A PHASE I/II TRIAL OF A COX-2 INHIBITOR, CELEBREX™ (CELECOXIB), WITH LIMITED FIELD RADIATION FOR INTERMEDIATE PROGNOSIS PATIENTS WITH LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER, WITH ANALYSIS OF PROGNOSTIC FACTORS

Study Chairs
Radiation Oncology
Elizabeth Gore, M.D.
Department of Radiation Oncology
Medical College of Wisconsin
9200 West Wisconsin Avenue
Milwaukee, WI 53226
(414) 805-4465
FAX (414) 805-4369
bethgore@mcw.edu

Medical Oncology
Corey Langer, M.D.
(215) 728-2985
FAX (215) 728-3639
cj_langer@fccc.edu

Geriatric Oncology
Martine Extermann, M.D.
(813) 979-3822
FAX (813) 972-8468
extermann@moffitt.usf.edu

Quality of Life
Benjamin Movsas, M.D.
(313) 916-5188
FAX (313) 916-3235
bmovsas1@hfhs.org

Translational Research
Paul Okunieff M.D.
(716) 273-1985
FAX (716) 275-1531
paul_okunieff@urmc.rochester.edu

Activation Date: July 30, 2002
Closure Date: June 30, 2005
Termination Date: March 21, 2012
Update Date: February 11, 2005
Version Date: March 24, 2010
Includes Amendments 1-5

This protocol was designed and developed by the Radiation Therapy Oncology Group (RTOG) of the American College of Radiology (ACR). It is intended to be used only in conjunction with institution-specific IRB approval for study entry. No other use or reproduction is authorized by RTOG nor does RTOG assume any responsibility for unauthorized use of this protocol.
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 - Sample Consent Forms
Appendix II - Performance Status Scoring
Appendix III - Staging System
Appendix IV - Toxicity Criteria
Appendix V - Adverse Reaction Reporting Guidelines
Appendix VI - Study Agent Shipment Form — U.S. Sites (4/13/04)
Appendix VII - Drug Supply Procedures — Canadian Sites
Appendix VIII - Site Information Sheet — Canadian Sites
Appendix IX - Comorbidity Assessments
RADIATION THERAPY ONCOLOGY GROUP

RTOG 0213

A PHASE I/II TRIAL OF A COX-2 INHIBITOR, CELEBREX™ (*CELECOXIB*), WITH LIMITED FIELD RADIATION FOR INTERMEDIATE PROGNOSIS PATIENTS WITH LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER, WITH ANALYSIS OF PROGNOSTIC FACTORS

**SCHEMA (5/21/04)**

R **COX-2 Inhibitor**

E Celecoxib 200 mg b.i.d, 7 days/week with dose escalation to 400 mg b.i.d;

G Begin 5 days prior to start of Radiation Therapy;

I Once RT begins, Celecoxib a.m. dose 1-2 hours prior to RT;

S Administer for 2 years or until disease progression

T **Concurrent Radiation Therapy**

E 2 Gy daily, 30-33 fractions, 5 days/week for 6-7 weeks, for a total dose of 60-66 Gy

R OR

3 Gy daily, 15 fractions, 5 days/week for 3-4 weeks for a total dose of 45 Gy

*The first 6 patients will be treated with 200 mg b.i.d. If less than 3 patients experience unexpected acute toxicity, then the dose will be escalated to 400 mg b.i.d. for the next 6 patients. If less than 3 of these patients experience unexpected acute toxicity, then the dose will be increased to 400 mg b.i.d. for patients already on study; all other patients will begin treatment at 400 mg b.i.d. (See Section 13.2.1.2 for details).

**ELIGIBILITY** *(See Section 3.0 for details) [10/3/02]*

- Histologically or cytologically proven diagnosis of non-small cell lung cancer *(NSCLC)*
- Inoperable stage IIB or unresectable stage IIIA or IIIB disease, without evidence of hematogenous metastases
- Patients with a Zubrod performance score of 2 and/or > 5% weight loss over 3 months prior to diagnosis
  OR
  - Patients with a Zubrod performance of 0-1, < 5% weight loss, and who refuse chemotherapy or who are medically unable to tolerate combined modality therapy
- No known hypersensitivity to celecoxib
- Patients who have developed allergic-type reactions to sulfonamides or who have experienced asthma, urticaria, or allergic-type reaction after taking aspirin or other NSAIDs are ineligible.
- Patients requiring therapy with NSAIDs, lithium, furosemide, corticosteroids, or ACE inhibitors are ineligible.
- Patients with intermediate-poor hepatic function as indicated by serum total bilirubin > 2 X ULN are ineligible.
- Patients with severe renal insufficiency *(CrCl < 50 mL/min)* are ineligible.
- Patients taking warfarin who have uncontrolled prothrombin time *(INR > 3.0)* are excluded.
- Patients who have undergone complete *(or subtotal)* tumor resection are excluded.
- No prior thoracic radiation or neoadjuvant chemotherapy
- Patients with active GI ulcers or bleeding within the last 3 months prior to study entry are ineligible.
- No synchronous or prior malignancy other than non-melanomatous skin cancer, unless disease free ≥ 3 years
- Pregnant women are ineligible as treatment involves unforeseeable risks to the participant and to the embryo or fetus.
- Patients must sign study-specific consent form prior to study entry.

**Required Sample Size:** 122
RTOG Institution # __________

RTOG 0213 | ELIGIBILITY CHECKLIST (10/3/02)
Case # __________ (page 1 of 2)

_____ (Y) 1. Does the patient have medically inoperable or unresectable histologically or cytologically proven NSCLC without evidence of hematogenous metastases?

_____ (IIB/III) 2. What is the stage?

_____ (Y) 3. Does the patient have a Zubrod of 2 and/or > 5% weight loss over 3 months prior to diagnosis?

OR

_____ (Y) 4. Does the patient have a Zubrod of 0-1, < 5% weight loss, and has refused chemotherapy or is medically unable to tolerate combined modality therapy?

_____ (N) 5. Does the patient have known hypersensitivity to celecoxib?

_____ (N) 6. Has the patient developed allergic-type reactions to sulfonamides?

_____ (N) 7. Has the patient experienced asthma, urticaria, or allergic-type reaction after taking aspirin or other NSAIDS?

_____ (N) 8. Does the patient require concomitant therapy with NSAIDs, lithium, furosemide, corticosteroids, or ACE inhibitors?

_____ (N) 9. Does the patient have intermediate-poor hepatic function as indicated by serum total bilirubin > 2 X ULN?

_____ (N) 10. Does the patient have severe renal insufficiency as indicated by CrCl < 50 mL/min?

_____ (N) 11. If taking warfarin, does the patient have uncontrolled prothrombin time (INR > 3.0)?

_____ (N) 12. Has the patient received prior thoracic radiation, or neoadjuvant chemotherapy, or complete or subtotal tumor resection?

_____ (N) 13. Does the patient have active GI ulcers or has the patient had bleeding within the last 3 months prior to study entry?

_____ (Y) 14. If the patient has a synchronous or prior malignancy, other than non-melanomatous skin cancer, is the patient disease-free for ≥ 3 years?

_____ (N) 15. Is the patient pregnant?

_____ (Y) 16. Have pre-study diagnostic evaluations been performed in accordance with Section 4.0?

The following questions will be asked at Study Registration:

______________ 1. Name of institutional person registering this case? (continued on next page)
(Y) 2. Has the Eligibility Checklist (above) been completed?

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

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

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

6. Verifying Physician

7. Patient’s ID Number

8. Date of Birth

9. Ethnic category (Hispanic or Latino; Not Hispanic or Latino; Unknown)

10. Race

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. Treatment Start Date

(Y/N) 17. Is the patient going to receive IMRT?

18. Medical Oncologist’s Name

(Y/N) 19. Tissue/Blood kept for cancer research?

(Y/N) 20. Tissue/Blood kept for medical research?

(Y/N) 21. Allow contact for future research?

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 BACKGROUND AND RATIONALE

1.1 Targeted Patient Population: Intermediate Prognosis

Combination chemotherapy and radiation in carefully selected patients with locally advanced non-small cell lung cancer (LA-NSCLC) is superior to radiation alone. Retrospective analyses of RTOG studies have shown that patients with weight loss, poor performance status, and advanced age do not benefit from aggressive multimodality therapy. Reasons for this are not clear. Poor tolerance to therapy is likely a partial explanation. Elderly patients and those with poor performance status frequently have a high incidence of comorbid conditions that may result in poor therapy tolerance and recovery. Patients with weight loss who are already nutritionally compromised tolerate esophageal toxicity poorly. There is no preferred therapy regimen for this diverse patient population. These patients are treated with radiation alone or a modified regimen of combination chemotherapy and radiation, extrapolating from data generated from patients with favorable prognostic factors. Radiation alone provides a very low chance of tumor control, while combination therapy is too toxic and of limited benefit for this patient population. Treatment with improved therapeutic ratio is needed.

A phase II SWOG trial treated poor risk patients with concurrent chemotherapy and radiation with favorable response rates and short-term survival, but with high acute esophageal toxicity. RTOG 97-01 was designed to test the SWOG regimen against standard radiation alone. Accrual was poor due to the reluctance of some physicians to treat patients with radiation alone and to the reluctance of others to treat with chemotherapy.

The proposed study is intended to target patients with LA-NSCLC with an intermediate prognosis, for whom there is no proven benefit to multimodality therapy. Patients with very poor performance status (Zubrod ≥ 3) are excluded. Eligible patients include those who do not meet the eligibility criteria for studies intended for patients with good prognostic factors or who refuse chemotherapy. Patients will be treated with concurrent, limited volume irradiation and celecoxib, a COX-2 inhibitor.

1.2 Radiation (5/21/04)

Limited volume irradiation will be used to minimize esophageal toxicity. Conventional radiation portals include prophylactic treatment of clinically uninvolved lymphatics in the mediastinum, ipsilateral hilum and, in some cases, the ipsilateral supraclavicular fossa and contralateral hilum. In this study, uninvolved regional lymphatics will not be included in the radiation portals. Investigators that have treated smaller than conventional volumes have not demonstrated a negative impact on outcomes. This can be explained by failures at involved sites as high as 90%, rendering the potential benefit of prophylactic nodal treatment negligible. Current dose escalation studies with 3D conformal radiation therapy do not include prophylactic treatment of uninvolved regional lymphatics. These limited fields decrease the length of esophagus and the amount of normal lung and other vital tissues in the treatment portals.

Standard radiation to the chest for unresectable NSCLC is 60-66 Gy at 2 Gy per fraction. Many patients with relatively poor prognostic factors may not be able to tolerate a 6-8 week course of radiation. An acceptable alternative is 3 Gy daily fractions, 5 days a week, to 45 Gy, and therefore, in this study, the treating physician will have the option to treat to 45 Gy at 3 Gy per fraction or to 60-66 Gy at 2 Gy per fraction.

Radiobiologic calculations indicate that the accelerated therapy regimen of 3 Gy/fraction to 45 Gy is similar to 2 Gy per fraction to 60 Gy, with regrowth delay time (time to progression) of 92% and late complication biologically effective dose (BED) of 90% of that calculated for standard radiation. Additionally, 45 Gy at 3 Gy per fraction has been shown to have similar clinical outcomes and toxicity. Nguyen, et al., from MD Anderson Cancer Center, retrospectively reviewed two cohorts of node positive patients with inoperable LA-NSCLC treated with radiation alone. One cohort (26 patients) had borderline prognostic factors (KPS < 70 but > 50, and/or weight loss of more than 5%) and was treated to 45 Gy over 3 weeks at 3 Gy/fraction. The second cohort (29 patients) had significantly better prognostic factors and was treated to 60-66 Gy over 6 to 6.5 weeks at 2 Gy per fraction during the same period. Despite having worse prognostic factors, the cohort treated to 45 Gy at 3 Gy per fraction over 3 weeks had response rates, locoregional control, and overall survival comparable to those in the cohort treated to a total dose of 60-66 Gy at 2 Gy per fraction over 6 to 6.5 weeks. There was no difference in acute or late toxicity.

Several other clinical studies (see the table below) have demonstrated that accelerated courses of radiation have similar response rates and survival as standard radiation.
<table>
<thead>
<tr>
<th>Study</th>
<th>Total Dose (Gy)</th>
<th>Duration Therapy (weeks)</th>
<th>Response Rate</th>
<th>Median Survival (months)</th>
<th>Two-year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>60</td>
<td>6</td>
<td>43%</td>
<td>8-11</td>
<td>13%</td>
</tr>
<tr>
<td>Nguyen</td>
<td>45</td>
<td>3</td>
<td>67%</td>
<td>NA</td>
<td>13%</td>
</tr>
<tr>
<td>Simpson</td>
<td>36</td>
<td>3</td>
<td>58%</td>
<td>NA</td>
<td>14.8%</td>
</tr>
<tr>
<td>Teo</td>
<td>45</td>
<td>4.5</td>
<td>53%</td>
<td>5</td>
<td>10%</td>
</tr>
<tr>
<td>Trovo</td>
<td>45</td>
<td>3</td>
<td>54.3%</td>
<td>12</td>
<td>20%</td>
</tr>
<tr>
<td>Abratt</td>
<td>45</td>
<td>3</td>
<td>68%</td>
<td>8.5</td>
<td>NA</td>
</tr>
<tr>
<td>Jeremic</td>
<td>51</td>
<td>3.5</td>
<td>65%</td>
<td>10</td>
<td>24%</td>
</tr>
</tbody>
</table>

Liao, et al. at MD Anderson Cancer Center recently completed a phase I dose escalation trial of celecoxib and concurrent radiation therapy for patients with NSCLC and poor prognostic factors. The trial consisted of 3 treatment groups. Group I received 45 Gy in 15 fractions. Group II received 66 Gy at 2 Gy per fraction, and Group III received 63 Gy at 1.8 Gy per fraction after induction chemotherapy. The celecoxib dose escalation schedule was 200 mg, 400 mg, 600 mg, and 800 mg daily divided into two equal doses starting five days prior to radiation and continuing through radiation. Nineteen patients were enrolled in Group I, and 22 patients were enrolled in Group II. The 800 mg dose level was completed without dose-limiting toxicities in Groups I and II.

### 1.3 COX-2 Inhibitor

Cyclooxygenase-2 (COX-2) is the enzyme that converts arachidonic acid to prostaglandins. It is overexpressed in a variety of different tumors, including colon, pancreatic, prostate, lung, and head and neck cancers. COX-2 is observed within human tumor neovasculature, suggesting that COX-2 derived prostaglandins contribute to tumor growth by inducing formation of new blood vessels. Up to 90% of non-small cell lung cancers have been shown to express COX-2 at a moderate to strong level. Although Hida et al. have reported only a 14% incidence of COX-2 over expression in squamous cell carcinoma, other investigators report much higher expression in squamous cell carcinoma. Soslow et al. reported COX-2 expression in 67% of squamous cell carcinomas. Wolff et al. reported COX-2 expression in 11/11 of squamous cell carcinomas evaluated. The expression level in non-small cell lung cancer (NSCLC) has been shown to be significantly higher than in normal lung tissue for both adenocarcinoma and squamous cell carcinoma. In stage I NSCLC, increased expression of COX-2 has been shown to correlate with shortened survival.

Celecoxib, a COX-2 inhibitor, is a potent inhibitor of angiogenesis and has been shown to inhibit neoplastic cells and neoangiogenic vasculature proliferation by 40–60% in these tumors. Hida et al. report that a selective COX-2 inhibitor, nimesulide, can inhibit proliferation of NSCLC cell lines in vitro in a dose-dependent manner in clinically-achievable low concentrations.

These and other data suggest that COX-2 dependent angiogenesis plays a major role in development of cancer. The ability of celecoxib to block neo-angiogenesis and tumor proliferation, regardless of the expression of the enzyme in the cancer cells, suggests the potential utility of this anti-inflammatory drug in the treatment of human cancer.

### 1.4 COX-2 Inhibitor and Concurrent Radiation

Preliminary published results suggest that irradiation upregulates VEGF and COX-2 production in tumor cells, which in turn stimulates tumor angiogenesis. Furthermore, Milas and co-workers reported that COX-2 inhibition on tumors improved the response to radiotherapy in an animal model, possibly through an antiangiogenic mechanism. More importantly, this enhancement came without markedly affecting normal tissue radioreponse. Evidence supporting this rationale comes from the work of Gallo et al. in which COX-2 inhibition reduced the synthesis of VEGF165 in A-431 and SCC-9 cell lines in vitro. The mechanism of COX-2 inhibited radiosensitivity is not completely known. COX-2 can be upregulated by ionizing radiation and blocked by the use of a COX-2 specific inhibitor prior to radiation. COX-2 also modulates immune function and the regulation of pro-inflammatory cytokines that may have a role in angiogenesis.

While it would be ideal to measure tissue and serum levels of angiogenesis markers and correlate to response and outcome, most patients on this study will not have sufficient tissue available for this. Similarly, immunohistochemical analysis of biopsy or resection material for expression of COX-2 will not be feasible since the usual FNA biopsy samples do not provide sufficient tissue for analysis. Nevertheless,
serum markers may be useful surrogates and will be measured before therapy, during radiation therapy and after radiation (during celecoxib “maintenance”).

The proposed translational studies will seek to answer the following questions:

1. Do circulating levels of VEGF, bFGF, and IL-8 correlate with response?

Celecoxib was chosen for lung cancer studies based on a nearly ideal set of pre-clinical data. As previously described, celecoxib in experimental animal and cell models improves tumor response to radiation. It accomplishes this by increasing human lung tumor cell kill in a direct manner, being additive with radiation, and by antiangiogenic mechanisms that indirectly decrease tumor growth and metastases.14-21

Local radiation alone has powerful local antiangiogenic effects22-27 that can include systemic lowering of circulating angiogenic factors such as bFGF and VEGF. As previously discussed, investigators have demonstrated decreases in VEGF, IL-8 and MCP-1 in tumor after celecoxib, probably due to decreased inflammation and thus decreased macrophage activation.10, 11 Among these angiogenic factors, bFGF, VEGF, and IL-8 are easily measured in the circulation, and have been makers of tumor aggressiveness and response in breast, melanoma, and bladder cancers.28-31 Therefore, we plan to collect blood to measure these factors and determine if the treatment regimen is associated with a decrease in these factors, and determine if angiogenic factors in the circulation correlate with prognosis.

2. Are circulating pro-angiogenic and pro-inflammatory cytokines altered by this novel, multi-targeted antiangiogenic approach?

Although COX-2 inhibitors are commonly used to treat arthritic conditions with no adverse side effects reported with concurrent radiation, the toxicity of concurrent RT and celecoxib has not been formally tested. This study will assess the toxicity of celecoxib with concurrent radiation. Celecoxib does not appear to sensitize normal tissue to radiation, and in fact, appears to achieve the opposite.18, 19 For example, fibrosis and acute inflammation following radiation is significantly reduced in several strains of mice if celecoxib is given orally to these mice for at least five days near the time of irradiation. The radioprotective effect is greater than that which can be achieved using another powerful radiation protector, FGF2. The strain differentiation appears to be related to the intrinsic differences in constitutive expression of inflammatory and fibrogenic cytokines including TGFß1. TGFß1 has been shown to predict susceptibility for the development of lung fibrosis in patients undergoing bone marrow transplantation, and lung irradiation.32-35

1.5 Prognostic Factor Assessment

Many factors have been implicated as prognostic for LA-NSCLC, but the only commonly accepted prognostic factors are performance status (PS) and weight loss. Patients with Zubrod PS 0 or 1 and 5% weight loss are said to have a favorable prognosis and are the focus of the majority of research for LA-NSCLC. Based on tumor registry analysis, the majority of patients with LA-NSCLC don’t meet these PS and weight loss criteria. Other patients, even though they may meet these strict eligibility criteria, are unwilling to accept the high rate of acute toxicity of multimodality therapy or are considered unsuitable for multimodality therapy because of age or comorbid conditions. These patients clearly represent a very diverse population. Many factors other than age, weight loss and performance status influence prognosis. Comorbid conditions and psychological status, in addition to functional status, are predictors of mortality in non-oncology patients. These factors likely influence prognosis in oncology patients and will be assessed to determine their impact on prognosis, toxicity to therapy and QOL in this study.

1.5.1 Comorbidity

Comorbid conditions affect prognosis in a variety of clinical situations and are independent of functional status. Although comorbid conditions influence a clinician’s decision regarding cancer therapy, these judgments are subjective and therefore, vary from physician to physician. In this study, comorbidity data will be collected and scored using the Charlson Comorbidity Index (CCI) and Cumulative Illness Rating Scales for Geriatrics (CIRS-G).

1.5.2 Functional Status

Functional status will be assessed with Activities of Daily Living (ADL)37 scales, and Lawton’s Instrumental ADL (IADL).38 ADL and IADL scales have been cornerstones of the Comprehensive Geriatric Assessment (CGA) since their creation in the mid-sixties.39-44 In patients with a good
performance status by oncologic criteria, there is a significant proportion of patients who present a
dependence in IADL.

1.5.3 Psychological Status
Cognitive problems are under-diagnosed and confounded in older patients. Screening tools can
improve detection and diagnosis and therefore, provide a more reliable assessment of the study
population for the psychological category of the CIRS-G, and as a control for quality of life (QOL)
assessment. The Mini-Mental Status Exam (MMSE) is a simple screening tool for cognitive disorders,
already in use in other RTOG studies. It is currently one of the most widely used brief mental status
exams and will be included in this study.

Depressive status as measured by Geriatric Depression Scale (GDS) is associated with an increased
mortality. Depression is often underdiagnosed in cancer patients. Symptoms of depression as assessed
with GDS have also been associated with unfavorable functional evolution in geriatric patients. The
GDS short form is a screening tool with good performance and will be used in this study.

Inouye et al. published a simple prognostic index using IADL, GDS, and MMSE that had a predictive
power for survival that was independent from comorbidity in hospitalized elderly patients. We will
assess whether these results can be reproduced in our study population.

1.5.4 Quality of Life
Prior studies, particularly in lung cancer, have demonstrated that Quality of Life (QOL) is a critical
prognostic factor for outcome. In a recent study of QOL in lung cancer, Montazeri et al. found that the
initial global quality of life was the most significant predictor of survival on multivariate analysis (p
<0.02), while some of the classic prognosticators (such as performance status and weight loss) were not
significant. Moreover, they found that of the patients who had died, more had perceived health problems,
a greater level of symptoms, and significantly lower physical functioning and global quality of life on
presentation (than those who were still alive). This type of study supports correlating quality of life data
with patients’ underlying health status/co-morbid conditions and overall functioning. Similarly, in a
study specifically of patients with inoperable non-small cell lung cancer treated with definitive
radiotherapy, Langendijk et al. found that pretreatment QOL was the strongest prognostic factor for
survival on multivariate analysis; performance status, however, was not significant.

This protocol provides a unique opportunity to correlate the important issue of co-morbid conditions
with that of quality of life, as well as functional status and psychological status. Indeed, other studies
have suggested an important correlation between the extent of co-morbid illness and QOL. For example,
Stier et al. studied a co-morbidity index, the Total Illness Burden Index (TIBI) and quality of life (via
the SF-36 QOL questionnaire) in 1638 men with prostate cancer. After adjusting for age and income,
they found that lower SF-36 scores were associated with a greater burden of co-morbid illness (as measured by TIBI), independent of the extent of prostate cancer. Even in patients without cancer, co-
morbid conditions have been found to significantly affect patient scores on QOL measures. For
example, Hussain et al. reported that the presence of co-morbid illness was the most important predictor
of health-related quality of life in patients with chronic hepatitis C.

Fatigue has been recognized as one of the most frequent symptoms experienced by patients with
cancer. In a study summarizing the findings of 2390 cancer patients in ten clinical trials, Pater et al.
reported that patients with lung or ovarian cancer experienced greater fatigue than those with other
cancers. A recent study of 157 patients with lung cancer found that approximately 60% experienced
clinical fatigue, (that interfered with any daily activities). Significantly correlated factors included
dyspnea, appetite loss and depression. Overall, this study indicated that fatigue is a frequent and
important symptom, associated with both physical and psychological distress in patients with lung
cancer. Fatigue has also been associated with the patient undergoing radiotherapy. Hickok et al.
retrospectively studied 50 lung cancer patients receiving radiotherapy and found that fatigue was a
frequent symptom (78%) that was not correlated with either disease or treatment variables.
However, only a few trials have prospectively studied fatigue in patients receiving definitive radiotherapy for lung
cancer. As fatigue is interwoven with underlying co-morbidities, functional status, and psychological
status, we felt this was an important component of QOL to include in this study. Indeed, Ferrell et al.
found that fatigue interfered with the physical, psychological, social, and spiritual dimensions of quality
of life. In another study, a significant correlation was found between fatigue and QOL.
QOL will be assessed through the use of one site-specific instrument and one symptom-specific instrument: the Lung Cancer Symptom Scale (LCSS) and Schwartz Cancer Fatigue Scale (SCFS).

CCI and CIRS-G will be correlated with QOL and functional status data to determine the relationship of comorbidity to symptoms of disease and therapy, QOL, and functional status. LCSS and SCFS will be correlated with functional assessment scales to determine which symptoms are related to functioning. LCSS, SCFS, IADL, ADL, MMSE, GDS, CCI, and CIRS-G will be correlated with survival by univariate and multiple regression analysis.

2.0 OBJECTIVES (8/26/03)

2.1 To determine the toxicity and efficacy of thoracic irradiation and two years of celecoxib for locally advanced non-small cell lung cancer in intermediate prognosis patients

2.2 To determine how predictors of mortality in the general population (comorbid conditions, functional status, quality of life, and psychological status) influence prognosis, toxicity of therapy, and outcomes of therapy in patients with locally advanced non-small cell lung cancer; this information will be used to develop prognostic indices

2.3 To determine if circulating levels of VEGF, bFGF, and IL-8 correlate with survival

2.4 To determine if circulating levels of IL-1, IL-6, and TGFβ correlate with development of pulmonary toxicity

3.0 PATIENT SELECTION

3.1 Eligibility (10/3/02)

3.1.1 Histologically or cytologically proven diagnosis of non-small cell lung cancer (NSCLC);

3.1.2 Inoperable stage IIB or unresectable stage IIIA or IIIB disease, without evidence of hematogenous metastases;

3.1.3 Patients with a Zubrod performance score of 2 and/or > 5% weight loss over 3 months prior to diagnosis

OR

3.1.4 Patients with a Zubrod performance score of 0-1, < 5% weight loss, and who refuse chemotherapy or who are medically unable to tolerate combined modality therapy;

3.1.5 Pre-study diagnostic evaluations must be performed as specified in Section 4.0.

3.1.6 Patients must sign a study specific consent form prior to study entry.

3.2 Conditions for Patient Ineligibility

3.2.1 Patients with known hypersensitivity to celecoxib;

3.2.2 Patients who have developed allergic-type reactions to sulfonamides;

3.2.3 Patients who have experienced asthma, urticaria, or allergic-type reaction after taking aspirin or other NSAIDs;

3.2.4 Patients requiring concomitant therapy with NSAIDs, lithium, furosemide, corticosteroids, or ACE inhibitors;

3.2.5 Intermediate-poor hepatic function as indicated by serum total bilirubin of > 2 X ULN;

3.2.6 Severe renal insufficiency: i.e., estimated Cr Clearance < 50 mL/min; Cockcroft-Gault Equation: Cr Clearance = (140-age) x wt (kg)/(Cr[mg/dl] x 72);

3.2.7 Patients taking warfarin with uncontrolled prothrombin time (INR > 3.0)

3.2.8 Patients who have undergone complete (or subtotal) tumor resection;

3.2.9 Patients who have received neoadjuvant chemotherapy;

3.2.10 Patients who have received prior thoracic radiation;

3.2.11 Patients with active GI ulcers or bleeding within the last 3 months prior to study entry;

3.2.12 Patients with synchronous or prior malignancy other than non-melanomatous skin cancer, unless disease free ≥ 3 years;

3.2.13 Pregnant women are ineligible as treatment involves unforeseeable risks to the participant and to the embryo or fetus; patients with childbearing potential must practice appropriate contraception.

4.0 PRETREATMENT EVALUATIONS

4.1 Complete detailed medical history & physical examination to include usual weight, recent weight loss, concurrent non-malignant diseases, and concurrent therapy

4.2 CT scan of chest, liver, adrenal glands is required, and it is recommended that CT be completed within 4-6 weeks prior to the start of therapy; up to 8 weeks is permitted, but in that case, CXR is required within 1 week of starting therapy.

4.3 CT scan or MRI of brain and radionuclide bone scan within 8 weeks prior to start of therapy
Location, type, and size of all measurable disease must be recorded.

CBC with differential, platelet count, SGOT, SGPT, total bilirubin, BUN, creatinine, and serum pregnancy test (for females of childbearing potential) within 14 days prior to study entry; for patients taking warfarin, prothrombin time (PT) within 14 days prior to study entry.

Completion of comorbidity measures (Comorbidity rating is based on pretreatment history/physical, laboratory results, and pretreatment medications; the rating does not have to be completed prior to treatment, but comorbidity data should be sent with the initial assessment data [See Sections 11.2.6 and 12.1]).

- Charlson Comorbidity Index (CCI)
- Cumulative Illness Rating Scales for Geriatrics (CIRS-G)

Completion of functional and psychological status scales:

- Zubrod Performance Scale
- Activities of Daily Living (ADL)
- Instrumental Activities of Daily Living (IADL)
- Geriatric Depression Scale (GDS)
- Mini-Mental Status Exam (MMSE)

Completion of quality of life measures:

- Lung Cancer Symptom Scale (LCSS)
- Schwartz Cancer Fatigue Scale (SCFS)

5.0 REGISTRATION PROCEDURES (8/26/03, 4/13/04)

5.1 For initial shipments of study drug, each U.S. institution must submit a Study Agent Shipment Form (Appendix VI) to the CTSU Regulatory Office (Fax 1-215-569-0206) prior to the registration of its first case. Canadian sites must submit drug shipment forms (see Appendices VII and VIII) to RTOG Headquarters (Fax 215-574-0300). Allow adequate processing time (7-10 days) before calling to register your first patient.

5.2 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 a.m. to 5:00 p.m. ET. The patient will be registered to a treatment arm 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.

6.0 RADIATION THERAPY (AN IMRT TREATMENT APPROACH IS NOT ALLOWED ON THIS PROTOCOL.)

6.1 Radiation Dose (5/21/04)

6.1.1 Radiation will be given at 2 Gy per fraction, 33 fractions, 5 days per week, for 6 plus weeks for a total dose of 60-66 Gy OR at 3 Gy per fraction, 15 fractions, 5 days per week for 3 weeks for a total dose of 45 Gy. The radiation dose will be specified at the ICRU-50 reference point, which is to be located in the central part of the PTV. This reference point is further described in Section 6.3.3. The dose is based upon a heterogeneity uncorrected model. The isodose curve representing 90% of the prescription dose must encompass the entire planning target volume (PTV), which is defined in Section 6.3.2. The maximum dose to the PTV should not exceed the prescription dose by > 15%. All fields are to be treated each day.

6.1.2 A volumetric treatment planning CT study will be required to define gross tumor volumes (GTV), and planning target volume (PTV). For this study, GTV will be equal to the clinical target volume (CTV). Each patient will be positioned in an individualized immobilization device in the treatment position on a flat table. Contiguous CT slices 3-5 mm separation of the regions harboring gross tumor and grossly enlarged nodes and 8-10 mm separation of the remaining lung. The GTV and PTV and normal organs will be outlined on all appropriate CT slices and displayed using beam's eye view. Normal tissues to be contoured include lungs, skin, heart, spinal cord, esophagus and liver (the liver only needs to be contoured if it is included in one or more of the treatment fields). A measurement scale for the CT image shall be included.

6.1.3 Intravenous contrast during the planning CT is optional provided a diagnostic chest CT was done with contrast to delineate the major blood vessels. If there is not a CT study which uses contrast, then intravenous contrast should be given during the planning CT.
6.1.4 Optimal immobilization is critical for this protocol. Alpha cradle or alternate individual immobilization system is required.

6.1.5 The reported dose shall include the dose to the ICRU-50 Reference Point. The maximum point dose within the PTV and the minimum point dose within the PTV shall also be reported.

6.1.6 The percentage of total lung volume (the volume of both lungs minus the PTV) exceeding 20 Gy (V20) should be less than 32%.

6.1.7 The total volume of the esophagus shall be contoured. (The PTV should NOT be subtracted from this volume.) The percentage of the esophageal volume exceeding 55 Gy should be ≤ 28% and the mean dose to the esophagus shall be ≤ 32 Gy.

6.1.8 The dose to the heart should be kept as low as possible. The whole heart dose should not exceed 30 Gy for patients treated at 3 Gy per fraction and should not exceed 40 Gy for patients treated at 2 Gy per fraction.

6.1.9 For patients whose lesion will require some of the liver to be treated, the entire liver should be imaged and defined. The dose to the liver should be kept to a minimum. The dose to half of the liver should not exceed 35 Gy. The whole liver dose should not exceed 30 Gy.

6.1.10 The maximum dose to any part of the spinal cord should not exceed 36 Gy for patients treated at 3 Gy per fraction to 45 Gy and should not exceed 45 Gy for patients treated at 2 Gy per fraction to 60-66 Gy.

6.2 Technical Factors

6.2.1 Beam Energy

6.2.1.1 Megavoltage equipment is required with effective photon energies ≥ 6 MV.

6.2.1.2 The use of 3D conformal radiotherapy capabilities is recommended, but not limited to the RTOG 3D CRT approved centers.

6.2.2 Treatment Distance

Minimal treatment distance to skin should be ≥ 100 cm for SSD technique, and minimum isocenter distance should be 100 cm for SAD techniques.

6.2.3 Blocking

Blocking most likely will be required in order to minimize the dose to the lung.

6.2.4 Compensating Filters or Wedges

In the case of a large sloping contour, such as is usually encountered when treating upper lobe tumors in large patients, compensating filters are recommended. A wedge may also be used as a two-dimensional tissue compensator. If necessary, appropriate reduction in field size must be done to avoid excessive irradiation to critical structures.

6.2.5 Therapy Interruptions

If interruptions of therapy up to one week become necessary, irradiation should be completed to the prescribed doses. Total number of fractions and elapsed days should be carefully reported. If more than one-week interruption is required, resumption of the treatment is at the discretion of the radiation oncologist.

6.3 Volume and ICRU Reference Point Definitions

The definition of volumes will be in accordance with the 1993 ICRU Report #50: Prescribing, Recording and Reporting Photon Beam Therapy.

6.3.1 Gross Tumor Volume (GTV) will be defined by the physician. It is equal to all known gross disease as defined by the planning CT and clinical information. Gross tumor includes the primary tumor (GTV-P) and abnormally enlarged regional lymph nodes > 1.0 cm (short axis measurement) (GTV-N). These volumes may be disjoint. (Note ICRU Report #50 also defines a clinical target volume (CTV) which includes the area of subclinical involvement around the GTV. In this study GTV= CTV.)

6.3.2 Planning Target Volumes (PTV) Planning target volume will provide margin around the GTV to compensate for variability in treatment setup, breathing, or motion during treatment. The PTV volume must include a minimum 10 mm margin around the GTV. Additional margin may be required based upon clinical judgment and/or respiratory motion. Respiratory motion should be checked by fluoroscopy at the time of simulation.

6.3.3 ICRU Reference Point is to be located in the central part of PTV. The specification of the target dose is in terms of a dose to a point at or near the center of target volume according to:

6.3.3.1 For arrangement of two or more intersecting beams: at the intersection of the central ray of the beams.

6.3.3.2 Other or complex treatment arrangements: at the center of the target area(s).

6.4 3D Planning

6.4.1 Planning Volume (PTV) - The PTV is to be treated with any combination of coplanar or noncoplaner three-dimensional conformal fields shaped to deliver the specified dose while restricting the dose to the
normal tissues. Field arrangements will be determined by 3D planning to produce the optimal conformal plan in accordance with volume definitions.

6.4.2 Localization Films All fields treated require filming on simulator units, or DRRs must be calculated in the case of virtual simulation. Portal verification must be done for all treated fields. Copies of both simulator or DRRs and portal fields must be submitted to RTOG Headquarters.

6.5 Compliance Criteria of Dose Distribution

6.5.1 No variation: The dose and volume criteria listed above are met.

6.5.2 Minor variation: The minimum dose to the PTV is \(\geq 85\%\) and < 90\% of the prescription dose and all of the volume criteria are met.

6.5.3 Major (unacceptable) deviation: The minimum dose to the PTV < 85\% of the prescription dose or any of the volume criteria (lung, esophagus, heart, liver, and spinal cord) are not met.

6.6 Treatment Planning Data

6.6.1 Submit isodose distributions, which are superimposed on the CT anatomy, through the ICRU 50 reference point(s) in the transverse, coronal, and sagittal planes. In addition, submit an isodose curve in the mid-sagittal plane to evaluate the dose to the cord. The isodose values to be represented shall include the 70, 66, 60, 56, 45, and 20 Gy surfaces.

6.6.2 Submit dose-volume histogram data for the PTV, lungs (both lungs together minus the PTV), esophagus, heart, and cord. If the liver receives more than scattered dose, i.e. the liver is included in one or more treatment fields, then submit a dose-volume histogram for the liver. The DVH's can be submitted in either graphical or tabular form.

6.7 Anticipated Side Effects or Toxicity

6.7.1 Reversible alopecia, bone marrow toxicity, skin pigmentation and esophagitis are expected side effects of radiation therapy, while radiation-induced myocarditis or transverse myelitis rarely occur at doses lower than 50 Gy of standard fractionation or 30 Gy for up to 5 Gy per fraction. Radiation pneumonitis and subsequent fibrosis or the lung will occur in 100\% of all patients receiving > 40 Gy to lung, usually within the first six months after initiation of treatment, so it is essential to spare all normal lung possible.

6.7.2 Acute toxicity monitoring: Acute (< 90 days from RT start) side effects of radiation therapy will be documented using the NCI Common Toxicity Criteria, version 2.0. A copy of version 2.0 can be downloaded from the CTEP homepage (http://ctep.info.nih.gov).

6.7.3 Late toxicity monitoring: Late (> 90 days from RT start) side effects will be evaluated and graded according to the RTOG/EORTC Late Radiation Morbidity Scoring Scheme. (Appendix IV)

6.7.4 Radiation therapy may be interrupted for periods of up to one week for grade 4 acute esophagitis: i.e., complete obstruction (cannot swallow saliva); ulceration with bleeding not induced by minor trauma or abrasion or perforation. Sucralfate slurries or topical anesthetics may provide symptomatic relief of esophagitis.

6.7.5 Post-treatment pneumonitis thought due to radiation should be treated with prednisone after excluding microbial causes.

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

6.7.7 All life-threatening (grade 4) toxicity from protocol treatment must be reported by telephone to Group Chairman, ACR Headquarters Data Management Staff and to the Study Chairman within 24 hours of discovery.

6.7.8 Appropriate data forms, and if requested a written report, must be submitted to headquarters within 10 working days of the telephone report.

7.0 CYCLOOXYGENASE-2 INHIBITOR THERAPY

7.1 Celecoxib (Celebrex™) [8/26/03]

7.1.1 Formulation: Celebrex™ is provided as 200 mg capsules to be taken orally. Celebrex™ is supplied in bottles of 100 or 500 capsules.

7.1.2 Storage: Store at 25º C (77º F); excursions permitted to 15-30º C (59-86º F).

7.1.3 Administration: Celebrex™ will be self-administered. Patients should take Celebrex™ with food to improve absorption. The first 6 patients on the Phase I portion of the study will start with one 200 mg capsule twice daily, 7 days per week. If less than 3 patients experience unexpected acute toxicity, then the dose will be escalated to 400 mg b.i.d. for the next 6 patients. If less than 3 of these patients experience unexpected acute toxicity, then the dose will be increased to 400 mg b.i.d. for patients already on study, except for patients that required a dose reduction in Celebrex™ for toxicity unrelated to radiation. All other patients will begin treatment at 400 mg b.i.d. (See Section 13.2.1.2 for details).
Celebrex™ will begin 5 days prior to the start of radiation. Once radiation therapy begins, it must be delivered 1-2 hours after the a.m. dose of Celebrex™. Celebrex™ should be given with food to improve absorption. Patients will take Celebrex™ for 2 years or until disease progression.

7.1.4 Adverse Effects: Incidence rates of adverse events associated with Celebrex™ are provided in the product package insert. The following events are expected with the administration of Celebrex™:

7.1.4.1 Gastrointestinal toxicity: Serious toxicity such as bleeding, ulceration, and perforation can occur with non-steroidal anti-inflammatory drugs (NSAIDs). Upper GI bleeding occurred in 0.04% of patients on controlled clinical trials at a daily dose of 200 mg or more. Patients that are at a higher risk of developing GI side effects include patients with a prior history of GI bleeding and/or peptic ulcer disease. Other therapies or co-morbid conditions that may increase the risk of GI bleeding include: treatment with anticoagulants, longer duration of NSAIDs, smoking, alcoholism, older age, and poor general health status. Other side effects include: abdominal pain, diarrhea, dyspepsia, flatulence, and nausea.

7.1.4.2 Hematologic toxicity: Anemia has been reported in patients on Celebrex™. Celebrex™ does not generally affect platelet counts, prothrombin time, partial thromboplastin time, and does not appear to inhibit platelet aggregation at indicated dosages.

7.1.4.3 Hepatotoxicity: Transient elevations in liver enzymes, especially SGOT (AST), and bilirubin, have been reported.

7.1.4.4 Renal toxicity: Celebrex™, like other NSAIDs, may decrease renal blood flow, which may precipitate renal decompensation.

7.1.4.5 Respiratory: Pharyngitis, rhinitis, sinusitis, upper respiratory tract infection

7.1.4.6 Anaphylactic-like reactions: Anaphylactic-like reactions may occur in patients previously exposed to nonsteroidal, anti-inflammatory drugs (NSAIDS). Symptoms include flushing, rash, urticarial reactions (acute), facial edema, wheezing, tachycardia, and hypotension. Very rare cases of anaphylactic reactions and/or angioedema have been reported in patients receiving Celebrex™.

7.1.4.7 Neurological: Dizziness, headaches, and insomnia

7.1.4.8 General: Back pain, peripheral edema

7.1.5 Drug Interactions: ACE-inhibitors, fluconazole, furosemide, aspirin, lithium, methotrexate, and warfarin. NOTE: Patients requiring therapeutic warfarin should have an INR of 2.0 to 3.0 prior to enrollment; given safety concerns and the remote but real possibility of bleeding, the INR should be monitored weekly during the course of the study (See Section 11.1).

7.1.6 Contraindication: Celebrex™ is contraindicated in patients with hypersensitivities to celecoxib, sulfonamides, and aspirin.

7.1.7 Supply (3/15/04)

Celebrex™ is manufactured by Pfizer/Searle Corporation. Pfizer will supply Celebrex™ free of charge to patients on study in 200 mg capsule form.

7.1.8 Celebrex™ Distribution for U.S. Sites (8/26/03, 3/15/04, 4/13/04)

For initial shipments, the Celebrex™ Shipment Form (Appendix VI) must be submitted to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified. This must be done prior to registration of the institution’s first case. RTOG will fax the completed Celebrex™ Shipment Form (sent to RTOG by CTSU) to Pfizer for the initial drug shipment. For re-supply of Celebrex™, sites can access Pfizer’s re-supply form at http://www.rtog.org/pdf_reports.html?members/reports=0213Pfizer_Clinical_Re-supply_Request_Form_sites.doc. An initial drug shipment of 24 bottles of Celebrex (100 capsules per bottle; 200 mg/capsule) will be provided to the institution after Pfizer, Inc. has received the appropriate documentation from RTOG. The trial inventory of Celebrex™ at each site should always include sufficient supply for two patients to complete three months of treatment. Pfizer will ship, using two-day express delivery, the requested number of bottles to the institution. Initial shipment will be sent within 15 business days following receipt of the request to Pfizer. Subsequent requests for re-supply will be made directly by the institution to Pfizer utilizing the Celebrex™ Drug Order Request Form (Appendix VIA). The re-supply shipment will be sent within 10 business days. Sites should order enough drug to ensure that an adequate supply is available between shipments. All unused Celebrex™ must be destroyed at the site and documented in the Drug Accountability Record Form.
Additional questions about supply and delivery should be directed to:

Susan M. Fritz, MBA
Associate Clinical Study Manager
Clinical / Scientific Operations
U.S. Medical Oncology
Pfizer, Inc.
Phone 212 733-8874
E-mail: susan.fritz@pfizer.com

7.1.9 **Celebrex™ Distribution for Canadian Study Sites (3/15/04)**

The Celebrex™ supplied for this study will not be used for any other purpose other than for this study or administered other than as described in the protocol. Pfizer Canada Inc. will ship Celebrex™ from its corporate office in Mississauga, Ontario, to participating Canadian institutions after Pfizer Canada Inc. has received the following documentation from RTOG:

- Ethics committee approval letter clearly identified with protocol title and study-specific consent form, version dated;
- Ethics Committee approved informed consent;
- Completed Site Information Sheet including the drug shipment address;
- Completed Trial Site Information Form and the fax confirmation sheet indicating that it has been filed with the Health Products and Food Branch (HPFB).

An initial drug shipment of 24 bottles of Celebrex (100 capsules per bottle; 200 mg/capsule) will be provided to the institution after Pfizer Canada Inc. has received the appropriate documentation from RTOG. The trial inventory of Celebrex™ at each site should always have sufficient supply for two patients to complete three months of treatment. To request additional supplies of Celebrex™, complete the Request for Trial Drug Shipment Form that is included with your original drug shipment and fax the request to the Pfizer Canada, Clinical Trials Supply Manager at FAX number 905-755-3151. The site pharmacist must confirm the receipt of the Celebrex™, and to comply with this request, the site pharmacist must sign and date the Drug Shipment Invoice and fax the invoice to the Pfizer Canada, Clinical Trials Supply Manager at FAX number 905-755-3151.

7.1.10 **Study Agent Accountability**

Patients will be issued diaries to record daily doses of Celebrex™. Pill diaries should be collected as specified in Section 11.1 and will be retained at the institution. These diaries are in addition to the completion by the institution of the Treatment Summary Form (TF) indicating daily doses of study agent (See Section 12.1). Celebrex™ will be dispensed to the patient as a three-month supply; a written prescription will be retained as source documentation of sponsor-supplied drug. Drug compliance will be recorded on the TF. All unused Celebrex™ must be destroyed at the site and documented in the Drug Accountability Record Form; unused drug will not be redispensed.

7.2 **Therapy Modification for Toxicity**

7.2.1 Radiation therapy will be interrupted for periods of up to one week for grade 4 acute esophagitis: i.e., complete obstruction (cannot swallow saliva); ulceration with bleeding not induced by minor trauma or abrasion or perforation.

7.2.2 (3/24/10) Toxicities that can be attributed to Celebrex™ should have dose modifications as follows:
<table>
<thead>
<tr>
<th>Toxicity*</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st appearance</td>
<td>Interrupt until resolved to grade 0-1, then continue at same dose with prophylaxis where possible</td>
<td>Interrupt until resolved to grade 0-1, then continue at 75% of starting dose</td>
<td>Discontinue permanently unless investigator deems it to be in the patient's best interest to continue at 50% once toxicity has resolved to grade 0-1</td>
</tr>
<tr>
<td>2nd appearance of same toxicity</td>
<td>Interrupt until resolved to grade 0-1, then continue at 75% of starting dose</td>
<td>Interrupt until resolved to grade 0-1, then continue at 50% of starting dose</td>
<td></td>
</tr>
<tr>
<td>3rd appearance of same toxicity</td>
<td>Interrupt until resolved to grade 0-1, then continue at 50% of starting dose</td>
<td>Discontinue treatment permanently</td>
<td></td>
</tr>
<tr>
<td>4th appearance of same toxicity</td>
<td>Discontinue treatment permanently</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*CTEP's Active Version CTCAE, except for grading of hand-foot syndrome

7.2.2.1 If dose reduction to 75% of the starting dose is required for patients receiving 200 mg b.i.d., patients should take 200mg for the a.m. dose and 100 mg for the p.m. dose (Celebrex™ in 100 mg capsules will be provided for patients needing this dose). If dose reduction to 75% of the starting dose is required for patients receiving 400 mg b.i.d., patients should take 400 mg for the a.m. dose and 200 mg for the p.m. dose.

7.2.2.2 If dose reduction to 50% of the starting dose is required for patients receiving 200 mg b.i.d., patients should take 200 mg for the a.m. dose only. If dose reduction to 50% of the starting dose is required for patients receiving 400 mg b.i.d., patients should take 200 mg for the a.m. dose and 200 mg for the p.m. dose.

7.3 Adverse Drug Reaction Reporting (3/24/10)

7.3.1 Beginning April 1, 2010, the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. The CTEP Active Version of the CTCAE is identified and located on the CTEP web site at: [http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE.

7.3.2 This study will be monitored by the Clinical Data Update System (CDUS) version 2.0. Complete cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

7.3.3 Reporting Requirements

The following guidelines for reporting adverse drug reactions (ADRs) apply to any research protocol that uses commercial anticancer agents.

- Any unexpected (not listed in the package label), life threatening (Grade 4) or unexpected, fatal (Grade 5) adverse event with an attribution of possible, probable, or definite should be reported in five (5) working days. The AE should be reported on the FDA Form 3500 MedWatch (available from the FDA:-www.fda.gov/medwatch)
- The completed form should be forwarded to the FDA:
  
  **MedWatch**
  
  5600 Fishers Lane
  
  Rockville, Maryland 20852-9787
  
  Fax: (800) 332-0178

  - A copy should be forwarded to the NCI:
    
    **Investigational Drug Branch**
    
    P.O. Box 30012
    
    Bethesda, Maryland 20824
    
    Fax: (301) 402-1584

7.3.4 Within 24 hours of discovery, the AE should be telephoned to RTOG Headquarters Data Management and to the Study Chairman; the report should be sent to RTOG, FDA, and IDB within five (5) working days.
Any death, regardless of cause, which occurs during protocol treatment must be reported to RTOG Headquarters by telephone within 48 hours of discovery.

Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported using the NCI/CTEP Secondary AML/MDS Report Form available at http://ctep.info.nih.gov. The report must include the time from original diagnosis to development of AML/MDS, characterization such as FAB subtype, cytogenetics, etc., and protocol identification. This form will take the place of the FDA Form 3500 and must be mailed within 30 days of AML/MDS diagnosis to the address on the form and to the RTOG Data Management Department:

Investigational Drug Branch (NCI/CTEP) RTOG Headquarters
P.O Box 30012 and 1101 Market Street, 14th floor
Bethesda, MD 20824 Philadelphia, PA 19107

7.4 Serious Adverse Event (SAE) Reporting for Pfizer, Inc. (3/15/04)

7.4.1 Definition of Adverse Event

All serious adverse events, regardless of relationship to study drugs, must be reported to RTOG in an expedited manner (see next section for reporting instructions). A serious adverse event (SAE) is any adverse event that:

7.4.1.1 Results in death;
7.4.1.2 Is life threatening;
7.4.1.3 Requires inpatient hospitalization or prolongation of existing hospitalization (excluding hospital admissions for study drug administration, transfusional support, scheduled elective surgery and admissions for palliative or terminal care);
7.4.1.4 Results in persistent or significant disability or incapacity.
7.4.1.5 Is a congenital anomaly/birth defect

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the events listed above.

7.4.2 Serious Adverse Event Reporting Instructions

All serious adverse events must be reported as follows:
Within 24 hours (of investigator knowledge of event) report event by faxing the FDA 3500 form to Medwatch and:

RTOG Data Management Investigational Drug Branch (NCI/CTEP)
1101 Market Street, 14th floor P.O. Box 30012
Philadelphia, PA 19107 Bethesda, MD 20824
1-800-227-5463 Ext. 4189 301-230-2330
Fax: 215-928-0153 Fax: 301-230-0159

If necessary, the initial report is to be followed by submission of more detailed adverse event information on the same FDA 3500 form within 5 working days of the event.

7.4.2.1 RTOG Headquarters Reporting Responsibilities for U.S. Sites (3/15/04)

All serious adverse events must be reported as follows:

RTOG will forward by fax a copy of all serious adverse events occurring at U.S. sites, regardless of relationship to protocol treatment, to Pfizer, Inc. within 24 hours of receipt by RTOG.
Please report SAE’s using the Serious Adverse Event Fax Coversheet. This form includes information for faxing to Pfizer, Inc. and must accompany the MedWatch form when faxed to Pfizer, Inc. The following information must be included: 1. protocol number 2. causality 3. date report was submitted to the FDA.

Reporting Information:
To: U.S. Pharmacovigilance
Fax: 1-616-337-9477 Phone: 1-800-253-8600
7.4.2.2  RTOG Headquarters Reporting Responsibilities for Canadian Sites (3/15/04)
All serious adverse events must be reported as follows:

RTOG will forward by fax a copy of all serious adverse events occurring at Canadian study sites, regardless of relationship to protocol treatment, to Pfizer Canada Inc. within 24 hours of receipt by RTOG. (Note: Only those SAE’s that occur at Canadian sites should be reported to Canadian Pharmacovigilance).

Please report SAE’s using the Serious Adverse Event Fax Coversheet. This form includes information for faxing to Pfizer, Inc. and must accompany the MedWatch form when faxed to Pfizer. The following information must be included: 1. protocol number 2. causality 3. date report was submitted to the FDA.

Reporting Information:
Drug Safety Unit
Pfizer Canada Inc.
555 Standish Court, Suite 1200
Mississauga, Ontario L4W 5J5
FAX: 800-353-0942
Phone: 888-391-2222 toll free

The Therapeutic Products Directorate (TPD) of the Canadian Health Protection Branch will be notified in an expedited manner of serious adverse events considered unexpected and related to protocol treatment. In addition, the RTOG will inform all investigators of all serious adverse events reported to TPD and request that local ethics boards (REB/IRB/IEC) be notified of the same.

7.4.2.3  Reporting Serious Adverse Events to Local Ethics Boards
Investigators must notify their Research Ethics Boards (REB/IRB/IEC) of any serious adverse events sent by RTOG for the purpose of reporting to REBs (as outlined in previous section). Documentation from the REB of receipt of these reportable serious adverse events must be kept on file in the centre.

8.0  SURGERY
Not applicable to this study.

9.0  OTHER THERAPY
No other nonsteroidal, anti-inflammatory drugs (NSAIDS) or chemotherapy are allowed while on protocol treatment. Concurrent aspirin (325 mg/day) is permitted for cardioprotection.

10.0  TRANSLATIONAL STUDY
For patients who have consented to participate in the use of their blood for research (See Appendix IB)

10.1  Rationale
The primary purpose of blood/serum collection in this study is to allow for the analysis of levels of VEGF, bFGF, and IL-8 before and after definitive radiotherapy/celecoxib (See sections 1.3, 1.4, 2.3, and 2.4). These proteins appear to be important in the development of angiogenesis and other aspects of the malignant phenotype; thus, it is relevant to determine if the therapy used in this study affects the protein blood levels. In addition to these primary “a priori” translational analyses, in the future, if new information suggests that other proteins may be important to study, additional analyses of these other proteins may be performed on remaining blood specimens in the Tissue Bank. It is expected that these future analyses will involve protein/peptide levels and NOT genetic (DNA) analysis.

10.2  Specimen Collection
Blood samples will be collected from each patient at 3 time points: (1) Pre-treatment; (2) during the last week of radiation treatment; and (3) 3 months from the start of radiation treatment. Ten ml of blood is to be collected in two purple-top 5 ml tubes (EDTA). Specimens should be placed on ice immediately and then spun on a desktop centrifuge for 10 min at 3000 rpm within 4 hours from sample collection. Specimens should be aliquoted into 1 ml eppendorf tubes, (~800 µl/tube; push-tab type preferred over screw caps). Care should be taken to avoid aspiration of the platelets in the sediment of the EDTA tube. Specimens should then be stored in a −70°C freezer after collection. Specimens should be labeled with the RTOG study and RTOG case number, institution type of tube, date of collection, and time point of collection (Pre-
treatment, during RT, 3 months after the start of RT). Usually it is best to label tubes before use in order to avoid condensation and moisture. When a complete collection of specimens is available for one or more patients, the specimens should be submitted to the RTOG Tissue Bank, with a Specimen Transmittal Form (ST) for each patient’s specimens that are shipped. The specimens will be analyzed by Ivan Ding M.D., University of Rochester Medical Center.

10.3 Shipping Instructions:
Specimens can be kept in -70°C until shipment. A batch of specimens can be shipped together on dry ice using Federal Express overnight service. Enough dry ice must be included to prevent thawing over 48 hours. Ship samples on Monday through Thursday, avoiding delivery days on weekends or national holidays. Notify the Tissue Bank by phone, fax, or email prior to shipping, with the specimen tracking number.

10.3.1 Ship specimens to:

LDS Hospital
Dept. of Pathology
E.M. Laboratory
8th Ave & C Street
Salt Lake City, UT 84143
(801) 408-5626
FAX (801) 408-5020
Idhflinn@ihc.com (8/26/03)

10.4 Reimbursement (8/26/03)
10.4.1 RTOG will reimburse institutions $300 per case for collection/shipping of blood samples. After confirmation from the Tissue Bank that appropriate materials have been received, RTOG Administration will prepare the proper paperwork and send a check to the institution. Pathology payment cycles are run twice a year in January and July and will appear on the institution’s summary report with the institution’s regular case reimbursement.

10.5.1 Upon receipt, the specimen is labeled with the RTOG protocol number and the patient’s case number only. The Tissue Bank database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

10.5.2 The specimens will be stored for an indefinite period of time. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.
### 11.0 PATIENT ASSESSMENTS

#### 11.1 Study Parameters (10/3/02)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Pretreatment (See Section 4.0 for timing)</th>
<th>Weekly During RT</th>
<th>3, 6, and 12 Months After Start of RT</th>
<th>Following Completion of RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>History &amp; Physical</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Height, Weight, &amp; Weight Loss</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Metastatic Evaluation (bone, brain)</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CBC with diff, platelets, liver and renal function tests</td>
<td>X</td>
<td>X&lt;sup&gt;2&lt;/sup&gt;</td>
<td>X&lt;sup&gt;3&lt;/sup&gt;</td>
<td>X&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Prothrombin time (PT)&lt;sup&gt;5&lt;/sup&gt;</td>
<td>X&lt;sup&gt;2&lt;/sup&gt;</td>
<td>X&lt;sup&gt;3&lt;/sup&gt;</td>
<td>X&lt;sup&gt;3&lt;/sup&gt;</td>
<td>X&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Serum pregnancy test&lt;sup&gt;6&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCI, CIRS-G</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zubrod, ADL, IADL, GDS, MMSE</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LCSS, SCFS</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient Pill Diary</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest x-ray, PA &amp; LAT</td>
<td>X&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest CT scan (liver &amp; adrenals)</td>
<td>X&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxicity Evaluation</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood samples for angiogenesis factor and cytokine analysis</td>
<td>X</td>
<td>X&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**a.** Patients will be seen at week 13 (day 90) from start of RT, then every 3 months for one year, then every six months for 2 years, then annually. The follow-up intervals are calculated from the start of therapy. The patient is to bring in the pill diary weekly during RT and at each follow-up visit to determine the number of pills consumed in the previous period.

**b.** CT scan of chest, liver, adrenal glands is required, and it is recommended that CT be completed within 4-6 weeks prior to the start of therapy; up to 8 weeks is permitted, but in that case, CXR is required within 1 week of starting therapy. CT of the chest is recommended every 6 months for 2 years from the start of therapy, then annually. CXR can be omitted when CT of the chest has been done.

**c.** CBC with differential and platelet count will be assessed within 14 days prior to study entry, weekly during RT, then at each follow-up visit; SGOT, SGPT, total bilirubin, BUN, and creatinine will be assessed at weeks 2, 4, and 6 during radiation and at each follow up.

**d.** CT scan or MRI of brain and radionuclide bone scan within 8 weeks prior to start of therapy; metastatic evaluation also should be done when appropriate for new symptoms or findings.

**e.** For patients on warfarin: It is recommended that PT be checked within 14 days prior to study entry and then weekly after start of Celebrex™, as increased bleeding times have been reported in patients on Celebrex™ and warfarin.

**f.** Blood samples for angiogenesis factor and cytokine analysis will be collected pretreatment, during the final week of radiation, and 3 months from the start of radiation therapy.

**g.** Required for females of childbearing potential within 14 days prior to study entry.

#### 11.2 Evaluation During Study

**11.2.1** An interval history and physical examination with particular attention to documentation of the weight and performance status on each visit.

**11.2.2** CBC, platelet count, and differential weekly during RT, then at each follow-up visit; liver and renal function studies at 2, 4, 6 weeks during RT and at each follow-up visit.

**11.2.3** CT of chest every 6 months for 2 years, then annually is recommended. Follow-up timing is based on the start of RT.

**11.2.4** Blood draws for cytokine and angiogenesis factor analysis will be done pretreatment, during the final week of radiation, and 3 months from the start of radiation.

**11.2.5** All relevant information including laboratory examinations, and treatment-related toxicity must be recorded before each treatment is given.
This study includes several assessment tools that are not commonly used in oncology studies, such as Instrumental Activities of Daily Living (IADL), Geriatric Depression Scale (GDS), Lung Cancer Symptom Scale (LCSS), or Schwartz Cancer Fatigue Scale (SCFS) [See forms packet]. Therefore, some training of site CRAs may be needed. This training can be provided at each institution by a local geriatric oncologist, geriatrician, geriatric nurse practitioner, or by a local CRA with a minimum experience of ten assessments with the study tools. The assessments will be used and rated in accordance with the instructions of the original authors. All assessment tools will be filled out prior to the start of therapy and at the 3, 6, and 12-month time points.

Comorbidity Rating
Comorbidity rating is based on pretreatment history/physical, laboratory results, and pretreatment medications; the rating does not have to be completed prior to treatment, but comorbidity data should be sent at the same time point as the initial assessment data (See Sections 12.1 and 12.2).

Site CRAs will complete the Comorbidity Recording Sheet and The Charlson CoMorbidity Index (CCI) following the instructions in Appendix IX; The Cumulative Illness Rating Scales for Geriatrics (CIRS-G) requires centralized rating; therefore, site CRAs will submit comorbidity data for the CIRS-G. The Recording Sheet and CCI must include the RTOG study number and case number, institution name and number, name of person completing the form, phone number of that person, and date of completion. The patient-specific label may be used; however, all pages must have a label affixed. The CIRS-G will be rated by Dr. Extermann, Geriatric Oncology study chair.

Credit/Reimbursement for Comorbidity Data Submission
CCOP institutions will receive 1 treatment credit and .3 cancer control credits per case for submission of comorbidity data. RTOG will reimburse non-CCOP institutions $300 per case for submission of comorbidity data. Credit or reimbursement will be given once valid data are submitted; Dr. Extermann will notify RTOG Headquarters by sending a copy of the CIRS-G for each case rated.

Assessment of acute toxicity will be made weekly during radiation and at week 13 (day 90) from start of radiation therapy. Late toxicity will be assessed at all follow-up visits beginning at 6 months from the start of therapy.

Criteria for Removal from Protocol Treatment
11.3.1 Disease progression at any time during therapy or the follow up period; the patient should be re-staged and sites of recurrence and/or progression documented. Re-biopsy is strongly encouraged.

11.3.2 Unacceptable toxicity

11.3.3 The patient may elect to withdraw from study treatment at any time for any reason.

11.3.4 Development of intercurrent, non-cancer related illnesses that prevent either continuation of therapy or regular follow-up

11.3.5 All reasons for discontinuation of treatment must be documented.

11.3.6 All patients will be followed until death.

DATA COLLECTION (8/26/03)
Data should be submitted to:
RTOG Headquarters
1101 Market Street, 14th Floor
Philadelphia, PA 19107

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

Summary of Data Submission (8/26/03)

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 2 weeks of randomization</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td></td>
</tr>
<tr>
<td>Baseline Mini-Mental Status Exam (MS)</td>
<td></td>
</tr>
<tr>
<td>Baseline Activities of Daily Living Scale (PQ)</td>
<td></td>
</tr>
<tr>
<td>Baseline Geriatric Depression Scale (QL)</td>
<td></td>
</tr>
<tr>
<td>Baseline Lung Cancer Symptom Scales (QP)</td>
<td></td>
</tr>
<tr>
<td>Baseline Schwartz Cancer Fatigue Scale (QF)</td>
<td></td>
</tr>
</tbody>
</table>
Initial Dosimetry Information:    Within 1 week of start of RT
RT Prescription (Protocol Treatment Form) (T2)
Films (simulation and portal) (T3)
Calculations (T4)
Planning CT and CT Report (C1, C3)

Final Dosimetry Information:    Within 1 week of RT end
Radiotherapy Form (T1)
Treatment Record (T5)
Isodose Distribution (T6)
Boost Film (simulation and portal) (T8)

Treatment Summary Form (TF) At week 13 from start of treatment, then
Patient Pill Diary (DP) with each follow up

Specimen Transmittal Form (ST) At 3 months from start of treatment

Activities of Daily Living Scale (PQ) At 3, 6, and 12 months from start of
Geriatric Depression Scale (QL) treatment
Mini-Mental Status Exam (MS)
Lung Cancer Symptom Scale (QP)
Schwartz Cancer Fatigue Scale (QF)

Initial Follow-up Form (FS) At week 13 (day 90) from start of RT

Follow-up Form (F1) Every 3 months for one year then q 6 months x 2
years, then annually. Also at progression/relapse,
onset of severe or unusual toxicity and at death.

Autopsy Report, final/microscopic (D3) As applicable

12.2 Comorbidity Data Submission
Comorbidity Recording Sheet
Charlson Comorbidity Index (CCI)

Submit these data collection tools to:
Martine Extermann, M.D.
H. Lee Moffitt Cancer Center
12902 Magnolia Drive
Tampa, Florida 33612-9497

13.0 STATISTICAL CONSIDERATIONS
13.1 Study Endpoints
13.1.1 Phase I portion
13.1.1.1 Determine safety of combined Celebrex™ and radiation therapy
13.1.2 Phase II portion
13.1.2.1 Overall survival
13.1.2.2 To determine how predictors of mortality in the general population (comorbid conditions, functional status, quality of life, and psychological status) influence prognosis, toxicity of therapy, and outcomes of therapy.
13.1.2.3 To correlate VEGF, bFGF, and IL8 with survival
13.1.2.4 To correlate IL, IL-6, and TGFB-1 with lung toxicity

13.2 Sample Size
13.2.1 Phase I component
13.2.1.1 Evaluation of Acute Toxicity (10/3/02)
Patients will be followed for a minimum of 90 days from the start of radiation therapy and carefully evaluated with respect to treatment morbidity. Grade 3 or 4 nonhematologic (excluding nausea, vomiting, and alopecia) and grade 4 hematologic toxicities will be referred to as dose limiting
toxicities (DLT). Acute toxicity is defined to be a toxicity occurring within 90 days from the start of radiotherapy treatment. The goal of this study is to determine if a maximum dose of 400 mg b.i.d. of Celebrex™ concurrent with radiation therapy can be tolerated, a dose at which no patients will develop acute grade 5 toxicity and less than 50% of patients will develop acute dose limiting toxicities. If, at any time, a Grade 5 toxicity is observed, then accrual will be suspended for that treatment sequence, and the Study Chair will review the event. Furthermore, if the combined acute DLTs estimate the toxicity rate to be greater than 50% within a treatment sequence, at any time, at any dose level, then the Executive Committee will be notified, and the committee will determine whether that arm should be closed.

13.2.1.2 Dose Escalation
There will be a maximum of one dose escalation of Celebrex™. For each arm, six patients will be accrued. After 90 days of evaluation, the current dose will be considered acceptable if less than three of the six patients experience DLTs. In which case, dose escalation will occur by accruing six new patients to the next arm. Otherwise, if three or more patients experience DLTs, the current dose will be considered too toxic, and the preceding dose will be declared the MTD. At a given dose level, the probability of halting dose escalation when the true toxicity is 50% or higher is at least 66% (power).

In addition, if the true DLT rate is instead 20%, there will still be a 10% probability of halting dose escalation at a given dose level (type I error). Maximum size for the phase I portion of the study will be 12 patients.

13.2.2 Phase II Component
13.2.2.1 RTOG 83-11 accrued 884 patients with a performance status of 0-2 and no weight loss criteria. All patients were treated with radiation therapy alone. RTOG 83-11 will be the basis for comparison of survival results for the current trial.

Using the Dixon-Simon method of calculating sample size for the comparison of survival against a historical control, a sample size of 110 evaluable patients followed over 12 months will ensure at least 87% probability of detecting a minimum of 40% improvement in MST compared to the RTOG 83-11 database at the 0.05 significance level (one-sided). Assuming 5% of the patients are either retrospectively ineligible or ineligible due to never starting any therapy, then 116 patients will be required. Combining patients from the phase I component, a total of 122 patients will be required.

It is expected that at the time of the analysis at least 90 events (deaths) will have occurred. It is anticipated that age, performance status, CCI, ADL, IADL, GDS, MMSE, LCSS, and SCFS will be examined for their prognostic importance for outcome. The above sample size should be sufficient to examine these factors for a substantial impact on outcome, both in univariate and multivariate models.

13.3 Patient Accrual
Patient accrual is projected to be 5 patients per month based upon the accrual of this patient group from RTOG 83-11. This trial should complete the accrual phase in 25 months. If the average monthly accrual is less than three cases, the study will be re-evaluated with respect to feasibility.

13.4 Analysis Plans
(5/21/04) Revision 3 of this study allows patients to be treated with either 2 Gy daily, 30-33 fractions, 5 days/week for 6-7 weeks, for a total dose of 60-66 Gy or 3 Gy daily, 15 fractions, 5 days/week for 3-4 weeks for a total dose of 45 Gy. There is no evidence of differences in acute or late toxicity or survival between these two dose/fractionation schedules; therefore, no change to the statistical design or analysis plan is required.

13.4.1 Phase I
13.4.1.1 Toxicities during the phase I component will be continuously monitored and assessed using the criteria stated in Section 13.2.1. All patients will reach the 90 day evaluation point prior to escalation of Celebrex™. If 400 mg b.i.d. of Celebrex™ is tolerable, than those patients will be included in the phase II analysis.

13.4.2 Phase II Interim Analyses of Accrual and Toxicity Data
Interim reports with statistical analyses will be prepared every six months until the initial paper reporting the treatment results has been submitted. In general, the interim reports will contain information about:
   a) The patient accrual rate with projected completion date for the accrual phase;
   b) The distribution of patients with respect to pretreatment characteristics;
   c) Compliance rate of treatment delivery with respect to the protocol prescription;
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.

13.4.3 Phase II Analysis and Reporting of Initial Treatment Results
The major analysis will be undertaken when each patient has been potentially followed for a minimum of twelve months. The usual components of this analysis are:

a) Tabulation of all cases entered and any excluded from the analysis with the reasons for such exclusions;
b) Reporting institutional accrual;
c) Distribution of the important prognostic baseline variables;
d) Observed results with respect to the study endpoints.

Survival will be compared to 83-11 using a one-sided log-rank test and a stratified Cox model. In addition, log-rank tests will be performed to determine if any of the nine factors listed in Section 13.2.2 are prognostic for survival. Factors with a p-value less than 0.25 will be included into a Cox model. Section 13.5 examines tumor marker evaluation.

13.5 Tumor Marker Evaluation
In addition to the clinical endpoints, this study also will consider translational questions with the idea of generating hypotheses for further testing in a phase III setting, should the combination of radiation therapy and Celebrex™ show a possible survival benefit. We will look at the markers VEGF, bFGF, and IL-8 and how they correlate with overall patient survival. Also, we will look at IL-1, IL-6, and TGFB-1 and how each marker correlates with lung toxicity.

13.5.1 Correlation of VEGF, bFGF, and IL-8 with survival
We want to determine the prognostic significance of each marker (VEGF, bFGF, and IL-8) on overall patient survival. Each marker will be measured at baseline (pre-treatment) and again during RT. The percentage change from baseline is the measurement of interest. The hypothesis is that the larger the positive change from baseline, the poorer the survival. Each marker will be evaluated separately.

Multivariate analysis will be used to evaluate the prognostic significance of each marker. We want to fit the best model for each marker. Cox models stratified by the RTOG Lung Recursive Partitioning Analysis (RPA) class will be used. Each model will contain the baseline value of each marker and the percentage change from baseline. We will test for the significance of the percentage change from baseline.

13.5.2 Correlation of IL-1, IL-6, and TGFB-1 with lung toxicity
We seek to determine the prognostic value of each of the 3 markers (IL-1, IL-6, and TGFB-1) on lung toxicity. Lung toxicity will be considered a binomial variable with patients falling into 1 of the following 2 groups: 1) Grade 2+ lung toxicity or 2) Grade 0 or 1 lung toxicity.

The hypothesis for IL-1 and IL-6 is that a higher pre-treatment value yields a higher probability for lung toxicity. The hypothesis for TGFB-1 is that the higher the positive change from baseline, the higher the probability of lung toxicity. To evaluate these hypotheses, IL-1 and IL-6 will be measured at baseline only, while TGFB-1 will be measured at baseline and during RT.

To evaluate the significance of IL-1 and IL-6, we will test for the significance of $\theta_2$ in the following logistic model (each marker will be evaluated separately):

\[ Y = \log \left( \frac{p}{1-p} \right) = \theta_0 + \theta_1 X_1 + \theta_2 X_2, \]

where

- $p$ = probability of lung toxicity in the first 2 years,
- $\theta_0$ = baseline effect (overall lung toxicity),
- $\theta_1$ = effect of RTOG lung RPA (adjustment for patient prognosis),
- $\theta_2$ = effect of tumor marker of lung toxicity,
- $X_1$ = RPA class number,
X₃ = baseline value of tumor marker.

To evaluate the significance of TGFB-1, we will test for the significance of θ₃ in the following logistic model:

\[ Y = \log \left( \frac{p}{1-p} \right) = \theta_0 + \theta_1 X_1 + \theta_2 X_2 + \theta_3 X_3, \]

where \( p \) = probability of lung toxicity in the first 2 years,

\( \theta_0 \) = baseline effect (overall lung toxicity),

\( \theta_1 \) = effect of RTOG lung RPA (adjustment for patient prognosis),

\( \theta_2 \) = effect of baseline value of TGFB-1 on lung toxicity,

\( \theta_3 \) = effect of change from baseline of TGFB-1 on lung toxicity,

\( X_1 \) = RPA class number,

\( X_2 \) = baseline value of TGFB-1,

\( X_3 \) = change from baseline of TGFB-1.

### 13.6 Gender and Minorities

Some investigators have shown gender to be a prognostic factor in NSCLC. 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 treatment. The projected gender and minority accruals are shown below.

**Planned Gender and Minority Inclusion**

<table>
<thead>
<tr>
<th>Ethnic Category</th>
<th>Sex/Gender</th>
<th></th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Females</td>
<td>Males</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>53</td>
<td>63</td>
<td>0</td>
<td>116</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Ethnic Category: Total of all subjects</strong></td>
<td><strong>56</strong></td>
<td><strong>66</strong></td>
<td><strong>0</strong></td>
<td><strong>122</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Racial Category</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>American Indian or Alaskan Native</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Asian</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Black or African American</td>
<td>7</td>
<td>9</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>White</td>
<td>46</td>
<td>54</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>More than one race</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Racial Category: Total of all subjects</strong></td>
<td><strong>56</strong></td>
<td><strong>66</strong></td>
<td><strong>0</strong></td>
<td><strong>122</strong></td>
</tr>
</tbody>
</table>
REFERENCES (5/21/04)


APPENDIX IA

RTOG 0213

SAMPLE CONSENT FOR RESEARCH STUDY

A PHASE I/II TRIAL OF A COX-2 INHIBITOR, CELEBREX™ (CELECOXIB), WITH LIMITED FIELD RADIATION FOR INTERMEDIATE PROGNOSIS PATIENTS WITH LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER, WITH ANALYSIS OF PROGNOSTIC FACTORS

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (NCI) booklet, “Taking Part in Clinical Trials: What Cancer Patients Need To Know,” is available from your doctor.

You are being asked to take part in this study because you have lung cancer.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to test the safety of the drug, Celebrex™, and find out what effects (good and bad) Celebrex™ and radiation therapy, have on you and your cancer. Celebrex™ is a drug commonly used to treat arthritis or similar conditions, and its effects in cancer patients is unknown. In addition, combining Celebrex™ with radiation therapy is investigational. This research is being done because some patients do not benefit from the standard treatment for lung cancer, a combination of chemotherapy and radiation therapy.

Tumors and spreading cancer need a new supply of blood vessels in order to grow. In animal research, Celebrex™ prevented the growth of new blood vessels; however, there is not yet any experience with research in humans with cancer. Celebrex™ also may improve your body’s response to radiation therapy. However, at this time, it is unknown if Celebrex™ will have any impact on radiation therapy or if it will have any effect on your cancer.

This study has two parts. In Part 1, the first six patients treated on this study will receive 200 mg of Celebrex™ twice a day during radiation therapy to see if this dose of the drug is safe. If less than 3 of these patients experience severe side effects, then the dose of Celebrex™ will be increased to 400 mg twice a day for the next 6 patients. If less than 3 of these patients experience severe side effects, then the dose of Celebrex™ will be increased to 400 mg twice a day during radiation therapy for patients already on the study. In part 2 of the study, all patients will begin treatment at 400 mg of Celebrex™ twice a day, if this dose has been determined to be safe in Part 1 of the study.
This study also will gather information about your health, activity level, thinking abilities, mood, and the quality of your life. This information will be used to find out if these are factors that can predict the recovery or outcome of patients with lung cancer.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY

About 122 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY? (5/21/04)

If you take part in this study, you will receive radiation therapy either once a day, 5 days a week, for 3-4 weeks or once a day, 5 days a week, for six to seven weeks. You and your doctor will discuss which radiation therapy schedule is best for you. Five days before starting radiation therapy, you will begin taking capsules of Celebrex™ (by mouth) twice each day, in the morning and the afternoon.

The dose of Celebrex™ you receive depends upon when you join the study. If you are among the first six patients, you will receive 200 mg of Celebrex™ twice a day. If this dose of Celebrex™ is found to be safe and you are among the next 6 patients on the study, you will receive 400 mg of Celebrex™ twice a day. If this dose is found to be safe, all patients already on study and all others that join the study will receive 400 mg of Celebrex™ twice a day.

You will continue taking two capsules of Celebrex™ twice each day during radiation therapy. The morning dose of Celebrex™ must be taken 1-2 hours before your radiation therapy. You will continue to take Celebrex™ after you finish radiation therapy for two years, unless there is evidence that your tumor is growing or you experience severe side effects. You will be provided with a pill diary and asked to keep track of your daily doses of Celebrex™. Celebrex™ will be supplied free of charge to patients who participate in this study.

Before beginning the study, you will have the following tests and procedures:

- Physical examination
- CT scan of your chest, liver, and adrenal glands
- Chest X-ray
- MRI or CT scan of your brain
- Bone scan
- Blood tests
- Pregnancy test for women who are able to have children
- A brief questionnaire that will measure your thinking abilities by asking you to answer questions and follow a few directions.
Several questionnaires that will measure your activity level, mood, and quality of your life; all of the questionnaires will take about 20 minutes to complete.

If you take part in this study, you also will have the following tests and procedures:

- Physical examination weekly during radiation therapy and during follow-up visits
- Blood tests: some tests weekly or every other week during radiation therapy; other tests 1, 3, and 6 months after the start of radiation therapy and then during follow-up visits
- CT scan of the chest every 6 months from the start of radiation for 2 years therapy, then annually, if recommended by your doctor
- A brief questionnaire that will measure your thinking abilities by asking you to answer questions and follow a few directions at 3, 6, and 12 months from the start of radiation therapy
- Several questionnaires that will measure your activity level, mood, and quality of your life at 3, 6, and 12 months from the start of radiation therapy
- After radiation therapy, follow-up visits 90 days from the start of radiation therapy, then every 3 months for one year, then every 6 months for 2 years, then annually for the rest of your life.

**HOW LONG WILL I BE IN THE STUDY? (5/21/04)**

You will receive radiation therapy for either 3-4 weeks or 6-7 weeks. You will begin taking Celebrex™ five days before starting radiation therapy, take it during radiation therapy, and continue taking it after you finish radiation therapy for 2 years, unless there is evidence that your tumor is growing or you experience severe side effects. You will see your doctor for follow-up visits 90 days from the start of radiation therapy, then every 3 months for one year, then every 6 months for 2 years, then annually for the rest of your life.

Your doctor may decide to take you off this study if it is in your medical best interest, drug supply is insufficient, your condition worsens, or new information becomes available and this information suggests the treatment will be ineffective or unsafe for you. It is unlikely, but the study may be stopped early due to lack of funding or participation.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.
WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the radiation therapy and Celebrex™ are stopped, but in some cases side effects can be serious or long-lasting or permanent.

Risks Associated with Radiation Therapy to the Chest

*Very Likely*
- Difficulty, pain, or a burning sensation when swallowing, which is temporary
- Fatigue, which is temporary
- Tanning, redness of skin, and hair loss within the treatment area, which is temporary
- Skin in treatment area may remain permanently dry, and chest hair may not grow back
- Decrease in blood counts while undergoing treatment that may result in bleeding and bruising easily
- Cough and some difficulty in breathing due to lung damage

*Less Likely, But Serious*
- Pericarditis - irritation of the heart sac
- Myocarditis - irritation of the heart muscle
- Transverse myelitis - irritation of the spinal cord
- Narrowing of the esophagus, which may require being fed through a feeding tube

Risks Associated with Celebrex™ (1/11/05)

*Likely*
- Upset stomach

*Less Likely*
- Headaches
- Dizziness
- Difficulty sleeping
- Skin rash
- Nausea, excess gas
- Diarrhea
- Fatigue, sluggishness
- Back pain
- Inflammation of the throat, nose, and/or sinuses
• Upper respiratory infection

Less Likely, But Serious
• Increase in blood pressure
• Anemia
• Water retention
• Bleeding from the stomach
• Ulceration (breakdown of skin) of the digestive tract
• Increase in blood tests that measure how well your kidneys are working
• Increase in blood tests that measure how well your liver is working; this may result in “flu-like” symptoms or jaundice – yellowing of the skin and whites of the eyes
• Increase in chloride in blood
• Serious allergic reactions, such as swelling of the face, hives, difficulty breathing, rapid heartbeat, low blood pressure

(1/11/05) Recently, an increased risk of heart attacks, strokes, and/or deaths resulting from heart or blood vessel disease has been reported among people taking celecoxib in clinical studies. Although the increased risk is 2 to 3 times greater than the risk of patients who did not take celecoxib, these serious side effects are rare. Taking celecoxib may increase your risk of one of these serious side effects.

Celebrex™ may interact with other drugs that you are taking, such as:
• aspirin
• lithium, a medicine for patients with certain types of emotional illnesses
• certain heart/blood pressure medications called ACE Inhibitors
• Diflucan®, a type of antibiotic
• Lasix, a diuretic (water pill)
• methotrexate, a powerful medicine sometimes used for patients with very bad arthritis or certain other diseases
• blood thinners, such as Coumadin®
• steroids, powerful medicines sometimes used for patients with bad asthma, arthritis, or certain other diseases

In addition, you should not take Celebrex™ if you are sensitive to it (celecoxib), to certain antibiotics called sulfa drugs, such as Bactrim™, or to nonsteroidal anti-inflammatory drugs, such as Motrin® or aspirin. You and your doctor should discuss these risks before you agree to participate in this study.

Risks Associated with Blood Drawing

You may experience some discomfort, bruising, and/or bleeding at the site of the needle insertion. Occasionally, some people experience dizziness or feel faint. In rare instances, infection may develop at the site of the needle insertion.

Reproductive risks: Because the drug and the radiation in this study can affect an unborn baby, you should not become pregnant or father a baby while on this
study. You should not nurse your baby while on this study. Ask about counseling and more information about preventing pregnancy.

**ARE THERE BENEFITS TO TAKING PART IN THE STUDY?**

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with lung cancer in the future.

Treatment with radiation (with or without Celebrex™) may keep your tumor from growing and may shrink it. This may provide relief from symptoms and improve your quality of life. Celebrex™ may improve control of lung cancer. However, none of these benefits is guaranteed.

**WHAT OTHER OPTIONS ARE THERE?**

You may choose to not participate in this study. Other treatments that could be considered for your condition may include the following: (1) radiation therapy; (2) chemotherapy; (3) no treatment except medications to make you feel better. With the latter choice, your tumor would continue to grow and your disease would spread. 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.

Another option may be to get the treatment described in this study even if you do not take part in the study. Please talk to your regular doctor about these and other options.

**WHAT ABOUT CONFIDENTIALITY? (8/26/03)**

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute 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). Your personal information may be disclosed if required by law.
Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Food and Drug Administration (FDA), the National Cancer Institute (NCI), Health Canada, qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in this study.

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems. Celebrex™ will be supplied free of charge to patients who participate in this study.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

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

WHAT ARE MY RIGHTS AS A PARTICIPANT? (8/26/03)

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. If you choose to stop participating in the study, you should first discuss this with your doctor. In order to provide important information that may add to the analysis of the study, he/she may ask your permission to submit follow-up data as it relates to the study. You may accept or refuse this request. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

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

A group of experts in lung cancer from the Lung Committee, the study chairs, and the study statistician will be reviewing the data periodically throughout the study.
WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
(This section must be completed)

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

__________________________  ______________________________           __________
Name                     Telephone Number

For information about this study, you may contact:

__________________________  ______________________________
Name                     Telephone Number

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

__________________________  ______________________________
Name                     Telephone Number

WHERE CAN I GET MORE INFORMATION?

You may call the NCI’s Cancer Information Service at 1–800–4–CANCER (1–800–422–6237) or TTY: 1–800–332–8615.

Visit the NCI’s Web sites for comprehensive clinical trials information at http://cancertrials.nci.nih.gov or for accurate cancer information including PDQ (Physician Data Query) visit http://cancernet.nci.nih.gov.

SIGNATURE (8/26/03)

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. I may also request a copy of the protocol (full study plan).

__________________________  ______________________________  __________
Patient’s Name              Signature                          Date

__________________________  ______________________________  __________
Name of Person Obtaining    Signature                          Date
Consent
APPENDIX IB

RTOG 0213

CONSENT FORM FOR USE OF BLOOD FOR RESEARCH

ABOUT USING BLOOD FOR RESEARCH

We would like to use some of your blood for future research. If you agree, your blood would be drawn three times during this study, when you are having blood drawn for other tests. This blood will be kept and may be used in research to learn more about cancer and other diseases.

The research that may be done with your blood is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your blood will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an affect on your care.

THINGS TO THINK ABOUT

The choice to let us keep your blood for future research is up to you. **No matter what you decide to do, it will not affect your care.**

If you decide now that your blood can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your blood and then any blood that remains will no longer be used for research; or, you may request that your blood be returned to you or your designee.

In the future, people who do research may need to know more about your health. While your doctor/institution may give them reports about your health, they will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes blood is used for genetic research (about diseases that are passed on in families). Even if your blood is used for this kind of research, the results will not be put in your health records.

Your blood will be used only for research and will not be sold. The research done with your blood may help to develop new products in the future.
BENEFITS

The benefits of research using blood include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

RISKS

The greatest risk to you is the release of information from your health records. Your doctor/institution will protect your records so that your name, address, and phone number will be kept private. The chance that this information will be given to someone else is very small.

MAKING YOUR CHOICE

Please read each sentence below and think about your choice. After reading each sentence, circle “Yes” or “No”. **No matter what you decide to do, it will not affect your care.** If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB’s phone number.

1. My blood may be kept for use in research to learn about, prevent or treat cancer.
   Yes  No

2. My blood may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer’s disease, or heart disease).
   Yes  No

3. Someone from doctor/institution may contact me in the future to ask me to take part in more research.
   Yes  No

Please sign your name here after your circle your answers.

Participant statement: (8/26/03)
I have read and received a copy of this consent form. I have been given an opportunity discuss the information with my doctor/nurse, and all of my questions/concerns have been answered to my satisfaction. My answers above and my signature below indicate my voluntary participation in this research.

______________________________  ________________________  _____________
Patient’s Name  Signature  Date
**Witness statement: (8/26/03)**
I have explained the information in this consent form to the patient and have answered any questions raised. I have witnessed the patient’s signature.

<table>
<thead>
<tr>
<th>Name of Person Obtaining Consent</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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)*

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>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.</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor.</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ.</td>
</tr>
<tr>
<td>T1</td>
<td>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,* <em>(i.e., not in the main bronchus).</em></td>
</tr>
<tr>
<td>T2</td>
<td>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.</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor of any size that directly invades any of the following: chest wall <em>(including superior sulcus tumors)</em>, 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.</td>
</tr>
<tr>
<td>T4</td>
<td>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.**</td>
</tr>
</tbody>
</table>

*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)*

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed.</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph nodes metastasis.</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes including involvement by direct extension of the primary tumor.</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s).</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s).</td>
</tr>
</tbody>
</table>
**APPENDIX III (cont'd)**

**ANATOMICAL STAGING FOR LUNG CANCER**

*(AJCC, 5th Edition)*

**Distant Metastasis (M)**

**MX**  Distant metastasis cannot be assessed

**M0**  No distant metastasis

**M1**  Distant metastasis present

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

**STAGE GROUPING**

<table>
<thead>
<tr>
<th>Occult Carcinoma</th>
<th>T</th>
<th>N</th>
<th>M</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 IIIB</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>
<tr>
<td>ORGAN TISSUE</td>
<td>0</td>
<td>GRADE 1</td>
<td>GRADE 2</td>
</tr>
<tr>
<td>----------------</td>
<td>---</td>
<td>------------------------------</td>
<td>----------------------------------------------</td>
</tr>
<tr>
<td>SKIN</td>
<td>None</td>
<td>Slight atrophy; Pigmentation change; Some hair loss</td>
<td>Patch atrophy; Moderate telangiectasia; Total hair loss</td>
</tr>
<tr>
<td>SUBCUTANEOUS TISSUE</td>
<td>None</td>
<td>Slight induration (fibrosis) and loss of subcutaneous fat</td>
<td>Moderate fibrosis but asymptomatic; Slight field contracture; &lt;10% linear reduction</td>
</tr>
<tr>
<td>MUCOUS MEMBRANE</td>
<td>None</td>
<td>Slight atrophy and dryness</td>
<td>Moderate atrophy and telangiectasia; Little mucus</td>
</tr>
<tr>
<td>SALIVARY GLANDS</td>
<td>None</td>
<td>Slight dryness of mouth; Good response on stimulation</td>
<td>Moderate dryness of mouth; Poor response on stimulation</td>
</tr>
<tr>
<td>SPINAL CORD</td>
<td>None</td>
<td>Mild L’Hermitte’s syndrome</td>
<td>Severe L’Hermitte’s syndrome</td>
</tr>
<tr>
<td>BRAIN</td>
<td>None</td>
<td>Mild headache; Slight lethargy</td>
<td>Moderate headache; Great lethargy</td>
</tr>
<tr>
<td>EYE</td>
<td>None</td>
<td>Asymptomatic cataract; Minor corneal ulceration or keratitis</td>
<td>Symptomatic cataract; Moderate corneal ulceration; Minor retinopathy or glaucoma</td>
</tr>
<tr>
<td>LARYNX</td>
<td>None</td>
<td>Hoarseness; Slight arytenoid edema</td>
<td>Moderate arytenoid edema; Chondritis</td>
</tr>
<tr>
<td>LUNG</td>
<td>None</td>
<td>Asymptomatic or mild symptoms (dry cough); Slight radiographic appearances</td>
<td>Moderate symptomatic fibrosis or pneumonitis (severe cough); Low grade fever; Patchy radiographic appearances</td>
</tr>
<tr>
<td>HEART</td>
<td>None</td>
<td>Asymptomatic or mild symptoms; Transient T wave inversion &amp; ST Changes; Sinus tachycardia &gt;110 (at rest)</td>
<td>Moderate angina on effort; Mild pericarditis; Normal heart size; Persistent abnormal T wave and ST changes ; Low ORS</td>
</tr>
<tr>
<td>ESOPHAGUS</td>
<td>None</td>
<td>Mild fibrosis; Slight difficulty in swallowing solids; No pain on swallowing</td>
<td>Unable to take solid food normally; Swallowing semi-solid food; Dilation may be indicated</td>
</tr>
<tr>
<td>SMALL/LARGE INTESTINE</td>
<td>None</td>
<td>Mild diarrhea; Mild cramping; Bowel movement 5 times daily Slight rectal discharge or bleeding</td>
<td>Moderate diarrhea and colic; Bowel movement &gt;5 times daily; Excessive rectal mucus or intermittent bleeding</td>
</tr>
<tr>
<td>LIVER</td>
<td>None</td>
<td>Mild lassitude; Nausea, dyspepsia; Slightly abnormal liver function</td>
<td>Moderate symptoms; Some abnormal liver; function tests; Serum albumin normal</td>
</tr>
<tr>
<td>KIDNEY</td>
<td>None</td>
<td>Transient albuminuria; No hypertension; Mild impairment of renal function; Urea 25-35 mg%;Creatinine 1.5-2.0 mg%; Creatinine clearance &gt; 75%</td>
<td>Persistent moderate albuminuria (2+); Mild hypertension; No related anemia; Moderate impairment of renal function; Urea &gt;36-60mg% Creatinine clearance (50-74%)</td>
</tr>
<tr>
<td>BLADDER</td>
<td>None</td>
<td>Slight epithelial atrophy; Minor telangiectasia (microscopic hematuria)</td>
<td>Moderate frequency; Generalized telangiectasia; Intermittent macroscopic hematuria</td>
</tr>
<tr>
<td>BONE</td>
<td>None</td>
<td>Asymptomatic; No growth retardation; Reduced bone Density</td>
<td>Moderate pain or tenderness; Growth retardation; Irregular bony sclerosis</td>
</tr>
<tr>
<td>JOINT</td>
<td>None</td>
<td>Mild joint stiffness; Slight limitation of movement</td>
<td>Moderate stiffness; Intermittent or moderate joint pain; Moderate limitation of movement</td>
</tr>
</tbody>
</table>
APPENDIX V

ADVERSE EVENT REPORTING GUIDELINES

Federal Regulations require that investigators report adverse events and reactions in a timely manner. This reporting improves patient care and scientific communication by providing information to the National Cancer Institute (NCI) whereby new findings can be more widely disseminated to investigators and scientists.

A. Definitions and Terminology
An adverse event is defined as an undesirable, unfavorable or unintended sign (including an abnormal laboratory finding), symptom or disease associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure. This may be a new event that was not pre-existing at initiation of treatment, a pre-existing event that recurs with increased intensity or frequency subsequent to commencement of treatment or an event, though present at the commencement of treatment, becomes more severe following initiation of treatment. These undesirable effects may be classified as “known or expected” or “unknown or unexpected”.

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

Unknown/unexpected events are those thought to have resulted from the agent, e.g. temporal relationship but not previously identified as a known effect.

Assessment of Attribution

In evaluating whether an adverse event is related to a procedure or treatment, the following attribution categories are utilized:

Definite: The adverse event is clearly related to the treatment/procedure.
Probable: The adverse event is likely related to the treatment/procedure.
Possible: The adverse event may be related to the treatment/procedure.
Unlikely: The adverse event is doubtfully related to the treatment/procedure.
Unrelated: The adverse event is clearly NOT related to the treatment/procedure.

B. Grading of Adverse Events (3/24/10)
Beginning April 1, 2010, the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized to grade severity of adverse events. The CTEP Active Version of the CTCAE is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

C. General Guidelines
In order to assure prompt and complete reporting of adverse events and toxicity, the following general guidelines must be observed. The guidelines apply to all RTOG studies. When protocol-specific guidelines indicate more intense monitoring than the standard guidelines, the study-specific reporting procedures supercede the General Guidelines. A protocol may stipulate that specific grade 4 events attributable to treatment are expected and therefore may not require the standard reporting; however, exceptions to standard reporting must be specified in the text of the protocol.

1. The Principal Investigator will report to the RTOG Group Chair, to the Headquarters Data Management Staff (215/574-3214) and to the Study Chair within 24 hours of discovery, the details of all unexpected severe, life-threatening (grade 4) and fatal (grade 5) adverse events if there is reasonable suspicion that the event was definitely, probably, or possibly related to protocol treatment.

2. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of attribution require telephone notification within 24 hours of discovery.

3. A written report, including all relevant clinical information and all study forms due up to and including the date of the event, will be sent by mail or FAX (215/928-0153) to RTOG Headquarters within 10 working days of the telephone report (unless specified otherwise within the protocol). The material must be labeled: ATTENTION: Adverse Event Reporting.

   a. The Group Chair in consultation with the Study Chair 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.

   b. For events that require telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB), the Food and Drug Administration (FDA), to another co-operative group or to the study sponsor, the investigator may first call RTOG (as outlined above) unless this will unduly delay the required notification process.

A copy of all correspondence sent to recipients of the call, e.g. NCI, IDB, another cooperative group office (non-RTOG coordinated studies) must be submitted to RTOG Headquarters. Copies must include the RTOG study and case numbers.
4. When participating in non-RTOG coordinated intergroup studies or in RTOG sponsored pharmaceutical studies, the investigator must comply with the reporting specification required in the protocol.

5. Institutions must comply with their individual Institutional Review Board policy regarding submission of documentation of adverse events. All “expedited” adverse event reports should be sent to the local Institutional Review Board (IRB).

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

7. When submitting reports and supporting documentation for reports to RTOG on an RTOG protocol patient, the study number and the case number must be recorded so that the case may be associated with the appropriate study file. This includes submission of copies of FDA Form 3500 (MedWatch).

8. All data collection forms through the date of the reported event and the applicable reporting form are submitted to RTOG Headquarters data management department (Attention: Adverse Event) within 10 working days of the telephone report or sooner if specified by the protocol. Documentation must include an assessment of attribution by the investigator as previously described in section A.

9. MedWatch Forms (FDA 3500) submitted on RTOG protocol patients must be signed by the Principal Investigator.

10. All neuro-toxicity (≥ grade 3) from radiosensitizer or radioprotector drugs are to be reported to RTOG Headquarters Data Management, to the Group Chair, and to the Study Chair within 10 days of discovery.

D. Adverse Event Reporting Related to Radiation Therapy (3/24/10)

1. All fatal events resulting from protocol radiation therapy must be reported by telephone to the Group Chair, to RTOG Headquarters Data Management department and to the radiation therapy protocol Study Chair within 24 hours of discovery.

2. All grade 4, (CTEP Active Version CTCAE and RTOG/EORTC Late Radiation Morbidity Scoring Scheme Criteria) and life-threatening events (an event, which in view of the investigator, places the patient at immediate risk of death from the reaction) and grade 4 toxicity that is related, possibly related or probably related to protocol treatment using non-standard fractioned radiation therapy, brachytherapy, radiopharmaceuticals, high LET radiation, and radiosurgery must be reported by telephone to the Group Chair, to RTOG Headquarters Data Management and to the radiation therapy Study Chair within 24 hours of discovery. Expected grade 4 adverse events may be excluded from telephone reporting if specifically stated in the protocol.

3. All applicable data forms and if requested, a written report, must be submitted to RTOG Headquarters within 10 working days of the telephone call.

E. Adverse Event Reporting Related to Systemic Anticancer Agents

Adverse drug reactions (ADRs) are adverse events that are related to an anticancer agent and meet certain criteria: are unexpected effects of the drug or agent, or are severe (grade 3), life-threatening (grade 4), or fatal (grade 5), even if the type of event has been previously noted to have occurred with the agent.

1. Commercial Agents/Non-Investigational Agents (3/24/10)

<table>
<thead>
<tr>
<th></th>
<th>Grade 4 or 5 Unexpected with Attribution of Possible, Probable, or Definite</th>
<th>Increased Incidence of an Expected AE&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Hospitalization During Treatment&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Secondary AML/MDS&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA Form 3500&lt;sup&gt;4,5&lt;/sup&gt; within 10 days</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>NCI/CTEP Secondary AML/MDS Form within 10 days of diagnosis&lt;sup&gt;4,5&lt;/sup&gt;</td>
<td>X&lt;sup&gt;6&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Call RTOG within 24 hrs of event†</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

<sup>1</sup> Any increased incidence of a known AE.

<sup>2</sup> Inpatient hospitalizations or prolongation of existing hospitalization for medical events equivalent to the CTEP Active Version CTCAE Grade 3-5 which precipitated hospitalization must be reported regardless of the requirements or phase of study, expected or unexpected and attribution.
Reporting required during or subsequent to protocol treatment. Submitted to Investigational Drug Branch, PO Box 30012, Bethesda, MD 20924-0012. Copy to RTOG Data Management labeled: Attention: Adverse Event Report. All grade 5 known toxicity. Call RTOG Data Management (215) 574-3214. To leave a voice mail message when the office is closed, announce that you’re reporting an “adverse event”, provide your name, institution number, and a telephone number where you may be contacted.

2. Investigational Agents

An investigational agent is one sponsored under an Investigational New Drug Application (IND). Reporting requirements and timing are dependent on the phase of the trial, grade, attribution and whether the event is expected or unexpected as determined by the NCI Agent Specific Expected Adverse Event List, protocol and/or Investigator’s Brochure. An expedited adverse event report requires submission to CTEP via AdEERS (Adverse Event Expedited Report). See the CTEP Home Page, http://ctep.info.nih.gov for complete details and copies of the report forms.

a. AdEERS (Adverse Event Expedited Reporting System)

Effective January 1, 2001, the NCI Adverse Event Expedited Reporting System (AdEERS) was implemented for all protocols for which NCI is the supplier of an investigational agent.

Attribution: An expedited report is required for all unexpected and expected Grade 4 and Grade 5 adverse events regardless of attribution for any phase of trial. An expedited report is required for unexpected Grade 2 and Grade 3 adverse events with an attribution of possible, probable or definite for any phase of trial. An expedited report is not required for unexpected or expected Grade 1 adverse events for any phase of the trial.

RTOG uses “decentralized” notification. This means that all reportable events will be directly reported to NCI, just as has been done with paper-based reporting. AdEERS is an electronic reporting system; therefore, all events that meet the criteria must be reported through the AdEERS web application. Once the report is filed with AdEERS, the institution need not send notification to RTOG, as the AdEERS system will notify the Group Office. Institutions that utilize this application are able to print the report for local distribution, i.e., IRB, etc.

For institutions without Internet access, if RTOG is the coordinating group for the study, contact RTOG Data Management (215-574-3214) to arrange for AdEERS reporting. In these instances, the appropriate Adverse Event Expedited Report template (Single or Multiple Agents) must be completed. The template must be fully completed and in compliance with the instruction manual; i.e., all mandatory sections must be completed including coding of relevant list of value (LOV) fields before sending to RTOG. Incomplete or improperly completed templates will be returned to the investigator. This will delay submission and will reflect on the timeliness of the investigators’ reporting. A copy of the form sent to RTOG must be kept at the site if local distribution is required. Do not send the template without first calling the number noted above.

Templates for Single or Multiple Agents may be printed from the CTEP web page or will be supplied from the RTOGRegistrar upon faxed request (FAX) (215) 574-0300.

When reporting an event on a patient in an RTOG-coordinated study, you must record the RTOG case number in the Patient ID field.

AdEERS reporting does not replace or obviate any of the required telephone reporting procedures.

Investigational Agent(s) used in a Clinical Trial Involving a Commercial Agent(s) on separate arms: An expedited adverse event report should be submitted for an investigational agent(s) used in a clinical trial involving a commercial agent(s) on a separate arm only if the event is specifically associated with the investigational agent(s).

Investigational Agent(s) used in a Clinical Trial in Combination with a Commercial Agent(s): When an investigational agent(s) supplied under an NCI-sponsored IND is used in combination with a commercial agent(s), the combination should be considered investigational and reporting should follow the guidelines for investigational agents.

b. Expedited Reporting for Phase 1 Studies

<table>
<thead>
<tr>
<th>Unexpected Event</th>
<th>Expected Event</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grades 2-3</strong>&lt;br&gt;Attribution: Possible, Probable or Definite</td>
<td><strong>Grades 4 &amp; 5</strong>&lt;br&gt;Regardless of Attribution</td>
</tr>
<tr>
<td>Grade 2: Expedited report within 10 working days.</td>
<td>Report by phone to IDB&lt;sup&gt;1,2&lt;/sup&gt; within 24 hrs. Expedited report to follow within 10 working days.</td>
</tr>
<tr>
<td>Grade 3: Report by phone to</td>
<td></td>
</tr>
<tr>
<td>IDB1,2 within 24 hrs. Expedited report to follow within 10 working days.</td>
<td>This includes deaths within 30 days of last dose of treatment with an investigational agent.</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Grade 1: Adverse Event Expedited Reporting <strong>NOT</strong> required.</td>
<td></td>
</tr>
</tbody>
</table>

1. Report by telephone to RTOG Data Management (215) 574-3214, to the Group Chair and to the Study Chair. To leave a voice mail message with RTOG when the office is closed, announce that you’re reporting an “adverse event”, provide your name, institution number and a telephone number where you may be contacted.

2. Telephone reports to IDB (301) 230-2330 available 24 hours a day (recorder after 5 PM to 9 AM ET).

c. Expedited Reporting for Phase 2 and Phase 3 Studies

<table>
<thead>
<tr>
<th>Unexpected Event</th>
<th>Grades 2-3 Attribution: Possible, Probable or Definite</th>
<th>Grades 4 &amp; 5 Regardless of Attribution</th>
<th>Expected Event</th>
</tr>
</thead>
</table>

| | Expedition report within 10 working days. | Report by phone to IDB\textsuperscript{1,2} within 24 hrs. Expedited report to follow within 10 working days. | Expedited including Grade 5 aplasia in leukemia patients within 10 working days. Grade 4 myelosuppression not to be reported, but should be submitted as part of study results. Other Grade 4 events that do not require expedited reporting would be specified in the protocol. |

1. Report by telephone to RTOG Data Management (215) 574-3214, to the Group Chair and to the Study Chair. To leave a voice mail message with RTOG when the office is closed, announce that you’re reporting an “adverse event”, provide your name, institution number and a telephone number where you may be contacted.

2. Telephone reports to IDB (301) 230-2330 available 24 hours a day (recorder after 5 PM to 9 AM ET).
APPENDIX VI (8/26/03, 4/13/04)

STUDY AGENT (CELEBREX™) SHIPMENT FORM — U.S. Sites

For initial shipment of Celebrex™, each institution must submit a Study Agent Shipment Form to the CTSU Regulatory Office as soon as the individual responsible for the study agent has been identified. This must be done prior to registration of the institution’s first case (the shipment form is only submitted once). Allow adequate processing time (7-10 days) before calling to register the first case. For re-supply of Celebrex™, sites can access Pfizer’s re-supply form at http://www.rtog.org/pdf_reports.html?members/reports=0213Pfizer_Clinical_Re-supply_Request_Form_sites.doc.

SHIP TO:

Name: ______________________________

Address: ______________________________

(no P.O. addresses)

____________________________________

____________________________________

Telephone: ______________________________

Fax#: ______________________________

RTOG Institution#: ______________________________

Institution Name: ______________________________

IRB Approval Date: ______________________________

(attach copies of IRB approval and sample consent form)

Investigator (PI) Signature ______________________________ Date: __________

Investigator Name (Print) ______________________________

Investigator NCI # ______________________________

Send Completed Form to:

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
FAX -215-569-0206

RTOG Headquarters Approval ______________________________ Date: __________
### APPENDIX VII  (3/15/04)

**RTOG 0213**

**DRUG SUPPLY PROCEDURE FOR CELEBREX™ - CANADIAN SITES**

**Initial Drug Shipment:**

<table>
<thead>
<tr>
<th>Role</th>
<th>Task</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site study coordinator</td>
<td>Sends originals of the trial site regulatory documents to the Radiation Therapy Oncology Group (RTOG) Registration/Randomization Department</td>
</tr>
<tr>
<td>RTOG Registration/Randomization Department</td>
<td>Informs the Therapeutic Area Manager at Pfizer Canada Inc. of local trial site activation by faxing (FAX number: 905-890-8522 the following documentation: Ethics Committee approval letter Ethics Committee approved Informed Consent Site Information Sheet Completed Clinical Trial Site Information Form and the fax confirmation sheet indicating that it has been filed with HPFB</td>
</tr>
<tr>
<td>Pfizer Canada Inc. Therapeutic Area Manager or designee, MMCR</td>
<td>Completes the request for initial trial drug shipment (Celebrex™). Forwards the request for initial trial drug shipment to the Clinical Trial Supplies Manager.</td>
</tr>
<tr>
<td>Pfizer Canada Inc. Clinical Trials Supplies Manager</td>
<td>Requests the Clinical Research Coordinator, MMCR, to notify the trial site of the shipment. Ships the following supplies to the trial site pharmacist. The initial shipment will supply enough study drug for 3 months of treatment for 2 patients. 1. 24 bottles of Celebrex™ (100 capsules per bottle; 200 mg capsules)</td>
</tr>
<tr>
<td>Pfizer Canada Inc. Clinical Research Coordinator, MMCR</td>
<td>Notifies the study site pharmacist and coordinator of the shipment by fax. Sends the following documents by courier to the study site pharmacist: 1. Investigational Medication Distribution Forms (drug accountability log) 2. Additional trial drug request forms 3. Product monographs: Celebrex™</td>
</tr>
<tr>
<td>Trial site pharmacist</td>
<td>Confirms receipt of the trial drugs by signing and dating the Drug Shipment Invoice that accompanies the trial drug supplies. Sends a signed/dated copy of the Drug Shipment Invoice to the Clinical Trial Supplies Manager, Pfizer Canada Inc. at FAX number 905- 755-3151.</td>
</tr>
</tbody>
</table>
### Requests for trial drug resupply:

<table>
<thead>
<tr>
<th>Role</th>
<th>Responsibilities</th>
</tr>
</thead>
</table>
| **Trial site pharmacist**                 | • Manages trial drug inventory ensuring sufficient supplies are maintained for 3 months of treatment for 2 patients  
• Completes the request for trial drug shipment on an “as needed” basis, depending upon patient accrual.  
• Sends the request for trial drug shipment to the Pfizer Canada Inc. Clinical Trial Supplies Manager at FAX number 905- 755-3151. |
| **Pfizer Canada Inc. Clinical Trial Supplies Manager** | • Forwards the request to the Therapeutic Area Manager, MMCR. |
| **Pfizer Canada Inc. Therapeutic Area Manager, MMCR** | • Approves and signs the request for trial drug shipment.  
• Forwards the request for trial drug shipment to the Clinical Trial Supplies Manager. |
| **Pfizer Canada Inc. Clinical Trial Supplies Manager** | • Ships drug supplies to the trial site.  
• Requests the Clinical Research Coordinator, MMCR to notify the trial site of the shipment. |
| **Pfizer Canada, Clinical Research Co-ordinator, MMCR** | • Notifies the trial pharmacist and site study coordinator of the shipment by fax. |
| **Trial site pharmacist**                 | • Confirms receipt of the trial drugs by signing and dating the Drug Shipment Invoice that accompanies the trial drug supplies.  
• Sends a signed/dated copy of the Drug Shipment Invoice to the Clinical Trial Supplies Manager, Pfizer Canada @ FAX number (905) 755-3151. |

### Return of trial drug supplies:

<table>
<thead>
<tr>
<th>Role</th>
<th>Responsibilities</th>
</tr>
</thead>
</table>
| **Pfizer Canada Inc. Clinical Research Co-ordinator, MMCR** | • Forwards the “Return of Clinical Supplies” form to the trial site.  
• Sends written instruction to the trial site regarding shipment of returned goods to Pfizer Canada offices for destruction. |
To facilitate the timely receipt of drug shipments, supplies and correspondence, we ask that you complete and promptly return this form to RTOG by faxing 215-574-0300. Your careful attention to the accuracy of this form will ensure the correct delivery of all items associated with this clinical trial.

<table>
<thead>
<tr>
<th>INVESTIGATOR:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>INSTITUTION/ORGANIZATION:</td>
<td></td>
</tr>
<tr>
<td>ADDRESS:</td>
<td></td>
</tr>
</tbody>
</table>

| CITY/PROVINCE: |  |
| POSTAL CODE: |  |
| PHONE NUMBER: | FAX NUMBER: |  |

| SUB-INVESTIGATOR(S): |  |
| ADDRESS ( if different form Investigator): |  |

| PHONE NUMBER: | FAX NUMBER: |  |

| SUB-INVESTIGATOR(S): |  |
| ADDRESS ( if different form Investigator): |  |

| PHONE NUMBER: | FAX NUMBER: |  |

| SUB-INVESTIGATOR(S): |  |
| ADDRESS ( if different form Investigator): |  |

| PHONE NUMBER: | FAX NUMBER: |  |

| PHARMACIST: |  |
| ADDRESS ( if different form Investigator): |  |

<p>| PHONE NUMBER: | FAX NUMBER: |  |</p>
<table>
<thead>
<tr>
<th>STUDY COORDINATOR:</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADDRESS (if different form Investigator):</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>PHONE NUMBER:</td>
</tr>
<tr>
<td>FAX NUMBER:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INSTITUTIONAL REVIEW BOARD</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAME:</td>
</tr>
<tr>
<td>ADDRESS (IF DIFFERENT FORM INVESTIGATOR):</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
Instructions for completing THE COMORBIDITY RECORDING SHEET:

1. Refer to Section 11.2.7 for assessments to be used as a basis for data collection.
2. Complete all patient/institution information or affix RTOG patient-specific label.
3. Extract all comorbidity elements you can identify and note them on the Recording Sheet. Place the elements in the most appropriate category. Be comprehensive. The rater (Dr. Extermann and/or staff) will determine the relevant diseases and modify the category if needed.
4. Include past surgeries, diseases, smoking history, and functional problems, such as incontinence or constipation.
5. If a functional problem appears to be related to tumor or treatment, place TR after the diagnosis.
6. Include medications, and specify as much as possible the dose/frequency. The rater may use this information to rate the severity of a disease.
7. Include all pertinent baseline laboratory values in your assessment of comorbidity.
8. Leave the scoring column blank.

Instructions for completing THE CHARLSON COMORBIDITY INDEX:

1. Complete all patient/institution information or affix RTOG patient-specific label.
2. Follow the “Rules for Completing The Charlson Comorbidity Index” in this appendix.
3. Complete the Charlson Comorbidity Index by noting “yes” or “no” for each disease.

Contact Martine Extermann, M.D. at 813-979-3822 or extermann@moffitt.usf.edu if you have questions.
<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>Score (Optional)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
</tr>
<tr>
<td>Eyes and ENT</td>
<td></td>
</tr>
<tr>
<td>Upper GI</td>
<td></td>
</tr>
<tr>
<td>Lower GI</td>
<td></td>
</tr>
<tr>
<td>Liver and Pancreas</td>
<td></td>
</tr>
<tr>
<td>Renal <em>(Creatinine: )</em></td>
<td></td>
</tr>
<tr>
<td>GU</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal/Integument</td>
<td></td>
</tr>
<tr>
<td>Neurological</td>
<td></td>
</tr>
<tr>
<td>Endocrine/Metabolic and Breast</td>
<td></td>
</tr>
<tr>
<td><em>(Weight:  Height:  )</em></td>
<td></td>
</tr>
<tr>
<td>Psychiatric</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medications</th>
<th></th>
</tr>
</thead>
</table>
APPENDIX IX (continued)

Rules for Completing the Charlson Comorbidity Index (CCI)

Adaptation: Do not count non-melanotic skin cancers or in situ cervical carcinoma.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarct</td>
<td>Hx of medically documented myocardial infarction</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Symptomatic CHF w/ response to specific treatment</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>Intermittent claudication, periph. arterial bypass for insufficiency, gangrene, acute arterial insufficiency, untreated aneurysm (&gt;=6cm)</td>
</tr>
<tr>
<td>Cerebrovascular disease (except hemiplegia)</td>
<td>Hx of TIA, or CVA with no or minor sequellae</td>
</tr>
<tr>
<td>Dementia</td>
<td>Chronic cognitive deficit</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>Symptomatic dyspnea due to chronic respiratory conditions (including asthma)</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>SLE, polymyositis, mixed CTD, polymyalgia rheumatica, moderate to severe RA</td>
</tr>
<tr>
<td>Ulcer disease</td>
<td>Patients who have required treatment for PUD</td>
</tr>
<tr>
<td>Mild liver disease</td>
<td>Cirrhosis without PHT, chronic hepatitis</td>
</tr>
<tr>
<td>Diabetes (without complications)</td>
<td>Diabetes with medication</td>
</tr>
<tr>
<td>Diabetes with end organ damage</td>
<td>Retinopathy, neuropathy, nephropathy</td>
</tr>
<tr>
<td>Hemiplegia (or paraplegia)</td>
<td>Hemiplegia or paraplegia</td>
</tr>
<tr>
<td>Moderate or severe renal disease</td>
<td>Creatinine &gt;3mg% (265 umol/l), dialysis, transplantation, uremic syndrome</td>
</tr>
<tr>
<td>2nd Solid tumor (non metastatic)</td>
<td>Initially treated in the last 5 years exclude non-melanomatos skin cancers and in situ cervical carcinoma</td>
</tr>
<tr>
<td>Leukemia</td>
<td>CML, CLL, AML, ALL, PV</td>
</tr>
<tr>
<td>Lymphoma, MM...</td>
<td>NHL, Hodgkin’s, Waldenström, multiple myeloma</td>
</tr>
<tr>
<td>Moderate or severe liver disease</td>
<td>Cirrhosis with PHT +/- variceal bleeding</td>
</tr>
<tr>
<td>2nd Metastatic solid tumor</td>
<td>Self-explaining</td>
</tr>
<tr>
<td>AIDS</td>
<td>AIDS and AIDS-related complex (Suggested: as defined in latest definition)</td>
</tr>
</tbody>
</table>
RTOG 0213
RTOG Institution Name/Number: ____________________________________________
Patient Initials (Last, First): ________________________________________________
RTOG Patient Case Number: ________________________________________________
Name of Person Completing Sheet: ____________________________________________
Phone Number: ____________________________________________________________________________
Date Completed: __________

CHARLSON COMORBIDITY INDEX (CCI)

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Present</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarct</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Cerebrovascular disease (except hemiplegia)</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Dementia</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Ulcer disease</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Mild liver disease</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Diabetes (without complications)</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Diabetes with end organ damage</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Hemiplegia</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Moderate or severe renal disease</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>2nd Solid tumor (non metastatic)</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Leukemia</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Lymphoma, MM...</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Moderate or severe liver disease</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>2nd Metastatic solid tumor</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>AIDS</td>
<td></td>
<td>6</td>
</tr>
</tbody>
</table>

Total points: __________

Comments: