PHASE II STUDY OF POSTOPERATIVE ADJUVANT IMMUNOTHERAPY AND RADIATION IN PATIENTS WITH COMPLETELY RESECTED STAGE II AND STAGE IIIA NON-SMALL CELL LUNG CANCER

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INDEX

Schema
Eligibility Check

1.0 Introduction
2.0 Objectives
3.0 Patient Selection
4.0 Pretreatment Evaluations
5.0 Registration Procedures
6.0 Radiation Therapy
7.0 Drug Therapy
8.0 Surgery
9.0 Other Therapy
10.0 Pathology
11.0 Patient Assessments
12.0 Data Collection
13.0 Statistical Considerations

References

Appendix I-a - Sample Consent Form
Appendix I-b - Sample Consent Form To Use Blood and Tissue for Research
Appendix II - Karnofsky and Zubrod Performance Status
Appendix III - Staging System
Appendix IV - Toxicity Criteria
Appendix V - Adverse Reaction Reporting Guidelines
Appendix VI - American Thoracic Society Regional Nodal Stations
Appendix VII - Suggested Radiation Fields of Initial AP:PA Portals
Appendix VIII - Immunologic Monitoring
Appendix IX - Biomarkers Correlative Study
Appendix X - Study Agents Shipment Form
Appendix XI - Designated Requestors Form
RADIATION THERAPY ONCOLOGY GROUP

RTOG 99-09

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SCHEMA

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Surgery ≤ 7 weeks

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PROTOCOL TREATMENT PLAN: (4/8/02)

**Immunotherapy:** 2 mg of CeaVac and 2 mg of TriAb intracutaneously at separate sites once a week x 3 starting weeks 2-7 after surgery, then monthly subcutaneously for two years. Vaccines will be given at separate sites on different arms. *(Vaccines should be given by day 49 following surgery.)*

**RT:** To start within 1 week following the 3rd weekly post-op vaccination *(and within 9 weeks after surgery).*

- 50.4 Gy/28 fractions/5-6 weeks
- *(1.8 Gy/day, 5 days/week)*
- 10.8 Gy/6 fractions boost to nodal stations if extracapsular extension of nodal metastases

**Eligibility:** *(See Section 3.0 for details)*
- Histologically determined non-small cell lung cancer
- Patients with pathologic N1 *( hilar)* and/or N2 nodal involvement from NSCLC which has been surgically resected *(peribronchial N1 only disease is excluded).*
- Zubrod Performance Status 0-1
- Post-op FEV₁ ≥ 1.0 L
- ANC ≥ 2000/mm³, platelets ≥ 100,000/mm³, serum creatinine ≤ 1.5 mg/dl
- No incompletely resected gross disease; no microscopic positive bronchial or vascular margins
- No brocho-alveolar carcinoma with lobar or multi-lobar involvement
- No prior chemotherapy, thoracic radiation, or prior immunotherapy
- No prior or concurrent malignancies, other than carcinoma in situ of the cervix and squamous/basal cell carcinoma of the skin, unless disease free for 3 years
- Patients with superior vena cava syndrome are excluded.
- No history of immune and immunodeficiency disorders; no active infection
- No history of hypersensitivity or contraindications to study treatments
- No history of colitis, inflammatory bowel disease, or pancreatitis within 10 years prior to first dose of study drugs
- Pregnant or nursing women are excluded due to possible harmful effects of immunotherapy to the unborn child
- Patients must sign a study-specific consent form.

Required Sample Size: 54
1. Has a diagnosis of non-small cell cancer of the lung been histologically confirmed?

2. Is the surgery in compliance with Section 8.0 of the protocol?

3. What was the stage at the time of surgical resection?

4. If the patient has stage II disease, is there only involvement of peribronchial lymph nodes?

5. Were contralateral mediastinal lymph nodes sampled?
   - If yes, were the locations designated according to the map in Appendix VI?
   - If no, were there no nodes or were there nodes < 1.5 cm visible on the contrast CT scan?

6. Are all surgical margins negative?

7. Does this patient have bronchioalveolar carcinoma with lobar or multi-lobar involvement or small cell (including “mixed”) histology?

8. Any evidence of superior vena cava syndrome?

9. Does the patient have any medical contraindications to thoracic irradiation?

10. Has the patient had any prior malignancy other than surgically treated carcinoma in situ of the cervix or squamous or basal cell carcinoma of the skin within the past 3 years?
    - If yes, has the patient been disease-free for at least 3 years?

11. Has this patient received any prior chemotherapy or immunotherapy within 3 years of study entry?

12. Has the patient received any prior thoracic radiation therapy?

13. Will protocol therapy begin within the time frame specified in Section 6.0?

14. Is the patient's Zubrod performance status 0-1?

15. Is the patient's ANC ≥ 2000/mm³?

16. Is the patient’s platelet count ≥ 100,000/mm³?

17. Is the patient’s creatinine ≤ 1.5 mg/dl? (See Section 3.1.8)

18. Has the patient undergone a comprehensive review of systems, and is the patient’s medical condition in compliance with Sections 3.1 and 3.2?

continued on page 2
Institution #  ________________
RTOG  99-09  ELIGIBILITY CHECK (8/1/01)
Case #  ________________  (page 2 of 3)

(Y) 19. Are the results of the postoperative pulmonary function tests in compliance with Section 3.1.7?
(Y) 20. Were laboratory values obtained within 3 weeks prior to registration?
(Y/N) 21. Were required scans and EKG obtained within 8 weeks prior to surgery and within 15 weeks prior to study registration?

(Y) If no, were the required studies obtained postoperatively?

The following questions will be asked at Study Registration:

1. Name of institutional person registering this case?
2. Has the Eligibility Checklist (above) been completed?
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 Name
6. Verifying Physician
7. Patient’s ID Number
8. Date of Birth
9. Race
10. Social Security Number
11. Gender
12. Patient’s Country of Residence
13. Zip Code
14. Patient’s Insurance Status
15. Will any component of the patient’s care be given at a military or VA facility?
16. Specify Lymph Node Status (N1 or N2).
17. Specify histology (squamous or non-squamous).

continued on page 3
Institution # ____________________________
RTOG 99-09 ELIGIBILITY CHECK (8/1/01, 4/8/02)
Case # ____________________________ (page 3 of 3)

_______________ 19. Immunotherapy Start Date

_______________ 20. Treatment Assignment

_______________ (Y/N) 21. Has the patient consented to participate in the optional Biomarkers Correlative Study (See Section 10.3)? (No=Option 1; Yes=Option 2 for data collection purposes)

The Eligibility Checklist must be completed in its entirety prior to calling RTOG. 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

1.1 Non-small cell lung cancer (NSCLC) represents the most common cause of cancer deaths in the United States among both men and women. Of all patients who present with NSCLC, approximately 30% are able to undergo complete resections. In a second randomized trial conducted by the Lung Cancer Study Group (LCSG) evaluated the role of post-operative chemoradiotherapy in patients with completely resected NSCLC. The majority of recurrences following curative resections are distant metastases. Even in stage I NSCLC, Feld documented distant metastases as the first site of recurrence in 65-75% of patients. Patients with resected stage II tumors have a similar recurrence pattern to those with stage I. In order to decrease the likelihood of recurrent disease following curative surgical resections, a variety of adjuvant therapies have been studied over the past several decades. Unfortunately, the majority of these studies have been unable to identify a subset of patients with an unequivocal benefit from adjuvant therapy.

In one study conducted by the Lung Cancer Study Group (LCSG-772), patients with completely resected stages II or III adenocarcinoma or large cell carcinoma of the lung were randomized to receive intrapleural BCG plus Levamisole versus post-operative chemotheraphy with cyclophosphamide, doxorubicin, and cisplatin (CAP, 400 mg/m²; 40 mg/m²; 40 mg/m², respectively). One hundred and forty-one patients were randomized after complete resection, of whom 130 were evaluable. Forty-five percent had stage II and 55% had stage III disease. This study reported significant differences in disease outcome between the groups favoring the CAP arm, consisting of a 7-month delay in median time to recurrence and a 15% survival advantage at one year (77% versus 62%). With a median follow-up of 8.5 years, the survival curves still favor the CAP arm, but the differences did not reach statistical significance. However, if the 15 patients randomized to chemotherapy, but who did not receive it, are excluded from the analysis, differences in survival reach statistical significance (p = 0.013). Of note, the majority of relapses (66%) occurred distantly indicating that systemic therapy more effective than CAP is required.

In a second randomized trial (LCSG-791), the Lung Cancer Study Group evaluated adjuvant therapy in patients with incompletely resected stages II and III NSCLC (all histologies). Incomplete resection was defined as either a tumor in the highest resected mediastinal node or the presence of positive surgical margins. One hundred and seventy-two patients were randomized to either post-operative thoracic RT (4000 cGy in a split, unconventional course) versus CAP plus RT. As in the previous study, CAP was administered every four weeks with 6 courses. Once again, the chemotherapy group experienced an improvement in median survival (20 months versus 13 months) and an improved median time to recurrence (14 months versus 8 months). In addition, the survival rate one year following randomization was 14% better (68% versus 54%) in the adjuvant chemoradiotherapy group. While these differences were not statistically significant, deaths due to cancer in the first post-operative year were less common in the chemoradiotherapy group (p = 0.02).

Another randomized trial conducted by the Lung Cancer Study Group evaluated the role of post-operative radiotherapy alone in patients with completely resected stages II and III squamous cell carcinoma of the lung. After complete resection, patients were randomized to observation versus post-operative radiotherapy (5000 cGy in 5 weeks). Although there was no difference in survival between the two groups, the patients who received radiotherapy had a significant decrease in local recurrence (1% versus 19% of all patients, p < 0.05). Although the study was not stratified to specifically address this issue, patients with N2 disease appeared to have a disease-free survival benefit from the post-operative radiotherapy. A similar result was found in another randomized trial by the Medical Research Council (MRC) of the United Kingdom. However, a recent meta-analysis of nine randomized trials from the same group (MRC) found a significant survival decrement with the addition of postoperative radiotherapy. This analysis has been criticized for including patients without pathologic nodal involvement (N0) and studies from the 1960’s and 1970’s employing older techniques (e.g. Cobalt irradiation) and different radiation fractionation schemes than are typically employed in this country. The interpretation of these older postoperative trials is also complicated by the fact that less vigorous staging was used before and during surgery compared to contemporary trials. Current trials typically require mediastinoscopy preoperatively and/or employ more consistent lymph node dissection/mapping.

The interpretation of these older postoperative trials is also complicated by the fact that less vigorous staging was used before and during surgery compared to contemporary trials. Current trials typically require mediastinoscopy preoperatively and/or employ more consistent lymph node dissection/mapping.
While many of these studies suggest that adjuvant therapy may improve outcome in patients with resected stage II and III NSCLC, the final answer is still not clear. These studies led to the emergence of RTOG 91-05, a prospective randomized trial of radiotherapy alone versus chemoradiation with cisplatin and etoposide, in patients with completely resected stage II and stage III-A NSCLC. The results of this study have recently been reported, showing no benefit with the addition of chemotherapy to radiotherapy.  

More recently, RTOG and others have decided to test newer, promising systemic agents, namely carboplatin and paclitaxel. Several investigators have accumulated considerable experience using carboplatin and paclitaxel with radiotherapy in patients with stage IIIB and bulky IIA non-small cell lung cancer. These studies indicate that chemoradiation with paclitaxel and carboplatin is active and well-tolerated in patients with inoperable locally advanced NSCLC. This approach was thus adapted to the “adjuvant” setting in patients who do not have bulky disease, i.e., into a setting in which cure rates may be substantially enhanced. RTOG 97-05, which employed adjuvant therapy with paclitaxel, carboplatin, and concurrent thoracic radiotherapy in completely resected stage II and IIIA NSCLC, completed accrual in June 1998. A total of 93 patients were entered, and the toxicity data is available for 62 patients. Overall, the treatment regimen was reasonably well tolerated with only one patient death reported after completing 4 cycles of chemotherapy secondary to sepsis and grade IV respiratory toxicity. There was one grade IV esophagitis after 2 cycles of chemotherapy. Overall, there was a 16% grade III/IV acute esophagitis rate and two late grade III esophageal toxicities. Five percent of the patients developed a grade III/IV acute respiratory toxicity.

As the role of chemotherapy in the adjuvant setting remains investigational, RTOG would like to explore a promising approach that could be added to radiotherapy without risking increased toxicity. The adjuvant approach selected for this study is active immunotherapy with vaccines directed against tumor-associated antigens. These antigens are seen as self-antigens by the immune system, and thus, the patient is typically immunologically tolerant to them.

Anti-idiotype antibodies can be used as vaccines to mimic tumor-associated antigens and generate an active immunity against these tumor-associated antigens. Two such anti-idiotype antibodies are available for clinical trials. One of these antibodies, 3H1 (CeaVac), mimics the carcinoembryonic antigen (CEA). CEA is an excellent tumor-associated antigen for active immunotherapy with anti-idiotype antibody for several reasons. First of all, CEA is typically present at high levels on the tumor cell surface. CEA is one of the most well-characterized antigens, its gene sequence is known, and its three-dimensional structures have been identified. CEA is a member of the immunoglobulin supergene family located on chromosome 19, which is thought to be involved in cell-cell interactions. Since CEA is considered an adhesion molecule, it might play an important role in the metastatic process by mediating attachment of tumor cells to normal cells. Thus, active immunotherapy targeted to CEA might be particularly beneficial in preventing metastasis. In this study, we will be using an anti-idiotype murine monoclonal antibody that identifies a specific epitope on CEA. This is a highly restricted CEA epitope that is not found on normal adult tissues and hematopoietic cells including granulocytes. In this way, the induction of a harmful auto-immune reaction can be avoided. Another anti-idiotype mimics the human milk fat globule antigen (HMFG) and is designated 11D10 (TriAb). Both of these vaccines are available through Titan Pharmaceuticals, Inc. Immunotherapy with vaccines likely should be most beneficial immediately after surgical resection of the primary tumor. Theoretically, the sooner the immune response is generated, the greater the likelihood of eradicating micrometastatic disease. Anti-idiotype antibodies can be used as vaccines to mimic tumor-associated antigens, and generate active immunity against these tumor-associated antigens. The 3H1 (CeaVac) vaccine has been studied extensively in patients with metastatic disease as well as in the post-surgical adjuvant setting. Thirty-two patients with resected Duke’s B, C and D and incompletely resected Duke’s D were treated with 2 mg of CeaVac every other week for 4 injections and then monthly until tumor recurrence or progression. Fourteen of the patients were treated concurrently with 5-fluorouracil (5-FU) chemotherapy regimens. All 32 patients generated high titer humoral immune responses against CEA. These responses were sustained over the course of therapy and were quantitated in the range of 125-135 mcg/ml serum. All IgG subclasses were present and the IgG1, IgG2 and IgG4 subclasses predominated. T-cell proliferative responses were reproducibly found in all 32 patients. Patients on 5-FU regimens did not exhibit a qualitative or quantitative difference in immune responses. A number of very high risk patients continue on study including 1 with incompletely resected Duke’s D at 14 months and 7 of 8 patients with resected Duke’s D from 12 to 33 months as well as 6 of 8 patients with Duke’s C2 disease from 14 to 40 months.
Over 100 breast cancer patients with either metastatic disease, patients in the post-surgical adjuvant setting, and patients receiving autologous bone marrow transplant have been treated with the second anti-idiotype, TriAb. In the post-surgical adjuvant setting, nearly 100% of patients have generated strong humoral and T-cell proliferative immune responses against HMFG. Breast cancer patients undergoing autologous bone marrow transplantation have been treated under two separate protocols. In one protocol, the vaccine is given following the stem cell infusion. In the second approach, the vaccine is given prior to conditioning high-dose chemotherapy, in order to generate a primary immune response prior to receiving intensive immunosuppressive therapy. Following three weekly immunizations with 11D10, these patients were leukopheresed, and stem cells were stored. Among these stem cells, it was hypothesized that lymphocytes resided that had a primary immune response against HMFG.

Twenty-two patients were treated with 4 weekly injections and then monthly injections of 11D10 following stem cell infusion. Five were unable to generate an immune response. Among the remaining patients, the immune response was delayed from 6 to 12 months following the stem cell infusion except for 3 patients who generated an immune response prior to 6 months. Thirty-four patients have been treated on the protocol in which three weekly vaccinations were given prior to high-dose chemotherapy and then continued monthly after stem cell infusion. All of these patients have thus far generated immune responses within 3 to 6 months of the stem cell infusion. These immune responses have been equivalent to immune responses seen in patients treated with the same vaccine in the post-surgical adjuvant setting without high-dose chemotherapy.

Patients treated with 3H1 or 11D10 following radiation therapy typically have a 6-12 month delay in their immune recovery, as radiation therapy is extremely immunosuppressive. Thus, it was felt to be critical to begin vaccine injections prior to radiation therapy in this non-small cell lung cancer population, in order to generate a primary immune response prior to immunosuppressive therapy.

An independent laboratory study of 20 NSCLC specimens demonstrated expressions of both CEA and HMFG on 19 of 20 patients sampled. HMFG was detected on a higher percentage of cells than CEA. This supports the strategy concept of a bivalent vaccine.

2.0 OBJECTIVES

2.1 To prospectively measure the immune (i.e., humoral and T-cell) response to each of two anti-idiotype vaccines (in combination with radiation).

2.2 To determine the qualitative and quantitative toxicity (and reversibility of toxicity) of this regimen.

2.3 To determine the recurrence-free and overall survival in patients with completely resected stage II and IIIA NSCLC treated with immunotherapy plus thoracic radiotherapy.

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility

3.1.1 Histologic documentation of non-small cell lung cancer.

3.1.2 Stage II (T1-2N1-2M0) and Stage IIIA (T1-2N2-3M0; T1-3N1-2M0) disease. Patients with N1 disease only are eligible only if there is pathologic involvement of hilar lymph nodes (and not only peribronchial lymph nodes). A pathologic diagnosis of Stage II/IIIA must have been made at the time of surgical resection (i.e., by postoperative pathologic diagnosis). Patients with T3N0M0 disease are not eligible.

3.1.2.1 Pre-operative cervical mediastinoscopy is required for any patient whose CT scan shows a mediastinal lymph node ≥ 1.5 cm in cross-sectional diameter. If the tumor is in the left upper lobe or left hilar region, level 5/6 lymph nodes with a cross-sectional diameter ≥ 1.5 cm must be biopsied by anterior mediastinotomy, extended mediastinoscopy or thoracoscopy. A complete cervical mediastinal staging includes nodal stations 2R, 4R, 7, 2L, 4L, 10R, and 10L, if possible. At least three stations should be sampled: one ipsilateral, 7 and one contralateral. If microscopic disease is present in one mediastinal nodal level, the patient is eligible for the study. If more than one level has tumor, or if extranodal disease is present in even one level, the patient is not eligible. Patients who are NOT required to undergo cervical mediastinoscopy and who are found to have extranodal disease at the time of surgical biopsy are eligible. (8/1/01)

3.1.2.2 N2 pre-operative patients should be considered for the NCI High Priority Study, RTOG 93-09 (INT 0139).

3.1.3 Surgery (within 7 weeks prior to study entry) consisting of lobectomy, sleeve resection, bilobectomy or pneumonectomy, as determined by the attending surgeon based on the intraoperative findings. See Section 8.0.
3.1.4 A complete nodal dissection is recommended but not required. For right thoracotomy lesions, the minimal mediastinal lymph nodes that must have been biopsied or resected include levels 4, 7 and 10 (Appendix VI). For left thoracotomy tumors, the minimum required for dissection of the mediastinum must include levels 5, 6 and 7. All surgical margins of resection must be negative for tumor.

3.1.5 Zubrod performance status of 0-1.

3.1.6 Consults by an attending thoracic surgeon, and radiation oncologist.

3.1.7 Post operative FEV1 ($\geq 1.0$ L) sufficient for patient to tolerate protocol radiation therapy.

3.1.8 ANC $\geq 2000$/mm$^3$ and platelet count $\geq 100,000$/mm$^3$; if serum creatinine is $> 1.5$ mg/dl, then creatinine clearance is needed; if creatinine clearance $> 60$ ml/min, patient is still eligible. Laboratory values must be obtained $\leq 3$ weeks prior to registration.

3.1.9 Scans as described in Section 4.4.

3.1.10 Signed study-specific informed consent prior to study entry.

3.2 Conditions for Patient Ineligibility

3.2.1 Prior chemotherapy within 3 years of study entry (other than topical therapy), any prior thoracic irradiation, or prior immunotherapy within 3 years of study entry.

3.2.2 No prior or concurrent malignancies, other than surgically treated carcinoma in situ of the cervix and squamous or basal cell carcinoma of the skin, are allowed unless disease-free for at least 3 years.

3.2.3 Medical contra-indication to surgery, irradiation, or immunotherapy.

3.2.4 Stage IIIB (i.e., contralateral N2 or N3) disease or Stage IV (M1) disease or T3 N0M0 disease.

3.2.5 Incompletely resected gross disease.

3.2.6 Microscopic positive bronchial or vascular margins.

3.2.7 Small cell lung carcinoma (including “mixed” histology).

3.2.8 Broncho-alveolar carcinoma with lobar or multi-lobar involvement.

3.2.9 Superior vena cava syndrome.

3.2.10 Pregnant or nursing women due to the unknown effects of immunotherapy on the unborn child (men and women of reproductive potential must use an accepted form of birth control).

3.2.11 Prior CeaVac or TriAb therapy or previous investigational CEA-derived therapies.

3.2.12 Prior exposure to murine antibodies (e.g. OncoScint® scan) or known sensitivity to rodent proteins.

3.2.13 Active infection.

3.2.14 Immunization (e.g. flu) within 30 days prior to the first dose of study drug.

3.2.15 Immunomodulatory therapy (e.g., gold, auranofin, hydroxychloroquine, sulfasalazine, penicillamine, levamisole, dapsone, azathioprine, IVIG, leukotriene antagonists, cromoglycate, ketotifen, nedocromil, PUVA, plasmapheresis, etc.) or investigational agent use within the 30 days prior to the first dose of study drug or five half-lives of the action of the agent, whichever is longer.

3.2.16 History of hypersensitivity or contraindication to study treatments (e.g., CeaVac, aluminum hydroxide, murine proteins, TriAb) or any excipients of the study treatments.

3.2.17 History of clinically significant hypersensitivity reactions (angioedema, anaphylaxis, serious dermatological manifestations) or asthmatic attacks requiring hospitalization.

3.2.18 History of immune and immunodeficiency disorders (e.g. HIV-positive, sarcoid, tuberculosis, rheumatoid arthritis, and autoimmune disorders).

3.2.19 History of colitis, inflammatory bowel disease or pancreatitis within ten years prior to the first dose of study drug.

3.2.20 History of drug or alcohol abuse (excluding nicotine) within 12 months prior to the first dose of study drug.

3.2.21 History of seizures requiring continuous medication and/or known CNS metastasis.

3.2.22 History of psychiatric or addictive disorders that would preclude obtaining informed consent.

3.2.23 History of celiac disease, familial polyposis, Turcot’s syndrome, Gardner’s syndrome, Peutz-Jegher’s syndrome, or hereditary non-polyposis colon cancer type B.

3.2.24 Systemic corticosteroids or immune suppressant use within 45 days prior to the first dose of study drug.

3.2.25 Expectation that systemic corticosteroids, other immunosuppressants (such as methotrexate, cyclophosphamide, cyclosporin) or chronic systemic antihistamines will be required by the patient during the study.

4.0 PRETREATMENT EVALUATIONS

4.1 A complete history and physical to include performance status, recent weight loss, percent of weight loss, usual weight, and concurrent non-malignant disease and its therapy must be recorded.

4.2 Immune bloodwork must be obtained within 21 days prior to the first dose of immunotherapy, and will be drawn in (2) 12 ml red top tubes (no serum separators) and (2) 12 ml green top tubes (preservative-free heparinized tubes); See Section 10.2 for specimen collection and handling; (Appendix VIII).
Laboratory studies will include a CBC with differential, platelet count, LFTs, electrolytes, creatinine, magnesium, total protein, and albumin, done within 3 weeks (21 calendar days) before study entry. Creatinine clearance is required if serum creatinine > 1.5 mg/dl. (8/1/01)

Chest X-ray, EKG, MRI or CT scans of brain (for neurologically symptomatic patients), chest, upper abdomen to include liver and adrenals, radionuclide bone scan (mandatory for symptomatic patients or alkaline phosphatase ≥ 2 x upper normal), are required within 8 weeks prior to definitive surgery. If any of the above required studies were not obtained preoperatively, they must be obtained postoperatively, prior to study enrollment. Maximum interval between scans and study registration is 15 weeks.

Pulmonary Functioning Tests (PFTs) must be obtained postoperatively since it is required for RT planning.

Serum pregnancy test as applicable.

Peripheral blood and patient questionnaire for optional Biomarkers Study; See Section 10.3 for specimen collection and handling; (Appendix IX).

REGISTRATION PROCEDURES (8/1/01, 4/8/02)

Prestudy Requirements

Prior to registering your first patient to this study, submit the following documents to RTOG Headquarters, Protocol Office (ATTN: Regulatory Documents for RTOG 99-09):

- IRB approval
- IRB approved, study-specific Consent Form
- Principal Investigator’s signed 1572 Form
- Conflict of Interest/Financial Disclosure Form for Principal Investigator and all sub-investigators
- Recent CV for Principal Investigator and all sub-investigators
- Study Agent Shipment Form (Appendix X)
- Investigational Product(s) Designated Requestors Form (Appendix XI)

RTOG will forward these documents to Titan for review and approval. Upon approval, Titan will send the site the Investigational Product Order Request Form, with instructions for completing the form. Upon registering a patient, sites are to complete the Investigational Product Order Request Form and fax it back to Titan who will ship vaccine to the site. Titan Pharmaceuticals will not ship vaccine until the above documents have been reviewed and approved (See Section 7.2.4).

Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday 8:30 am to 5:00 pm ET. The patient will be registered and a case number will be assigned and confirmed by mail. The Eligibility Checklist must be completed in its entirety prior to calling RTOG. 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.

RADIATION THERAPY

Radiation therapy is to be initiated no earlier than 4 weeks following surgery. Radiation therapy must begin by no later than 9 weeks after surgery and within one week after the third immunotherapy injection.

Equipment

All patients will be treated with isocentric equipment with a minimum SAD of 80 cm. Treatment should be given with photon energies of 4-18 MV. The use of electron beams is not permitted.

Treatment Planning

All patients must be simulated prior to the start of radiation therapy. Both the initial portion of treatment, which is to be given with AP/PA portals and the off-cord boost to be given with lateral and/or oblique portals should be simulated at this time with the patient in the same position for both phases of treatment to facilitate the construction of composite isodose plans. Portal verification films should be taken of each field, copied, and submitted for review. The use of custom immobilization and support devices such as styrofoam molds is encouraged. A CT scan of the chest for radiation treatment planning may suffice for the postoperative scan.

Target Volume

The desired target volume for treatment on this study will encompass the mediastinal and ipsilateral hilar nodes. The tumor bed is to be included only if invasion of the parietal pleura is documented in the operative pathology report. The target volume is thus to be defined in terms of anatomic landmarks rather than the preoperative appearance of the tumor. A postoperative CT scan is required to document post surgical anatomic changes and to serve as a baseline study for comparison with follow-up studies. The target volume will include the hilum ipsilateral to the primary tumor as well as bilateral peritracheal nodes. Either the contralateral hilum nor the supraclavicular fossae are to be included on a routine basis.
If, however, it is necessary to treat the tumor bed for a T3 lesion of the upper lobe, the supraclavicular fossae may be included. The exact placement of the field borders will vary somewhat from case to case depending on the postoperative shift of the mediastinal structures. See Appendix VII for suggested radiation fields for initial AP/PA portals. The following are guidelines:

6.3.1 **Superior border** – at the level of the thoracic inlet for patients with N1 disease. Supraclavicular fossae for patients with N2 disease.

6.3.2 **Inferior border** – 5 cm below the carina for upper lobe lesions and 8 cm below the carina for lesions of the lower or middle lobe, or for lesions of any primary site if the subcarinal nodes are histologically involved.

6.3.3 **Ipsilateral border** – 2 cm beyond the tracheal edge and encompassing the ipsilateral hilum with a 2 cm margin. In patients who have undergone pneumonectomy, the bronchial stump and associated peribronchial nodes should be included with margins based on the preoperative appearance of the hilum.

6.3.4 **Contralateral border** – 2 cm lateral to the edge of the trachea as defined on the postoperative simulator film and CT scan.

6.3.5 In patients in whom nodal (N1 or N2) disease breaches the nodal capsule, these nodal stations as mapped on the intraoperative staging forms, and not the entire mediastinum, will be included in a boost field which should encompass the nodal region with 1 cm margins.

6.4 **Treatment Technique**

6.4.1 The initial portion of the treatment will be given with parallel opposed AP/PA portals with equal weighing. These will typically be used for approximately 36-42 Gy of the planned total of 50.4 Gy to the full mediastinal volume.

6.4.2 To deliver the remainder up to 50.4 Gy, the same mediastinal target volume will be used excluding the spinal cord from the high dose region. The spinal cord should not receive greater than 45 Gy. Specifically, the supraclavicular areas should be excluded from the oblique field. Oblique fields using angles between 20 and 40 degrees, with medial borders defined by the ipsilateral pedicle of the spine and including the subcarinal space and contralateral mainstem bronchus, are the preferred method. Lateral fields may not be used. Direct posterior spinal cord shields are not acceptable.

6.4.3 If the boost is required (Section 6.5), then the target volume should be reduced to include only the involved lymph node area or area of T3 invasion plus a 1 cm margin.

6.5 **Dose**

The entire mediastinal target volume will receive 50.4 Gy/28 fractions 5-6 weeks. 1.8 Gy once a day 5 days/week.

Patients requiring mediastinal boost of 10.8 Gy in 6 fractions include: (1) patients with pathologically documented extracapsular extension of the nodal metastasis and (2) T3 lesions. This boost is not optional.

6.5.1 Dose will be prescribed to the midplane on the central axis for AP/PA treatment and to the isocenter for oblique and/or lateral treatment.

6.5.2 Dose inhomogeneity corrections (lung corrections) will NOT be used.

6.5.3 The dose inhomogeneity across the target volume in the central transverse plane will be no more than +/- 5%. A composite isodose distribution will be calculated, copied, and submitted in one transverse plane at the central axis.

6.5.4 Tissue compensators for sloping chest surfaces are required if separations measured from top-to-bottom of the field result in variations in top-to-bottom dose of ≥ 10%, or if the slope between the upper and lower borders has a difference in depth of ≥ 2 cm.

6.6 **Suggested Maximum Doses to Critically Sensitive Normal Structures**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal Cord</td>
<td>45 Gy</td>
</tr>
<tr>
<td>Heart</td>
<td>Not more than 35 Gy to &gt; 50% cardiac volume</td>
</tr>
<tr>
<td>Lung</td>
<td>20 Gy to entire lung</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Will tolerate doses required by protocol</td>
</tr>
</tbody>
</table>

6.7 **Treatment Interruptions**

The majority of esophageal complaints are self-limited and do not require breaks, which are specifically discouraged. Dietary and medicinal regimens of local choice are encouraged. **Amifostine may not be given in this study.** Indications for interruption include > 10% weight loss and the inability to swallow solids and liquids. Please call Dr. Benjamin Movsas or, in his absence, Dr. David Johnstone with questions.

6.8 Treatment is to be given 5 days per week, once each day. If there are holidays, equipment failure, or treatment interruption, the treatment should recommence as early as possible, and the cause of the delays documented.
7.0 DRUG THERAPY

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

7.1 Treatment Plan

7.1.1 Immunotherapy (4/8/02)

CeaVac and TriAb intracutaneously at separate sites once a week x 3, starting weeks 2-7 after surgery, then monthly subcutaneously for two years.

7.1.2 Concurrent XRT: To start within 1 week following the 3rd weekly post-op vaccination (and within 9 weeks after surgery).

50.4 Gy/28 fractions/5-6 weeks (1.8 Gy/day, 5 days/week)

10.8 Gy/6 fractions boost to nodal stations if extracapsular extension of nodal metastases

7.2 Immunotherapy

7.2.1 Immunotherapy Treatment Plan (8/1/01, 4/8/02)

2 mg of TriAb and 2 mg of CeaVac will be administered at separate injection sites on different arms on the same schedule. The first three injections will be intracutaneous and all subsequent injections will be subcutaneous. Vital signs need to be obtained every 15 minutes for at least 30 minutes following injections. Therapy will be given every week for three immunizations (starting 2-7 weeks after surgery) and then monthly (every four weeks) for a total of 26 injections over a two-year period. (Vaccines should be given by day 49 following surgery. If it becomes absolutely necessary to deviate from this schedule, the vaccine should be administered within a window of 1 day from the target date for the first three injections, and within a window of 7 days from the target date for subsequent injections).

The combination of vaccines (CeaVac and TriAb) will be administered for two years. The administration should continue for this duration even if the patient progresses, and can be given concurrently with chemotherapy. The rationale for this comes from the fact that patients may require six or more injections to achieve an adequate immune response, which can then be maintained with monthly booster injections in order to have a continuing anti-tumor effect. This immune response can be generated and maintained even when concurrent standard or high-dose chemotherapy is administered.

7.2.2 Chemical Properties of TriAb Anti-Idiotype Monoclonal Antibody (4/8/02)

The TriAb anti-idiotype monoclonal antibody was produced as ascites and then purified. General safety, sterility, pyrogenicity, polynucleotides and mycoplasma and adventitious virus contamination have been tested in accordance with a Notice of Claimed Investigational Exemption for a new drug (IND) from the Office of Biologics, Food and Drug Administration (BB-IND 5745).

7.2.3 Chemical Properties of CeaVac Anti-Idiotype Monoclonal Antibody (4/8/02)

The CeaVac anti-idiotype monoclonal antibody was grown as ascites in BALB/c mice. General safety, sterility, pyrogenicity, polynucleotides and mycoplasmas and adventitious virus contamination has been tested in accordance with a Notice of Claimed Investigational Exemption for a new drug (IND) from the Office of Biologics, Food and Drug Administration. The IND application was supervised by Dr. Malaya Chatterjee of the University of Kentucky and has been approved (BB-IND 5533).

7.2.4 Supply and Distribution (8/1/01, 4/8/02)

Titan Pharmaceuticals will supply and distribute CeaVac and TriAb. Prior to registering their first patient, sites must submit the following documents to RTOG: IRB approval; IRB approved, study-specific Consent Form; Principal Investigator’s signed 1572 form; Conflict of Interest/Financial Disclosure Form for Principal Investigator and all sub-investigators; recent CV for Principal Investigator and all sub-investigators; Study Agents Shipment Form (Appendix X); and Investigational Product(s) Designated Requestors Form (Appendix XI). RTOG will forward these documents to Titan for review and approval. Upon approval, Titan will send the site the Investigational Product Order Request Form, with instructions for completing the form. Upon registering a patient, sites are to complete the Investigational Product Order Request Form and fax it back to Titan who will ship CeaVac and TriAb separately in 2 ml vials, packaged in boxes of 6 vials each, and on cold packs. Although the supply will not be patient-specific and may be used as needed for study patients, Titan will only ship CeaVac and TriAb after a site has registered a patient. Sites can request subsequent shipments by completing the Investigational Product Request Form and faxing it to Titan. Only requests from individuals listed on the Investigational Product(s) Designated Requestors form will be processed. CeaVac and TriAb will be shipped overnight to sites Monday through Thursday to arrive at the sites Tuesday through Friday. There will be no Saturday or holiday shipments. Allow three business days for processing, i.e. if a request is received at Titan on Friday, then the shipment will arrive at the site on Wednesday. For questions about investigational product shipments, please contact Kristen Yen, CRA II, at Titan, at (650) 244-4990, ext. 269. Drug inventory logs must be kept by the site for review by RTOG and Titan upon
request. At the completion of the study, remaining CeaVac and TriAb supplies should be inventoried and destroyed on site.

7.2.5 Immunotherapy Information

7.2.5.1 Drug Classification
- Biological response modifier

7.2.5.2 Mode of Action
- Immunomodulatory; direct effects

7.2.5.3 Availability
- 2 mg vial; free to study patients from Titan Pharmaceuticals, Inc.

7.2.5.4 Storage
- Refrigerate at 2-8°C (Do Not Freeze)

7.2.5.5 Shelf Life
- Two years at refrigeration

7.2.5.6 Stability After Withdrawal from Vial
- 30 minutes at room temperature

7.2.5.7 Vaccine Administration
- Vaccines will be supplied in vials and will require no reconstitution prior to injection. The step-by-step instructions for the intracutaneous (intradermal) and subcutaneous administrations of the CeaVac and TriAb vaccines (to be injected at separate sites in different arms) are as follows:
  1) Prepare the injection site by cleansing an area of skin on the upper arm (deltoid) with an alcohol swab and allow the skin to dry. Use clean needle for each patient injection.
  2) Withdraw the study drug from the vial (2 mg dose from 2 mg/1ml vial) and expel all bubbles and air from the syringe.
  3) Stretch the skin taught at the injection site and insert the needle with the bevel at a 45º angle or less.
  4) The needle should come to rest in the dermis (for the initial three weekly intracutaneous injections) or just below it (for the subsequent monthly subcutaneous injections).
  5) A small bleb should form at the injection site. Continue to inject until the entire solution has been administered.
  6) Quickly withdraw the syringe/needle and discard appropriately.
  7) Gently blot any solution on the skin surface with gauze pads or paper tissue.
  8) Repeat this procedure (steps 1-8) with the other vaccine in the other arm.
  9) Observe the patient for 30 minutes, and instruct the patient not to scratch or apply pressure to the injection site for 30 minutes. Vital signs should be recorded at 15 and 30 minutes post injection.
  10) All previous injection sites should be observed and any adverse events recorded at each visit. Document the date/time (and site – left vs. right arm) of each injection.

7.2.6 Expected Toxicities and Management of Immunotherapy

7.2.6.1 The most likely immunization side effects anticipated in this study are local skin reaction, fever, chills, and sweats as the direct effect of antibody. These seldom require therapy and persist for only a few hours. Anti-pruritics will be used symptomatically post therapy. Premedication with anti-pruritics or steroids will be avoided. The injections will continue despite these symptoms. Ice packs or heat applications to the injection sites will be avoided due to the potential change in the drug’s absorption rate.

7.2.6.2 The next most likely side effects are urticaria and/or pruritus secondary to allergic reactions to mouse protein. They may be treated symptomatically with diphenhydramine (Benadryl) or hydroxyzine (Atarax) but prophylactic administration of these is not recommended. Therapy will be continued despite the appearance of urticaria or pruritus. Ice packs or heat applications to the injection sites will be avoided due to the potential change in the drug’s absorption rate.

7.2.6.3 Less common but more severe allergic reactions include bronchospasm and anaphylaxis. In the presence of these, treatment should be immediately discontinued and the patient treated with epinephrine, steroids, oxygen, volume support, other bronchodilators such as theophylline as needed, and other supportive care as needed. The injections will not be resumed.

7.2.6.4 Uncommon mild to moderate side effects include nausea, vomiting, diarrhea, and increased serum transaminases. These generally require no specific therapy and resolve spontaneously.

7.2.6.5 Theoretically, immune complex disease as manifested by skin, joint, renal, or other manifestations could occur, but these should be rare in the absence of prior exposure to mouse protein. More severe
generalized skin reactions (acute or chronic) and necrotic reaction at injection sites can rarely occur as well.

7.2.6.6 Study drug administration for a patient will be discontinued if any study drug related Grade 3 or 4 toxicity is observed. This would include, but not be limited to, events described in Section 7.2.5.3 (bronchospasm and anaphylaxis) and in Section 7.2.5.5 (immune complex disease, severe generalized skin reactions and necrotic reactions at injection sites). The adverse event would be reported to and discussed with the medical monitor. Treatment may be resumed following discussion and at the discretion of the medical monitor in consultation with appropriate parties (e.g., the principal investigator, the FDA, and Titan).

7.3 Monitoring for Safety and Toxicity

7.3.1 This study will utilize the Common Toxicity Criteria (CTC) version 2.0 for toxicity and Adverse Event Reporting (occurring ≤ 90 days from start of treatment). A copy of the CTC version 2.0 can be downloaded from the CTEP Home page (http://ctep.info.nih.gov). All appropriate treatment areas should have access to a copy of the CTC version 2.0. This study will be monitored by the Clinical Data Update System (CDUS) version 1.1. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

7.3.2 General Guidelines
Adverse event (AE), safety and toxicity monitoring will be performed throughout the study. All AEs, regardless of causality, will be recorded on the appropriate case report form. In addition, AEs which are included in the National Cancer Institute Common Toxicity Criteria (NCI CTC) will be graded accordingly. Appropriate medical intervention will be provided and, if necessary, study drug administration will be discontinued.

7.3.3 Definitions
The following definitions, developed in conjunction with the Code of Federal Regulations (CFR) and the International Committee on Harmonization (ICH) Guidance for Industry, E6, Good Clinical Practice (ICH GCP guidelines) will be used for the purpose of identifying adverse events in this clinical trial.

7.3.3.1 Adverse Event (AE) or Adverse Experience
Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product. An Adverse Event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or increase in severity of a pre-existing abnormality, temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (ICH GCP Guidelines, April 1996).

7.3.3.2 Serious Adverse Event (SAE) (21 CFR § 312.32, revised April 1, 1998). A serious adverse event or reaction is any untoward medical occurrence at any dose that:
- Results in death
- Is life-threatening (at the time of the event) or
- Requires inpatient hospitalization or prolongation of existing hospitalization or
- Results in persistent or significant disability/incapacity or
- Is a congenital anomaly/birth defect (in an offspring)

Medical and scientific judgment should be exercised in deciding whether the designation of an event as serious is appropriate in other situations, such as medical events that may not be immediately life-threatening but may require intervention to prevent one of the outcomes listed in the above definition.

7.3.4 Hospitalizations as Serious Adverse Events
All adverse events requiring hospitalization or prolongation of hospitalization should be reported as serious adverse events unless they occur greater than 30 days after the final study drug administration AND are not drug related, or are listed as follows. Hospitalizations meeting the following criteria will not be reported as a SAE but must be recorded on the appropriate form in the CRF: study drug/chemotherapy administration, transfusion support, disease staging/re-staging procedures, concomitant radiotherapy, thoracentesis or paracentesis, or placement of an indwelling catheter.

7.3.5 Adverse Event Reporting
All adverse events regardless of causality must be entered on the Adverse Event CRF. Adverse events include: new adverse events; worsening baseline conditions; clinically significant laboratory findings; disease-related signs and symptoms that were not present at baseline, and any event or findings that the Investigator feels is clinically significant. Disease related signs and symptoms that are present at baseline should not be recorded as adverse events unless they worsen in severity or frequency with causality appropriately identified. Information collected concerning AEs will include the:
- Name of the event,
Onset date, Resolution date, Severity, NCI CTC Grade, Relationship to study drug administration determination, and Outcome

All AEs will be followed while a subject is receiving study drug, and for 30 days following the last study drug administration. Those AEs which have been designated as study drug related will be followed until resolution, or until the end of the follow-up period.

7.3.6 **Serious Adverse Event Reporting (4/8/02)**

Serious Adverse Events (SAEs) must be reported to the Medical Monitor at RTOG within 24 hours of knowledge of the event. RTOG will then forward SAEs to Titan Pharmaceuticals within 24 hours of receipt. All Serious Adverse Events that occur while a patient is receiving study drug *(or within 30 days of the final study drug administration)* are reportable. During the follow-up period beyond 30 days from the final study drug administration, only those SAEs which are considered to be study drug related should be reported. This does not apply to those subjects who have not received study drug in more than 30 days due to treatment delays, but are still on study.

The procedure for reporting a SAE is as follows:

Within 24 hours of knowledge of the event, the site must contact the Medical Monitor at RTOG by telephone or facsimile to report the event.

The initial report should include all information known at the time of the report *(additional information can be reported as discovered).*

The site will complete a MedWatch form *(FDA Form 3500A)* that includes the following information, as available:

- Subject ID,
- Basic demographic information *(age, gender, weight)*,
- The outcomes attributed to the event *(death, life-threatening, hospitalization [new or prolonged], disability, congenital anomaly, required medical intervention to prevent permanent impairment/damage, etc.)*,
- The onset date,
- A brief description of the event including frequency and severity of symptoms leading to diagnosis and investigator's assessment of causality,
- A list of relevant test results and lab data,
- Any other relevant history,
- The first and last dates of study drug administration,
- Whether the study drug was discontinued or schedule modified,
- Dates that study drug was discontinued or schedule modification,
- Whether the event abated after study drug stopped/modified,
- Investigator assessment of causality.

The completed MedWatch form should be faxed to RTOG as soon as possible following the initial telephone and/or fax report. RTOG and/or the Medical Monitor may contact the Investigator to request additional information regarding the event or to confirm information. All SAEs must also be entered on the AE CRF.

The Investigator is responsible for reporting all SAEs to the Medical Monitor via RTOG, following up on completion of the MedWatch form, and notifying the appropriate Institutional Review Board *(IRB/EC)*/Ethics Committee *(EC)* of the occurrence and details of the event. RTOG is responsible for forwarding SAEs to Titan Pharmaceuticals, within 24 hours of receipt. In the event there is a question as to whether the experience is serious, the event should be reported.

7.3.7 **Special Reporting for this Study** *(fax 215/928-0153)*

7.3.7.1 Any grade ≥ 2 pulmonary, renal, or gastrointestinal adverse event related to study drug will be considered to be reportable to the FDA as an expedited event. These adverse events also should be reported to RTOG within 24 hours. RTOG will then forward this information to Titan within 24 hours of receipt for submission to the FDA.

7.3.7.2 All grade ≥ 3 non-hematologic toxicities must be reported to RTOG within 24 hours.

7.3.7.3 All grade ≥ 4 hematologic toxicities except lymphopenia must be reported to RTOG within 24 hours.

7.3.7.4 Data submission must adhere to the timetable specified in Section 12.0 and the patient calendar issued by RTOG.
8.0 SURGERY (PRE-REGISTRATION)

8.1 Accurate intraoperative surgical staging will be ensured by strict attention to the anatomic boundaries between nodal groups described by the American Thoracic Society regional nodal stations definitions (Appendix VI).

8.1.1 A pathologically complete surgical resection of the tumor mass by lobectomy, bilobectomy, sleeve resection, or pneumonectomy will be performed.

8.1.2 A complete mediastinal lymph node dissection or nodal sampling is recommended but not required.

The minimal acceptable lymph node sampling includes levels R4, R10 & 7 from right-sided tumors and levels 5, 6, 7 from left-sided tumors. Complete lymph node dissection involves removing all lymph nodes of the anatomically defined level. Lymph node sampling necessitates opening the pleura and removing representative tissue from each lymph node level. All nodal tissue obtained must be carefully labeled by lymph node level. This must be performed by the operating surgeon in the operating room. Complete mediastinal dissection or sampling includes the following nodal levels:
- Levels 2 and 4*
- Levels 8
- Levels 5 and 6 in all patients when the primary lesion is located in the left lung
- Level 7
- Level 9
- Level 10

*It is recognized that Levels 2L and 4L are often difficult to dissect.

All ipsilateral lymph node levels 11-13 should be removed en bloc with the primary surgical specimen. In addition, any lymph nodes which are not mentioned above but which appear grossly abnormal at surgery should be removed and their locations identified. The presence or absence of evidence of invasion of the nodal capsule must be noted on the pathology reports for hilar and/or mediastinal nodes. Patients in whom there is extracapsular extension of nodal metastases will have these nodal stations boosted with an additional 10.8 Gy in 6 fractions.

9.0 SUPPORTIVE THERAPY

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

9.2 The use of non-protocol radiotherapy and corticosteroids should be clearly indicated on the data forms, as should dose and reason for continuation.

9.3 Hyperalimentation may be used, but details must be clearly outlined on data forms.

9.4 Amifostine may not be given.

10.0 PATHOLOGY

10.1 RTOG Tissue Bank

10.1.1 Patients entered on this study should also participate in the RTOG Tissue Bank.

10.1.2 The following must be provided:

10.1.2.1 One paraffin block of tumor and/or 15 unstained slides. It is strongly encouraged that immunoperoxidase staining with MC10 and 8019 be performed on all blocks. Block/slides must be clearly labeled with the pathology identification number that agrees with the pathology report.

10.1.2.2 Pathology report documenting that submitted block or slides contain tumor.

10.1.2.3 A Pathology Submission Form must be included and must clearly state that it is being submitted for the RTOG Tissue Bank.

10.1.3 RTOG will reimburse pathologists from submitting institutions $100 per case if proper materials are submitted. RTOG Administration will prepare the proper paperwork and send a check to your institution after confirmation that LDS Hospital has received the appropriate number of slides/blocks. (4/8/02)

10.1.4 Patient consent form, Appendix I-b, should give the Pathology Department authority and responsibility to comply with this request (pathology blocks belong to the patient from whom tissue has been removed).

10.1.5 Materials will be sent to:

LDS Hospital
Department of Pathology
E.M. Pathology
8th Avenue and C Street
Salt Lake City, UT 84143
(801) 408-5626
FAX (801) 408-5020
Ldafurme@ihc.com
10.2 Immunologic Monitoring – Specimen Collection, Preparation/Storage, and Shipping (8/1/01)

10.2.1 The Immunologic Monitoring and Cellular Products Laboratory (IMCPL), located at the University of Pittsburgh Cancer Institute and under the direction of Dr. Theresa Whiteside, will perform the immunologic studies. These studies will include the following tests: binding of Ab1' from patient serum to CEA, proliferation in response to Anti-id 3H1, binding of Ab1' from patient serum to HMFG, proliferation in response to Anti-id 11D10, post-heat CEA (regular CEA at baseline) and human anti-mouse antibody (HAMA) response (see Appendix VIII).

10.2.2 Whole blood specimens collected for immunologic studies must be handled in a special way. Prior to the start of protocol treatment, obtain specimen shipping kits for sample submission to the laboratory by calling the Study Coordinator responsible for RTOG protocol 99-09 at 412-624-3277. The laboratory is open for regular business Monday through Friday from 8:30 AM to 5:00 PM. If you are unable to reach the RTOG Study Coordinator, you may call the laboratory at 412-624-0080 or e-mail Dr. Whiteside at whitesidetl@msx.upmc.edu with a copy to Dr. Elder at elderem@msx.upmc.edu.

10.2.3 Specimens are shipped at room temperature (no refrigeration). Specific directions for handling and shipping of the specimens will be included with the specimen shipment kit supplied by the IMCPL and must be followed explicitly. The temperature checks will be included with each kit to monitor the sample temperature during shipment. Samples that have exceeded the limits defined in the kit will not be processed. Samples must be shipped immediately after collection to reach the laboratory no later than 24 hours after their collection. If shipment is delayed, samples must be kept at room temperature. Do not freeze or refrigerate the venous blood samples.

10.2.4 Samples may be shipped on Sunday through Friday only by Overnight Priority delivery service, so that the samples arrive at the laboratory between 8:30 AM and 5:00 PM on Monday through Friday and between 8:30 AM and 12:00 PM on Saturday. Federal Express is the preferred courier. Do not ship samples on Saturdays or prior to legal holidays. If blood cannot be drawn for delivery as specified above, please call the laboratory to make special arrangements. Otherwise, the samples that arrive without prior notification on Saturday afternoon or Sunday or on a holiday will not be processed. Samples that are more than 24 hours old will not be processed. Please ship to:

RTOG 99-09 Study Coordinator
IMCPL
W1041 Biomedical Science Tower
200 Lothrop Street
Pittsburgh, PA 15213-2582
Phone: 412-624-0080
FAX 412-624-0264

An IMCPL specimen requisition/shipment form must be submitted with each sample. Specimens must be identified by using RTOG study number and case number assigned at registration (example: 9909-001). Institutions must notify the RTOG Study Coordinator in the laboratory prior to shipping samples by faxing a Notice of Shipment Form to the laboratory. This will allow the laboratory to track the package in the event that there are any problems in delivery. If you are unable to get through to the laboratory by fax, telephone the RTOG Study Coordinator.

10.3 Optional Translational Research/Biomarkers Correlative Study - Specimen Collection, Preparation/Storage, and Shipping (4/8/02)

10.3.1 Two tubes (yellow top tubes) of peripheral blood (approximately 8 mls each) will be collected from each patient preferably prior to start of radiation, but it is acceptable to do so at any time while the patient is on protocol. A blood collection kit can be obtained in advance by calling Dr. Cindy Spittle at (215) 214-1696 (See Appendix IX for details). Institutions must notify Dr. Cindy Spittle (215-214-1696) or Dr. Clapper (215-728-4301) prior to shipping the yellow top tubes. The tubes must be labeled with the RTOG study number and case number assigned at registration (e.g., 9909-01). Blood must be shipped on the same day as it is drawn (Monday-Thursday) at room temperature, by Federal Express for overnight delivery.
10.3.2 Corresponding hormonal supplementation data and tobacco/alcohol history will be obtained by data form and returned to RTOG Headquarters.

10.3.3 RTOG will reimburse submitting institutions $100 per case (in addition to the reimbursement described in Section 10.1) if proper materials are submitted (This reimbursement is handled through an invoice submitted to RTOG Administration, ATTN: Path Reimbursement, 1101 Market Street, 14th Floor, Philadelphia, PA 19107-2914).

10.3.4 Patient consent form, Appendix I-b, must be signed by the patient to give authority and responsibility to comply with this request.

10.3.5 Materials will be sent to:

Margie L. Clapper, Ph.D.
Division of Population Science, P2044
Fox Chase Cancer Center
7701 Burholme Avenue
Philadelphia, PA 19111
(215) 728-4302

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (8/1/01, 4/8/02)

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<td></td>
<td></td>
<td>X&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Toxicity Evaluation</td>
<td></td>
<td>X&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
<td>X&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Pregnancy Test</td>
<td></td>
<td>X&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
<td>X&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Blood for biomarkers study</td>
<td>X&lt;sup&gt;p&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>X&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Patient questionnaire</td>
<td></td>
<td>X&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
<td>X&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

a. LFTs include bilirubin, SGOT, alkaline phosphatase, LDH.
b. Chest X-ray, EKG, MRI or CT scans of brain (for neurologically symptomatic patients), chest, upper abdomen to include liver and adenals, radionuclide bone scan (mandatory for symptomatic patients or alkaline phosphatase ≥ 2 x upper normal), are required within 8 weeks prior to definitive surgery. If any of the above required studies were not obtained preoperatively, they must be obtained postoperatively, prior to study enrollment. Maximum interval between scans and study registration is 15 weeks.
c. Abdominal CT not necessary if a chest CT includes the entire liver and the adrenal glands. Any adrenal gland showing loss of normal contour, regardless of size, must be biopsied.
d. Head CT, or preferably an MRI, is required only in neurologically symptomatic patients. At relapse, patients should undergo a head scan to document status of CNS only if they are neurologically symptomatic.
e. A pre-registration bone scan is desirable but not required in an asymptomatic patient with a normal alkaline phosphatase. A bone scan is required if the patient has bone tenderness or bone pain or an alkaline phosphatase twice the upper limits of normal or higher.
f. PFTs should be obtained prior to the initiation of XRT. In addition, repeat PFTs should be obtained at the six-month follow-up visit upon completion of XRT, and 1 year after completion of XRT.
g. Obtain chest CT if symptoms. If no symptoms, obtain chest CT every 6 months during years 1 and 2, then every 12 months thereafter up to 5 years.
h. Obtain creatinine clearance if serum creatinine > 1.5 mg/dl.
i. Electolytes include Na, K, Cl, HC03.

j. Serum pregnancy test pre-study entry as applicable. Urine pregnancy test before each vaccination for women of child-bearing potential.

k. Immune blood work will be drawn in two (2) 12 ml red top tubes (no serum separators) and two (2) 12 ml green top tubes (preservative-free heparinized tubes) and must be obtained within 21 days prior to the first dose of immunotherapy, and at 6, 12, 18, 24, 36, and 48 months (Section 10.2) Note: HAMA response is only tested at baseline and month 6. (4/8/02)

l. See Section 7.3.

m. Follow-up is at day 90 from start of RT, then every 3 months x 1 year, then every 4 months x 1 year, then every 6 months x 3 years, then yearly.

n. A chest x-ray should be obtained at each follow-up (unless a chest CT has been done).

o. Vital signs need to be obtained every 15 minutes for at least 30 minutes following injection of the vaccines.

p. Optional Biomarkers Correlative Study: two tubes (yellow top tubes) of peripheral blood (approximately 8 mls) will be collected from each patient preferably prior to start of RT, but at any time while on protocol (Section 10.3).

q. If patient participates in Biomarkers Correlative Study: Part I to be completed by all patients; Part II for females only (PF form).

11.2 Evaluation During Study (4/8/02)

11.2.1 A brief interim history and directed physical examination will be done weekly regarding radiation-related toxicity.

11.2.2 History and physical with performance status and weight will be recorded.

11.2.3 Electrolytes and LFT’s will be performed every 3 weeks during radiotherapy, as will CBC, Differential, and Platelets. (8/1/01, 4/8/02)

11.2.4 Women of child-bearing potential will have a serum pregnancy test before the first vaccination and a urine pregnancy test prior to each subsequent vaccination. (4/8/02)

11.2.5 All relevant information regarding drug dosage, laboratory data, and treatment-related toxicity must be recorded on the data forms.

11.2.6 Immune blood work at 6, 12, 18, 24, 36, and 48 months, drawn in two (2) 12 ml red top tubes (no serum separators) and two (2) 12 ml green top tubes (preservative-free heparinized tubes). (4/8/02)

11.3 Duration of Therapy

11.3.1 Regardless of the actual number of doses of immunotherapy received, all patients will be evaluated for toxicity and survival.

11.3.2 Development of local, regional or distant recurrence (including CNS metastases) must be documented on the data forms. Biopsy of recurrence is encouraged.

11.3.3 The development of unacceptable toxicity, which is defined as unpredictable, irreversible, or grade 4 (excluding myelosuppression) from therapy despite attempts to modify toxicity of treatment will constitute grounds for a patient’s discontinuation of treatment. This must be documented on the data forms.

11.4 Measurement of Effect

Outcome measures will include the immune response to both antibodies, (CeaVac and TriAb), recurrence, disease-free survival, survival and toxicity.

11.4.1 Recurrence (8/1/01)
The development of a loco-regional and/or distant recurrence. Whenever possible, recurrence should be histologically confirmed. However, to confirm recurrence in some organs, invasive diagnostic procedures might be required. In this case, biopsy may be deferred because the clinical course will clarify the time of recurrence in almost all patients. An abnormal chest, abdominal, or head CT scan consistent with metastatic disease is considered sufficient evidence to document recurrent disease. Abnormal blood studies are not adequate for documentation of recurrence (e.g., elevated LFTs, etc.).

11.4.2 Definitions of Site of Recurrence
Local - within RT port
Chest - outside RT port
Distant - brain, other

11.4.3 Disease-Free Survival
Date of definitive resection to the date of first treatment failure (recurrence or death before recurrence). Survival is defined as the time from definitive resection until death.

11.4.4 Survival
The cause of death (cancer versus non-cancer related) should be documented and explained. Survival is measured from the date of definitive resection to the date of death.
### 11.5 Data and Protocol Management

11.5.1 The attending physician and oncology research nurse see each patient prior to drug administration. All required interim and pre-treatment data should be available, and the physician must have made a designation as to tumor response and toxicity grade.

11.5.2 A brief explanation for required but missing data must be recorded.

11.5.3 Dr. Movsas will be the final arbiter of responses or toxicity should a difference of opinion exist.

11.5.4 Patients who refuse protocol treatment or withdraw consent will be considered canceled. No follow-up need be submitted.

11.5.5 Patients who start radiotherapy will be evaluable regardless of when therapy is discontinued. All data will be required.

11.5.6 Patients who are found to be ineligible after enrolling onto the trial will be removed from the study. A letter will be sent to the institution by RTOG Headquarters to acknowledge the ineligible status.

### 12.0 DATA COLLECTION

(RTOG, 1101 Market Street, Philadelphia, PA 19107, FAX#215/928-0153)

#### 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 first dose of immunotherapy</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td>Have the patient fill out a questionnaire</td>
</tr>
<tr>
<td>Pathology Report (P1)</td>
<td></td>
</tr>
<tr>
<td>Pathology Block/Slides (P2)</td>
<td></td>
</tr>
<tr>
<td>Surgery Form (S1)</td>
<td></td>
</tr>
<tr>
<td>Surgical Op Note (S2)</td>
<td></td>
</tr>
<tr>
<td>Surgical Path Report (S5)</td>
<td></td>
</tr>
<tr>
<td>Specimen Transmittal Form (ST)*.TCBS</td>
<td></td>
</tr>
<tr>
<td>Patient Questionnaire (PF)*.TCBS</td>
<td></td>
</tr>
<tr>
<td>*Applicable only if patient participates in Biomarkers Correlative Study (Appendix IX)</td>
<td></td>
</tr>
<tr>
<td>Treatment Summary Form (TF)</td>
<td>At the completion of first of 3 weekly injections, including all pre-treatment lab values; then every 3 months for 2 years or until immunotherapy is discontinued</td>
</tr>
<tr>
<td>Preliminary Dosimetry Information:</td>
<td></td>
</tr>
<tr>
<td>RT Prescription (Protocol Treatment Form) (T2)</td>
<td>Within 1 week of start of RT</td>
</tr>
<tr>
<td>Films (simulation and portal) (T3)</td>
<td></td>
</tr>
<tr>
<td>Calculations (T4)</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy Form (T1)</td>
<td>Within 1 week of RT end</td>
</tr>
<tr>
<td>Final Dosimetry Information:</td>
<td></td>
</tr>
<tr>
<td>Daily Treatment Record (T5)</td>
<td></td>
</tr>
<tr>
<td>Isodose Distribution (T6)</td>
<td></td>
</tr>
<tr>
<td>Boost Films (simulation and portal) (T8)</td>
<td></td>
</tr>
<tr>
<td>Initial Followup Form (FS)</td>
<td>Day 90 (week 13) from start of RT</td>
</tr>
<tr>
<td>Follow-up Form (F1)</td>
<td>Every 3 months for 1 year; q 4 months x 1 year; q 6 months x 3 years, then annually. Also at progression/relapse and at death</td>
</tr>
<tr>
<td>Autopsy Report (D3)</td>
<td>As applicable</td>
</tr>
</tbody>
</table>
13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints
13.1.1 Percentage of patients with immune response to CEA and HMFG anti-idiotypes at six months from start of protocol treatment.
13.1.2 Acute and late toxicities.
13.1.3 Overall and recurrence-free survival.

13.2 Sample Size
The primary endpoint of this study is the proportion of patients with an immune response (as defined in Section 13.1.1) to the CEA and HMFG vaccines at six months from start of protocol treatment. The two vaccines will be addressed independently. With 46 patients, a one group chi-square test with a 0.05 one-sided significance level will have 88% power to detect the difference between the null hypothesis proportion of 30% of patients exhibiting an immune response and the alternative proportion of 50% of patients. The median survival time for completely resected stage II and IIIA non-small cell lung cancer patients treated with 50.4 Gy in the intergroup study RTOG 91-05 was 38.6 months. We therefore expect 90% of patients to be alive at six months, and must adjust the sample size accordingly. Assuming 90% survival at six months and a 5% ineligibility/inevaluability rate results in 54 patients required for this study.

13.3 Patient Accrual
13.3.1 The patient accrual is projected at 10 cases per month, based upon accrual to RTOG 97-05. Therefore, it will take 6 months to reach the required accrual of 54 patients. If the average monthly accrual is less than three patients, the study will be re-evaluated with respect to feasibility.

13.4 Suspension of Accrual Due to Morbidity
If there is any study-drug related fatal treatment morbidity, the accrual will be suspended, and all data pertaining to the event will be reviewed by the Executive Committee and the committee will determine whether the study should be closed.

13.5 Analyses Plans
13.5.1 Interim Analyses
Interim reports with statistical analyses are prepared every six months until the initial manuscript reporting the treatment results has been submitted. In general, the interim reports will contain information about:
   a) patient accrual rate with a projected completion date for the accrual phase.
   b) quality of submitted data with respect to timeliness, completeness, and accuracy.
   c) frequency and severity of toxicities.
Through examination of the above items, the statistician can identify problems with the execution of the study. These problems will be reported to the RTOG committee responsible for this study and, if necessary, the RTOG Executive Committee so that corrective action can be taken.

13.5.2 Analysis for Reporting the Initial Treatment Results
This analysis will be undertaken when each patient has been potentially followed for a minimum of six months, and immune response laboratory work has been completed. The usual components of this analysis are:
   a) tabulation of all cases entered and any excluded from the analysis with reasons for the exclusion;
   b) reporting institutional accrual;
   c) distribution of important prognostic baseline variables;
   d) observed results with respect to the endpoints described in Section 13.1.

The observed results (d) consist of a one-sample comparison of the proportion of patients exhibiting immune response to CEA and HMFG vaccines, comparing each separately to a rate of 30%, using a significance level of 0.05, and testing only if the observed rate is greater than 30%.

13.5.3 Inclusion of Women and Minorities
Some investigators have shown gender to be a prognostic factor in non-small cell lung cancer. However, the RTOG did not show this to be the case in a recent analysis. Furthermore, an analysis of race did not indicate an association with outcome. In conformance with the National Institute of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we have also considered the possible interaction between gender/to race and treatments. The participation rates of men and women will be examined according to Section 13.5.1.
REFERENCES


APPENDIX I-a

RTOG 99-09

PHASE II STUDY OF POSTOPERATIVE ADJUVANT IMMUNOTHERAPY AND RADIATION IN PATIENTS WITH COMPLETELY RESECTED STAGE II AND STAGE IIIA NON-SMALL CELL LUNG CANCER

SAMPLE CONSENT FOR RESEARCH STUDY

THERE IS A RESEARCH STUDY ABOUT YOUR CONDITION AND ITS TREATMENT. THIS CONSENT FORM WILL TELL YOU ABOUT THIS STUDY AND HOW THE TREATMENT MAY OR MAY NOT HELP YOU.

IT IS IMPORTANT THAT YOU READ AND UNDERSTAND THIS FORM, THE STUDY, AND THE TREATMENT BEFORE YOU DECIDE TO BE PART OF THIS STUDY. IF YOU HAVE ANY QUESTIONS ABOUT THIS STUDY, THE TREATMENT, OR HOW IT WILL AFFECT YOU, PLEASE ASK YOUR DOCTOR.

RESEARCH STUDY

You have the right to know about the procedures used in this research study and the risks, benefits, and alternatives to the treatment in this study. You should know and understand the treatment proposed in this study, how it will be given, how the treatment may help you, how the treatment may harm you, and the choices available to you. This form will tell you about the study, the benefits, the risks, and the alternatives so you can decide whether to be a part of this research study.

PURPOSE OF THIS STUDY (4/8/02)

It has been explained to you that you have non-small cell lung cancer. You have been invited to participate in this research study to determine if additional treatment, immunotherapy (vaccines), after surgery can reduce the incidence of tumor recurrence and thereby prolong survival. At the present time, individuals with completely removed non-small cell lung cancer are usually given no additional treatment or get radiation therapy alone.

You are being offered two vaccines (called CeaVac and TriAb anti-idiotype monoclonal antibodies) as a part of this clinical research study. The vaccines will be given in addition to radiation therapy to try and prevent recurrent disease. The vaccines are mouse proteins which are similar to the proteins (antigens) found on your tumor cells. The combination of the two vaccines may make your own immune system work against the cancer cells. This vaccine has not yet been proven to help in the treatment of human cancer but based on laboratory studies, it may be helpful. If you decide to participate in this study, you will be one of 54 patients.

RTOG is conducting this study with support from the National Cancer Institute (NCI) and Titan Pharmaceuticals. You will be provided with these two experimental vaccines free of charge. Should these agents become commercially available or approved for this indication during the course of this study you, or your insurance carrier, may be billed for subsequent doses of the medicine.

DESCRIPTION OF PROCEDURES (4/8/02)

1 month then monthly for 2 years

Surgery --------------->v-->v-->v-------------------------------->v--------------------------------etc.

RT XXXXX XXXXX XXXXX XXXXX XXXXX XXX

v= injection of two vaccines, once a week for three weeks, then monthly for two years.

X= daily radiation (RT) will begin within one week of the third vaccine injection. The total number of radiation treatments can range from 28 to 34 depending on lymph node status.

The immunotherapy consists of two vaccines injected into the skin starting within 7 weeks after your surgery. This procedure takes only a few minutes. The two vaccines will be given (outpatient) once a week for 3 weeks and then once a month for two years. The radiation therapy will begin within a week after the third injection. Radiation treatment is given on an outpatient basis once a day, five days a week for 6-7 weeks. Blood work will be obtained every 3 weeks during
radiotherapy. Women able to have children will have a blood test for pregnancy before the first vaccination and a urine pregnancy test before each subsequent vaccination.

Inflammation of the esophagus (esophagitis) which causes pain and difficulty swallowing is one of the main acute side effects of radiation to the chest. If medications are needed to relieve your symptoms of esophagitis, they will be offered to you as needed.

Following completion of treatment, you will be followed on a regular basis by your physician for your lifetime. Blood samples will be taken before the first treatment, every six months for one year, then at sixteen months, then once per year for three years in order to determine if your immune system is responding to the antibody. You will also have CT scans of the chest and liver. CT scans will be done prior to starting any treatment and every six (6) months thereafter for 2 years and then once a year up to five years. A breathing test (pulmonary function test) will be done before the radiation treatment, at the six month follow-up visit and then at one year. Imaging of the brain will be done only if you have symptoms. The studies, however, may be done whenever you may have symptoms of disease or your doctor thinks you need to have them repeated. If your disease worsens at any time during the study, you will be removed from the study and alternative treatments will be discussed.

**RISKS AND DISCOMFORTS (4/8/02)**

Cancer treatments, whether given in a research study or in the ordinary practice of medicine, may often hurt or harm you (side effects). The treatment used in this study may cause all, some, or none of the side effects listed. In addition, there is always the risk of very uncommon or previously unknown side effects occurring.

*Risks from Immunotherapy:*

As with any experimental treatment, there may be unexpected side effects. The long-term side effects of monoclonal antibody in humans are not fully known at this time. Based on preliminary studies with these antibodies, these side effects may include allergic reactions, (fever, hives, wheezing, and swelling). Also, you may experience flu-like symptoms (fevers, chills, sweats, headache, fatigue, nausea, malaise) as a direct effect of the antibody. Therapy is seldom required, and the symptoms usually persist for only a few hours. Rarely, patients may experience vomiting, diarrhea or a transient increase in some lab values that test the liver’s function. These generally require no specific treatment and often go away on their own. Earlier studies have shown temporary shortness of breath in some patients. Even though it has not been reported in previous experience with the study drugs, there is a possibility that you may develop side effects related to your immune system reacting with the antibodies given. This could result in reactions involving your skin, joints, kidneys, or other organs. You will be watched closely for these problems. Antibody treatment will be reduced or stopped if any of the above side effects occur. It is not likely that you will suffer most of these side effects. The monoclonal antibody vaccine can cause pain, tenderness, swelling, erythema, redness or sores (induration of the skin), bruising and scarring at the site of the injection. More severe generalized skin reactions (acute or chronic) and necrotic reactions at injection site can rarely occur as well.

Treatment on the study may exclude you from mouse monoclonal antibody therapies in the future because you will be developing an immune response to mouse antibodies due to the vaccine. This vaccine therapy may interfere with future CEA lab tests (measurements) as you may develop an immunity to the mouse protein.

*Risks from Radiation Therapy:*

Chest Radiation Therapy may cause: 1) difficulty, pain, or a burning sensation on swallowing. This effect (esophagitis) usually begins after the second week of radiotherapy and goes away within 1 month of completion of radiotherapy; 2) fatigue - a tiredness without having done anything to make you tired. Also, a temporary effect which resolves within 1 month of completion of treatment; 3) skin damage within the port of radiation - the skin may develop a sunburn-like appearance which may itch, feel dry, or burn slightly. Although skin color and the sunburn-like reaction resolves within 2-6 weeks after treatment, the skin will permanently be more dry than other skin, and chest hair (if any) may not regrow; 4) decrease in white blood cells and platelets. Decrease in white cell production may predispose you to infection. Decreases in platelets may make you bleed or bruise easily; 5) inflammation and/or scarring of the lung (i.e., radiation pneumonitis/fibrosis) which may result in shortness of breath and a cough.

This study may be harmful to a nursing infant or an unborn child. Sufficient medical information is not available to determine whether the study treatment administered to a pregnant woman causes significant risks to the fetus. If you are a woman of childbearing age and have not been surgically sterilized (tubal ligation or hysterectomy), you should have a pregnancy test before enrolling in this study as well as prior to every vaccination. If you are unwilling to use adequate birth
control measures to prevent pregnancy, you should not participate in this study. If you should become pregnant while on study, you must tell your doctor immediately.

If you are a man of reproductive potential, the treatment you receive may risk harm to an unborn child unless you use a form of birth control approved by your doctor. If you are unwilling to use adequate birth control measures to prevent pregnancy, you should not participate in this study. If you suspect you have caused anyone to become pregnant, you must tell your doctor immediately.

COSTS

There is no charge for the vaccine therapy. However, routine blood tests and scans will be done to evaluate the effects of treatment. There may also be laboratory testing and procedures required by this study for research purposes. These additional tests may increase your medical bills although the impact will be dependent on your insurance company. If injury occurs as a result of this research, treatment will be available. The use of medication to help control side effects could result in added costs. This institution is not financially responsible for the treatment of side effects caused by the study treatment. You will not be reimbursed for medical care other than what your insurance carrier may provide. You will not be paid for your participation in this research study.

CONTACT PERSONS
(This section must be completed)

For information about your disease and research-related injury, you may contact:

<table>
<thead>
<tr>
<th>Name</th>
<th>Telephone Number</th>
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</thead>
</table>

For information about this study, you may contact:

<table>
<thead>
<tr>
<th>Name</th>
<th>Telephone Number</th>
</tr>
</thead>
</table>

For information about your rights as a research subject, you may contact:
(OPRR suggests that this person not be the investigator or anyone else directly involved with the research)

<table>
<thead>
<tr>
<th>Name</th>
<th>Telephone Number</th>
</tr>
</thead>
</table>

ALTERNATIVES

Treatment options that could be considered for your condition may include the following: (1) radiation therapy; (2) chemotherapy; or (3) no treatment (observation).

These treatments could be given either alone or in combination with each other.

Your doctor can tell you more about your condition and the possible benefits of the different available treatments. You should discuss your condition and the expected outcome with your doctor. Your doctor will be available to answer any questions. You are encouraged to ask your doctor any questions you have about this research study and the choices of treatment available to you. If you have any questions at all, please ask your doctor.

If your disease returns, if side effects become very severe, or if developments occur that indicate the research study is not in your best interest, the treatment would be stopped. Further treatment would be discussed at that time.

BENEFITS

It is not known whether the treatment you will be given in this research study will help your condition more than any other treatment for this disease would. The information from this study may also help others by providing information about your type of cancer and its response to treatment. The information will be used scientifically. A possible personal benefit of this research study may be a decrease in the size of your tumor and a longer survival. None of these possible benefits is certain or guaranteed.
VOLUNTARY PARTICIPATION (4/8/02)

You do not have to take part in this research study. You are free to withdraw or withhold your consent from taking part in this research study at any time. You or your legally acceptable representative will be informed in a timely manner of any new information that may affect your willingness to continue participation in this study. If you refuse to participate, there will be no penalty or loss of benefits. You may seek care from a doctor of your choice at any time. If you do not take part in this study or if you withdraw from the study, you will continue to receive care.

CONFIDENTIALITY

Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology Group (RTOG). The confidentiality of the central computer record is carefully guarded. During their required reviews, representatives of the Food and Drug Administration (FDA), the National Cancer Institute (NCI), qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in this study may have access to medical records that contain your identity. However, no information by which you can be identified will be released or published.

I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.

I willingly give my consent to participate in this program. Upon signing this form I will receive a copy.

Patient Signature (or legal Representative) ____________________________ Date ____________________________
APPENDIX I-b

RTOG 99-09

PHASE II STUDY OF POSTOPERATIVE ADJUVANT IMMUNOTHERAPY AND RADIATION IN PATIENTS WITH COMPLETELY RESECTED STAGE II AND STAGE IIIA NON-SMALL CELL LUNG CANCER

SAMPLE CONSENT TO COLLECT, STORE, AND USE BLOOD AND TUMOR TISSUE FOR RESEARCH

The RTOG would like to keep some of your blood and tumor tissue that is not needed for your care. If you agree, the RTOG will keep some of the tumor tissue in a specimen bank. These samples may be used in future research to learn more about cancer. In addition, some of your blood and tissue will be sent to another central office for review and research into biologic factors and inherited traits that may help predict lung cancer as early as possible.

Researchers are trying to learn more about cancer, such as what causes cancer, how to prevent it, how to treat it better, and how to cure it. Causes of cancer may come from the environment or from genetic causes. Genetic causes are causes that people are born with and that can also affect other family members. Your cancer may come from one or both of these causes. You may, however, be concerned that research about genetic causes may give information not only about yourself, but also about your relatives and other groups of people who are like you. When genetic testing is done on your blood and tissue, the testing will be done with only coded samples so that your identity remains unknown. Because the value of the research is not known at this time and the researcher will not know who you are, results of this research will not be given to you or to your doctor. Even if the research that is done on your blood and/or tissue cannot be used to help you, it might help other people who have cancer or other medical problems.

The RTOG will be responsible for making sure your samples and information are protected and kept confidential in the specimen bank and at the central office. Your samples will be given a code number to protect your identity. The samples will only be given to researchers approved by the RTOG. The research study must also be approved by the Institutional Review Board (IRB) at your hospital. An IRB is a group of people who look after the rights and welfare of people taking part in research.

The choice to let the RTOG keep your blood and tissue for research is up to you. **No matter what you decide to do, it will not affect your care.** If you decide that your blood and tissue can be kept for research but you later change your mind and tell your doctor, the specimen bank and the central office will destroy any of your samples that they still have. Otherwise, the blood and tissue may be kept until they are used up or until the RTOG decides to destroy them.

The people using your samples to do research into biological factors and inherited traits need to know more about your health and habits. When your blood is drawn, you also will be asked to answer some questions about your hormonal history (females only) and your tobacco and alcohol use. These questions will only take a few minutes to answer. As mentioned before in the main consent form, the RTOG, the NCI, and the FDA will be allowed to review and copy your medical records as related to this research.

Your blood and/or tissue will be used only for research and will not be sold. There will be no cost to you for any specimens collected and stored in the RTOG specimen bank or at the central office.
VOLUNTARY PARTICIPATION

You do not have to take part in this research study. You are free to withdraw or withhold your consent from taking part in this research study at any time. If you refuse to participate, there will be no penalty or loss of benefits. You may seek care from a doctor of your choice at any time. If you do not take part in this study or if you withdraw from the study, you will continue to receive care.

I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.

I willingly give my consent to participate in this program. Upon signing this form I will receive a copy.

Patient’s Signature (or legal Representative)  Date
# APPENDIX II

## KARNOFSKY PERFORMANCE SCALE

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Normal; no complaints; no evidence of disease</td>
</tr>
<tr>
<td>90</td>
<td>Able to carry on normal activity; minor signs or symptoms of disease</td>
</tr>
<tr>
<td>80</td>
<td>Normal activity with effort; some sign or symptoms of disease</td>
</tr>
<tr>
<td>70</td>
<td>Cares for self; unable to carry on normal activity or do active work</td>
</tr>
<tr>
<td>60</td>
<td>Requires occasional assistance, but is able to care for most personal needs</td>
</tr>
<tr>
<td>50</td>
<td>Requires considerable assistance and frequent medical care</td>
</tr>
<tr>
<td>40</td>
<td>Disabled; requires special care and assistance</td>
</tr>
<tr>
<td>30</td>
<td>Severely disabled; hospitalization is indicated, although death not imminent</td>
</tr>
<tr>
<td>20</td>
<td>Very sick; hospitalization necessary; active support treatment is necessary</td>
</tr>
<tr>
<td>10</td>
<td>Moribund; fatal processes progressing rapidly</td>
</tr>
<tr>
<td>0</td>
<td>Dead</td>
</tr>
</tbody>
</table>

## ZUBROD PERFORMANCE SCALE

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all predisease activities without restriction (<em>Karnofsky 90-100</em>).</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work (<em>Karnofsky 70-80</em>).</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (<em>Karnofsky 50-60</em>).</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (<em>Karnofsky 30-40</em>).</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (<em>Karnofsky 10-20</em>).</td>
</tr>
</tbody>
</table>
APPENDIX III

ANATOMICAL STAGING FOR LUNG CANCER
(AJCC, 5th Edition)

TNM CATEGORIES (Note Definitions)

**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 cytopathological examination of pleural fluid are negative for tumor. In these cases, fluid is non-bloody and is not an exudate. Where 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).
APPENDIX III  (cont'd)

ANATOMICAL STAGING FOR LUNG CANCER
(AJCC, 5th Edition)

**Distant Metastasis  \((M)\)**

<table>
<thead>
<tr>
<th>MX</th>
<th>Distant metastasis cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis present</td>
</tr>
</tbody>
</table>

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

**STAGE GROUPING**

<table>
<thead>
<tr>
<th>Occult Carcinoma</th>
<th>TX</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IA</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T2</td>
<td>N0</td>
<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>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</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>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>
APPENDIX V

ADVERSE EVENT REPORTING GUIDELINES

A. GENERAL GUIDELINES

In order to assure prompt and complete reporting of toxicities, the following general guidelines are to be observed. These apply to all RTOG studies and Intergroup Studies in which RTOG participates. When a protocol toxicity requires more intense, special handling, study-specific reporting procedures supersede the General Guidelines. For specific reporting procedures for this study, please refer to Section 7.3.

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman and to the Headquarters Data Management Staff (215/574-3214) within 24 hours of discovery. When telephone reporting is required, the Principal Investigator should have all relevant material available. See the protocol-specific criteria to grade the severity of the reaction.
   a. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of cause requires telephone notification within 24 hours of discovery.

2. The Principal Investigator will also report the details of the significant reaction to the Study Chairman by telephone.

3. A written report, including all relevant study forms, containing all relevant clinical information concerning the reported event will be sent to RTOG Headquarters by the Principal Investigator. This must be sent within 10 working days of the discovery of the toxicity unless specified sooner by the protocol (FAX #215/928-0153).

4. The Group Chairman in consultation with the Study Chairman will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures if this is warranted.

5. For those incidents requiring telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB) or Food and Drug Administration (FDA), the Principal Investigator should first call RTOG (as outlined above) unless this will unduly delay the notification process required by the federal agencies.
   A copy of all correspondence submitted to NCI, or to another Cooperative Group (in the case of RTOG-coordinated intergroup studies) must also be submitted to RTOG Headquarters when applicable.

6. The Principal Investigator, when participating in RTOG-coordinated Intergroup studies, is obligated to comply with all additional reporting specifications required by an individual study.

7. Institutions must also comply with their individual Institutional Review Board policy with regard to toxicity reporting procedure.

8. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

B. RADIATION TOXICITY GUIDELINES

1. All fatal toxicities (grade 5) resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.

2. All life-threatening (grade 4) toxicities resulting from protocol treatment using non-standard fractionated treatment, brachytherapy, radiopharmaceuticals and radiosurgery must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.

C. ADVERSE DRUG REACTIONS DRUG AND BIOLOGICS

An adverse reaction is a toxicity or an undesirable effect usually of severe nature. Specifically, this may include major organ toxicities of the liver, kidneys, cardiovascular system, central nervous system, skin, bone marrow, or anaphylaxis. These undesirable effects may be further classified as "known" or "unknown" toxicities.

Known toxicities are those which have been previously identified as having resulted from administration of the agent. They may be identified in the literature, the protocol, the consent form or noted in the drug insert.

Unknown toxicities are those thought to have resulted from the agent but have not previously been identified as a known side effect.

Commercial and Non-Investigational Agents

i. Any fatal (grade 5) or life threatening (grade 4) adverse reaction which is due to or suspected to be the result of a protocol drug must be reported to the Group Chairman or to RTOG Headquarters’ Data Management Staff and to the Study Chairman by telephone within 24 hours of discovery. Known grade 4 hematologic toxicities need not be reported by telephone.

ii. Unknown adverse reactions (> grade 2) resulting from commercial drugs prescribed in an RTOG protocol are to be reported to the Group Chairman or RTOG Headquarters’ Data Management, to the Study Chairman and to the IDB within 10 working days of discovery. FDA Form 3500 is to be used in reporting details. All relevant data forms must accompany the RTOG copy of Form 3500.

iii. All neurotoxicities (> grade 3) from radiosensitizer or protector drugs are to be reported within 24 hours by phone to RTOG Headquarters and to the Study Chairman.

iv. All relevant data forms must be submitted to RTOG Headquarters within 10 working days on all reactions requiring telephone reporting. A special written report may be required.

Reactions definitely thought not to be treatment related should not be reported, however, a report should be made of applicable effects if there is a reasonable suspicion that the effect is due to protocol treatment.

Investigational Agents

Prompt reporting of adverse reactions in patients treated with investigational agents is mandatory. Adverse reactions from NCI sponsored drugs are reported to:

Investigational Drug Branch (IDB)
P. O. Box 30012
Bethesda, MD 20824
Telephone number available 24 hours
(301) 230-2330 FAX # 301-230-0159

i. Phase I Studies Utilizing Investigational Agents

- All deaths during therapy with the agent. Report by phone within 24 hours to IDB and RTOG Headquarters.
  **A written report to follow within 10 working days.
- All deaths within 30 days of termination of the agent. As above

- All life threatening (grade 4) events which may be due to agent. As above

- First occurrence of any toxicity (regardless of grade). Report by phone within 24 hours to IDB drug monitor and RTOG Headquarters. **A written report may be required.

** See attached (if applicable to this study) NCI Adverse Drug Reaction Reporting Form

ii. Phase II, III Studies Utilizing Investigational Agents

- All fatal (grade 5) and life threatening (grade 4) known adverse reactions due to investigational agent. Report by phone to RTOG Headquarters and the Study Chairman within 24 hours. **A written report must be sent to RTOG within 10 working days with a copy to IDB. (Grade 4 myelosuppression not reported to IDB)

- All fatal (grade 5) and life threatening (grade 4) unknown adverse reactions resulting from or suspected to be related to investigational agent. Report by phone to RTOG Headquarters, the Study Chairman and IDB within 24 hours. **A written report to follow within 10 working days.

- All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent. **Report in writing to RTOG Headquarters and IDB within 10 working days.
APPENDIX VI

Lymph Node Map Definitions

Table 1

N2 Nodes – All N2 nodes lie within the mediastinal pleural envelope

1. Highest mediastinal nodes
2. Upper paratracheal nodes
3. Prevascular and retrotracheal nodes
4. Lower paratracheal nodes

N1 nodes – All N1 nodes lie distal to the mediastinal pleural reflection and within the visceral pleura

5. Subaortic (aorto-pulmonary window)
6. Para-aortic nodes (ascending aorta or phrenic)
7. Subcarinal nodes
8. Paracarinal nodes (below carina)
9. Pulmonary ligament nodes

N1 nodes – All N1 nodes lie distal to the mediastinal pleural reflection and within the visceral pleura

10. Hilar nodes
11. Interlobar nodes
12. Lobar nodes
13. Segmental nodes
14. Subsegmental nodes

Nodes lying above a horizontal line at the upper rim of the brachiocephalic (left innominate) vein where it ascends to the left, crossing in front of the trachea at its midline

Nodes lying above a horizontal line drawn tangential to the upper margin of the aortic arch and below the inferior boundary of No. 1 nodes

Prevascular and retrotracheal nodes may be designated 3A & 3P; midline nodes are considered to be ipsilateral

The lower paratracheal nodes on the right lie to the right of the midline of the trachea between a horizontal line drawn tangential to the upper margin of the aortic arch and a line extending across the right main bronchus at the upper margin of the upper lobe bronchus, and contained within the mediastinal pleural envelope; the lower paratracheal nodes on the left lie to the left of the midline of the trachea between a horizontal line drawn tangential to the upper margin of the aortic arch and a line extending across the left main bronchus at the level of the upper margin of the left upper lobe bronchus, medial to the ligamentum arteriosum and contained within the mediastinal pleural envelope

Subaortic nodes are lateral to the ligamentum arteriosum or the aorta or left pulmonary artery and proximal to the first branch of the left pulmonary artery and lie within the mediastinal pleural envelope

Nodes lying anterior and lateral to the ascending aorta and aortic arch or the innominate artery, beneath a line tangential to the upper margin of the aortic arch

Nodes lying caudal to the carina of the trachea, but not associated with the lower lobe bronchi or arteries within the lung

Nodes lying adjacent to the wall of the esophagus and to the right or left of the midline, excluding subcarinal nodes

Nodes lying within the pulmonary ligament, including those in the posterior wall and lower part of the inferior pulmonary vein

The proximal lobar nodes, distal to the mediastinal pleural reflection and the nodes adjacent to the bronchus intermedius on the right; radiographically, the hilar shadow may be created by enlargement of both hilar and interlobar nodes

Nodes lying between the lobar bronchi
Nodes adjacent to the distal lobar bronchi
Nodes adjacent to the segmental bronchi
Nodes around the subsegmental bronchi
APPENDIX VII
SUGGESTED RADIATION FIELDS OF INITIAL AP-PA PORTALS

Suggested radiation therapy fields for initial AP-PA portals. Treat same volume with obliques or lateral to reach 50.4 Gy.

N1 disease with no extranodal extension.

Boost volume for N1 disease with extranodal extension. Use steep obliques off cord to boost nodal bed.

N2 disease with no extranodal extension.

Boost volume for N2 disease with extranodal extension. Use steep obliques off cord to boost nodal bed.
Immunologic Monitoring of Patients Treated with CeaVac (Anti-Id 3H1) and TriAb (Anti-Id 11D10) Vaccines

The Immunologic Monitoring and Cellular Products Laboratory (IMCPL) at the University of Pittsburgh Cancer Institute, under the direction of Dr. Theresa Whiteside, has extensive experience in evaluating patients’ immune responses following immunization with anti-idiotypic (anti-id) antibody vaccines.

The following procedures outlined below are planned for this study. See Section 10.2 for specimen collection, preparation/storage, and shipping.

1.0 Binding of Ab1’ from patient serum to CEA
To assess humoral immune responses that are directed against the CEA tumor antigen, patients’ whole or partially-purified sera will be tested by ELISA or radioimmunoassay (RIA) for specific immunoreactivity to a commercial preparation of purified recombinant human CEA coated onto microtiter plates. The specific antigen Ab1’ antibody complex will be detected using enzyme-conjugated anti-human IgG (H + L chain) reagents, or with 125I-labeled or enzyme-conjugated anti-id 3H1 antibody (Ab2). Patients’ pre-immune sera will be used as an independent control for the assay.

2.0 Proliferation in Response to Anti-id 3H1
Peripheral blood mononuclear cells (PBMC) separated by Ficoll Hypaque gradient centrifugation from venous blood will be cryopreserved in vials using a Cryomed. The cells will be thawed immediately before the assay, counted in the presence of Trypan Blue dye, and plated in 96-well plates.

Following the addition of the anti-id 3H1 antibody (Ab2), isotype control antibody, or Phaseolus vulgaris phytohemagglutinin-protein (PHA-P) as a positive control, the plates will be incubated for 5 days in a CO2 incubator. On day 5, the cultures will be pulsed with [3H] thymidine for 24 hours. The counts/min obtained from triplicate wells will be averaged, and the stimulation indices determined for all cultures.

3.0 Binding of Ab1’ from patient serum to HMFG
To assess humoral immune responses that are directed against the HMFG tumor antigen, patients’ whole or partially-purified sera will be tested for specific immunoreactivity by ELISA or radioimmunoassay (RIA) to a preparation of purified HMFG antigen coated onto microtiter plates. The specific antigen Ab1’ antibody complex will be detected using enzyme-conjugated anti-human IgG (H + L chain) reagents, or with 125I-labeled or enzyme-conjugated anti-id 11D10 antibody (Ab2). Patients’ pre-immune sera will be used as an independent control for the assay.

4.0 Proliferation in Response to Anti-id 11D10
Peripheral blood mononuclear cells (PBMC) separated by Ficoll Hypaque gradient centrifugation from venous blood will be cryopreserved in vials using a Cryomed. The cells will be thawed immediately before the assay, counted in the presence of Trypan Blue dye, and plated in 96-well plates.

Following the addition of the anti-id 11D10 antibody (Ab2), isotype control antibody, or PHA-P as positive control, the plates will be incubated for 5 days in CO2 incubator. On day 5, the cultures will be pulsed with [3H] thymidine for 24 hours. The counts/min obtained from triplicate wells will be averaged, and the stimulation indices determined for all cultures.

5.0 Post-heat CEA
Due to the presence of immune complexes in the serum and HAMA, the standard CEA assay may not reliably measure serum CEA levels while a patient is receiving CeaVac. Heating the serum precipitates out the interfering immunoglobulins, allowing the soluble CEA, which is heat stable, to be measured in the supernatant following centrifugation. This post-heat CEA assay has been validated under GLP. Note that
CEA levels in patients treated with CeaVac may be misleading because CEA bound in immune complexes may be cleared more rapidly from the circulation than unbound CEA, resulting in decreased circulating CEA levels. Baseline CEA measurements will be done as regular CEA assays as well. All CEA measurements will be done by the IMCPL and results will not be available to investigators during the conduct of the study.

6.0 Human Anti-Mouse Antibody (HAMA)
This assay measures the level of human anti-mouse antibodies (HAMA), which are endogenous antibodies that may exist against mouse immunoglobulins. Since CeaVac and TriAb are injected as intact murine IgG1, subjects are expected to mount HAMA responses. With other antibody therapies, this HAMA response is usually unwanted. However, in this case, when the HAMA response is directed at the CEA-mimicking/HMFG-mimicking portion of Ab2, it results in Ab3, which is a desired outcome. There may be a HAMA response to other portions of Ab2 which, coupled with clinical signs or symptoms, may be considered an incidental unwanted effect. However, in several hundreds of patients treated with these vaccines, there have been no deleterious clinical signs or symptoms derived from a HAMA response.
APPENDIX IX (4/8/02)

OPTIONAL TRANSLATIONAL RESEARCH/BIOMARKERS CORRELATIVE STUDY

1. Principal Investigator: Margie L. Clapper, Ph.D.
   Co-Investigator: Benjamin Movsas, M.D.

2. Institution
   Fox Chase Cancer Center
   Division of Population Science, P2044
   7701 Burholme Avenue
   Philadelphia, PA 19111
   Tel.: (215) 728-4301

3. Tumor Site: Lung
   A Correlative Study to RTOG 99-09, A Phase II Study of Postoperative Adjuvant Immunotherapy and Radiation in Patients with Completely Resected Stage II and Stage IIIA Non-Small Cell Lung Cancer.

4. Title of Research Project: Biomarkers in Resected Non-Small Cell Lung Cancer

5. Research Objectives
   A. To determine the frequency of genetic polymorphisms in cytochrome P450 1A1 (CYP1A1) and glutathione S-transferase M1 (GSTM1) in men and women with NSCLC.
   B. To correlate polymorphisms in CYP1A1 and GSTM1 with disease outcome (survival/disease-free survival).
   C. To measure the expression of cyclooxygenase 2 (COX-2) and vascular endothelial growth factor (VEGF) in tumors from patients with non-small cell lung cancer and correlate these data with disease outcome (survival/disease-free survival).

6. Research Plan
   Two yellow top tubes of peripheral blood (approximately 8 mls each) will be collected from each patient preferably prior to start of radiation, but it is acceptable to do so at any time while the patient is on protocol. Fasting is NOT necessary. A blood collection kit can be obtained in advance by calling Dr. Cindy Spittle at (215) 214-1696. Institutions must notify Dr. Cindy Spittle (215-214-1696) or Dr. Clapper (215-728-4301) prior to shipping samples. The blood collection kit contains: 2 yellow top tubes, 2 plastic bags, 1 box with a Styrofoam shell, and 1 Fed Ex Diagnostic Specimen envelope for packaging and shipping the YELLOW TOP TUBES ONLY. NOTE: All tubes must be labeled with RTOG study number and case number assigned at registration (e.g., 9909-01). Place the two yellow top tubes inside the Styrofoam shell, and seal the shell with tape. Place the shell inside the large plastic bag, and close. Place the bagged Styrofoam shell inside the cardboard box, and close. Place the cardboard box inside the Fed Ex Specimen envelope, and seal. Keep the box with the blood samples at ROOM TEMPERATURE. Any questions regarding sample handling and/or shipping, please contact Dr. Cindy Spittle at (215) 214-1696. Corresponding hormonal supplementation data and tobacco/alcohol history will be obtained by data form and returned to RTOG Headquarters (see Section 12.0 of protocol). Blood will be shipped on the same day the blood was collected (Monday – Thursday) at room temperature by Federal Express for overnight delivery to the following address:
A. Genotypic Analyses

Peripheral mononuclear cells will be isolated from whole blood by lysing the red blood cells in buffer containing 77 mM ammonium acetate, 5 mM potassium bicarbonate and 0.05 mM EDTA. DNA will be extracted using a salting-out procedure, and its purity and concentration will be determined spectrophotometrically by measuring the absorbance at 260 and 280 nm.

1. CYP1A1 The presence of an isoleucine to valine substitution in exon 7 of the CYP1A1 gene will be identified by PCR and NcoI restriction enzyme digestion as described previously. PCR reactions will be run in duplicate and either digested with NcoI or left unrestricted. Electrophoretic separation of the amplified fragments on a 3% agarose gel will distinguish between a 163 bp “wild type” fragment and a 195 bp fragment bearing the mutation.

2. GSTM1 Assays for detection of the GSTM1 null polymorphism will be performed according to the method of Fryer et al. using primers to exon 4 and exon 6. The β globin gene will be amplified as an internal positive control. PCR reactions will be carried out in duplicate, and amplified products will be electrophoresed in 2% w/v agarose gels, stained with ethidium bromide and photographed under UV light.

B. Immunohistochemistry

Fifteen unstained slides of formalin-fixed lung tissue will be obtained from each patient following curative resection and shipped to LDS Hospital (see Section 10.1.5). Immunohistochemical staining for VEGF and COX-2 will be performed according to standard protocols. Negative controls will be run in parallel using nonimmune immunoglobulin as the primary antibody. Immunoreactivity will be expressed as the percentage of total neoplastic cells showing positivity.

C. Statistical Analyses

All analyses will be performed by the Biostatistic Division of RTOG. Associations between gender and CYP1A1 and GSTM1 status will be evaluated using the $\chi^2$ test and, when appropriate, the Cochran-Mantrel-Haenszel and Cochran-Armitage trend tests. A $\chi^2$ test with Fisher’s correction and an unpaired t-test will be used to evaluate associations between immunohistochemical and clinical variables.

7. Background

Epidemiological studies continue to suggest that lung cancer may be the result of a complex interaction between genetic and environmental factors (i.e., cigarette smoke, occupational exposures, hormones). Although cigarette smoke continues to be the critical etiologic agent associated with this malignancy, only 20% of individuals who smoke develop lung cancer. Efforts to elucidate the genetic basis of lung cancer susceptibility have to date focused on DNA repair genes, oncogenes, tumor suppressor genes, and the metabolic enzymes of detoxication.

A. Phase I and II Detoxication Enzymes

Detoxication enzymes play a critical role in the metabolism of tobacco-related carcinogens. Maintenance of an appropriate balance between the Phase I and II detoxication enzymes is required to ensure optimal cellular protection. Phase I enzymes, including the cytochrome P450s, metabolically activate carcinogens, such as the polycyclic aromatic hydrocarbons in cigarette smoke, to highly reactive intermediates (i.e., epoxides and reactive oxygen species) which are both carcinogenic and mutagenic. In contrast, Phase II detoxication enzymes, including the glutathione S-transferases, both compete with the Phase I carcinogen-activating enzymes to inhibit the formation of electrophiles and catalyze the conversion of reactive intermediates to inactive conjugates which are more water soluble and more readily excreted. Recent data from this group suggest that the
increased risk of women for lung cancer may be attributed in part to differences in the ability of men and women to metabolize tobacco-related carcinogens.²

Genetic polymorphisms in both Phase I and II detoxication enzymes have been identified and associated with increased risk for smoking-related cancers. A point mutation in exon 7 of the aryl hydrocarbon hydroxylase gene, CYP1A1, leads to enhanced enzyme inducibility and bioactivation of benzo(a)pyrene, a polycyclic aromatic hydrocarbon found in cigarette smoke. Several studies have demonstrated that this CYP1A1 mutation (NcoI) occurs more frequently in lung cancer patients than in noncancer controls.³,⁶ The most common polymorphism among the Phase II detoxication enzymes is the GSTM1 null genotype, which is present in 40-60% of the general population due to a gene deletion.⁷ This polymorphic expression, when combined with the ability of M1 to inactivate highly reactive epoxides in smoke such as the benzo(a)pyrene-4,5-oxide⁸, has prompted a detailed investigation of the role of the null genotype in determining personal susceptibility to a variety of cancers. Several studies have suggested an association between the GSTM1 null genotype and increased risk for smoking-related cancers including lung⁷,⁹, larynx¹⁰ and bladder.¹⁰,¹¹ A recent meta-analysis of the relationship between GSTM1 status and lung cancer risk in twelve case control studies classified the GSTM1 null genotype as a moderate risk factor for all histological subtypes of cancer (OR = 1.4) and estimated to be responsible for 17% of all lung cancer cases.¹² The unavailability of standardized data on both gender and smoking history prohibited the inclusion of these variables in the analysis. Although several independent investigations have demonstrated that patients with both the CYP1A1 and GSTM1 polymorphisms are at a significantly increased risk of developing cancer¹³-¹⁵, gender differences in susceptibility have not been investigated.

Previous studies from this laboratory have investigated the basis for the increased susceptibility of women for lung cancer by comparing the frequency of genetic polymorphisms in CYP1A1 and GSTM1 among males and females.² Lung cancer patients (N = 180) and healthy controls (N = 167) completed a smoking history questionnaire and donated a blood sample for genotypic analysis. No gender differences were observed among cancer patients in either age at presentation or histological diagnosis. Female lung cancer patients and controls smoked significantly less than males (p ≤ 0.03). Women, but not men, had an increased risk for lung cancer if they possessed a CYP1A1 polymorphism (OR 4.98 and 1.37, respectively). The combined mutant CYP1A1 and GSTM1 null genotypes conferred an OR for lung cancer of 6.54 for women and 2.36 for men, independent of age or smoking history. These data provide a genetic basis for the enhanced predisposition of female smokers to lung cancer and an approach to identify a target population of early intervention. Further analysis of the association between genotype and disease outcome may lead to the establishment of tailored treatment regimens for genetically defined high-risk patients.

B. Expression of Vascular Endothelial Growth Factor

In 1971, Folkman proposed that tumor growth depends on angiogenesis. Several studies describe an association of high microvessel density with a greater incidence of metastases and decreased patient survival.¹⁶ Evidence has subsequently accumulated showing that tumor cells can produce diffusible angiogenic regulatory molecules.¹⁶ One of the current leading candidates is VEGF. VEGF binds to at least two specific tyrosine kinase receptor proteins found on epithelial cells.¹⁷ In contrast to microvessel density, only a few studies concerning the association of angiogenic factor expression on prognosis have been published. Toi et al.¹⁸ reported that the expression of VEGF is an independent prognostic factor in patients with breast cancer. Maeda et al.¹⁹ found that among patients with gastric carcinoma, those with VEGF-positive tumors had a significantly poorer prognosis than those with VEGF-negative tumors. Similarly, Volm et al.²⁰ found that VEGF expression was an independent prognostic factor for patients with squamous cell carcinoma of the lung. Patients with VEGF-stained tumors had significantly lower median survival times (47 weeks) than patients with negative tumors (128 weeks), p = 0.02.

C. Expression of COX-2

Clinical research studies continue to implicate a role for COX-2 in the development of lung carcinomas. Examination of COX-2 expression in primary NSCLC, metastatic lymph nodes and normal lung tissue (N = 76) by RT-PCR revealed significantly higher levels in NSCLC, both adenocarcinomas and squamous cell carcinomas, than in normal lung tissue.¹⁸ Higher levels of COX-2 expression have also been observed in well-differentiated adenocarcinomas than in poorly differentiated ones.¹⁹ While COX-2 expression was detected in 70% of invasive adenocarcinomas, a greater percentage of expressing cells were present in lymph node metastases than in corresponding primary tumors.²⁰

The prognostic significance of elevated COX-2 expression has been evaluated for 130 adenocarcinoma patients who underwent curative lung resections. Seventy-two percent of the cases exhibited tumor cells with markedly increased COX-2 immunoreactivity. A trend was observed between increased COX-2 expression and outcome (p = 0.099). This relationship
achieved significance in patients with Stage I disease where elevated COX-2 expression correlated with decreased patient survival ($p = 0.034$). In contrast, although Hosomi et al. detected COX-2 overexpression in over 80% of cuboidal cell hyperplasias, atypical adenomatous hyperplasias, bronchioalveolar carcinomas and invasive carcinomas, inhibition of NSCLC COX activity and proliferation has been demonstrated.

8. **Research Facilities**

Dr. Clapper's laboratory is located in the Cancer Prevention Pavilion, occupies 900 sq. ft., and is fully equipped with state-of-the-art instrumentation. Laboratory equipment that is pertinent to this project includes Techni Genius and Progene thermal cyclers and gel electrophoresis equipment (including a DNA slab gel system). Dr. Clapper has access to an adjacent community dark room with a UV box and an Alpha Imager. One hood within the laboratory is dedicated exclusively to the preparation of PCR reactions.

A room adjacent to Dr. Clapper's laboratory has been designated a P2 facility for the handling of potentially hazardous biological materials, including human blood. This self-contained area is equipped with a laminar flow hood with Hepa filters, a table-top centrifuge and -80°C freezers.

9. **Qualifications of the Investigator and Laboratory to Perform Studies**

All genotypic assays will be performed in the laboratory of Dr. Margie Clapper, the Principal Investigator of this proposal. For the past 15 years, her research has focused on the role of detoxication enzymes in both drug resistance and cancer prevention. Her chemoprevention laboratory has extensive experience detecting polymorphisms in Phase I and II detoxication enzymes in various high-risk populations.

All immunohistochemical analyses will be performed in collaboration with Harry S. Cooper, M.D., Director of Clinical Laboratories and Chief of Surgical Pathology and Immunohistochemistry at Fox Chase Cancer Center. Drs. Clapper and Cooper have worked closely on several research projects during the past four years. This established collaboration will be extended to the present study.

10. **Duration of Study:** 18 months
REFERENCES FOR TRANSLATIONAL RESEARCH


APPENDIX X (8/1/01, 4/8/02)

RTOG 99-09

STUDY AGENTS (CeaVac and TriAb) SHIPMENT FORM

Titan Pharmaceuticals, Inc. will ship CeaVac and TriAb only to institutions that have completed this form and returned it to RTOG Headquarters prior to registering any patients on study. See Section 5.1 for additional requirements (IRB approval; IRB approved, study-specific Consent Form; PI’s 1572 form; Conflict of Interest/Financial Disclosure Form for PI and all sub-investigators; recent CV for PI and all sub-investigators; this form; and Designated Requestors Form). **Titan Pharmaceuticals will not ship vaccine until the above documents have been reviewed and approved.** Allow adequate processing time at Headquarters and Titan before calling to register your first patient.

**SHIP TO:**

Name: ________________________________

Address: ________________________________  
(No P.O. Box numbers)  
________________________________________  
________________________________________  
________________________________________

Telephone: ________________________________

Fax#: ____________________________________

RTOG Institution#: ____________________________

Institution Name: ____________________________

IRB Approval Date: ____________________________

Investigator (PI) Signature ____________________________ Date: __________

Investigator Name (Print) ____________________________

Investigator NCI # (Required) ____________________________

Return to:  
RTOG Headquarters  
1101 Market Street  
Philadelphia, PA 19107  
RANDOMIZATION OFFICE  
ATTN: FAX# 215-574-0300

RTOG Headquarters Approval ____________________________ Date: __________
APPENDIX XI (4/8/02)

TITAN PHARMACEUTICALS, INC.
INVESTIGATIONAL PRODUCT(S) DESIGNATED REQUESTORS

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I confirm that the above-listed shipping address is correct, and that the individuals noted above are authorized to request Investigational Product(s) for the above-mentioned study. I understand that Titan Pharmaceuticals will only accept IP requests from those individuals.

__________________________________ ____________________________
Investigator Signature Date

CR Form #014 Version Date: 2/23/2005