NRG ONCOLOGY
RTOG 0839
RANDOMIZED PHASE II STUDY OF PRE-OPERATIVE CHEMORADIOOTHERAPY +/- PANITUMUMAB (IND #110152) FOLLOWED BY CONSOLIDATION CHEMOTHERAPY IN POTENTIALLY OPERABLE LOCALLY ADVANCED (STAGE IIIA, N2+) NON-SMALL CELL LUNG CANCER
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NRG ONCOLOGY
RTOG 0839

RANDOMIZED PHASE II STUDY OF PRE-OPERATIVE CHEMORADIOTHERAPY +/- PANITUMUMAB (IND #110152) FOLLOWED BY CONSOLIDATION CHEMOTHERAPY IN POTENTIALLY OPERABLE LOCALLY ADVANCED (STAGE IIIA, N2+) NON-SMALL CELL LUNG CANCER

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NRG ONCOLOGY

RTOG 0839

Randomized Phase II Study of Pre-operative Chemoradiotherapy +/- Panitumumab (IND #110152)
Followed by Consolidation Chemotherapy in Potentially Operable Locally Advanced
(Stage IIIA, N2+) Non-Small Cell Lung Cancer

SCHEMA (8/16/12)

| R | Arm 1: Induction Chemoradiation  
|   | Paclitaxel & Carboplatin: 1x/week for 6 weeks  
|   | Concurrent RT: 2 Gy/day, 5x/week, for 6 weeks, for a total of 60 Gy
| A | Arm 2: Induction Chemoradiation and Panitumumab  
|   | Panitumumab 1x/week for 6 weeks  
|   | Paclitaxel & Carboplatin: 1x/week for 6 weeks  
|   | Concurrent RT: 2 Gy/day, 5x/week, for 6 weeks, for a total of 60 Gy
| N | D
| O | M
| I | Z
| E

All Patients

4 weeks after Induction treatment

Reassessment

Resectable Patients with No Disease Progression
Surgery within 2 weeks of reassessment and within 6 weeks of completion of induction treatment

Inoperable Patients (inoperable for medical, anatomical, or other reasons) with No Disease Progression
Patient proceeds to consolidation treatment within 6 weeks of completion of induction treatment

Arms 1 and 2: Consolidation Chemotherapy
Paclitaxel & Carboplatin: q21 days x 2

† Note: See Sections 6.0 and 6.6 regarding instructions concerning the V20.

Patient Population: (See Section 3.0 for Eligibility)
Pathologically proven diagnosis Stage IIIA (T1-T3) with a single primary lung parenchymal lesion and N2 positive ipsilateral mediastinal nodes

Required Sample Size: 97
ELIGIBILITY CHECKLIST (10/9/14)  
(page 1 of 4)

______(Y)  1. Did the patient have a pathologically proven diagnosis of Stage IIIA (T1-T3) with a single primary lung parenchymal lesion within 12 weeks of registration?

______(Y)  If yes, does the patient have positive ipsilateral mediastinal node or nodes (N2), with or without positive ipsilateral hilar nodes (N1)?

______(Y)  Are the N2 nodes separate from the primary tumor (by CT scan or surgical exploration)?

______(Y)  Is the largest diameter of any involved N2 node ≤ 3.0 cm?

______(Y)  Has the patient’s N2 status been pathologically confirmed as positive within 12 weeks of registration by one of the following methods listed in Section 3.1.3?

______(Y)  2. Was there histologic proof that the patient has non-small cell history (adenocarcinoma, adenosquamous, large cell carcinoma, squamous carcinoma, non-lobar and non-diffuse bronchoalveolar cell carcinoma or non-small cell lung cancer NOS) within 12 weeks of registration?

______(Y)  3. Does the patient have measurable disease?

_____(NA/Y)  4. If the patient has a right sided lesion, were the nodal levels biopsied as listed in Section 3.1.3?

____(NA/Y/N)  5. If the patient has ipsilateral mediastinal lymph nodes associated with a left sided lesion, was it biopsied?

______(Y)  If no, was the biopsy omitted because all of the following were true?
- The tumor is left sided;
- Paralyzed left true vocal cord documented by bronchoscopy or indirect laryngoscopy;
- Nodes visible in the AP (Level 5) region on CT scan;
- Distinct primary tumor separate from the nodes is visible on CT scan;
- Histologic (biopsy) or cytologic (needle aspiration or sputum) proof of non-small cell histology from the primary tumor.

______(NA/Y)  6. If pleural effusion is present, have the following criteria been met to exclude malignant involvement (incurable M1a disease)?
- When pleural fluid is visible on both the CT scan and on a chest x-ray, a pleuracentesis is required to confirm that the pleural fluid is cytologically negative.
- Exudative pleural effusions are excluded, regardless of cytology.
- Effusions that are minimal (i.e. not visible under ultrasound guidance) that are too small to safely tap are eligible.

_____(N)  7. Does the patient have distant metastases?

______(Y)  8. Was a history/physical examination, including a neurological assessment, performed within 8 weeks of registration?

______(Y)  9. Was the patient evaluated by a thoracic surgeon within 4 weeks of registration?

______(Y)  If yes, was the patient deemed potentially operable and resectable?

(Continued on the next page)
10. Did the patient have a whole body FDG-PET or PET/CT within 6 weeks of registration?  
11. Did the patient have an MRI with contrast of the brain (or CT scan with contrast, if the MRI was medically contraindicated) CT scan with contrast of the lungs and upper abdomen within 5 weeks of registration, or whole body PET/CT scan within 6 weeks of registration?  
12. Is the patient’s Zubrod performance status 0-1?  
13. Is the patient at least 18 years of age?  
14. Did the patient have an EKG within 8 weeks of registration?  
15. Were all pre-registration labs done within the specified timeframes and are the patient’s lab values within the parameters of eligibility in Section 3.1?  
16. If female, was there a negative serum pregnancy test performed within 2 weeks of registration for women of childbearing potential?  
17. Were pulmonary function tests done within 8 weeks of registration and are the patient’s FEV1 and diffusion capacity within the parameters of eligibility in Section 3.1?  
18. Did the patient provide study-specific informed consent prior to any protocol-specified procedure(s)?  
19. Does the patient have palpable lymph nodes present in the supraclavicular areas or higher in the neck? (nodes proven benign on fine needle aspiration or biopsy are permitted)  
20. Is there evidence of invasive malignancy within the past 3 years other than those stated in Section 3.2?  
21. Has the patient had prior systemic chemotherapy or biologic agents (including erlotinib or similar agents) for the study cancer?  
22. Has the patient had prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields?  
23. Does the patient have any severe co-morbidities as defined in Section 3.2?  
24. Has patient had unintentional weight loss ≥ 5% of body weight over the preceding 6 months?  
25. If a woman of childbearing potential or a sexually active man, is the patient willing/able to use medically acceptable forms of contraception during the trial and for 6 months after completion of treatment?  
26. Has the patient had prior therapy that specifically and directly targets the EGFR pathway?  
27. Has the patient had a prior severe infusion reaction to a monoclonal antibody?  
28. Does patient have a pre-existing ≥ grade 2 peripheral motor or sensory neuropathy?
The following questions will be asked at Study Registration:

3D-CRT or IMRT CREDENTIALING IS REQUIRED BEFORE REGISTRATION. LUNG IGRT CREDENTIALING IS REQUIRED IF TREATMENT PLANNING USES REDUCED MARGINS.

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<td>Have you obtained the patient’s consent for his or her tissue to be kept for use in research to learn about, prevent, treat, or cure cancer?</td>
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<td>Have you obtained the patient’s consent for his or her blood to be kept for use in research to learn about, prevent, treat, or cure cancer?</td>
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<tr>
<td>Have you obtained the patient’s consent for his or her urine to be kept for research to learn about, prevent, treat, or cure cancer?</td>
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23. Have you obtained the patient's consent for his or her tissue to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease or heart disease)?

24. Have you obtained the patient's consent for his or her blood to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease or heart disease)?

25. Have you obtained the patient's consent for his or her urine to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease or heart disease)?

26. Have you obtained the patient's consent to allow someone from this institution to contact him or her in the future to take part in more research?

27. Use of IMRT.

28. Will reduced margins be used for treatment planning (0.2-0.3 cm)?

If yes, have the pre-registration requirements in Section 5.3.2 been met?

29. Is the maximum nodal diameter > 3.0 cm in any N2 node(s)?

The Eligibility Checklist must be completed in its entirety prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/NRG Oncology audit.

Completed by ________________________________ Date ________________________________
1.0 INTRODUCTION

1.1 Background

Of 150,000 patients who develop non-small cell lung cancer (NSCLC) in the United States in the next year, at least 40% will present with Stage III NSCLC. Surgical resection or radiotherapy alone will result in cure in less than 10% of patients (Mountain 1997). Recent randomized studies have demonstrated that chemotherapy followed by surgery or chemoradiotherapy without surgery can result in superior survival compared to surgery or radiotherapy alone (Edelman 1996). Both strategies, however, have a substantial rate of local relapse as the first site of failure. Therefore, the possibility of improving outcome utilizing trimodality therapy (i.e., chemotherapy, radiotherapy and surgery) is attractive.

1.2 Experience with Trimodality Therapy

Pulmonary resection following induction therapy with chemotherapy and radiotherapy to 45 Gy has now been well documented to be feasible and safe. Two large prospective cooperative group studies, Southwest Oncology Group 8805 and the recent Pancoast Intergroup study (INT 0160), demonstrated the ability to perform either lobectomy or pneumonectomy following neoadjuvant concurrent chemotherapy and radiotherapy in a multi-institutional setting (Rusch 1993; Kraut 2000). The induction radiotherapy in these trials was limited to 45 Gy, primarily due to concern of excess morbidity and mortality that has been attributed to surgical resection following high dose radiotherapy.

The rationale for the use of combined pre-operative chemoradiotherapy, rather than chemotherapy induction alone, may be appreciated by the impact that local control may ultimately have on long-term survival. Combined therapy targeted to improve local and systemic control in non-operative studies has demonstrated that improvements in local control may as well lead to improved overall survival. In both small cell and in non-small cell carcinoma of the lung the addition of concurrent radiotherapy to systemic therapy has been shown to improve survival versus chemotherapy alone or sequentially delivered chemotherapy and radiotherapy (Turrisi 1999; Furuse 1999; Curran 2000). In the most recent non-operative phase III study by the West Japan Lung Cancer Group, patients with Stage III NSCLC were randomized to concurrent versus sequential chemoradiotherapy treatment. In the 323 patients that were studied, the response rate (84% vs. 66%, p=.0002), and the median survival (16.5 months vs. 13.3 months, p=0.039), were both improved with the delivery of concurrent versus sequential therapy. Of interest, 35% (42/117) of the patients who failed in the sequential arm of the study recurred with local disease only, the highest single site of recurrence, an indication of the possible role of surgical resection following even optimal medical therapy. Taken as a whole, the surprising improvement in outcome in small cell lung cancer (SCLC), an ostensibly systemic disease with a more aggressive approach to local control as well as the Japanese results, strongly imply that enhanced local control may yield benefits in terms of systemic disease as well and favorably impact survival.

RTOG 93-09 tested the need for surgery as part of the treatment plan for locally advanced (N2) NSCLC (Albain 2005). The primary endpoint for the study (improved overall survival) was not met at the time of the initial report of results. However, there was a significant improvement in progression-free survival. The discrepancy is due to an unacceptably high mortality in patients undergoing pneumonectomy. This may be an artifact of lack of surgical expertise with the post-operative management of these patients.

The recently completed trimodality trial, RTOG 0229, required certification of surgical expertise and enrolled 60 patients from 19 RTOG institutions. The median age was 59, 61% of the patients were male, and 77% had a Zubrod performance status of 0. All patients had pathologically documented N2 or N3 disease. Ninety-five percent received radiation therapy per protocol, and 91% received induction chemotherapy per protocol, 49% with dose modifications. Toxicity was comparable to that of other studies of chemoradiotherapy, despite the higher radiation dose. Grade 3-4 toxicities included hematologic toxicity (12%), GI (8%), and pulmonary (13%). Forty-three patients (75%) were evaluable for the primary endpoint of mediastinal sterilization. Thirty-seven patients were resected, 34 with lobectomy and 3 with pneumonectomy. Seven patients had residual mediastinal disease and were not offered resection. Twenty-seven of 43 (63%) achieved mediastinal clearance. There was a 14% (5/37) incidence of grade 3 postoperative pulmonary complications. There was only 1 post-operative grade 5 adverse event (3%). With a median follow up of 20 months, the overall median survival is 26.6 months with a 1-year survival of 77%. Median and 1-year progression-free survival are 13.1 months and 52%, respectively. The primary sites of failure were brain (19%), ipsilateral lung (18%), and regional nodes (16%) [Suntharalingam 2010]. In summary, this trial implies that with appropriate surgical expertise, an aggressive multimodality treatment of locally advanced lung cancer can be accomplished in the cooperative group setting with low levels of surgical morbidity and mortality.
1.3 Use of a Carboplatin and Paclitaxel Regimen

The combination of carboplatin and paclitaxel with concurrent radiotherapy has been employed by a large number of investigators and cooperative groups (Choy 1998). At the University of Maryland, this regimen has been employed in trimodality therapy with excellent results in 40 patients (Sonett 1999). Utilizing radiation therapy to 61.6 Gy and lobectomy or pneumonectomy, there were no post-operative deaths and the complications rate was acceptable. This approach yielded excellent short and long-term results. A 47% complete pathologic response and 87% mediastinal nodal sterilization rate were documented in this study. Two- and three-year survivals were 71% and 62%, respectively. Disease-free survival at two years was 68%. Median survival has not yet been reached. These single institution results demonstrated the feasibility of concurrent carboplatin/paclitaxel and radiotherapy followed by surgery, and lead to RTOG 0229, which confirmed the tolerability of the regimen.

1.4 Radiotherapy Dose

The largest experiences with trimodality therapy for the treatment of Stage IIIa NSCLC in clinical trials in the United States are SWOG 8805 and the RTOG 93-09 (INT 0139). The cumulative radiotherapy dose administered was 45Gy. RTOG 0229 has demonstrated that higher dose radiotherapy (61 Gy) can be administered and can safely be followed by surgical resection with a high rate of mediastinal sterilization (see above). Therefore, 60 Gy will be adopted as pre-operative dose in the current study.

1.5 EGFR Antibodies, Radiation, and Non-Small Cell Lung Cancer (2/9/12)

Epidermal growth factor receptor (EGFR) is frequently overexpressed in many malignancies including NSCLC and is associated with poor prognosis. Constitutive EGFR activation may be a critical step in malignant proliferation, angiogenesis, and metastasis (Woodburn 1999). Gefitinib, erlotinib, and related quinazoline molecules are small molecule inhibitors of the intracellular domain of the EGFR (Woodburn 1999). These agents have demonstrated activity in multiple tumor types including NSCLC. Erlotinib is currently approved for treatment of recurrent NSCLC on the basis of a positive phase III trial (erlotinib versus supportive care).

Cetuximab is an antibody to the extracellular domain of the EGFR. A phase III trial in head and neck cancer has demonstrated superior survival of cetuximab combined with radiotherapy versus radiotherapy alone (Bonner 2006). This study indicates that EGFR antibodies have marked radiosensitizing properties that can result in improved outcome in a locally advanced malignancy. Importantly, there was no evidence of the development of antibodies to the drug (Khazaeli 2000). Overall, the combination of cetuximab with radiation has been well tolerated; however, there is an increase in cutaneous toxicity. Specific guidelines for the management of cutaneous toxicity in the setting of radiation and cetuximab have now been formulated (Bernier 2008). Although it has not been reported, it is possible that anti-EGFR antibodies such as cetuximab or panitumab could increase the risk of pneumonitis when utilized with chemoradiotherapy. Impaired wound healing also is possible.

In vitro studies have demonstrated substantial synergistic interaction between cetuximab and other chemotherapeutic agents, including cisplatin and vinorelbine. Cetuximab was additive with paclitaxel (Raben 2001). These in vitro interactions were not clearly related to EGFR expression. As a result, initial phase III studies utilized cetuximab in addition to chemotherapy without testing for EGFR expression. While there was a trend towards superiority, these studies did not meet planned goals (Lynch 2010). An evaluation of EGFR expression by FISH in SWOG 0342 demonstrated a marked advantage when FISH+ patients received cetuximab (Herbst 2007). In contrast, the FLEX trial combined cisplatin, vinorelbine, and cetuximab versus cisplatin and vinorelbine in a population of advanced lung cancer patients (stage IIIB, IV) and found that the EGFR inhibitor resulted in a significantly improved overall survival (Pirker 2008). These 2 trials indicate that there is biological activity of EGFR antibodies in NSCLC, though the degree of benefit in advanced NSCLC is very modest.

RTOG 0324 (n=93) combined carboplatin, paclitaxel, radiotherapy, and cetuximab in treatment of inoperable stage III patients. There was no selection based upon EGFR status. Preliminary survival data demonstrates a 24-month overall survival, which is among the best ever demonstrated for a cooperative group study population. Importantly, other than rash, there was little evidence that the use of cetuximab was associated with increased toxicity (Blumenschein 2008). Another cooperative group study, CALGB 30407, evaluated carboplatin, pemetrexed, cetuximab, and concurrent radiotherapy versus carboplatin, pemetrexed, and concurrent radiotherapy. Other than increased skin rash, there was no difference in toxicity (Govindan 2008). Specifically, in neither trial was the use of the EGFR antibody associated with increased pulmonary toxicity.
Panitumumab is a high-affinity fully human IGG2 monoclonal antibody against EGFR. Compared with cetuximab, it is much less likely to cause severe infusion reactions, does not require premedications nor a loading dose. It is currently approved as a single agent in advanced colorectal cancer in Kras wild type disease. Studies in advanced NSCLC demonstrate excellent tolerance in combination with carboplatin and paclitaxel (Crawford, 2004). There were no pharmacokinetic interactions noted. Several studies have combined panitumumab with chemotherapy (including carboplatin/paclitaxel, carboplatin, and cisplatin) and radiotherapy (70Gy) in head and neck cancer (Wirth, 2008; Fortin 2009, Tabernero 2008). Doses utilized ranged from 1.5-2.5 mg/kg weekly and 1.0-9.0 mg/kg q 3 weeks. No unexpected toxicities were encountered either with the antibody alone, when combined with radiation, or when combined with chemotherapy and radiation. Therefore, it is likely that panitumumab will demonstrate comparable levels of efficacy to cetuximab with a more favorable toxicity profile in the setting of concurrent thoracic chemoradiotherapy. However, as this regimen has not been previously evaluated in this specific setting, we will evaluate toxicity after the first 10 patients have been randomized to receive panitumumab in order to formally evaluate toxicity. Accrual will continue during this evaluation.

1.6 Surgery (3/21/13)
As noted above, the feasibility of surgical resection after full dose (e.g., 61Gy) radiotherapy has been demonstrated. Importantly, in RTOG 0229, it was demonstrated that a process that required certification of thoracic surgeons as able to perform the resection prior to allowing an institution to join the trial resulted in a very acceptable degree of postoperative mortality, in contrast to the prior Intergroup study.

The current study will preserve this approach and hopefully, expand the number of institutions participating. All patients are assessed by a thoracic surgeon prior to enrollment. After completion of induction chemoradiotherapy +/- panitumumab, patients will be reassessed to determine whether they remain surgical candidates. At this point, protocol treatment for any patient with evidence of disease progression will be discontinued; these patients will be followed as specified in the protocol. Patients without disease progression that are still considered to be good candidates for resection will proceed to surgery. Surgery will be performed within 6 weeks of completion of induction treatment. The surgical procedure will consist of lobectomy or pneumonectomy and will be decided upon at the time of surgery to ensure an R0 resection. A complete systematic mediastinal lymph node evaluation will be performed.

Patients with disease that has not progressed but who have had a significant deterioration in their medical condition during neoadjuvant therapy to the point that they are no longer considered a suitable candidate for surgical resection by the thoracic surgeon (such as for the following reasons) will be deemed unresectable:

- Worsened pulmonary status to the point that the patients lack sufficient reserve for resection;
- New, unstable cardiac arrhythmia, ischemia, or decrease in ejection fraction;
- Deterioration of mental status;
- Acute renal insufficiency;
- Severe malnutrition;
- Uncontrolled infection;
- Significant neurologic impairment.

1.6.1 Mediastinal Sterilization
Emerging from recent studies of aggressive bimodality and tri-modality treatment of locally-advanced NSCLC is the importance of mediastinal clearance. Mediastinal sterilization after chemoradiotherapy is strongly associated with overall survival and can serve as a surrogate marker for long-term benefit. In SWOG 8805, 107 patients who underwent concurrent chemoradiotherapy followed by surgical resection were evaluated. The median and 3-year survival were 30 months and 44% for the 48 patients (45% of the surgical population, 38% of the intent to treat population) who were mediastinal node negative versus 10 months and 18% for all others (p=.0005) [Albain 1995]. Notably, pathologic complete response was a significant predictor of long-term benefit. Very similar results were reported by a multicenter trial in Switzerland. Ninety patients with stage IIIa disease were enrolled and were treated with induction chemotherapy (docetaxel/cisplatin). Seventy-five patients underwent resection, of whom 23 had mediastinal clearance (26% of the intent to treat population). The strongest predictor of long-term survival was mediastinal nodal clearance, which had a hazard ratio of .22, (p=.0003) [Betticher 2003]. Most importantly, in the phase III trial, INT 0139, nodal clearance predicted outcome. Patients with N0 resection specimens demonstrated a 41% 5-year survival versus 24% for those with pN1-3 in the surgical specimen (Albain 2005). Clearly, studies of induction therapy (chemotherapy or chemoradiotherapy) followed by surgical
resection have consistently demonstrated that mediastinal nodal sterilization is a powerful predictor of outcome and can serve as a surrogate marker.

1.7 Correlative Studies
There is considerable controversy regarding the value of predictive markers for EGFR antibody therapy. Some recent trials with cetuximab in addition to chemotherapy have demonstrated that the benefit of the agent may be primarily seen in patients with tumors that demonstrate high levels of expression of EGFR by immunohistochemistry (IHC) [FLEX] or chromosomal amplification by fluorescence in situ hybridization (FISH) [SWOG 0342]. It is unknown if this finding also will apply to the use of EGFR antibodies in addition to radiation. Therefore, in this study an exploratory analysis will be conducted to correlate response (mediastinal sterilization) and overall survival with EGFR expression by IHC and FISH in the primary tumor tissues. Conversely, ras mutations have been associated with lack of response to EGFR antibodies in patients with advanced colorectal cancer. There are no patient data regarding either of these variables in multimodality therapy (i.e., chemotherapy and radiation therapy). This trial, which will obtain tissue both prior to and after therapy, is uniquely positioned to address the question of whether either or both of these markers is potentially relevant. Primary tumor tissue will be used as a surrogate because nodal tissues will not be readily available in the post-treatment setting for patients who achieve complete mediastinal clearance. To verify that primary tumor can act as a surrogate for nodal tissues, EGFR expression and ras mutation will be assessed in as subset of patients with available pre-treatment tumor and nodal tissues.

A previous study (Taguchi 2007) has performed MALDI mass spectrometry from serum samples of a training set of 139 metastatic/recurrent NSCLC patients treated with EGFR tyrosine kinase inhibitor (EGFR TKI, either erlotinib or gefitinib). Based on these results, they have developed a classifying algorithm using eight distinct m/z features that was able to predict outcomes after EGFR TKI therapy in both the training set and 2 validation sets from different institutions. The classifier did not predict outcomes in patients who did not receive EGFR TKI treatment. In addition, they showed that classifications based on spectra acquired at 2 different institutions were highly reproducible with a concordance rate of 97.1%. Since these studies have not been applied to EGFR targeting with antibodies and non-metastatic stage, we propose to determine if the same classifier can be used to predict for treatment response, as measured by (1) pathologic response and (2) overall survival in RTOG 0839 patients.

Osteopontin (OPN), a secreted protein involved in cell invasion, migration and metastasis, has been previously identified as a hypoxia regulated secreted protein and a prognostic marker for both head and neck and NSCLC (Le 2003; Petrik 2006; Le 2006; Mack 2008). Specifically, plasma OPN level has been shown to correlate with survival in a small group of early stage NSCLC patients (Stage I-II) treated with definitive surgical resection (Le 2006). Similarly, plasma OPN levels were significantly associated with treatment response, progression-free survival, and overall survival in 172 chemotherapy-treated patients for stage NSCLC in a cooperative group setting (SWOG 0003) [Mack 2008]. OPN has never been evaluated as a prognostic marker in stage III NSCLC patients treated with definitive chemoradiation, panitumumab, and surgical resection; therefore, 0839 will validate plasma OPN as a prognostic marker for survival.

MicroRNA (miRNA), a class of naturally occurring small non-coding RNAs of 19-25 nucleotides in length, recently have been linked to cancer development and prognosis (Esquela-Kerscher 2006; Calin 2006). Altered miRNA expression has been reported in various cancers, including NSCLC (Esquela-Kerscher 2006; Calin 2006). Since miRNAs are very small, they are remarkably stable and therefore can be readily detected in either plasma or serum of cancer patients. A recent study showed that the levels of several miRNA are elevated in the sera of diffuse large B-cell lymphoma (DLBCL) patients compared to controls and that high circulating miR-21 expression was associated with worse relapse free survival in these patients (Lawrie 2008). A more comprehensive study showed that serum and plasma contained a large amount of stable miRNA derived from various tissues in both cancer patients and controls and that miR-25 and miR-223 were significantly elevated in the sera of 152 lung cancer patients compared to non-cancer controls (Chen 2008). Both of these studies used a quantitative PCR approach to detect circulating miRNA levels. In patients enrolled on RTOG 0839, the levels of miR-25 and miR-223 will be measured before, during and after all active therapy with the goal of evaluating the change in the levels of these biomarkers during therapy and whether pre-treatment levels of these markers can be used to correlate with pathologic response or survival in these patients.
Preliminary work in an animal model of skin toxicity induced by EGFR antagonistic antibodies supports the hypothesis that EGFR inhibition deregulates IL-1 and TNF-α expression and production in the skin and, potentially, other sites. While this requires confirmation in additional model systems and in humans, these findings also set the stage for the development and optimization of interventional strategies in patients treated with EGFR inhibitors. A component of the translational research of this protocol is to monitor inflammatory biomarker expression in patients treated with EGFR inhibitors in situ in the skin and in plasma. This will serve to validate that deregulation of the IL-1/TNF-α axis occur not only in mice but also in patients. It also is expected to provide a basis for monitoring treatment efficacy and will be evaluated for the identification of surrogate markers for the intensity of ‘skin rash’ as it relates to therapeutic efficacy. Collectively, the proposed work will serve to further test the role of specific molecular mechanisms of skin toxicity associated with the use of EGFR inhibitors, validate biomarkers useful to monitor not only skin toxicity but also therapeutic effects of EGFR antagonists, and develop topical therapeutics for treatment of skin toxicity.

1.8 Imaging Research
This study includes an exploratory correlative component to evaluate the utility of PET/CT after concurrent chemoradiotherapy. The surgical aspect of 0839 provides a unique opportunity to evaluate PET/CT, as there will be actual pathologic assessment of lesions. PET/CT has been widely adopted for the staging of NSCLC. Its value after chemoradiotherapy is less certain. A number of single institution studies have documented decreased standardized uptake values (SUV) after radiation or chemoradiotherapy. Cerfolio, et al. (2004), in a retrospective study of 56 patients found that a decline of SUV max by > 80% predicted for a complete pathologic response after receiving neoadjuvant chemoradiotherapy. The same group performed a prospective study (n=93) and were able to relate pathologic response to change in SUV. However, they found a high rate of false positive (25%) and false negative (20%) results (Cerfolio 2006). Pottgen, et al. (2006) similarly correlated pathologic response in a retrospective study of 50 consecutive patients treated with chemoradiotherapy prior to resection for whom PET/CT data were available. They employed a methodology that evaluated both changes from maximal SUV as well as changes in tumor volume. MacManus, et al. (2005) noted improved survival with decreasing SUV utilizing a qualitative scale after radiotherapy or radical radiotherapy. Others also have found prognostic value for PET/CT scanning after chemoradiation utilizing a variety of methods to compare pre and post-treatment scans (Xu 2008).

1.9 Aspects of Trial Design
This study employs a randomized phase II design. One arm will utilize the regimen employed in RTOG 0229. The second arm will employ the same regimen with the addition of panitumumab. The “control” arm (the 0229 arm) will serve several purposes: 1) it will allow for direct comparison of toxicities both acute and late that may result from the addition of panitumumab; 2) it will anchor the present trial as this arm will be directly comparable to the 0229 study and will assure that the population treated on 0839 is similar; 3) it will provide adequate samples to allow for the correlative studies described above. As 0839 is not a definitive trial and we already have results from the 0229 trial for the primary endpoint of mediastinal sterilization and for secondary endpoints of overall survival, patterns of failure, etc, there will be a 2:1 randomization between the panitumumab containing arm and the “control” arm (0229 arm). This will allow for the evaluations described while minimizing the required numbers of patients.

2.0 OBJECTIVES
2.1 Primary Objective
Mediastinal nodal clearance following completion of induction chemoradiation +/- panitumumab

2.2 Secondary Objectives
2.2.1 Overall survival;
2.2.2 Patterns of first failure;
2.2.3 Acute and late adverse events;
2.2.4 Surgical morbidities among resectable patients at reassessment;
2.2.5 Correlation between biomarkers (including at least EGFR and ras mutation status) in pre- and post-therapy and outcomes (mediastinal nodal clearance and overall survival);
2.2.6 Evaluation of the prognostic value of plasma osteopontin and microRNA for overall survival;
2.2.7 Assess the ability of PET/CT scan re-staging to predict outcome;
2.2.8 Estimate response rate.
3.0 PATIENT SELECTION (10/9/14)
NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED. For questions concerning eligibility, please contact the study data manager.

3.1 Conditions for Patient Eligibility (10/9/14)

3.1.1 Pathologically proven diagnosis of Stage IIIA (T1-T3) [AJCC Staging, 7th edition; see Appendix II] with a single primary lung parenchymal lesion and ipsilateral positive mediastinal nodes within 12 weeks of registration; Note: The primary tumor does not require tissue diagnosis; documentation of non-small cell carcinoma may originate from the mediastinal node biopsy or aspiration.

3.1.1.1 Histologic proof of non-small cell histology (adenocarcinoma, adenosquamous, large cell carcinoma, squamous carcinoma, non-lobar and non-diffuse bronchoalveolar cell carcinoma, or non-small cell lung cancer NO) within 12 weeks of registration; note: mixed small cell and non-small cell histologies are not eligible for this study.

3.1.2 Measurable disease as determined by contrast-enhanced CT scan with the primary lung tumor distinct from mediastinal lymph nodes;

3.1.3 Positive ipsilateral mediastinal node or nodes (N2), with or without positive ipsilateral hilar nodes (N1); N2 nodes must be separate from primary tumor by either CT scan or surgical exploration, and the maximum nodal diameter of involved N2 nodes cannot exceed 3.0 cm. N2 status must be pathologically confirmed to be positive within 12 weeks prior to registration by one of the following:
- mediastinoscopy;
- mediastinotomy (Chamberlain procedure);
- transesophageal needle biopsy using endoscopic ultrasound (EUS-TBNA);
- endobronchial ultrasound biopsy using endoscopic ultrasound guidance (EBUS-TBNA);
- thoracotomy;
- video-assisted thoracoscopy;
- transbronchial needle biopsy by Wang technique (TBNA);
- fine needle aspiration under CT guidance.

Note: Demonstration of N2 status DOES NOT require sampling of all potentially positive nodes. It is adequate to document any N2 node as positive at the time of registration. For left sided lesions, the following nodal levels should be biopsied: 2L, 4L, 2R, 4R and 7 or stations 5 and 6 whenever possible to rule out microscopically involved lymph nodes. For right sided lesions levels 2R, 4R, 2L, 4L and 7 should be sampled whenever possible to rule out microscopically involved lymph nodes. Investigators are strongly encouraged to biopsy multiple stations of mediastinal lymph nodes at the time of invasive staging in addition to those nodes that are abnormal on PET/CT or CT scan. PET/CT positivity in the ipsilateral mediastinal lymph nodes will not be sufficient to establish N2 nodal status.

Ipsilateral mediastinal lymph nodes associated with right sided tumors must be biopsied. The mediastinal nodal biopsy or aspiration can only be omitted in the special circumstance in which ALL of the following are true:
- The tumor is left sided;
- Paralyzed left true vocal cord documented by bronchoscopy or indirect laryngoscopy; Note: bronchoscopy is not required but is at the discretion of the patient’s surgeon. It is recommended in patients who have central tumors or disease near the carina or in another position that may impact resectability, or to document paralyzed recurrent laryngeal nerve, in cases of AP nodal involvement.
- Nodes visible in the AP (level 5) region on CT scan;
- Distinct primary tumor separate from the nodes is visible on CT scan;
- Histologic (biopsy) or cytologic (needle aspiration or sputum) proof of non-small cell histology from the primary tumor.

Regardless of method of documentation of N2 disease (see Section 3.1.3), the following must be documented:
- From the Operative and Pathology reports, all mediastinal nodes shown to be both positive and negative (including contralateral nodes) must be designated on the I1 form according to the Lymph Node Map in Appendix IV.
- If the procedures to document N2 eligibility were done at a non-member facility, the patient is still eligible if the institution PI reviews the outside pathology slides and
report with the institution's pathologist in conjunction with the outside operative report, and generates a report that verifies the original diagnosis and lymph node mapping, as consistent with the staging requirements of the protocol.

3.1.4 If a pleural effusion is present, the following criteria must be met to exclude malignant involvement (incurable M1a disease):

- When pleural fluid is visible on both the CT scan and on a chest x-ray, a pleuracentesis is required to confirm that the pleural fluid is cytologically negative.
- Exudative pleural effusions are excluded, regardless of cytology;
- Effusions that are minimal (i.e. not visible under ultrasound guidance) that are too small to safely tap are eligible.

3.1.5 Appropriate stage for protocol entry, including no distant metastases, based upon the following minimum diagnostic workup:

- History/physical examination, including a neurological assessment, within 8 weeks of registration;
- Evaluation by a thoracic surgeon within 4 weeks of registration; the patient must be deemed potentially operable and resectable to be eligible for the study. Operability is defined as having adequate pulmonary, cardiac, renal, nutritional, musculoskeletal, neurologic, and cognitive capacity to undergo major pulmonary resection with acceptable morbidity and mortality. Resectable is defined as an R0 resection possible either by lobectomy or pneumonectomy at the time of initial evaluation.
- Whole body FDG-PET (or PET/CT) scan within 6 weeks of registration; **Note:** PET/CT data will be used for the analysis of a secondary endpoint (Section 2.2.7). To be included in this analysis, the patient’s PET/CT studies must be performed with a dedicated BGO, LSO, or GSO PET or PET/CT scanner. PET/CT scanners with sodium iodide (NaI) detectors are not acceptable. PET/CT DICOM images, diagnostic reports, and assessment forms must be submitted as described in Section 12.1. If an additional treatment planning FDG PET/CT (in the treatment position, see Section 6.3.3) is performed after the initial diagnostic staging PET/CT, the most recent scan data prior to initiation of treatment should be submitted as described.

If the baseline PET/CT study is performed at the treating institution (or its affiliated PET facility), it is recommended but not required that the reassessment PET/CT scan (see Section 8.1.2) will be performed at the same site. **Note:** National Cancer Institute recommendations regarding performance of the scans should be followed as closely as possible (Shankar 2006).

- An MRI with contrast of the brain (or CT scan with contrast of brain, if an MRI is medically contraindicated) within 5 weeks of registration;
- A CT scan with contrast of the lungs and upper abdomen to complete T and N staging and exclude other ipsilateral or contralateral parenchymal lesions and liver or adrenal metastases within 5 weeks of registration; note: a whole body FDG-PET/CT scan within 6 weeks of registration will satisfy this criterion. An additional chest x-ray is optional.

3.1.6 Zubrod Performance Status 0-1 within 8 weeks of registration;

3.1.7 Age ≥ 18;

3.1.8 EKG within 8 weeks of registration;

3.1.9 Adequate bone marrow function defined as follows:

- Absolute neutrophil count (ANC) ≥ 1,500 cells/mm³ based on a CBC/differential obtained within 2 weeks prior to registration;
- Platelets ≥ 100,000 cells/mm³ based on a CBC/differential obtained within 2 weeks prior to registration;
- Hemoglobin ≥ 10.0 g/dl based on a CBC/differential obtained within 2 weeks prior to registration (Note: The use of transfusion or other intervention to achieve Hgb ≥ 10.0 g/dl is acceptable.);

3.1.10 Adequate renal function, defined as follows: creatinine clearance within 2 weeks of registration must be at least 60 ml/min; this may be measured or calculated according to the following formula:

\[(140 - \text{age}) \times (\text{body weight in kg}) \times 0.85 \text{ for females}
\]
\[72 \times \text{serum creatinine}\]
3.1.11 Adequate hepatic function, defined as follows: Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for the institution; ALT, AST, and alkaline phosphatase ≤ 2.5 x ULN for the institution within 2 weeks of registration;
3.1.12 Serum albumin > 3.0 g/dl within 2 weeks of registration;
3.1.13 Serum magnesium within normal range within 2 weeks of registration; patients may receive magnesium supplementation to achieve normal levels.
3.1.14 For women of childbearing potential, a negative serum pregnancy test within 2 weeks of registration;
3.1.15 Adequate pulmonary function based on the following pulmonary function tests done within 8 weeks of registration:
   • FEV1 at least 2.0 liters; if less than 2.0 liters, the predicted post-resection FEV1 must be at least 0.8 liters based on the following formula using the quantitative V/Q scan:
     \[
     \text{Predicted post-resection FEV1} = \text{FEV1} \times \% \text{ perfusion to the residual, unresected lung or segment counting (predicted post-resection FEV1 = preopFEV1 x (# segments remaining/total # of segments).}
     \]
   • Diffusion capacity should be ≥ 50% predicted;
3.1.16 Patient must provide study specific informed consent prior to study entry.

3.2 Conditions for Patient Ineligibility (8/16/12)
3.2.1 Palpable lymph nodes present in the supraclavicular areas or higher in the neck, unless proven to be benign on fine needle aspiration or biopsy;
3.2.2 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years (For example, carcinoma in situ of the breast, oral cavity, or cervix are all permissible);
3.2.3 Prior systemic chemotherapy or biologic agent (including erlotinib or similar agents) for the study cancer; note that prior chemotherapy for a different cancer is allowable.
3.2.4 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields;
3.2.5 Severe, active co-morbidity, defined as follows:
   • Current uncontrolled cardiac disease; i.e., uncontrolled hypertension, unstable angina, recent myocardial infarction (within prior 6 months), uncontrolled congestive heart failure, and cardiomyopathy with decreased ejection fraction (< 50%);
   • Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;
   • Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 4 weeks of registration;
   • Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for coagulation parameters are not required for entry into this protocol.
   • Patients with acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition or patients known to be HIV positive; note, however, that HIV testing is not required for entry into this protocol. The need to exclude these patients from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immuno-compromised patients.
3.2.6 Unintentional weight loss ≥ 5% of body weight over the preceding 6 months;
3.2.7 Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception during the trial and for 6 months after completion of treatment; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.
3.2.8 Prior therapy that specifically and directly targets the EGFR pathway;
3.2.9 Prior severe infusion reaction to a monoclonal antibody;
3.2.10 Pre-existing ≥ grade 2 peripheral motor or sensory neuropathy.
4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

4.1 Highly Recommended Evaluations/Management

Note that the following evaluations/interventions are highly recommended as part of good clinical care of patients on this trial but are not required:

- Echocardiogram;
- Formal consultation by a nutritionist.

5.0 REGISTRATION PROCEDURES (11/26/13)

Access requirements for OPEN and TRIAD:

Site staff will need to be registered with CTEP and have a valid and active CTEP Identity and Access Management (IAM) account. This is the same account (user id and password) used for the CTSU members’ web site. To obtain an active CTEP-IAM account, go to https://eapps-ctep.nci.nih.gov/iam.

Note: This trial is not utilizing the services of the ITC for dosimetry digital treatment data submission. See below for information on installing TRIAD for submission of digital RT data and PET imaging data prior to enrolling patients.

Pencil beam and Clarkson integration algorithms cannot be used for this protocol. Superposition/convolution algorithms or Monte Carlo calculations must be used.

5.1 Pre-Registration Requirements for IMRT Treatment Approach (TBD)

5.1.1 In order to utilize IMRT on this study, the institution must have met specific technology requirements and have provided baseline physics information. Instructions for completing these requirements or determining if they already have been met are available on the IROC Houston QA Center (formerly the Radiological Physics Center [RPC]) web site. Visit http://irochouston.mdanderson.org and select “Credentialing” and “Credentialing Status Inquiry”. Institutions that have been successfully credentialed for prior RTOG lung studies will automatically qualify for this study without the need of re-credentialing.

An IMRT phantom study with the IROC Houston must be successfully completed (if the institution has not previously met this IMRT credentialing requirement). Instructions for requesting and irradiating the phantom are available on the IROC Houston web site at http://irochouston.mdanderson.org; select “Credentialing” and “RTOG”. Upon review and successful completion of the phantom irradiation, the IROC Houston will notify both the registering institution and RTOG Headquarters that the institution has completed this requirement. Subsequently, RTOG Headquarters will notify the institution that IMRT credentialing requirements have been met.

5.1.2 The institution or investigator must update or complete the electronic Facility Questionnaire (available on the IROC Houston website at http://irochouston.mdanderson.org) and then complete a Credentialing Status Inquiry Form, also found on the IROC Houston, web site to determine if your site has met all of the requirements. This will be completed in place of updating the previous Facility Questionnaire. When the requirements are met, the site and RTOG will be notified. RTOG will then update the RSS database. Before any cases can be entered, a TRIAD account must also have been set up for data submission.

5.2 Pre-Registration Requirements for 3D-CRT Treatment Approach (10/9/14)

5.2.1 Only institutions that have met the technology requirements and that have provided the baseline physics information may enter patients onto this study.

5.2.2 The institution or investigator must update or complete a Facility Questionnaire (available on the IROC Houston website at http://irochouston.mdanderson.org) and complete a Credentialing Status Inquiry Form, also found on the IROC Houston web site, to determine if your site has met all of the requirements. This will be completed in place of updating the previous Facility Questionnaire. When the requirements are met, the site and RTOG will be notified. RTOG will then update the RSS database prior to entering any cases. A TRIAD account must also have been set up for data submission prior to submitting any data. IROC Houston will notify the institution and RTOG when all requirements have been met and the institution is eligible to enter patients onto this study. RTOG will update the RSS database.
5.3 Pre-Registration Requirements for IGRT Treatment Approach (3/10/14)

5.3.1 In order to be eligible to enroll patients onto this trial, the center must be credentialed both for 3D-CRT and/or IMRT and if the institution intends to use reduced margins as described in the next paragraph, for lung image-guided radiotherapy (IGRT).

In order to utilize IGRT, the center must be credentialed for its use. This means the institution must have met technology requirements and have provided the baseline physics information. This information is available on the IROC Houston web site, at http://irochouston.mdanderson.org.

In order to become credentialed for lung IGRT, the institution must have already become credentialed for either 3DCRT and/or IMRT. Institutions that have not been credentialed by the RTOG to perform 3DCRT and/or IMRT MUST apply for 3DCRT and/or IMRT credentialing as described in Sections 5.1 and 5.2.

5.3.2 IGRT Credentialing Process (10/9/14)

The use of IGRT in this study is optional. The RTOG has a strict definition of IGRT, defined here to include only those procedures in which an x-ray imaging technique is used in combination with some form of computer-assisted manual or automatic registration with the image information obtained during the patient’s planning CT. If daily IGRT is used and the institution is credentialed for its use in lung, the setup margin can be set to 0.2-0.3 cm. If daily IGRT is not used, the setup margin must be 0.5 cm in all directions.

- Each institution wishing to avoid using the 0.5 cm margin described in the above subsection will be required to undergo credentialing for lung IGRT. It should be noted that institutions can credential for 3D-CRT or IMRT and start to accrue patients to this protocol before credentialing for IGRT, but they are strictly forbidden from eliminating the required 0.5 cm margin until IGRT credentialing is complete. The first step is for the institution or investigator to complete the Facility Questionnaire and set up a TRIAD account for digital data submission. See Section 5.4 for TRIAD access and installation. Additional IGRT information is provided on the RTOG web site at http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0839.

- Next, the institution must submit a series of daily treatment images along with a spreadsheet of IGRT data from an anonymized lung cancer patient. This patient should have a lesion similar to what is required for protocol accrual. The purpose of sending this information is to credential the institution’s method of IGRT. See the RTOG web site, http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0839, for the spreadsheet. This series must include a minimum of 5 daily pre-treatment images as well as the DICOM planning data (CT, RT Dose, RT Structure and RT Plan files). Pre-treatment images may include three-dimensional (3D) volumetric images (either fan- or cone-beam CT with Megavoltage (MV) or kilovoltage (kV) x-ray or Orthogonal (kV) 2D images. These images and the spreadsheet will be reviewed prior to certification.

5.3.3 Respiratory Motion Correction Credentialing Process

Each institution will be required to undergo credentialing for respiratory motion correction if they employ target tracking or gating. This applies to both IMRT and 3D-CRT techniques. Institutions will have to irradiate a moving lung phantom provided by IROC Houston unless the institution declares they will use an Automatic Breathing Coordinator (ABC) device, abdominal compression or other method that restricts the target motion to staying within the stated internal margins (IM) for motion, at which time the institution can irradiate for IMRT a static lung phantom or use previous credentialing using the appropriate IROC Houston IMRT phantom in lieu of irradiating the lung phantom for IMRT. If an institution has been credentialed for IMRT with the lung phantom and has not changed TPS or delivery machine, then the institution would also be credentialed for 3D-CRT. Please contact IROC Houston to determine if you already meet this requirement based on previous IMRT credentialing. Instructions for requesting and irradiating the phantom are available on the RPC web site at http://irochouston.mdanderson.org; select “Credentialing” and “RTOG”. Upon review and successful completion of the phantom irradiation, IROC Houston will notify both the registering institution and RTOG Headquarters that the institution has completed this requirement. Institutions must use the same respiratory motion correction for all patients enrolled in this protocol from that institution.
5.4 Digital RT Data Submission to RTOG Using TRIAD (11/26/13)
TRIAD is the American College of Radiology’s (ACR) image exchange application and it is used by NRG Oncology. TRIAD provides sites participating in RTOG clinical trials a secure method to transmit DICOM RT and other objects. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:
- Site physics staff who will submit images through TRIAD will need to be registered with The Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account. Please refer to Section 5.0 of the protocol for instructions on how to request a CTEP-IAM account.
- To submit images, the site physics user must have been assigned the ‘TRIAD site user’ role on the relevant Group or CTSU roster. RTOG users should contact your site Lead RA to be added to your site roster. Users from other cooperative groups should follow their procedures for assignment of roster roles.
- RAs are able to submit standard of care imaging through the same method.

TRIAD Installations:
When a user applies for a CTEP-IAM account with proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found on the RTOG website Core Lab tab.

This process can be done in parallel to obtaining your CTEP-IAM account username and password.

If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org.

5.5 Pre-Registration Requirements for Surgeon Credentialing (10/9/14)
Note: Surgeons previously credentialed for RTOG 0229 are credentialed for this trial and do not need to submit any additional documentation.

Participating surgeons must complete and sign the Thoracic Surgeon's Questionnaire, Appendix VII, prior to the institution entering any patients onto this study. The institution will e-mail the completed form to Dr. Donington, Thoracic Surgery Co-Chair, jessica.donington@nyumc.edu, for review. Dr. Donington will then e-mail the reviewed form to CTSU, CTSURegOffice@ecogchair.org and to NRG Oncology, rtog0839@acr.org. Institutions should allow adequate processing time (7-10 days) before calling to register the first patient.

5.6 Regulatory Pre-Registration Requirements (10/9/14)
This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Prior to the recruitment of a patient for this study, investigators must be registered members of a lead protocol organization. Each investigator must have an NCI investigator number and must maintain an “active” investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch (PMB), CTEP, DCTD, NCI. These forms are available on the CTSU registered member web site or by calling the PMB at 240-276-6575 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org.

Requirements for RTOG 0839 site registration:
- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet
- CTSU RT Facilities Inventory Form (if applicable)
NOTE: Per NCI policy all institutions that participate on protocols with a radiation therapy component
must participate in the IROC Houston (former Radiological Physics Center [RPC]) monitoring program.
For non-lead group institutions an RT Facilities Inventory Form must be on file with CTSU. If this form
has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred
at the RT facility.

5.6.1 In addition to the requirements noted above, ALL institutions must fax copies of the
documentation below to the CTSU Regulatory Office (215-569-0206 study-related regulatory
documentation also may be e-mailed to the CTSU at CTSURegulatory@ctsu.coccg.org. This
must be done prior to registration of the institution’s first case:
- IRB approval letter;
- IRB approved consent (English version);
  *Note: Institutions must provide certification/verification of IRB/REB consent
translation to NRG Oncology (described below)
- IRB assurance number

5.6.2 Pre-Registration Requirements for the Initial Shipment of Panitumumab (6/24/11)

U.S. Institutions Only:

All pre-registration requirements must be met before registering the first case. Institutions
must electronically complete (versus hand write) a Study Agent Shipment Form (SASF) available on the web site, www.rtog.org (under protocol-
specific materials/regulatory resources). U.S. institutions must fax the SASF to the CTSU Regulatory
Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has
been identified.

5.7 Registration (10/9/14)

5.7.1 OPEN Registration Instructions

Patient registration can occur only after evaluation for eligibility is complete, eligibility criteria
have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have
signed and dated all applicable consents and authorization forms.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN).
OPEN is a web-based registration system available on a 24/7 basis. All site staff will use OPEN
to enroll patients to this study. OPEN can be accessed at https://open.ctsu.org or from the
OPEN tab on the CTSU members' web site https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following:
- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPPA authorization form (if applicable).

Access requirements for OPEN:
- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM
  account. This is the same account (user id and password) used for the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role on
  the relevant Group roster.
- To perform registrations on protocols for which you are a member of NRG Oncology, you
  must have an equivalent 'Registrar' role on the NRG Oncology roster. Role assignments
  are handled through the Groups in which you are a member.
- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead
  Group registrations) you must have the role of Registrar on the CTSU roster. Site and/or
  Data Administrators can manage CTSU roster roles via the new Site Roles maintenance
  feature under RSS on the CTSU members' web site. This will allow them to assign staff
  the "Registrar" role.

The OPEN system will provide the site with a printable confirmation of registration and
treatment information. Please print this confirmation for your records.
Further instructional information is provided on the CTSU members’ web site OPEN tab or within the OPEN URL. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

In the event that the OPEN system is not accessible, participating sites can contact web support for assistance with web registration: websupport@acr.org or call the Registration Desk at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask the site to fax in the eligibility checklist and will need the registering individual’s e-mail address and/or return fax number. This information is required to assure that mechanisms usually triggered by the OPEN web registration system (e.g. drug shipment and confirmation of registration will occur.

6.0 RADIATION THERAPY (10/9/14)
NOTE: Participating sites must complete RT pre-planning prior to registration to determine that the V20 is no greater than 37% and the Mean Lung Dose (MLD) is no greater than 20 Gy. This pre-plan is not to be submitted but must be reviewed by the treating physician to ensure the dose constraint will be achieved prior to registering the patient.

NOTE: See Section 5.4 for information on installing TRIAD for submission of digital RT data prior to enrolling patients.

IMRT OR 3D-CRT WILL BE USED FOR THIS STUDY. See Section 5.1 for details of credentialing requirements.

Protocol treatment must begin within 14 days after registration and must begin on the same day as the first dose of carboplatin and paclitaxel. It is recommended that radiation therapy be delivered after chemotherapy.

6.1 Dose Specifications (11/26/13)
6.1.1 Patients will receive treatment 5 days per week, in a once-daily fraction, 2 Gy per fraction, for a total dose of 60 Gy in 30 fractions. There will be no field reduction. Either Intensity Modulated Radiation Therapy (IMRT) or Three-dimensional Conformal Radiotherapy (3D-CRT) will be used for this protocol. All fields and the entire PTV must be treated daily. Radiation therapy (RT) commences on day 1 of chemotherapy. Post-operative thoracic radiation is not permitted.

6.1.2 Normalization of the treatment plan will cover 95% of the PTV with the prescription dose. The minimum PTV dose (to a volume of at least 0.03 cc) must not fall below 95% of the prescription dose. The maximum dose within the PTV must not exceed 120% of the prescribed dose. All RT doses will be calculated with inhomogeneity corrections that take into account the density differences within the irradiated volume (i.e., air, lung, soft tissues, and bones).

6.1.3 Heterogeneous Dose Calculations
For the purpose of this protocol, acceptable TPS/algorithms should be used to demonstrate agreement between planned versus delivered dose. As described in subsection 5.1.1, institutions intending to use IMRT must perform a phantom irradiation. For this phantom credentialing test, doses falling within criteria established by the Medical Physics Committee will be deemed acceptable.

6.2 Technical Factors (2/9/12)
6.2.1 Beam Energy: 6-10 MV beams are to be used.
6.2.2 Beam Shaping: Multileaf collimation (MLC) or custom made compensators can be used for IMRT, and shaped fields using MLC or custom blocks must be used to protect normal tissues outside the target volumes for 3D-CRT.

6.3 Localization, Simulation, and Immobilization
6.3.1 A volumetric treatment planning CT study will be required to define gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV) (see Section 6.4 for definitions). For this trial, an internal target volume (ITV) can be used for respiratory motion management. If respiratory motion management is utilized during CT simulation, the resulting ITV will be scored/classified as the CTV. Each patient will be positioned in an immobilization device in the treatment position on a flat table. Contiguous CT slices, having ≤ 3 mm thickness are required through the region harboring the gross tumor, grossly enlarged lymph nodes and adjacent...
slices that are within the path of non-coplanar beams or contain critical structures. A slice thickness of 4-10 mm can be used for the remaining regions. The CT images must extend from the level of the cricoid cartilage and extend inferiorly through the entire liver volume. The GTV, CTV or ITV, PTV and normal organs will be outlined on all appropriate CT cross-sectional slices.

6.3.2 Intravenous (IV) contrast during the planning CT is optional provided a diagnostic chest CT was done with contrast to delineate the major blood vessels. If not, IV contrast should be given during the planning CT. If contrast is used, the densities corresponding to the CTV can be overridden or the contrast scan must be registered to a non-contrast scan for planning purposes.

6.3.3 A treatment planning FDG PET/CT scan (or FDG-PET alone) with the patient in the treatment position is recommended for treatment planning. In the case in which the PET/CT is obtained in the treatment position, the CT from this study may be used as the planning CT scan provided that the following is observed: 1) simulation is performed on a flat table-top; 2) the CT scan is a ‘conventional dose’ CT (as opposed to a low-dose CT); and 3) one of the approaches correcting for tumor motion is employed.

6.3.4 Optimal immobilization is critical for this protocol. Immobilization to assure reproducibility of daily set up is necessary.

6.3.5 Accounting for tumor motion is required. See Section 6.4.2 for details of the approaches recommended to account for tumor motion in this study.

6.4 Target Volumes/Tumor Motion/Treatment Planning/Treatment Delivery (10/9/14)

6.4.1 Target Volumes: The definition of volumes will be in accordance with the 1993 ICRU report #62.

- **GTV:** The GTV consists of the primary tumor, clinically positive lymph nodes seen either on the planning CT (> 1 cm short axis diameter) or on pre-treatment PET/CT scan (SUV > 3), and any known involved nodal level found on mediastinoscopy or biopsy, regardless of CT or PET/CT findings. Volume(s) may be disjointed. In the event of a collapsed lobe or lung segment, the use of PET/CT to distinguish tumor from fluid/atelectasis is encouraged.

- **CTV:** CTV is defined as the GTV plus a 0.5-1 cm margin to account for microscopic tumor extension. In addition, the CTV should include all known levels of mediastinal nodal involvement (defined both clinically as above and pathologically).

- **ITV:** ITV is defined as the union of the CTV volumes (primary tumor and nodes) contoured on each 3D CT data set and includes the envelope that encompasses the tumor motion for a complete respiratory cycle.

- **PTV:** PTV consists of CTV + Tumor motion margin (Section 6.4.2) + Setup margin (Section 6.4.4). See the margin summary table in Section 6.5.

6.4.2 Accounting for Tumor Motion Approaches and Internal Margins for Treatment Planning

One of the following 4 approaches will be employed to take tumor motion into account and define the internal margin (IM), which is part of the PTV margin.

- **Free Breathing, Non-ITV Approach (Required Tumor Volumes: GTV, CTV, PTV)**
  This approach will involve a standard CT simulation without 4D CT or fusion of inhalation or exhalation scans. The IM margin will consist of the CTV contoured on the free-breathing CT plus 1 cm in the inferior-superior direction and 0.5 cm in the axial plane.

- **Breath-hold or Gating Non-ITV Approach (10/9/14) (Required Tumor Volumes: GTV, CTV, PTV)**
  For breath-hold (assisted, such as the Elekta ABC device, or voluntary) or gated CT simulation (such as the Varian RPM device), a single 3D CT image will be acquired at a pre-determined respiration level. The IM margin will consist of the CTV plus 0.5 cm in the superior-inferior direction and 0.3 cm in the axial plane. If this approach is adopted, the institution must use breath-hold or gating-guided treatment delivery. Treatment delivery under free-breathing conditions is not acceptable for this approach.

- **4D CT Approach (Required Tumor Volumes: GTV, ITV, PTV)**
  A 4D CT may be employed (with the acquisition of at least 2 sets of 3D CT images at end-inhale and end-exhale and up to 10 sets of 3D CT data sets corresponding to various levels of the respiration cycle). The ITV is the union of the CTV volumes (primary tumor and nodes) contoured on each 3D CT data set and includes the envelope that encompasses the tumor motion for a complete respiratory cycle. While the 4D CT will be used to define the target volumes, a separate free-breathing CT must be acquired for treatment planning and dose calculation (normal tissues must be delineated on this free-
breathing CT and target volumes will be merged from the 4D CT). No additional margin is required for the ITV. The IM will be equal to the ITV.

- **Abdominal Compression (Required Tumor Volumes: GTV, ITV, PTV)**
  If abdominal compression is used during CT simulation, the IM margin will consist of the CTV contoured on a free-breathing CT with abdominal compression plus 0.8 cm in the superior-inferior direction and 0.5 cm in the axial plane. If abdominal compression is used in conjunction with breath-holds or gating, then the CTV to IM margin will be as described in Section 6.4.2.

- **Normal Anatomy to be Defined on Treatment-Planning CT Images:** These images should include the lungs (right and left done separately as well as a combined structure excluding CTV/ITV), heart, external contour of patient, esophagus, brachial plexus (for upper lobe tumors) and spinal cord. The heart should be contoured from its base to apex, beginning at the CT slice where the ascending aorta originates. The esophagus should be contoured from the bottom of the cricoid to the gastroesophageal junction. The external patient contour and spinal cord should be contoured on each CT slice.

### 6.4.3 Treatment Planning

**3D-Conformal Therapy (3D-CRT):** The PTV is to be treated with any combination of coplanar or non-coplanar 3-D 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 and corresponding dose constraints. The treatment plan used for each patient will be based on an analysis of the volumetric dose including DVH analyses of the PTVs and critical normal structures. Each field is to be treated daily.

**Intensity Modulated Radiation Therapy (IMRT):** IMRT is allowed as long as the participating institution is credentialed by IROC for intra-thoracic IMRT treatments. See Section 5.1 for details of credentialing.

### 6.4.4 Treatment Delivery

Treatment will be delivered using one of the following approaches: free-breathing, breath-hold or gating. **Daily IGRT may be employed. IGRT is defined here to include only those procedures where an x-ray imaging technique is used in combination with some form of computer-assisted manual or automatic registration with the image information obtained during the patient's planning CT procedure.** The standard use of MV EPID images as a visual comparison to DRRs does not fall under this definition. Also, the use of silver halide film radiographs alone is not accepted under this definition of IGRT. If daily IGRT is not employed, irrespective of the approach used to account for tumor motion (Section 6.4.2), the PTV will consist of a 0.5 cm margin added to the ITV in Section 6.4.2. If daily IGRT is utilized irrespective of the approach used to account for tumor motion, the PTV will consist of a 0.2-0.3 cm margin added to the ITV in Section 6.4.2.

### 6.5 Tumor Motion and Setup Margin Summary

The table below provides a summary of the margins corresponding to the various approaches to accounting for tumor motion and setup.

<table>
<thead>
<tr>
<th>Approach</th>
<th>Internal Margin</th>
<th>Set up Margin</th>
<th>PTV Margin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free-breathing CT + Free-breathing delivery without daily IGRT</td>
<td>1 cm in superior-inferior direction and 0.5 cm in axial directions</td>
<td>0.5 cm uniform expansion</td>
<td>1.5 cm in the superior-inferior direction and 1 cm in the axial directions</td>
</tr>
<tr>
<td>Free-breathing CT + Free-breathing delivery + daily IGRT</td>
<td>1 cm in the superior-inferior direction and 0.5 cm in axial directions</td>
<td>0.2-0.3 cm uniform expansion</td>
<td>1.2-1.3 cm in the superior-inferior direction and 0.7-0.8 cm in axial directions</td>
</tr>
<tr>
<td>Breath-hold or gating CT + breath-hold or gating delivery without IGRT</td>
<td>0.5 cm in the superior-inferior direction and 0.3 cm in axial directions</td>
<td>0.5 cm uniform expansion</td>
<td>1 cm in the superior-inferior direction and 0.8 cm in axial directions</td>
</tr>
<tr>
<td>Breath-hold or gating CT</td>
<td>0.5 cm in the superior-inferior direction</td>
<td>0.2-0.3 cm uniform</td>
<td>0.7-0.8 cm in the superior-inferior direction</td>
</tr>
<tr>
<td>Technique</td>
<td>CTV Expansion</td>
<td>ITV Expansion</td>
<td>PTV Expansion</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>---------------</td>
<td>---------------</td>
<td>---------------</td>
</tr>
<tr>
<td>+ breath-hold or gating delivery + daily IGRT</td>
<td>Inferior direction and 0.3 cm in axial directions</td>
<td>0.5 cm uniform expansion</td>
<td>Inferior direction and 0.5-0.6 cm in axial directions</td>
</tr>
<tr>
<td>4D CT + Free-breathing delivery without daily IGRT</td>
<td>ITV</td>
<td>0.5 cm uniform expansion</td>
<td>ITV + 0.5 cm uniform expansion</td>
</tr>
<tr>
<td>Abdominal compression CT + abdominal compression free-breathing delivery without IGRT</td>
<td>0.8 cm in the superior-inferior direction and 0.5 cm in axial directions</td>
<td>0.5 cm uniform expansion</td>
<td>1.3 cm in the superior-inferior direction and 1 cm in axial directions</td>
</tr>
<tr>
<td>Abdominal compression CT + abdominal compression free-breathing delivery + IGRT</td>
<td>0.8 cm in the superior-inferior direction and 0.5 cm in axial directions</td>
<td>0.2-0.3 cm uniform expansion</td>
<td>1.0-1.1 cm in the superior-inferior direction and 0.7-0.8 cm in axial directions</td>
</tr>
<tr>
<td>Abdominal compression CT + abdominal compression breath-hold or gating delivery without IGRT</td>
<td>0.5 cm in the superior-inferior direction and 0.3 cm in axial directions</td>
<td>0.5 cm uniform expansion</td>
<td>1 cm in the superior-inferior direction and 0.8 cm in axial directions</td>
</tr>
<tr>
<td>Abdominal compression CT + abdominal compression breath-hold or gating delivery + IGRT</td>
<td>0.5 cm in the superior-inferior direction and 0.3 cm in axial directions</td>
<td>0.2-0.3 cm uniform expansion</td>
<td>0.7-0.8 cm in the superior-inferior direction and 0.5-0.6 cm in axial directions</td>
</tr>
</tbody>
</table>

### 6.6 Critical Structures (10/9/14)

**Note:** All required structures must be labeled as listed in the table below for digital RT data submission. Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed.

<table>
<thead>
<tr>
<th>Standard Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTV_6000</td>
<td>Gross Tumor with positive lymph nodes</td>
</tr>
<tr>
<td>CTV_6000</td>
<td>GTV plus 0.5-1 cm margin to account for microscopic extension</td>
</tr>
<tr>
<td>ITV_6000</td>
<td>ITV is the union of the CTV volumes (primary tumor and nodes) contoured on each 3D CT dataset and includes the envelope that encompasses the tumor motion for a complete respiratory cycle</td>
</tr>
<tr>
<td>PTV_6000</td>
<td>CTV + Tumor motion margin + Set up margin (depends on imaging technique)</td>
</tr>
<tr>
<td>Lung_L</td>
<td>Left Lung</td>
</tr>
<tr>
<td>Lung_R</td>
<td>Right Lung</td>
</tr>
<tr>
<td>Lungs</td>
<td>Both Lungs minus CTV or ITV (depending upon the inclusion of respiratory motion management during CT simulation)</td>
</tr>
<tr>
<td>SpinalCord</td>
<td>Spinal Cord</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Esophagus</td>
</tr>
<tr>
<td>BrachialPlexus</td>
<td>Brachial Plexus (required only for upper lobe tumors)</td>
</tr>
<tr>
<td>Heart</td>
<td>Heart</td>
</tr>
<tr>
<td>External</td>
<td>Single External Contour or the calculation of non-target and unspecified tissue DVHs</td>
</tr>
<tr>
<td>NonPTV_6000</td>
<td>Constructed by taking the External contour and subtracting the PTV</td>
</tr>
</tbody>
</table>

Normal tissue constraints will be prioritized for treatment planning in the following order:

1. Spinal cord;
2. Lungs;
3. Esophagus;
4. Brachial plexus;
5. Heart.

6.6.1 Spinal Cord: The spinal cord dose limitation is the highest priority dose constraint, and thus must be met irrespective of other constraints. The dose to the spinal cord must not exceed 50.5 Gy to any contiguous volume that is ≥ 0.03 cc.

6.6.2 Lungs: The dose-volume constraint to the lungs is the second highest priority and must be met, except if it conflicts with the spinal cord dose constraints. The volume of both lungs that receive more than 20 Gy (the V20) should not exceed 37% of the total. Alternatively, the mean lung dose should optimally be < 20 Gy. (Total lung volume = the total lung minus CTV or ITV, depending upon inclusion of respiratory motion management during CT simulation).

If either of these constraints is exceeded, several solutions can be entertained:
- Increase the weighting of the AP-PA portion and reduce the weighting of the oblique portion; this can be done as long as the cord dose (above), which takes precedence, is not exceeded.
- Also reduce the CTV/ITV to the minimal range suggested above.
- Reduce the PTV by using recommended respiratory gating management approaches above and IGRT.

If all the attempts to reduce the V20 below 37% fail, then the patient should not be treated on this study.

If the V20 is between 35% and 37% or if the mean lung dose (MLD) is > 20 Gy, contact the Radiation Oncology Co-chair, Quynh-Thu Le, MD to obtain permission to begin treatment.

6.6.3 Esophagus: The mean dose to the esophagus optimally is kept below 40 Gy. This is not an absolute requirement but is strongly recommended unless other, more critical constraints force the situation. The V60 (% volume of esophagus exceeding 60 Gy) should be calculated for each patient.

6.6.4 Brachial Plexus: The maximal brachial plexus dose should be kept < 66 Gy. This contour is required only for those cases treating upper lobe tumors.

6.6.5 Heart: The following limits are recommended: 60 Gy to < 1/3, 45 Gy to < 2/3, and 40 Gy to < 100% of the heart.

### Normal Tissue Dose Limits

<table>
<thead>
<tr>
<th>Organ</th>
<th>Priority</th>
<th>Dose parameter</th>
<th>Volume Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal cord</td>
<td>1</td>
<td>Maximum dose</td>
<td></td>
</tr>
<tr>
<td>Lungs</td>
<td>2</td>
<td>Mean lung dose</td>
<td>&lt; 37% V20</td>
</tr>
<tr>
<td>Esophagus</td>
<td>3</td>
<td>Mean dose</td>
<td></td>
</tr>
<tr>
<td>Brachial Plexus</td>
<td>4</td>
<td>Maximum dose</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>5</td>
<td>&lt; 60 Gy</td>
<td>&lt; 1/3 volume</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 45 Gy</td>
<td>&lt; 2/3 volume</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 40 Gy</td>
<td>100% volume</td>
</tr>
</tbody>
</table>

6.7 Documentation Requirements (10/9/14)

6.7.1 Isodose plan for 3-D radiotherapy and IMRT and DVH of GTV, CTV or ITV, PTV, and critical normal structures must be submitted.

6.7.2 Portal image of each field of 3-D radiotherapy or orthogonal images that localize the isocenter placement of IMRT must be obtained on the first day of therapy but should not be submitted.

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

6.8 Compliance Criteria

6.8.1 Variation of Dose Prescription
- **Per Protocol**: See section 6.1.2.
- **Variation Acceptable**: Deviations of this magnitude are not desirable, but are acceptable.
  - The minimum dose to a volume that is at least 0.03 cc is less than 95% of the prescribed dose, but not less than 93%. The maximum dose for a contiguous volume of at least 0.03 cc inside the PTV exceeds 120% but is not greater that 125% of the prescribed dose.
• Deviation Unacceptable: Exceeding the dose limits stated in Variation Acceptable; doses in this region are not acceptable.

6.9 R.T. Quality Assurance Reviews (3/10/14)
The Radiation Oncology Co-Chair, Quynh-Thu Le, MD, will perform an RT Quality Assurance review after complete data for the first 15 cases enrolled has been received at IROC Philadelphia-RT. Dr. Le will perform the next review after complete data for the next 15 cases enrolled has been received at IROC Philadelphia-RT. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at IROC Philadelphia-RT, whichever occurs first.

6.10 Radiation Therapy Adverse Events
6.10.1 Reversible or permanent alopecia, bone marrow toxicity, skin pigmentation, and esophagitis are expected side effects of radiation therapy. Radiation-induced myocarditis or transverse myelitis rarely occurs at doses lower than 50 Gy. Radiographic evidence of radiation change and subsequent fibrosis of the lung will occur within lung volume receiving > 20 Gy, usually within the first 6 months after initiation of treatment. It is essential to spare as much normal lung as possible in order to avoid symptomatic lung injury.

6.10.2 Esophagitis: Esophageal complaints are common with combined modality therapy. Esophagitis does not constitute a reason to interrupt or delay radiotherapy or chemotherapy provided oral intake is sufficient to maintain hydration. Patients should be advised to avoid alcoholic, acidic, or spicy foods or beverages. Viscous xylcaine, carafate, or other medications should be used for symptomatic relief. In some cases, narcotics may be required.

It is not necessary to biopsy acute esophagitis in the first 2 weeks of combined therapy since it is rarely due to underlying viral or fungal disease. Acute esophagitis may persist for 4-6 weeks. If grade 4 esophagitis occurs, radiation treatment can be held until esophagitis improves to grade 2 or less. Every effort should be made to limit the interruption to ≤ 3 treatment days. Patients requiring hospitalization because of esophagitis may have their treatment interrupted. In this event, please notify Dr. Le.

Esophagitis should be graded according to CTCAE, v. 4.0 as follows:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Clinical Scenario</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Asymptomatic; pathologic, radiographic or endoscopic findings only</td>
</tr>
<tr>
<td>2</td>
<td>Symptomatic; altered eating/swallowing (e.g. altered dietary habits, oral supplements), IV fluids indicated &lt; 24 hrs</td>
</tr>
<tr>
<td>3</td>
<td>Symptomatic and severely altered eating/swallowing (e.g. inadequate oral caloric or fluid intake), IV fluids, tube feeding, or TPN indicated &gt; 24 hrs.</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening consequences</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
</tr>
</tbody>
</table>

6.10.3 Treatment should be interrupted for ≥ grade 4 dysphagia or odynophagia. Acute esophageal toxicity, which typically occurs within 2 weeks of the initiation of treatment and manifests as dysphagia, odynophagia, reflux symptoms, etc., should be pharmacologically managed as recommended by following approaches and should be initiated at the first signs or symptoms of esophageal toxicity. Recommended treatments are shown below:

Suggested Management Of Radiation Esophagitis
• Ketoconazole 200 mg PO q day OR
• Fluconazole 100 mg PO a day until completion of radiation.
• Mixture of:
  – 2% viscous lidocaine 60 cc;
  – Mylanta 30 cc;
  – Sucralfate (1 gm/cc) 10 cc;
Take 15-30 cc PO q 3-4 hrs prn (Contraindications: patients on dilantin, ciprofloxacin, digoxin).
• Ranitidine 150 mg PO BID (or other H2 blockers or proton pump inhibitors such as omeprazole) until completion of radiation.
• Grade 4 esophagitis: Hold RT + chemotherapy + panitumumab until ≤ grade 2. It is expected that a significant portion of patients will experience grade 3 esophagitis.
6.11 Adverse Events (AEs) and Serious Adverse Events (SAEs) Reporting Requirements
See Section 7.11 for Adverse Event Reporting.

7.0 DRUG THERAPY (10/9/14)
Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology
Quality Control guidelines.

Protocol treatment must begin within 14 days after registration. Chemotherapy and radiation therapy
(RT) must begin on the same day. It is recommended that RT be delivered after chemotherapy.

7.1 Induction Chemoradiotherapy +/- Panitumumab
Arm 1 patients will receive induction chemotherapy and concurrent radiation therapy as described below
and in Section 7.1.3.

<table>
<thead>
<tr>
<th></th>
<th>Dose</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>50mg/m²</td>
<td>Days 1, 8, 15, 22, 29, and 36</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>AUC=2</td>
<td>Days 1, 8, 15, 22, 29, and 36</td>
</tr>
<tr>
<td>Radiation</td>
<td>60 Gy</td>
<td>Days 1-5, 8-12, 15-19, 22-26, 29-33, 36-40</td>
</tr>
<tr>
<td></td>
<td>5 X per week for 6 weeks</td>
<td></td>
</tr>
</tbody>
</table>

Arm 2 patients will receive weekly panitumumab before administration of chemotherapy and radiation
therapy. Drug therapy for Arms 1 and 2 must be administered on Monday Tuesday, or Wednesday
of each week.

7.1.1 Arm 2: Panitumumab with Induction Chemoradiation (Weeks 1-8)
Beginning Day 1, patients will receive weekly treatment with panitumumab 2.5 mg/kg IV over 60
minutes before administration of chemotherapy and RT for 6 weeks (see Section 7.3.4 for
details of administration). Patients will receive the panitumumab on the following days of RT:
Days 1, 8, 15, 22, 29, 36.

After the administration of panitumumab, patients will receive paclitaxel 50 mg/m² over 60
minutes and carboplatin AUC=2 over 30 minutes administered weekly for 6 weeks during
concurrent RT.

<table>
<thead>
<tr>
<th></th>
<th>Dose</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panitumumab</td>
<td>2.5 mg/kg</td>
<td>Days 1, 8, 15, 22, 29, 36</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>50mg/m²</td>
<td>Days 1, 8, 15, 22, 29, 36</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>AUC=2</td>
<td>Days 1, 8, 15, 22, 29, 36</td>
</tr>
<tr>
<td>Radiation</td>
<td>60 Gy</td>
<td>Days 1-5, 8-12, 15-19, 22-26, 29-33, 36-40</td>
</tr>
<tr>
<td></td>
<td>5 X per week for 6 weeks</td>
<td></td>
</tr>
</tbody>
</table>

7.1.2 Arms 1 and 2: Induction Chemotherapy
Chemotherapy should be delivered after the administration of panitumumab and prior to RT.
Carboplatin will be given after paclitaxel. Both paclitaxel and carboplatin will be administered by
intravenous drip on the following days of RT: 1, 8, 15, 22, 29, and 36.

- Carboplatin, AUC=2/week, will be given over 30 minutes with standard antiemetics.
  This study uses the Calvert formula (below) for calculation of carboplatin dose.

**Calvert Formula**
Total Dose (mg)=(target AUC) X (GFR + 25)

**NOTE:** The GFR used in the Calvert formula to calculate AUC-based dosing should not exceed 125 mL/min.
Therefore, the maximum carboplatin dose (mg) = target AUC (mg x min/mL) x 150 mL/min.

For males:
\[ \text{CrCl (mL/min)} = \frac{(140\text{-age}) \times \text{weight in kg}}{72 \times \text{serum creatinine in mg/dL}} \]

For females:
\[ \text{CrCl (mL/min)} = 0.85 \times \frac{(140\text{-age}) \times \text{weight in kg}}{72 \times \text{serum creatinine in mg/dL}} \]

- Paclitaxel, 50 mg/m²/week, will be given over 1 hour with standard premedication consisting of diphenhydramine 25-50 mg, an H2-blocker, and dexamethasone 20 mg (oral or intravenous is acceptable according to local custom) at least 30 minutes prior to paclitaxel.
- See Section 7.7.3 for dose modifications for non-hematologic toxicity. If the day of chemotherapy falls on a holiday, chemotherapy should be administered on the next full working day following the holiday (e.g., if the day 8 dose falls on Thanksgiving, the next chemotherapy dose would be given the following Monday). Doses that are missed during the weekly schedule concurrent with RT will not be made up but will be documented. If breaks from chemotherapy are required for longer than 15 days, protocol chemotherapy will be discontinued. RT will continue, and the patient will remain on study and will be followed as specified in the protocol.

### 7.2 Consolidation Chemotherapy (3/21/13)
Both Arm 1 and Arm 2 patients will receive consolidation chemotherapy consisting of carboplatin and paclitaxel. Patients will not receive panitumumab as part of consolidation therapy. To begin consolidation chemotherapy, all previous toxicities including neuropathy must have resolved to < grade 2, CTCAE, v. 4.0.

For patients who undergo surgical resection, chemotherapy will resume no earlier than 6 weeks and no later than 12 weeks post-operatively. Patients not undergoing surgical resection for medical reasons or for failure to sterilize the mediastinum should proceed within 6 weeks of the completion of induction chemoradiotherapy +/- panitumumab to consolidation chemotherapy. For patients with progressive disease, protocol treatment will be discontinued, and these patients will be followed as specified in the protocol.

If the patient is unable to initiate chemotherapy at the specified time points above, the chemotherapy may be delayed up to an additional 4 weeks. If the chemotherapy cannot be given during this time interval, protocol treatment will be discontinued and the patient will be followed as specified in the protocol.

#### 7.2.1 Arms 1 and 2: Consolidation Chemotherapy
Carboplatin will be given after paclitaxel. Both paclitaxel and carboplatin will be administered by intravenous drip q 21 days x 2.
- Carboplatin, AUC=6, will be given over 30 minutes with standard anti-emetics.
- Paclitaxel, 200 mg/m², will be given over 3 hours with standard premedication consisting of diphenhydramine 25-50 mg, an H2-blocker, and dexamethasone (oral or intravenous is acceptable according to local custom) at least 30 minutes prior to paclitaxel.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>200mg/m²</td>
<td>Days 1 and 22</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>AUC=6</td>
<td>Days 1 and 22</td>
</tr>
</tbody>
</table>
7.3 Panitumumab (Vectibix®) [IND # 110152] (10/9/14)

To supplement the toxicity information contained in this document, investigators must obtain the current version of the investigator brochure for comprehensive pharmacologic and safety information. Sites can request the investigator brochure from Barbara Allen, Amgen, ballen@amgen.com. Refer to the text in this section and Appendix VI for Panitumumab Clinical Safety Experience.

Note: The panitumumab being administered in this study is not a commercially marketed product. Although it is expected to be very similar in safety and activity to the commercially marketed drug, it is possible that some differences may exist. Because this is not a commercially marketed drug, panitumumab can only be administered to patients enrolled in this clinical trial and may only be administered under the direction of physicians who are investigators in this clinical trial.

7.3.1 Formulation
Each vial of panitumumab will contain 10 mL of a sterile, colorless, preservative-free protein solution containing a 20-mg/mL solution of panitumumab.

7.3.2 Packaging and Labeling
Each vial of panitumumab will contain approximately 200 mg of panitumumab and is for single dose use only. Boxes of panitumumab will contain 12 vials of panitumumab. Each vial of panitumumab will be labeled in accordance with current ICH GCP, FDA and specific national requirements.

7.3.3 Storage
Upon receipt, panitumumab must be stored at 2-8°C (36° to 46°F) in a secured area. Vials are to be stored in the original carton under refrigeration at 2-8°C (36° to 46°F) until time of use. The product should be protected from direct sunlight and should not be frozen or shaken excessively. Exposure of the material to excessive temperature above or below this range should be avoided. Do not allow panitumumab to freeze and do not use if contents freeze in transit or in storage. If vials fall out of specified temperature requirement, please contact Amgen for instructions.

As panitumumab contains no preservative, vials are designed for single use only. Any unused portion of panitumumab remaining in the vial must not be used. The diluted solution should be used ≤ 6 hours after dilution, if stored at room temperature, or ≤ 24 hours after dilution if stored refrigerated at 2-8°C (36° to 46°F).

Records of the actual storage condition during the period of the study should be maintained.

7.3.4 Preparation and Administration

NOTE: Panitumumab is a protein and should be handled gently to avoid foaming, which may lead to denaturation of the protein product. This precaution applies not only to panitumumab stored in the vial, but also for diluted panitumumab prepared in the IV bag. It is, therefore, essential to avoid medication delivery methods, particularly pneumatic tube systems, that could potentially lead to excessive shaking or vibration that would lead to particulate formation in the protein product.

The pharmacist, using aseptic techniques, will prepare panitumumab infusion. The dose of panitumumab will be 2.5 mg/kg and will be based upon the patient’s baseline weight. The dose will not be recalculated unless the weight changes at least + 10% from the baseline weight. It is recommended that the calculated amount of panitumumab (may be rounded to the nearest tenth milligram [e.g., 456 mg rounded to 460 mg or 312 mg rounded to 310 mg]) to be removed from the vials and added to a total volume of 100 mL of pyrogen-free 0.9% sodium chloride solution USP. The maximum concentration of the diluted solution to be infused should not exceed 10 mg/mL. Doses higher than 1000 mg should be diluted to 150 mL with 0.9% sodium chloride injection USP. The diluted solution should be mixed by gentle inversion. Do not shake. Once diluted, panitumumab should be used ≤ 6 hours after dilution if stored at room temperature, or ≤ 24 hours after dilution if stored refrigerated at 2-8°C (36° to 46°F). The bag should be labeled per site pharmacy standard operating procedures and promptly forwarded to the clinic center for infusion.

No incompatibilities have been observed between panitumumab and sodium chloride injection in polyvinyl chloride bags, polyolefin bags, or glass bottles (study specific per EU label).
Panitumumab, 2.5 mg/kg will be administered IV by an infusion pump through a peripheral line or indwelling catheter using a nonpyrogenic, low protein binding filter with a 0.2- or 0.22-micron pore size in-line filter infusion set-up over 60 minutes ± 15 minutes by a trained healthcare professional. In the event a patient’s actual body weight requires greater than a 150-mL volume infusion, panitumumab will be administered over 60 to 90 minutes ± 15 minutes, as tolerated. If a dose of panitumumab is well tolerated (i.e., without any serious infusion related reactions), then subsequent IV infusions of panitumumab may be administered over 30 minutes ± 10 minutes.

Panitumumab should not be administered as an IV push or bolus.

Panitumumab should not be mixed with or administered as an infusion simultaneously with other medicinal products. The infusion line should be thoroughly flushed with saline (supplied by the center) before and after administration of panitumumab to avoid mixing with other drug products or IV solutions.

7.3.5 Adverse Events (3/10/14)

The most common adverse events of panitumumab are skin rash with variable presentations, hypomagnesemia, paronychia, fatigue, abdominal pain, nausea, and diarrhea, including diarrhea resulting in dehydration. The most serious adverse events of panitumumab are pulmonary fibrosis, severe dermatologic toxicity, including the rare risk of Stevens-Johnson syndrome and toxic epidermal necrolysis complicated by infectious sequelae and septic death, infusion reactions, abdominal pain, hypomagnesemia, nausea, vomiting, and constipation. See Appendix VI.

7.3.6 U.S. Sites Only: Drug Ordering and Accountability (11/26/13)

Amgen provides panitumumab free of charge to patients on study. Panitumumab will be distributed by Fisher Clinical Services. No supplies will be shipped to any site until the case has been registered.

The drug supply is study specific. Investigational sites will be supplied with sufficient panitumumab to treat each registered patient.

Panitumumab will be shipped from Fisher Clinical Services directly to the institution according to the following schedule:

<table>
<thead>
<tr>
<th>Patient Randomized</th>
<th>Initial e-order sent by RTOG</th>
<th>Initial e-order received by Fisher (before 5 p.m. EST)</th>
<th>Initial order shipped by Fisher</th>
<th>Initial order received at site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monday</td>
<td>Monday</td>
<td>Monday</td>
<td>Tuesday</td>
<td>Wednesday</td>
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<tr>
<td>Tuesday</td>
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<td>Monday</td>
<td>Tuesday</td>
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<tr>
<td>Friday</td>
<td>Friday</td>
<td>Friday</td>
<td>Monday</td>
<td>Tuesday</td>
</tr>
</tbody>
</table>

All questions regarding drug supply and anticipated delivery dates should be addressed directly to Fisher Clinical Services:

FCS Help Desk: 877-260-3956

This study will be conducted under an IND to be held by RTOG/NRG Oncology and will require FDA submission and approval as part of the IND.

The Study Agent Shipment Form [SASF; available on the NRG Oncology/RTOG web site, www.rtog.org (under protocol-specific materials/regulatory resources)] for U.S. sites 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. The drug supply will not be shipped by Fisher Clinical Services until the patient has been registered. NRG Oncology will notify Fisher Clinical Services to initiate each of these shipments after registration of the patient. Please contact the drug distributor
listed in the protocol directly for shipment tracking information and anticipated delivery
dates or if a shipment has not been received by the expected date.

The institution is responsible for acquiring any drug specified in the protocol as commercially
available.

7.3.7 Handling and Dispensing of Investigational Product
Investigational product should be stored in a secure area according to local regulations. It is
the responsibility of the Investigator to ensure that investigational product is only dispensed to
study patients. The investigational product must be dispensed only from official study sites by
authorized personnel according to local regulations.

7.3.8 Drug Destruction
All drug should be discarded according to the site’s guidelines, and their disposition should be
recorded on the NCI Investigational Agent Accountability Record Form or an accountability form
containing the equivalent information at a minimum.

7.4 Paclitaxel (7/24/13)
Refer to the package insert for detailed pharmacologic and safety information.

7.4.1 Formulation
Paclitaxel is a poorly soluble plant product from the Pacific yew, Taxus brevifolia. Improved
solubility requires a mixed solvent system with further dilutions of either 0.9% sodium chloride
or 5% dextrose in water. Vials will be labeled with shelf life. All solutions of paclitaxel exhibit a
slight haziness directly proportional to the concentration of drug and the time elapsed after
preparation, although when prepared as described above, solutions of paclitaxel (0.3-1.2
mg/ml) are physically and chemically stable for 27 hours.

7.4.2 Preparation
A sterile solution concentrate, 6 mg/ml in 5 ml vials (30 mg/vial) in polyoxyethylated castor oil
(Cremophor EL) 50% and dehydrated alcohol, USP, 50%. The contents of the vial must be
diluted just prior to clinical use. Paclitaxel for injection must be diluted before administration with
5% dextrose USP, 0.9% sodium chloride USP, or 5% dextrose in Ringer's injection to a final
concentration of 0.3 to 1.2 milligrams/milliliter. This solution is stable for 27 hours under
ambient temperature (25 degrees Celsius) and room lighting (Prod Info Taxol®, 1997). Use 5%
polyolefin containers due to leaching of diethylhexphthalate (DEHP) plasticizer from polyvinyl
chloride (PVC) bags and intravenous tubing by the Cremophor vehicle in which paclitaxel is
solubilized. Each bag/bottle should be prepared immediately before administration. NOTE: Formation of a small number of fibers in solution has been observed after preparation of paclitaxel (NOTE: acceptable limits established by the US
Particular Matter Test for LVP’s). Therefore, in-line filtration is necessary for administration of paclitaxel solutions. In-line filtration should be accomplished by incorporating a hydrophilic, microporous filter of pore size not
greater than 0.22 microns (e.g., Millex-GV Millipore Products) into the IV fluid pathway distal to
the infusion pump. Although particulate formation does not indicate loss of drug potency,
solutions exhibiting excessive particulate matter formation should not be used.

7.4.3 Administration
Paclitaxel will be administered as a 1-hour IV infusion using non-PVC tubing and connectors,
such as the IV administration sets (polyethylene or polyolefin) that are used to infuse parenteral
nitroglycerin and/or fat emulsion during the weekly induction period and as a 3-hour infusion
during the consolidation treatment. A 22 micron filter must be placed on the distal end of the
infusion line. Nothing else is to be infused through the line where paclitaxel is being
administered.

Patients will receive prophylactic antiallergy premedication prior to paclitaxel administration as
follows:

Dexamethasone: 20 mg oral or IV (according to local custom) approximately 30 minutes prior to
paclitaxel
Diphenhydramine: 25-50 mg IV x 1 dose 30 minutes prior to paclitaxel

The premedication schedule can be altered at the discretion of the treating physician after the
first paclitaxel dose.

7.4.4 Storage
Paclitaxel vials should be stored between 2°-25°C (36°-77°F).
7.4.5 Adverse Effects:
- Hematologic: Myelosuppression;
- Gastrointestinal: Nausea and vomiting; diarrhea, stomatitis, mucositis, pharyngitis, typhilitis, ischemic colitis, neutropenic enterocolitis, increased liver function tests (SGOT, SGPT, bilirubin, alkaline phosphatase); hepatic failure, hepatic necrosis;
- Heart: Arrhythmias, heart block, ventricular tachycardia, myocardial infarction (MI), bradycardia, atrial arrhythmia, hypotension, hypertension, lightheadedness;
- Neurological: Sensory (taste), peripheral neuropathy, seizures, mood swings, hepatic encephalopathy, encephalopathy, sensation of flashing lights; blurred vision, scintillating scotoma;
- Allergy: Anaphylactoid and urticarial reactions (acute); Stevens-Johnson Syndrome; flushing, rash, pruritus;
- Other: Alopecia, fatigue, arthralgia, myopathy, myalgia, infiltration (erythema, induration, tenderness, rarely ulceration); radiation recall reaction.

7.4.6 Supply
Paclitaxel is commercially available.

7.5 Carboplatin (7/24/13)
Refer to the package insert for detailed pharmacologic and safety information.

7.5.1 Formulation
Carboplatin is supplied as a sterile lyophilized powder available in a single-dose vial containing 50 mg, 150 mg, and 450 mg of carboplatin for administration by intravenous infusion. Each vial contains equal parts by weight of carboplatin and mannitol.

7.5.2 Preparation
Immediately before use, the content of each vial must be reconstituted with either sterile water for injection, USP, 5% dextrose in water, or 0.9% sodium chloride injection, USP, according to the following schedule:

<table>
<thead>
<tr>
<th>Vial Strength</th>
<th>Diluent Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg</td>
<td>5 ml</td>
</tr>
<tr>
<td>150 mg</td>
<td>15 ml</td>
</tr>
<tr>
<td>450 mg</td>
<td>45 ml</td>
</tr>
</tbody>
</table>

These dilutions all produce a carboplatin concentration of 10 mg/ml. When prepared as directed, Paraplatin solutions are stable for eight hours at room temperature; since no antibacterial preservative is contained in the formulation, it is recommended that Paraplatin solutions be discarded eight hours after dilution.

7.5.3 Administration
Carboplatin will be administered after paclitaxel as an IV infusion over 30 minutes. The dose will be calculated based on the patient's actual body weight at each treatment visit and the AUC (area under curve) dosing.

This study uses the Calvert formula (below) for calculation of carboplatin dose.

**Calvert Formula**
Total Dose (mg) = (target AUC) X (GFR + 25)

**NOTE:** The GFR used in the Calvert formula to calculate AUC-based dosing should not exceed 125 mL/min.

Therefore, the maximum carboplatin dose (mg) = target AUC(mg x min/mL) x 150 mL/min.

For males:

\[
CrCl \ (mL/min) = \frac{(140 - \text{age}) \times (\text{weight in kg})}{72 \times \text{serum creatinine in mg/dL}}
\]
For females:

\[
CrCl (\text{mL/min}) = 0.85 \times \frac{(140 - \text{age}) \times \text{weight in kg}}{72 \times \text{serum creatinine in mg/dL}}
\]

7.5.4 Storage
Unopened vials of Paraplatin are stable for the life indicated on the package when stored at controlled room temperature and protected from light.

7.5.5 Adverse Events
- Hematologic: Myelosuppression;
- Gastrointestinal: Nausea and vomiting; hepatic toxicity; electrolyte imbalance; hypomagnesemia; hypercalcemia;
- Neurological: Peripheral neuropathy, ocular changes;
- Other: Ototoxicity, myalgia, fatigue, allergic reaction.

7.5.6 Supply
Carboplatin is commercially available.

7.6 Dose Modifications
7.6.1 Paclitaxel and carboplatin infusions will not be concurrently withheld if panitumumab is withheld. Likewise, if paclitaxel, carboplatin, or RT are delayed or withheld, panitumumab will not be concurrently delayed or withheld, unless required by parameters described in Section 6.10 and/or Section 7.6.3.

7.6.2 Dose Levels
Patients will be treated at the following dose levels:

<table>
<thead>
<tr>
<th>Dose Levels of Paclitaxel and Carboplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting Dose</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td><strong>Concurrent Therapy</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Paclitaxel</td>
</tr>
<tr>
<td>Carboplatin</td>
</tr>
<tr>
<td><strong>Consolidation Therapy</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Paclitaxel</td>
</tr>
<tr>
<td>Carboplatin</td>
</tr>
</tbody>
</table>

Panitumumab: Only administered during chemoradiotherapy

<table>
<thead>
<tr>
<th>Starting Dose</th>
<th>Dose Level -1</th>
<th>Dose Level -2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panitumumab</td>
<td>2.5 mg/kg</td>
<td>2.0 mg/kg</td>
</tr>
</tbody>
</table>

<sup>a</sup> For concurrent therapy, paclitaxel and carboplatin doses will not be adjusted.

<sup>b</sup> For consolidation therapy, dose reductions of paclitaxel and carboplatin below the -1 dose level will not be allowed.

7.6.3 Panitumumab Dose Modifications
Panitumumab dose reductions below the −2 dose level will not be allowed. All dose reductions are permanent; that is, there will not be any re-escalation of panitumumab dose. If panitumumab is omitted for more than 4 consecutive infusions for toxicity due to panitumumab or for an intercurrent illness (e.g., infection) requiring interruption of therapy, the patient should be discontinued from further panitumumab therapy. If toxicities prevent the administration of panitumumab, the patient may continue to receive paclitaxel, carboplatin, and RT without panitumumab.
It is recommended that patients be closely monitored for treatment-related adverse events, especially infusion reactions, during the infusion and the post-infusion observation hour. For the initial panitumumab infusion, vital signs should be monitored pre-infusion, 1/2 hour into the infusion, at the end of the infusion and 1 hour post-infusion. For subsequent infusions, vital signs should be taken pre- and post-infusion.

**Treatment of Panitumumab Infusion Reactions**

Cytokine release syndromes/acute infusion reactions are different from allergic/hypersensitivity reactions, although some of the manifestations are common to both adverse events. Cytokine release syndrome/acute infusion reactions may occur with an agent that causes cytokine release, e.g., with a monoclonal antibody such as panitumumab. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms are similar to those of allergic reaction/hypersensitivity: arthralgia, bronchospasm, cough, dizziness, dyspnea, fatigue, fever, headache, hypertension, hypotension, myalgia, nausea, pruritus/itching, rash/desquamation, rigors/chills, sweating, tachycardia, tumor pain, urticaria, and vomiting.

Severe infusion reactions require the immediate interruption of panitumumab therapy and permanent discontinuation from further treatment. Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Patients should be carefully observed until the complete resolution of all signs and symptoms.

In previous clinical trials, mild to moderate infusion reactions were managed by slowing the infusion rate of panitumumab and by continued use of antihistamine pre-medications (e.g., diphenhydramine) in subsequent doses. If the patient experiences a mild or moderate (Grade 1 or 2) infusion reaction, the infusion rate should be permanently reduced by 50%. For grade 1 or 2 reactions manifesting only as delayed drug fever, see paragraph below. Panitumumab should be immediately and permanently discontinued in patients who experience severe (Grade 3 or 4) infusion reactions.

**Treatment of Isolated Drug Fever**

In the event of isolated drug fever, the investigator must use clinical judgment to determine if the fever is related to the study drug or to an infectious etiology. If a patient experiences isolated drug fever, for the next dose, pretreat with acetaminophen or non-steroidal anti-inflammatory agent (investigator discretion), repeat antipyretic dose 6 and 12 hours after panitumumab. The infusion rate will remain unchanged for future doses.

If a patient experiences recurrent isolated drug fever following premedication and post-dosing with an appropriate antipyretic, the infusion rate for subsequent dosing should be 50% of previous rate. If fever recurs following infusion rate change, the investigator should assess the patient’s level of discomfort with the event and use clinical judgment to determine if the patient should receive further panitumumab.

**Management of Pulmonary Toxicity**

In the event of acute onset (grade ≥ 2) or worsening pulmonary symptoms which are not thought to be related to underlying cancer, panitumumab therapy should be interrupted and a prompt investigation of these symptoms should occur. Panitumumab retreatment should not occur until these symptoms have resolved to grade 1. If interstitial lung disease is confirmed, panitumumab should be discontinued and the patient should be treated appropriately.

**Preemptive Management of Panitumumab-Associated Skin Toxicities**

Clinical trial data with panitumumab therapy indicate that integument and eye toxicities are consistent with what has been observed for other EGFR inhibitors. Most integument- and eye-related toxicity events were mild or moderate in intensity. For patients on panitumumab, dermatologic toxicities should be managed according to institutional standard procedures. The following information is provided for reference.
In a study investigating preemptive skin treatment, patients treated with panitumumab received the following regimen starting 24 hours before study day 1 and continuing for at least 6 weeks (Mitchell 2008):

- Skin moisturizer (e.g., Lubriderm): apply to face, hands, feet, neck, back, and chest daily in the morning upon rising;
- Sunscreen (para-aminobenzoic acid [PABA]–free, sun protection factor [SPF] 15 or higher, UV-A, and UV-B protection): apply to exposed skin areas before going outdoors;
- Topical steroid (1% hydrocortisone cream): apply to face, hands, feet, neck, back, and chest at bedtime, and
- Oral antibiotic (such as doxycycline, 100 mg, twice a day); since doxycycline is a tetracycline derivative, subjects should avoid long exposure to direct sunlight or ultraviolet light. Such exposure may result in subjects experiencing an exaggerated sunburn reaction (skin erythema). Doxycycline should not be used in subjects with a history of hypersensitivity to doxycycline or tetracycline.

The optimal duration of preemptive skin treatment is not known and, if implemented, should be individually tailored for each patient. Patients who subsequently experience skin toxicities ≥ grade 2 should be managed appropriately according to the institution’s standard procedures.

Examples of various alternative or complementary treatment options suggested in the literature include the following (Lynch 2007; Perez-Solar 2005; Segaerts 2005):

- Avoidance of sun exposure: use of sunscreen with a high SPF that blocks both UV-A and UV-B and wearing a hat;
- Prophylactic use of alcohol-free emollient creams and moisturizers to combat dryness (xerosis);
- Topical hydrocortisone (1% or 2.5%) cream and/or Clindamycin 1% gel for mild cases (grade 1); tetracycline oral antibiotics for more severe ( ≥ grade 2 ) cases along with the topical treatments for grade 1 events, and use of an oral antihistamine for itch is recommended;
- IV antibacterial or antifungals, as clinically appropriate, for superinfection.

Patients developing dermatologic toxicities while receiving panitumumab should be monitored for the development of inflammatory or infectious sequelae, and appropriate treatment of these symptoms initiated. Panitumumab should be held for the following dermatological adverse events:

- Any grade 3 or 4 (CTCAE, v. 4.0) skin or nail-related adverse events;
- Skin or nail infection requiring IV antibiotic or IV antifungal treatment;
- Need for surgical debridement;
- Any skin- or nail-related SAE.

**Panitumumab Dose Modification Guidelines for Dermatologic Toxicity**

In patients with mild and moderate skin toxicity, treatment should continue without dose modification. In the event of grade 3 or 4 cutaneous toxicity, hold the infusion for up to 2 weeks, until toxicity resolves to ≤ grade 1, and resume at dose level -1, 2.0 mg/kg. If grade 3 or 4 toxicity recurs, discontinue panitumumab.

**Management of Hypomagnesemia and Electrolyte Abnormalities**

Hypomagnesemia has been reported with panitumumab when administered as a single agent and in combination with multiple different chemotherapeutic regimens. The incidence of hypomagnesemia (both overall and severe [CTCAE, v. 4.0 grades 3 & 4]) is increased in patients receiving chemotherapy and panitumumab as compared with those receiving chemotherapy alone based on controlled clinical trials. Patients receiving panitumumab therapy should be periodically monitored for hypomagnesemia, hypocalcemia, and hypokalemia, during and for at least 8 weeks following the completion of panitumumab. Replete electrolytes as necessary.
Based on previous experience with panitumumab reactions, the following treatment guidelines may be applicable:

<table>
<thead>
<tr>
<th>CTCAE, v. 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1 Allergic reaction</strong> (including drug fever): Transient flushing or rash; drug fever &lt; 38°C (&lt; 100.4°F); intervention not indicated</td>
</tr>
<tr>
<td>or <strong>Grade 1 Cytokine release syndrome/infusion reaction</strong>: Mild reaction; infusion interruption not indicated; intervention not indicated</td>
</tr>
<tr>
<td><strong>Treatment</strong>: Decrease the panitumumab infusion rate by 50%, and monitor closely for any worsening.</td>
</tr>
</tbody>
</table>

| **Grade 2 Allergic reaction** (including drug fever): Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours |
| or **Grade 2 Cytokine release syndrome/infusion reaction**: Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours |
| **Treatment**: Stop panitumumab infusion; administer bronchodilators, oxygen, etc. as medically indicated. Resume infusion at 50% of previous rate once allergic reaction has resolved or has decreased to Grade 1 in severity, and monitor closely for any worsening. |

| **Isolated drug fever (Grade 1 or 2 Allergic reaction or Cytokine release syndrome/infusion reaction)**: |
| **Treatment**: Pre-treat for next dose with acetaminophen or NSAID (Investigator’s discretion). Repeat antipyretic dose 6 and 12 hours after panitumumab infusion. The infusion rate will remain unchanged. See Section 7.5.3 for dose modification of subsequent courses. |

| **Grade 3 or Grade 4 Allergic reaction** (including drug fever): |
| **Grade 3**: Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates). |
| **Grade 4**: Life-threatening consequences; urgent intervention indicated |
| or **Grade 3 or Grade 4 Cytokine release syndrome/infusion reaction**: |
| **Grade 3**: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae |
| **Grade 4**: Life-threatening; urgent intervention indicated |
| **Treatment**: Stop the panitumumab infusion immediately, and disconnect infusion tubing from the patient; administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc., as medically indicated. Report as a serious adverse event (see Section 7.11). |

**Retreatment with Panitumumab Following Allergic or Cytokine Release Reactions**

Once a panitumumab infusion rate has been decreased due to an allergic or cytokine release reaction, it will remain decreased for all subsequent infusions. If the patient has a second allergic or cytokine release reaction with the slower infusion rate, the infusion should be stopped, and the patient should receive no further panitumumab treatment. If a patient experiences a Grade 3 or 4 allergic or cytokine release reaction at any time, the patient should receive no further panitumumab treatment. If there is any question as to whether an observed reaction is an allergic or cytokine release reaction of Grades 1 – 4, the Study Chair should be contacted immediately to discuss the reaction.

If the patient experiences recurrent isolated drug fever following pre-medication and post-dosing with an appropriate antipyretic, the infusion rate for subsequent dosing should be 50% of the previous rate. If fever recurs following infusion rate changes, the investigator should assess the patient’s level of discomfort with the event and use...
clinical judgment to determine if the patient should receive further panitumumab therapy.

The first time a patient experiences a grade 3 acne/acneiform rash associated with pain, disfigurement, ulceration, or desquamation, panitumumab therapy is to be held for up to four consecutive infusions with no change in the dose level. The Investigator also can consider concomitant treatment with topical and/or oral antibiotics; topical corticosteroids are not recommended. If the toxicity resolves to Grade 2 or less by the following treatment period, treatment may resume. With subsequent occurrences of a Grade 3 acne/acneiform rash, panitumumab therapy again may be omitted for up to four consecutive weeks. Treatment may resume with reduced dose of panitumumab if skin toxicity has resolved to Grade 2 or less. **Panitumumab dose reductions are permanent.** Panitumumab will be discontinued if there are more than 4 consecutive infusions held or if there is a subsequent occurrence of a fourth episode of Grade 3 acne-like rash (rash/desquamation). The patient should be followed weekly until resolution of the rash.

7.7 **Dose Modifications During Induction Chemoradiation and Panitumumab (7/24/13)**

7.7.1 **Paclitaxel/Carboplatin/Panitumumab Dose Modifications for Hematologic Toxicity**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Paclitaxel Dose at Start of Subsequent Cycles of Therapy a</th>
<th>Carboplatin Dose at Start of Subsequent Cycles of Therapy b</th>
<th>Panitumumab Dose at Start of Subsequent Cycles of Therapy b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>1 (1500-1999/mm³)</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>2 (1000-1499/mm³)</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>3 (500-999/mm³)</td>
<td>Hold therapy a</td>
<td>Hold therapy a</td>
<td>Hold therapy a</td>
</tr>
<tr>
<td>4 (&lt; 500/mm³)</td>
<td>Hold therapy a</td>
<td>Hold therapy a</td>
<td>Hold therapy a</td>
</tr>
<tr>
<td>Neutropenic fever</td>
<td>Hold therapy a</td>
<td>Hold therapy a</td>
<td>Hold therapy a</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>1 (&lt; LLN-75,000/mm³)</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>2 (50,000-74,999/mm³)</td>
<td>Hold therapy b</td>
<td>Hold therapy b</td>
<td>Hold therapy b</td>
</tr>
<tr>
<td>3 (25,000-49,999/mm³)</td>
<td>Hold therapy b</td>
<td>Hold therapy b</td>
<td>Hold therapy b</td>
</tr>
<tr>
<td>4 (&lt; 25,000/mm³)</td>
<td>Hold therapy b</td>
<td>Hold therapy b</td>
<td>Hold therapy b</td>
</tr>
<tr>
<td>Other Hematologic</td>
<td>Dose modifications for leukopenia are based on CTCAE, v. 4.0 and are the same as recommended for neutropenia above.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>toxicities</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

aDose levels are relative to the starting dose in the previous cycle. Dose reductions of panitumumab below the –2 dose level will not be allowed. For induction therapy, paclitaxel and carboplatin doses will not be adjusted.
bRepeat lab work weekly and resume chemotherapy based on this table.

7.7.2 If paclitaxel and/or carboplatin doses must be withheld for greater than two consecutive weeks, the drug(s) will be held permanently for the duration of induction therapy.
### 7.7.3 Paclitaxel/Carboplatin/Panitumumab Dose Modifications for Non-Hematologic Toxicity

<table>
<thead>
<tr>
<th>Worst Toxicity</th>
<th>Paclitaxel Dose At Start of Subsequent Cycles of Therapy</th>
<th>Carboplatin Dose At Start of Subsequent Cycles of Therapy</th>
<th>Panitumumab Dose At Start of Subsequent Cycles of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paronychia</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
<td>Decrease by 1 dose level</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>≤ Grade 1</td>
<td>Hold therapy until Grade ≤ 1; restart at full dose&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Discontinue therapy</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>Paclitaxel Infusion Reaction&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Premedicate 24 hours before and/or desensitization</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>Grades 1, 2, 3</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Discontinue paclitaxel</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>Other non-hematologic toxicities&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Hold treatment until ≤ Grade 2</td>
<td>Hold treatment until ≤ Grade 2</td>
<td>Hold treatment until ≤ Grade 2</td>
</tr>
<tr>
<td>≥ Grade 3</td>
<td>Hold treatment until ≤ Grade 2</td>
<td>Hold treatment until ≤ Grade 2</td>
<td>Hold treatment until ≤ Grade 2</td>
</tr>
</tbody>
</table>

- For ≤ Grade 2 CTCAE, v. 4.0 non-hematologic toxicity not described above, excluding neuropathy, maintain dose level of all study. For neuropathy, follow the guidelines listed above.
- Dose levels are relative to the starting dose in the previous cycle. Dose reductions of panitumumab below the – 2 dose level will not be allowed. For concurrent therapy, paclitaxel and carboplatin doses will not be adjusted.
- With the exception of allergic or cytokine release reaction (see Section 7.6.3), acne-like rash (rash/desquamation), anorexia, and viral infections. See Section 7.6.3 for treatment modifications for and skin toxicity management.
- Most patients with hypersensitivity reactions to paclitaxel can be successfully treated by administration of steroid, H1 and H2 blocker prophylaxis or increased infusion time. If the patient experiences repeated severe episodes (grade 3) then paclitaxel should be discontinued. Carboplatin, radiation, and panitumumab should be continued. Substitution with docetaxel, nabpaclitaxel, etc. is not permitted.
- Radiation therapy should continue to be delivered for ≤ Grade 3 non-hematologic toxicities in or outside the radiation treatment field. RT should be held for all Grade 4 non-hematologic toxicity in or outside the treatment field and resumed only when toxicity is ≤ Grade 2.

In any case of panitumumab treatment delay, all subsequent treatments will be at the current dose level.

### 7.7.4 Carboplatin Dose Modifications for Renal Toxicity

A > 25% change in the serum creatinine will warrant a recalculation of the carboplatin dose (see Section 7.8.3).

### 7.7.5 Paclitaxel for Neuropathy

If paclitaxel doses must be withheld for greater than two consecutive weeks, the drug will be held permanently for the duration of concurrent therapy (see Section 7.8.4).

### 7.7.6 If there is a decline in Zubrod performance status to ≥ 2 for greater than 2 weeks while under treatment, RT should be held with no further chemotherapy administered. Re-evaluate patient after one week for resumption of radiotherapy.
### Treatment Modification for In-field Non-Hematologic Toxicity

<table>
<thead>
<tr>
<th>In-field</th>
<th>CTCAE, v. 4.0 Toxicty Grade</th>
<th>XRT</th>
<th>Paclitaxel</th>
<th>Carboplatin</th>
<th>Panitumumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagus/pharynx (on day of XRT)</td>
<td>4</td>
<td>Hold treatment until ≤ Grade 2</td>
<td>Hold treatment until ≤ Grade 2</td>
<td>Hold treatment until ≤ Grade 2</td>
<td>Hold treatment until ≤ Grade 2</td>
</tr>
<tr>
<td>Esophagus/pharynx (on day of chemo)</td>
<td>3</td>
<td>No change or hold ≤ 5 days (See Sections 6.10.2 &amp; 6.10.3)</td>
<td>Hold treatment until ≤ Grade 2</td>
<td>Hold treatment until ≤ Grade 2</td>
<td>Hold treatment until ≤ Grade 2</td>
</tr>
<tr>
<td>Esophagus/pharynx (on day of chemo)</td>
<td>2</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>4</td>
<td>Discontinue</td>
<td>Hold treatment until ≤ Grade 2</td>
<td>Hold treatment until ≤ Grade 2</td>
<td>Discontinue panitumumab</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>3</td>
<td>Hold treatment until ≤ Grade 2</td>
<td>Hold treatment until ≤ Grade 2</td>
<td>Hold treatment until ≤ Grade 2</td>
<td>Discontinue panitumumab</td>
</tr>
<tr>
<td>Skin</td>
<td>4</td>
<td>Hold treatment until ≤ Grade 2</td>
<td>Hold treatment until ≤ Grade 2</td>
<td>Hold treatment until ≤ Grade 2</td>
<td>Follow guidelines in Section 7.6.3</td>
</tr>
<tr>
<td>Skin</td>
<td>3</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>Follow guidelines in Section 7.6.3</td>
</tr>
</tbody>
</table>

**For infield esophagitis**, see the table above.

**For dermatitis or other in-field RT-related toxicity**, see the table above. On day of chemotherapy administration during any treatment week, omit paclitaxel and carboplatin until toxicity resolves to ≤ grade 2 as detailed in the table above. For panitumumab skin toxicity management, follow the guidelines in Section 7.6.3.

**Radiotherapy** should be interrupted for Grade 4 toxicity, including Grade 4 esophagitis or pulmonary toxicity and resumed according to the table above. If treatment is interrupted for > 2 weeks, the patient should be removed from study treatment. If the patient experiences esophagitis so that IV fluid support is needed, insertion of a feeding tube should be considered.

In the event of acute onset of grade 2 or greater pulmonary symptoms, worsening of pulmonary symptoms not thought to be related to the underlying cancer, or pre-existing pulmonary disease, panitumumab therapy should be interrupted and a prompt investigation of these symptoms should occur.

**Dose Modifications During Consolidation Chemotherapy (7/24/13)**

To begin consolidation chemotherapy, all previous toxicities including neuropathy must have resolved to < grade 2, CTCAE, v. 4.0.

**Paclitaxel and Carboplatin Dose Modifications for Hematologic Toxicity**

<table>
<thead>
<tr>
<th>Toxicty NCI CTCAE Grade (CTCAE, v. 4.0)</th>
<th>Paclitaxel Dose at Start of Subsequent Cycles of Therapy</th>
<th>Carboplatin Dose at Start of Subsequent Cycles of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia 1 (1500-1999/mm³)</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
</tr>
</tbody>
</table>
Hold therapy\(^b\). Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when \(\geq 1,500 \text{ mm}^3\)

### Neutropenic fever

<table>
<thead>
<tr>
<th>NCI CTCAE Grade (CTCAE, v. 4.0)</th>
<th>Paclitaxel Dose At Start of Subsequent Cycles of Therapy</th>
<th>Carboplatin Dose At Start of Subsequent Cycles of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paronychia</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>Infusion Reaction(^c)</td>
<td>Premedicate 24 hours before and/or desensitization</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>Other non-hematologic toxicities</td>
<td>Discontinue paclitaxel</td>
<td>Maintain dose level</td>
</tr>
</tbody>
</table>

**a.** Dose levels are relative to the worst toxicities in the previous cycle. For consolidation therapy, dose reductions of paclitaxel and carboplatin below the –1 dose level will not be allowed.

**b.** Repeat lab work weekly and resume chemotherapy based on this table.

**c.** Dose delays greater than 2 weeks will warrant discontinuation of chemotherapy for the consolidation cycles.

### Paclitaxel and Carboplatin Dose Modifications for Non-Hematologic Toxicity

<table>
<thead>
<tr>
<th>Worst Toxicity</th>
<th>Paclitaxel Dose At Start of Subsequent Cycles of Therapy</th>
<th>Carboplatin Dose At Start of Subsequent Cycles of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paronychia Grade 2</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>Neuropathy (\leq) Grade 1</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Hold therapy until Grade (\leq 1); restart at full dose</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Discontinue therapy</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>Infusion Reaction(^c) Grade 1, 2, 3</td>
<td>Premedicate 24 hours before and/or desensitization</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Discontinue paclitaxel</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>Other non-hematologic toxicities</td>
<td>Hold treatment until (\leq) Grade 2</td>
<td>Hold treatment until (\leq) Grade 2</td>
</tr>
</tbody>
</table>
a. For ≤ Grade 2 CTCAE, v. 4.0 non-hematologic toxicity not described above, excluding neuropathy, maintain dose level of all study drugs. For neuropathy, follow the guidelines above. 

b. Dose levels are relative to the worst toxicities in the previous cycle. For consolidation therapy, paclitaxel and carboplatin doses will not be adjusted.

c. Most patients with hypersensitivity reactions to paclitaxel can be successfully treated by administration of steroid, H1 and H2 blocker prophylaxis, increased infusion times and/or desensitization. If the patient experiences repeated severe episodes (grade 3) or refuses further therapy with paclitaxel then paclitaxel should be discontinued. Carboplatin, should be continued. Substitution with docetaxel, nabpaclitaxel etc is not permitted.

When a chemotherapy dose reduction is required during the consolidation course of therapy, re-escalation of the chemotherapy dose will not be allowed for subsequent doses during that specific course.

7.8.3 Carboplatin Dose Modifications for Renal Toxicity
The dose of carboplatin is only recalculated for major changes; for example, a > 25% change in the serum creatinine, based on weekly calculated creatinine clearance, will warrant a recalculation of the carboplatin dose. It is not necessary to recalculate the carboplatin dose based on the patient’s weekly body weight.

7.8.4 Paclitaxel Dose Modifications for Neuropathy
See Section 7.8.2 for details. If paclitaxel doses must be withheld for > 2 consecutive weeks, the drug will be held permanently for the duration of consolidation therapy.

7.8.5 If protocol treatment is discontinued for any reason, follow up and data collection will continue as specified in the protocol. The reason(s) for discontinuation of protocol treatment should be documented in the patient’s medical record and appropriate case report form (see Section 12.0).

7.9 Modality Review
The Principal Investigator, Martin Edelman, MD, will perform a Systemic Therapy Assurance Review of all patients who receive or are to receive chemotherapy +/- panitumumab in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of treatment data as specified in Section 12.1. The scoring mechanism is: Per Protocol/Acceptable Variation, Not Per Protocol, and Not Evaluable. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

Dr. Edelman will perform an Assurance Review after complete data for the first 15 cases enrolled has been received at NRG Oncology. Dr. Edelman will perform the next review after complete data for the next 15 cases enrolled has been received at NRG Oncology. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at NRG Oncology, whichever occurs first.

7.10 Adverse Events (3/10/14)
This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for adverse event (AE) reporting. The CTCAE version 4.0 is located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

Adverse events (AEs) that meet expedited reporting criteria defined in the table(s) below will be reported via the CTEP-AERS (the CTEP Adverse Event Reporting System) accessed via the CTEP web site ((https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613).

7.10.1 Adverse Events (AEs)
Definition of an AE: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm]
7.10.2 **Serious Adverse Events (SAEs)** — Serious adverse events (SAEs) that meet expedited reporting criteria defined in the table in section 7.11 will be reported via CTEP-AERS. SAEs that require 24 hour CTEP-AERS notification are defined in the expedited reporting table in section 7.11. Contact the CTEP-AERS Help Desk if assistance is required.

**Definition of an SAE**: Any adverse drug event (experience) occurring at any dose that results in any of the following outcomes:
- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect;
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported via CTEP-AERS in an expedited manner.

7.10.3 **Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS)** (3/10/14)
AML or MDS that is diagnosed as a secondary malignancy during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the CTEP-AERS system within 30 days of AML/MDS diagnosis.

**Secondary Malignancy**
A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:
- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

**Second Malignancy**
A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

7.11 **CTEP-AERS Expedited Reporting Requirements** (10/9/14)
All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via CTEP-AERS, the CTEP Adverse Event Reporting System, accessed via the CTEP website, [https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613](https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613).

Submitting a report via CTEP-AERS serves as notification to NRG Oncology and satisfies NRG Oncology requirements for expedited adverse event reporting.

CTEP-AERS provides a radiation therapy-only pathway for events experienced that involve radiation therapy only. These events must be reported via the CTEP-AERS radiation therapy-only pathway.
In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to 1-800-227-5463, ext. 4189, for instances when Internet fails. Once internet connectivity is restored, an AE report submitted by phone must be entered electronically into CTEP-AERS.

- CTEP-AERS-24 Hour Notification requires that an CTEP-AERS 24-hour notification is electronically submitted within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by an CTEP-AERS 5 Calendar Day Report. Serious adverse events that require 24 hour CTEP-AERS notification are defined in the expedited reporting table below.
- Supporting source document is not mandatory. However, if the CTEP-AERS report indicates in the Additional Information section that source documentation will be provided, then it is expected. If supporting source documentation accompanies an CTEP-AERS report, include the protocol number, patient ID number, and CTEP-AERS ticket number on each page, and fax supporting documentation to the NRG Oncology dedicated SAE FAX, 215-717-0990.
- A serious adverse event that meets expedited reporting criteria outlined in the following table but is assessed by the CTEP-AERS as “expedited reporting NOT required” must still be reported to fulfill RTOG safety reporting obligations. Sites must bypass the "NOT Required" assessment; the CTEP-AERS allows submission of all reports regardless of the results of the assessment.

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

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention ¹,²

<table>
<thead>
<tr>
<th>Hospitalization</th>
<th>Grade 1 Timeframes</th>
<th>Grade 2 Timeframes</th>
<th>Grade 3 Timeframes</th>
<th>Grade 4 &amp; 5 Timeframes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resulting in Hospitalization ≥ 24 hrs</td>
<td>10 Calendar Days</td>
<td>24-Hour 5 Calendar Days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not resulting in Hospitalization ≥ 24 hrs</td>
<td>Not required</td>
<td>10 Calendar Days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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

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

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

**Expedited AE reporting timelines are defined as:**

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

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

**Expedited 24-hour notification followed by complete report within 5 calendar days for:**
- All Grade 4, and Grade 5 AEs

**Expedited 10 calendar day reports for:**
- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

**2** For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote “1” above applies after this reporting period.

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

Not applicable for this study.

### 8.0 SURGERY

**8.1 Evaluation for Surgery (7/24/13)**

#### 8.1.1 Mediastinal Sampling

N2 status must be pathologically confirmed to be positive within 12 weeks prior to registration (see Section 3.1.3).

For left sided lesions, the following nodal levels should be biopsied: 2L, 4L, 2R, 4R and 7 or stations 5 and 6. For right sided lesions levels 2R, 4R, 2L, 4L and 7 should be sampled whenever possible to rule out microscopically involved lymph nodes. Investigators are strongly encouraged to biopsy multiple stations of mediastinal lymph nodes at the time of invasive staging in addition to those nodes that are abnormal on PET/CT scan. N2 status must be pathologically confirmed to be positive within 12 weeks prior to registration by one of the following:

- mediastinoscopy;
- mediastinotomy (Chamberlain procedure);
- transesophageal needle biopsy using endoscopic ultrasound (EUS-TBNA);
- endobronchial ultrasound biopsy using endoscopic ultrasound guidance (EBUS-TBNA);
- thoracotomy;
- video-assisted thoracoscopic;
- transbronchial needle biopsy by Wang technique (TBNA);
- fine needle aspiration under CT guidance.

PET/CT positivity in the ipsilateral mediastinal lymph nodes will not be sufficient to establish N2 nodal status.

#### 8.1.2 Nodal Documentation

Review of pre-treatment studies (PET/CT, CT, pathologic results of mediastinal staging) will define mediastinal lymph node status for appropriate analysis, as follows:
Number of Stations Involved

- If, on review of the pathology report, only one station has been biopsied and that station is positive for cancer, the patient will be classified as N2LX (nodes not evaluable); patients with a paralyzed vocal cord and enlarged aorto-pulmonary window nodes also will fall into this category.
- If, on review of the pathology report, more than one station has been biopsied and only one station is positive for cancer, the patient will be classified as N2L1 (one station involved);
- If, on review of the pathology report, more than one station has been biopsied and two or more stations are positive for cancer, the patient will be classified as N2L2 (two or more stations involved).

Nodal Micrometastases And Lymph Node Size

- Patients with either any non-subcarinal nodes with a short axis diameter on CT > 1 cm or subcarinal nodes with a short axis diameter on CT > 1.2 cm shall be classified as cN2 (clinically involved lymph nodes);
- Patients in whom all non-subcarinal nodes are ≤ 1 cm and subcarinal nodes ≤ 1.2 cm shall be classified as mN2 (microscopically involved lymph nodes).

If lymph nodes in the contralateral (opposite the primary) mediastinum and neck are visible on the contrast CT scan of the chest and are > 1.0 cm in short axis or if contralateral involvement is suggested by PET/CT scan, then the nodes must be confirmed to be negative by one of the diagnostic procedures listed in Section 3.1.3.

8.1.3 Reassessment After Completion of Induction Chemoradiotherapy +/- Panitumumab

Four weeks following completion of induction chemoradiation +/- panitumumab and within 2 weeks of anticipated surgery, all patients will be re-evaluated as follows to assure that their medical condition has not deteriorated to the point that the patient is no longer medically fit to withstand resection:

- History and physical by medical oncologist;
- Evaluation by thoracic surgeon;
- EKG;
- Pulmonary Function Tests with diffusion capacity; the quantitative V/Q scan or split functions need not be repeated unless the FEV1% decreases by > 5 percentage points from the pre-induction therapy study or the predicted post-resection FEV1 falls below .8L;
- Laboratory: Repeat lab evaluations for bone marrow and hepatic function (repetition of the creatinine clearance is not necessary);
- Imaging:
  - Chest and upper abdominal CT scan to include entire liver;
  - Brain MRI with contrast (substitute CT scan if the MRI is medically contraindicated);
  - Whole body FDG-PET scan is recommended but not required. This PET/CT scan should ideally be performed at the same facility as the pre-treatment PET/CT scan (see Section 3.1.6) so that the data can be used for analysis of the secondary objective (Section 2.2.7) Note: To be included in this analysis, the patient's PET/CT studies must be performed with a dedicated BGO, LSO, or GSO PET or PET/CT scanner. PET scanners with sodium iodide (NaI) detectors are not acceptable. A bone scan is not required unless there is new bone pain or new elevation of the alkaline phosphatase or LDH. PET/CT DICOM images, diagnostic reports, and assessment forms must be submitted as described in Section 12.1.
  - Repeat bronchoscopy is performed at the discretion of the surgeon. It is recommended in those patients who have disease near the carina or in another position where small amounts of progression which may not be well visualized on CT scan may impact resectability.

8.1.4 Radiographic response determinations (CR, PR, SD, PD) will be required for this study (see Section 11.2). Whenever possible, a biopsy should be obtained to confirm distant progression. All patients who fit the criteria for no progression in the chest or elsewhere, including all patients who have stable disease on re-evaluation, are eligible to proceed to surgery. A repeat pathological assessment mediastinum by mediastinoscopy or EBUS-TBNA may be done at the
option of the participating surgeon. Since many of these patients will have their initial pathologic evaluation of the mediastinum performed by mediastinoscopy and EBUS-TBNA has decreased diagnostic yield following induction therapy in this setting and repeat mediastinoscopy has significant increase in complication and decreased diagnostic yield (DeWaele 2008), this step is not required. The individual institution will have the option of proceeding to resection if there is pathologic evidence of persistent mediastinal disease or forgoing surgery and proceeding directly to full dose chemotherapy. All patients without pathologic evidence of persistent mediastinal disease, without clinical evidence for disease progression, or whose medical condition has not deteriorated to the point that they are no longer fit for surgery are expected to be taken to resection. Not undergoing resection without documentation of the one of the above reasons would be considered a protocol violation. Institutions will be notified of the first such violation and upon a second such violation, will not be permitted to enroll further patients to the study.

8.1.5 If there is progressive disease (PD) or distant disease identified, protocol treatment will be discontinued. Further treatment is at the discretion of the treating medical oncologist. Patients who have not progressed but are inoperable for medical or anatomic reasons, should proceed to consolidation chemotherapy as detailed in the protocol. Sites will submit Post-Induction Evaluation Form (FS). If it is the opinion of the attending thoracic surgeon that the patient has developed a problem that makes surgery medically or technically unsafe, or if the patient refuses surgery, the Thoracic Surgery Co-Chair, Dr. Donington, or, in her absence, the Principal Investigator, Dr. Edelman, should be notified and this information documented. Patients with progressive disease will receive further non-operative, non-protocol therapy at the discretion of their treating physician(s).

8.1.6 Surgery will be performed 4-6 weeks after completion of induction therapy. Occasionally, an extra week will be required to recover from toxicity of induction chemoradiotherapy and panitumumab. If longer than a week is deemed necessary, Dr. Donington or Dr. Edelman should be notified immediately. The site will document the reason(s) for delay on the Post-Induction Evaluation Form (FS). If the delay is approved by Drs. Donington or Edelman, the delay will not be considered a protocol violation.

8.2 Surgical Guidelines/Extent of Resection (3/21/13)

8.2.1 A lobectomy, or a pneumonectomy will be performed at the discretion of the attending thoracic surgeon. A sublobar resection (e.g., a wedge or segmentectomy) will be considered a major protocol deviation. The type of resection chosen should provide complete removal of the primary lesion with negative gross margins; this is not subject to quality assurance review. If the resection margins are close, documentation of margins by frozen section at surgery is strongly recommended.

8.2.2 Lesions with direct extension into parietal pleura or chest wall should be resected with an en bloc chest wall resection. Lesions with direct extension into pericardium or diaphragm should have en bloc resection of those structures with an attempt made to achieve a minimum of 2 cm gross or 1 cm microscopic margins. These are recommendations subject to quality assurance review (i.e., if it is not a chest wall lesion but a pleura invasion, this must be reviewed).

8.2.3 A formal systematic mediastinal lymph node evaluation will be performed in all cases. The primary endpoint of this trial is clearance of disease from mediastinal lymph nodes at the time of resection. Numbering and/or nomenclature outlined in the Lymph Node Map will be used (see Appendix IV). Mediastinal lymph nodes removed at the time of resection should include nodes from the following regions:

- For right sided lesions: 4R, 7, 9R, 10R; and if accessible, 2R. If the 4R, 7, 9R, and 10R levels are not performed, it will be considered a major protocol deviation. 2R is recommended but is not subject to quality assurance review.
- For left sided lesions: 5, 6, 7, 9L, 10L; and if accessible, 4L. If the 5, 6, 7, 9L, and 10L levels are not performed, it will be considered a major protocol deviation. 4L is recommended but is not subject to quality assurance review.

8.2.4 The attending thoracic surgeon must review and sign all post-surgical forms.

8.2.5 At the time of surgical resection, after the completion of a lobectomy or pneumonectomy, it is a requirement of the study that an autologous tissue flap be placed on the bronchial stump to buttress the bronchus and prevent air leak or infection. In the case of an anticipated lobectomy, it is recommended that an intercostal muscle, pericardial fat or thymic flap be used. In the case of a pneumonectomy, a serratus anterior or intercostal muscle flap is required. The serratus anterior muscle should be harvested in its anterior and inferior portions, left attached to the...
scapula superiorly and placed through the 2nd intercostal space anteriorly. The intercostal muscle flap should be harvested from the 5th intercostal space with neurovascular pedicle at the time of the thoracotomy before placing the rib spreader. It is suggested that the tissue flaps should be secured with at least 4 interrupted 4-0 vicryl sutures to the adventitia overlying the bronchus. Performing a lobectomy without soft tissue coverage or performing a pneumonectomy without a muscle flap to buttress the bronchus will be considered a major protocol violation.

8.2.6 Care should be taken with the use of minimally invasive techniques (video-assisted thoracoscopic surgery (VATS) or robotic approaches) because of the extensive pretreatment and the need for thorough mediastinal nodal assessment. Minimally invasive approach does not preclude the requirement for soft tissue coverage to the bronchus.

8.3 Post-operative Period (3/21/13)

During the post-operative period the use of minimal IV fluids is recommended. After pneumonectomy, a strict fluid restriction of < 1500 cc/day adhered to for the first 4 days is recommended. In addition, diuretic therapy is strongly encouraged, and additional doses of Lasix are used if blood transfusions are necessary.

8.3.1 Surgical Adverse Events

All acute and late adverse events from protocol surgery will be reported and scored for severity using the revised NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 for grading all adverse events. CTCAE, v. 4.0 is identified and located on the CTEP web site at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. See Section 7.11 for Adverse Event Reporting.

8.3.2 Post-Operative Complications

Major morbidities are scored as any event occurring within 30 days following surgery. The complications of surgery will be documented on the Surgical Evaluation Form (S1) as part of the secondary objectives of this study. All patients undergoing surgical resection will be included in the analysis of surgical adverse events. Data collection also will include Surgical Operative (S2) and Surgical Pathology (S5) Reports documenting duration of surgery; estimated blood loss; blood transfusions required intra- and peri-operatively; and number of post-operative days intubated. The adverse events attributed to surgery will include any of the following complications listed below:

- **Bronchial, pleural, and lung infections**: includes pneumonia and empyema that was diagnosed during the post-operative period; specify the organism causing the infection
- **Infection** (other than pulmonary). **NOTE**: This includes wound infection of surgical incisions for thoracotomy. When there is a wound infection, specify the organism causing the infection in the space provided, and record which wound was infected.
- **Atelectasis**: includes collapse of either an entire lung or a lobe of the lung or atelectasis severe enough to require medical/operative intervention; **NOTE**: Do not include instances of incidental post-operative basilar atelectasis
- **Pneumothorax**: includes lung collapse that is due to air leakage from the lung into the pleural space; the pneumothorax must be severe enough that treatment, i.e., insertion of reinsertion of a chest tube is required
- **Bronchopleural fistula**: includes all air leaks > 5 days and bronchial stump leaks, includes any fistula that developed within the post-operative period; **NOTE**: A patient with a bronchopleural fistula associated with an intrathoracic infection should be reported as having both the intrathoracic infection and a fistula, pulmonary/upper respiratory.
- **Pleural effusion (non-malignant)**: includes any effusion within the post-operative period that requires treatment, i.e., pleural tap
- **Chylothorax**
- **Myocardial infarction, Acute coronary syndrome**: includes any myocardial infarction that occurred within the post-operative period
- **Thromboembolic event**: includes any pulmonary embolus that occurred within the post-operative period
- **Atrial fibrillation, atrial flutter**: includes any new atrial arrhythmia that developed within the post-operative period that requires treatment
- **Ventricular arrhythmia**: includes any new ventricular arrhythmia that developed within the post-operative period that requires treatment
• **Post-operative hemorrhage**: Post-operative period is defined as ≤ 72 hours after surgery; includes hemorrhage that required reoperation for control.
• **Death**: Any grade 5 adverse event occurring within 30 days of surgery, regardless of attribution
• **Other**: includes any surgical or medical complication that occurred during the post-operative period, e.g., cerebrovascular accident; specify details

### 8.4 Surgical Quality Assurance Reviews (3/21/13)

#### 8.4.1 The Thoracic Surgery Co-Chair, Jessica Donington, MD, will perform a Surgical Quality Assurance Review of all patients who complete neoadjuvant therapy and proceed to surgical reassessment and resection in this trial. The goal of the review is to evaluate protocol compliance related to staging prior to induction therapy, indications for non-resection, adherence to time line for resection, compliance with use of soft tissue coverage and completeness of mediastinal node dissection. The review process is contingent on timely submission of treatment data as specified in Section 12.1. The scoring mechanism is: Per Protocol/Acceptable Variation, Not Per Protocol, and Not Evaluable. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

#### 8.4.2 Dr. Donington will perform a Quality Assurance Review on each case after complete data for has been received at NRG Oncology for that case.

#### 8.4.3 Goals of Surgical Quality Assurance

- To assure eligibility and correct surgical staging of patients prior to Induction Therapy;
- To assure safety of patients undergoing resection after Induction Therapy;
- To assure adequate resection of primary and lymph node dissection after Induction Therapy.

#### 8.4.4 Surgical Protocol Compliance Criteria (6/24/11)

- **Deviations Minor**: Surgical resection outside the defined window (unless prior approval from the Thoracic Surgery Co-Chair was obtained);
- **Deviations Unacceptable**: Those deviations that affect patient safety/outcome, which will result in an institution being suspended from further participation in the study, such as:
  - Inadequate nodal dissection and/or numbering at thoracotomy;
  - No documentation of post neoadjuvant/pre-operative PFTs or evidence of calculated post-resection FEV 1 < 800 cc;
  - Inadequate assessment of pathologic evidence of mediastinal nodal involvement or documentation of decline in medical condition which precludes resection prior to initiation of Consolidation Chemotherapy.
  - Noncompliance with soft tissue coverage to bronchial stump

### 9.0 OTHER THERAPY

#### 9.1 Permitted Supportive Therapy

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

#### 9.2 Non-permitted Supportive Therapy

Agents not approved by the U.S. FDA as pharmaceuticals are discouraged (i.e., so called “nutracitcals” etc.) given the potential for drug interactions. Any use should be recorded. Use by a patient will not constitute a study violation, but it should be documented that the patient was advised regarding possible harm.

### 10.0 TISSUE/SPECIMEN SUBMISSION

For patients who have consented to participate in the tissue/blood component of the study (See the informed consent form). **NOTE: Patients must be offered the opportunity to participate in the correlative components of the study, such as tissue/specimen submission.** If the patient consents to participate in the tissue/specimen component of the study, the site is required to submit the patient’s specimens as specified below. Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent.

#### 10.1 Tissue/Specimen Submission

The NRG Oncology Biospecimen Bank at the University of California San Francisco acquires and maintains high quality specimens from NRG Oncology trials. Tissue from each block is preserved through
careful block storage and processing. NRG Oncology encourages participants in protocol studies to consent to the banking of their tissue. The NRG Oncology Biospecimen Bank provides tissue specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions.

In this study, it is strongly encouraged that tumor tissue, blood (serum/plasma/lymphocytes), and urine be submitted to the NRG Oncology Biospecimen Bank for the purpose of tissue banking and translational research. EGFR represents one of the most promising biomarkers studied to date with regard to clinical outcome in cancer. The tissue submitted will be tested for evidence of EGFR expression and other biomarkers in an effort to expand and refine investigation of EGFR relationship to clinical outcome. This may lead to identification of promising similar or new biomarkers with the goals of 1) identifying factors predictive of outcome such that patients may be better stratified in future trials; and 2) developing novel treatment strategies which target the molecular abnormalities identified. In this particular trial, specific information regarding any correlation between various forms of the EGFR (along with several related markers, such as TGF-alpha, IL1) as well as other biomarkers such as MALDI proteomic, osteopontin and circulating microRNA will be collected as will clinical outcome in patients receiving an EGFR inhibitory agent.

Institutions will submit the following specimens for each patient:
1. A specimen of the primary tumor at the time of diagnosis (before any treatment);
2. If available, a sample specimen of the documented involved mediastinal node at the time of diagnosis (before any treatment);
3. A sample specimen of the primary tumor at the time of surgical resection (after concurrent chemoradiation +/- panitumumab).
4. Blood and urine will be collected at 4 time points: pre-treatment, at reassessment, prior to and after consolidation treatment.

10.2 (11/26/13) Tissue Collection for Banking and Translational Research (Highly recommended but not required)
The following must be provided in order for the case to be evaluable for the Biospecimen Bank:

10.2.1 One H&E stained slide (slide can be a duplicate cut stained H&E of the diagnostic slide (block); it does not have to be the diagnostic slide itself)
10.2.2 A corresponding paraffin-embedded tissue block of the tumor (the block must match the H&E being submitted) or a 2 mm diameter core of tumor tissue, punched from the tissue block containing the tumor with a skin punch and submitted in a plastic tube labeled with the surgical pathology number. NOTE: A kit with the punch, tube, and instructions can be obtained free of charge from the Biospecimen Resource (see Appendix V). Block or core must be clearly labeled with the pathology identification number and block number that corresponds to the Pathology Report.
- The submitted material must be from malignant tumor, not necrotic or fibrotic tissue. If the submitted material is reviewed and is not tumor, the site may be assessed a protocol violation.
10.2.3 A Pathology Report documenting that the submitted block or core contains tumor. The report must include the NRG Oncology protocol number and patient’s case number. The patient’s name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.
10.2.4 A Specimen Transmittal (ST) Form clearly stating that tissue is being submitted for the NRG Oncology Biospecimen Bank; if for translational research, this should be stated on the form. The form must include the NRG Oncology protocol number and patient’s case number.

10.3 Serum, Plasma, and Lymphocyte Collection for Translational Research (Highly recommended but not required) [6/24/11]

See Appendix V for blood collection kit and detailed collection instructions.

10.3.6 Storage of Blood Specimens
Store at –80°C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:
- Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday).

OR:
- Samples can be stored in plenty of dry ice for up to one week, replenishing daily (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

OR:
• Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only Canada: Monday-Tuesday).

Please indicate on the ST Form the storage conditions used and time stored.

10.4 **Urine Collection for Translational Research** (Highly recommended but not required) [6/24/11]
See Appendix V for detailed collection instructions.

10.5 **Documentation for Submission of Serum, Plasma, Lymphocytes, and Urine**
The following materials must be provided to the NRG Oncology Biospecimen Bank: A Specimen Transmittal Form documenting the date of collection of the serum, plasma, lymphocytes, and urine; the NRG Oncology protocol number; the patient’s case number; and method of storage (e.g., stored at -80°C), must be included.

10.6 **Specimen Collection Summary (11/26/13)**

<table>
<thead>
<tr>
<th>Specimens for Tissue Banking and Translational Research</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specimens taken from patient:</td>
</tr>
<tr>
<td>--------------------------------------------------------</td>
</tr>
<tr>
<td>Representative H&amp;E stained slides of the primary tumor</td>
</tr>
<tr>
<td>A paraffin-embedded tissue block of the primary tumor taken before initiation of treatment or a 2 mm diameter core of tissue, punched from the tissue block with a punch tool</td>
</tr>
<tr>
<td>SERUM: 5-10 mL of whole blood in 1 red-top tube and centrifuge</td>
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<tr>
<td>PLASMA: 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/lavender top) and centrifuge</td>
</tr>
<tr>
<td>DNA: 5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/lavender top) and mix</td>
</tr>
<tr>
<td>10-20 mL clean-catch urine</td>
</tr>
</tbody>
</table>

10.7 **Submit materials for Tissue Banking and Translational Research as follows:** (11/26/13)

**U.S. Postal Service Mailing Address:** For Non-frozen Specimens Only
NRG Oncology Biospecimen Bank
University of California San Francisco
Campus Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

**Courier Address (FedEx, UPS, etc.):** For Trackable FFPE and All Frozen Specimens
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115
10.8 Reimbursement (10/9/14)
Please note that with the start of the NCI National Clinical Trials Network (NCTN) Program, NCI funds for reimbursement for protocol-specified biospecimen materials will be distributed per the requirements/methods specified by the new NCTN Program. This information will be made available with the other registration materials in the Oncology Patient Enrollment Network (OPEN) portal system. OPEN will serve as the registration system for all patient enrollments onto NCI-sponsored NCTN trials, including this study, which will be transitioned into the new Program from the NCI-sponsored Cooperative Group Clinical Trials Program.

10.9 Confidentiality/Storage (2/9/12)

10.9.1 Upon receipt, the specimen is labeled with the NRG Oncology protocol number and the patient’s case number only. The NRG Oncology Biospecimen 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.

10.9.2 Specimens for tissue banking will be stored for an indefinite period of time. Specimens for the translational research component of this protocol will be retained until the study is terminated, unless the patient has consented to storage for future studies. 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: (8/16/12) See Appendix I for a summary of assessments. See details and exceptions in Sections 11.1.1-11.1.6 below:

11.1.1 The pre-treatment history/physical should include a neurological assessment, documentation of the patient’s usual weight and any recent weight loss, and documentation of concurrent non-malignant disease and therapy. A whole body FDG-CT-PET scan within 6 weeks of registration will satisfy the required pre-treatment CT scan with contrast of the lungs and upper abdomen (see Section 3.1.5). PET/CT DICOM images, diagnostic reports, and assessment forms must be submitted as described in Section 12.1.

11.1.2 Mediastinal staging must be confirmed by one of the following:
- mediastinoscopy;
- mediastinotomy (Chamberlain procedure);
- transesophageal needle biopsy using endoscopic ultrasound (EUS-TBNA);
- endobronchial ultrasound biopsy using endoscopic ultrasound guidance (EBUS-TBNA);
- thoracotomy;
- video-assisted thoracoscopy;
- transbronchial needle biopsy by Wang technique (TBNA);
- fine needle aspiration under CT guidance.

11.1.3 At the reassessment (4 weeks following completion of induction chemoradiation and within 2 weeks of anticipated surgery) [see Sections 8.1.2 through 8.1.5 for details]:
- History and physical, evaluation by thoracic surgeon, EKG, and pulmonary function tests with diffusion capacity;
- Repeat lab evaluations for bone marrow and hepatic function (repetition of the creatinine clearance is not necessary);
- Chest and upper abdominal CT scan to include entire liver; note: a whole body FDG-PET/CT scan will satisfy this requirement.
- A brain MRI with contrast;
- The PET/CT scan at reassessment is recommended but not required (the pre-treatment PET/CT scan is required; see Section 3.1.5). The reassessment PET/CT scan should ideally be performed at the same facility as the pre-treatment PET/CT scan so that the
data can be used for analysis of the secondary objective (Section 2.2.7). Note: To be included in this analysis, the patient’s PET/CT studies must be performed with a dedicated BGO, LSO, or GSO PET or PET/CT scanner. PET scanners with sodium iodide (NaI) detectors are not acceptable. PET/CT DICOM images, diagnostic reports, and assessment forms must be submitted as described in Section 12.1.

- A bone scan is not required unless there is new bone pain or new elevation of the alkaline phosphatase or LDH.
- The bronchoscopy should be repeated at the discretion of the operating surgeon. It is recommended is a pretreatment bronchoscopy demonstrated disease close to the carina or in a position where small amounts of progression which may not be well assessed by CT scan may make the patient unresectable.

11.1.4 In follow-up visits, an EKG, pulmonary function tests, and a PET/CT scan should be done at the discretion of the treating physician.

11.1.5 If the patient consents, tumor tissue will be collected in the pre-treatment biopsy/aspiration and in surgery. Blood and urine will be collected at 4 time points: pre-treatment, at reassessment, prior to and after consolidation treatment.

11.2 Measurement of Response: Radiologic, Pathologic, and Extent of Resection (11/26/13)
Response will be evaluated in this study using the revised RECIST guideline, v. 1.1 [European Journal of Cancer. 45: 228-247, 2009] will be used as a guideline to determine study eligibility. See http://ctep.cancer.gov/protocolDevelopment/docs/recist_guideline.pdf for further details.

11.2.1 Radiographic Response
Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.

- Measurable lesions
  Tumour lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
  - 10 mm by CT scan (CT scan slice thickness no greater than 5 mm; see Appendix II of the RECIST guideline, v1.1 on imaging guidance).
  - 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
  - 20 mm by chest X-ray.
  Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

- Non-measurable lesions – All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with ≥10 to <15mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special considerations regarding lesion measurability
Bone lesions:
- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.
Cystic lesions:
- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- ‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Response Criteria: Evaluation of target lesions

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

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

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

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.2 Criteria for Pathologic Response of Target Lesions
- **Pathologic Complete Response** (PCR): Complete resection (R0 resection) achieved and no evidence of viable tumor in the entire resection specimen;
- **Mediastinal Pathologic Complete Response** (MCR): Complete resection achieved with no evidence of residual viable tumor in the mediastinal lymph nodes, regardless of the primary tumor status;
- **Progressive Disease** (PD): New sites of disease identified pathologically (e.g., malignant pleural studding, multiple pulmonary metastases, etc.);
- **Stable Disease** (SD): Not meeting the criteria of any of the three categories above.

11.2.3 Extent of Surgical Resection
- **R0**: Complete resection of all disease with negative margins and the highest lymph node resected negative for residual tumor;
- **R1**: Complete resection of all gross disease with pathologically positive margins and/or pathologic evidence of tumor cells in the highest lymph node resected in the mediastinum and/or extracapsular nodal spread;
- **R2**: Gross residual disease left behind after surgical resection.

11.3 Criteria for Discontinuation of Protocol Treatment
Protocol treatment may be discontinued for any of the following reasons:
- Progression of disease (further treatment will be at the discretion of the treating physician);
- Pregnancy;
- Any clinical adverse event, laboratory abnormality, or intercurrent illness that, in the opinion of the Investigator, indicates that continued treatment with all study therapy is not in the best interest of the patient;
- A delay in protocol treatment of greater than 15 days during induction treatment and more than 4 weeks during the consolidation treatment.

If protocol treatment is discontinued for any reason, follow up and data collection will continue as specified in the protocol.
12.0 DATA COLLECTION
Data should be submitted to:

NRG Oncology*
1818 Market Street, Suite 1600
Philadelphia, PA 19103

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

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

12.1 Summary of Data Submission (11/26/13)

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 2 weeks of registration</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td></td>
</tr>
<tr>
<td>Pathology Report (P1)</td>
<td></td>
</tr>
<tr>
<td>Slides/Blocks (P2)</td>
<td></td>
</tr>
<tr>
<td>Pre-Treatment PET/CT Scan and Report (MR,ME)</td>
<td>Within 2 weeks of study entry</td>
</tr>
<tr>
<td>Scans must be submitted via TRIAD in DICOM format</td>
<td></td>
</tr>
<tr>
<td>PET/CT Assessment Form (IM)</td>
<td></td>
</tr>
<tr>
<td>PET/CT Technical Assessment Form (TA)</td>
<td></td>
</tr>
<tr>
<td>Induction XRT/Chemo +/- Panitumab Treatment Form (TF)</td>
<td>Within 1 week of end of induction XRT/chemo +/- panitumab treatment</td>
</tr>
<tr>
<td>Post-Induction Evaluation Form (FS)</td>
<td>Within 1 week of reassessment after completion of induction XRT/chemo +/- panitumab</td>
</tr>
<tr>
<td>Surgical Form (S1)</td>
<td>Within 4 weeks after protocol surgery</td>
</tr>
<tr>
<td>Surgical Procedure Report (S2)</td>
<td></td>
</tr>
<tr>
<td>Surgical Pathology Report (S5)</td>
<td></td>
</tr>
<tr>
<td>Consolidation Chemo Treatment Form (SF)</td>
<td>Within 1 week of end of consolidation chemo treatment</td>
</tr>
<tr>
<td>Radiotherapy Form (T1)</td>
<td>Within 1 week of the end of RT</td>
</tr>
<tr>
<td>Complete Daily Treatment Record (T5)</td>
<td></td>
</tr>
<tr>
<td>Post-RT PET/CT Scan and Report (MR,ME)</td>
<td>Within 12 weeks of study entry</td>
</tr>
<tr>
<td>Scans must be submitted via TRIAD in DICOM format</td>
<td>See Section 8.1.3</td>
</tr>
<tr>
<td>Post RT PET/CT Assessment Form (IM)</td>
<td></td>
</tr>
<tr>
<td>Post RT PET/CT Technical Assessment Form (TA)</td>
<td></td>
</tr>
<tr>
<td>Follow-up Form (F1)</td>
<td>At 6, 9, and 12 months from start of treatment for 1 year, then every 6 months for years 2-3, then annually</td>
</tr>
</tbody>
</table>
12.2 Summary of Dosimetry Digital Data Submission (Submit to TRIAD; see Section 5.0 for account access and installation instructions) (10/9/14)

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preliminary Dosimetry Information (DD)</td>
<td>Within 1 week of start of RT</td>
</tr>
</tbody>
</table>

**ALL DIGITAL DATA MUST BE IN DICOM FORMAT**

Digital Data Submission – Treatment Plan submitted to RTOG via TRIAD account exported from treatment planning machine by TRIAD user

Digital data submission includes the following:

- CT data, critical normal structures, all GTV, CTV or ITV, and PTV contours (CT File, RT Structure File)
- All required structures **MUST** be labeled per the table in Section 6.6 or resubmission may be required.
- Digital beam geometry (RT Plan File)
- Doses (RT Dose File)
- Digital DVH data for all required critical normal structures, GTV, CTV or ITV, and PTVs for total dose plan

Upon submission of all digital data via TRIAD, complete a new online digital data transmission form (DDSI) located in the Core Lab section on the RTOG/NRG Oncology web site at [http://www.rtog.org/LinkClick.aspx?fileticket=0-PuBILfs4Q%3d&tabid=399](http://www.rtog.org/LinkClick.aspx?fileticket=0-PuBILfs4Q%3d&tabid=399)

**Final Dosimetry Information**

Radiotherapy Form (T1) [web data entry]

Daily Treatment Record (T5) [copy to HQ]

Upon submission of all digital data via TRIAD, complete an online digital data transmission form (DDSI) located in the Forms section on the RTOG/NRG Oncology web site at [http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0839](http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0839)

**NOTE:** ALL SIMULATION AND PORTAL IMAGES WILL BE KEPT BY THE INSTITUTION AND ONLY SUBMITTED IF REQUESTED.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Primary Objective

Mediastinal nodal clearance following completion of induction chemoradiation +/- panitumumab

13.1.2 Secondary Objectives

- Overall survival;
- Patterns of first failure;
- Acute and late adverse events;
- Surgical morbidities among resectable patients at reassessment;
- Correlation between biomarkers (including at least EGFR and ras mutation status) in pre- and post-therapy and outcomes (mediastinal nodal clearance and overall survival);
- Evaluation of the prognostic value of plasma osteopontin and MicroRNA for overall survival;
- Assess the ability of PET/CT scan data to predict outcome;
- Estimation of response rate.

13.2 Sample Size

The primary endpoint of this study is the rate of mediastinal nodal clearance (p) as the proportion of patients who have a mediastinal nodal clearance following completion of induction chemoradiation +/- panitumumab among all eligible patients. Assessment of mediastinal clearance will occur either prior to or at the time of planned definitive surgery. RTOG 0229 met its accrual objective and closed on November 19, 2008. At the time of the interim analysis, the study met the predefined goal of >50% mediastinal sterilization. As of December 9, 2008, the preliminary results of RTOG 0229 shows a 52% rate of...
mediastinal sterilization. We hypothesize that the experimental treatment of this study, carboplatin/taxol in combination with panitumumab, will improve the rate of mediastinal sterilization by 20% over the rate of RTOG 0229 (odds ratio of 2.374).

This study is a Phase II screening study (Rubinstein 2005) in which preliminary and non-definitive randomized comparisons of Arm 2 (experimental treatment arm) to Arm 1 (standard treatment arm) are made. This design allows assessment of whether the experimental Arm 2 is more promising than Arm 1. The unbalanced randomization method is applied (Machin and Campbell 1987), specifically 2 to 1 for Arm 2 vs. Arm 1. The purpose of Arm 1 is to ensure that the adverse events of Arm 1 are similar to those of RTOG 0229 and also to have control samples (i.e., patients not treated with the EGFR inhibitor) for the proteomic and other studies.

The sample size is calculated with a 1-sided significance level of 0.15 (the probability of false positive) and 80% statistical power (the probability of a false-negative result is 0.2) with one interim analysis using East software for a two-sample test for odds ratio of proportions with a 1-sided test. The null hypothesis \( H_0 \) is that that the experimental treatment is not effective versus the alternative hypothesis \( H_A \) that the experimental treatment is effective. The hypotheses are:

\[
H_0: \text{OR} \leq 1 \quad \text{vs.} \quad H_A: \text{OR} > 1
\]

where, odds ratio (OR) = \([p_2(1-p_1)]/[p_1(1-p_2)]\), \( p_1 \) denotes the mediastinal clearance rate in Arm 1 and \( p_2 \) denotes the mediastinal clearance rate in Arm 2.

Ninety-two patients are required, 61 for Arm 2 and 31 for Arm 1. This gives an actual statistical power of 78.7%. Adjusting the number of cases for ineligible patients or those who do not start protocol treatment by 5% for each arm, a maximum of 97 patients, 64 for Arm 2 and 33 for Arm 1, is required for this trial.

13.3 Patient Accrual

Based upon patient accrual in previous RTOG NSCLC studies, there will be negligible accrual during the initial 6 months while institutions are obtaining IRB approval. The patient accrual is projected to be 3 patients per month considering the previous RTOG NSCLC studies and the anticipated number of participating institutions. We expect to complete accrual in 3.1 years.

13.4 Analysis Plan

13.4.1 Primary Endpoint

We hypothesize at least 72% of patients will have a mediastinal clearance with the experimental treatment (Arm 2). The rate of a mediastinal clearance, rate \( p \), will be calculated as the number of patients who have a mediastinal clearance by the total number of analyzable patients at 4 weeks following completion of induction chemoradiation +/- panitumumab and within 2 weeks prior to anticipated surgery in each arm. Patients who do not undergo mediastinal assessment will not be considered as having a mediastinal clearance. Analyzable patients are defined as eligible patients who received any protocol treatment. The test will be calculated by the two-sample test statistics for odds ratio of proportions at the significance level of 0.15.

The results from phase II screening trials are not definitive. However, we will consider the results from this trial as convincing if the \( p \)-value is less than 0.005. If this level of evidence favoring a beneficial effect for the experimental treatment is absent, a phase III study should be considered in order to reliably define the treatment’s contribution to the therapy.

Group Sequential Testing for Early Termination and Reporting of Efficacy and Futility

A group sequential test with one planned interim analysis and a final analysis will be performed. The interim analysis will be carried out when the cumulative accrual is met. At the planned interim analysis, the \( p \)-value from the two-sample test for the odds ratio of proportion assessing treatment efficacy and futility with respect to the primary endpoint, the rate of a mediastinal clearance, will be compared to the nominal significance level. The efficacy testing is based on the power family of test (Pampallona 1994) with \( \Delta=0 \) (see table below for nominal significance level for efficacy testing) and for the futility testing boundary, a less aggressive boundary, Rule C (at a nominal significance level of 0.005) will be used (Freidlin 2005). The following hypotheses are tested:

\[
H_0: \text{OR} \leq 1 \quad \text{vs.} \quad H_A: \text{OR} > 1
\]

where, odds ratio (OR) = \([p_2(1-p_1)]/[p_1(1-p_2)]\), \( p_1 \) denotes the mediastinal clearance rate in Arm 1 and \( p_2 \) denotes the mediastinal clearance rate in Arm 2. If the \( H_0 \) is rejected, then
we will conclude that the mediastinal clearance rate of Arm 2 is better than Arm 1, and accrual will be stopped, if applicable.

### Schedule for the Planned Interim Analysis

<table>
<thead>
<tr>
<th>Information Time</th>
<th>Estimated Analysis Time*</th>
<th>Cumulative Number of Patients in the 2 Arms</th>
<th>Nominal Significance Level for Efficacy (Z-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>1.9 years</td>
<td>46</td>
<td>0.056 (1.59)</td>
</tr>
<tr>
<td>1.00</td>
<td>3.9 years</td>
<td>92</td>
<td>0.15 (1.12)</td>
</tr>
</tbody>
</table>

* Time to the analysis is from the first patient entry without considering ineligibility or lack-of-data rate and under the null hypothesis.

For futility testing, the alternative hypotheses, HA (OR =2.374) will be tested at 0.005 level (the futility nominal significance level). If the computed p-value is less than 0.005, then stopping the trial will be considered in favor of the H0, and we will conclude that the mediastinal clearance rate of Arm 2 is not better than Arm 1. Otherwise, the trial will continue.

If a grade 5 adverse event definitely, probably or possibly related to treatment is reported during the protocol treatment, it will be reviewed by the study chairs, the study statistician, the RTOG Lung Cancer Committee chair, and the RTOG Executive Committee. Case report forms (CRFs), source documentation, and a statistical report summarizing the study data will be reviewed as soon as possible. During this review, accrual will be suspended (if applicable). Following this review, the study chairs, the study statistician, the RTOG Lung Cancer Committee chair, and the RTOG Executive Committee will discuss the findings and make a decision about amending and/or continuing the study.

Multivariate logistic regression (Agresti 1990) will be used to model the association of factors with the occurrence of a mediastinal clearance. Both unadjusted and adjusted odds ratios and the respective 95% confidence interval will be computed. Appropriate covariates, such as age or race (or other factors as appropriate) will be adjusted for in this analysis.

### Interim Analysis for Unacceptable Adverse Events in Arm 2

Adverse events will be evaluated using the Common Terminology Criteria for Adverse Events (CTCAE), v. 4.0. One interim analysis for unacceptable treatment-related adverse events (AEs) is planned after 15% (10 patients) of analyzable patients in Arm 2 have been accrued and followed for at least 30 days from the end of induction chemoradiation and panitumumab. A treatment-related AE is defined as any adverse event with an attribution of possibly, probably, or definitely related to treatment.

The rate of grade 3 or worse AEs will be calculated as the proportion of patients among the 10 analyzable patients in Arm 2 who have a grade 3 or worse AE by 30 days from the end of induction chemoradiation and panitumumab. We expect at most a 65% rate of grade 3 or worse treatment-related non-hematologic AEs in Arm 2 of this study based on data from RTOG 0229, and so we will consider a 75% or higher rate of grade 3 or worse treatment-related non-hematologic AEs in Arm 2 to be too excessive. For these 10 patients, in the time period described above, there will be a real-time, independent review of all treatment-related grade 3 or worse non-hematologic AEs so that the rate will be evaluated on an ongoing basis, starting with a minimum of 3 patients. If this occurs, the study chairs, RTOG Lung Cancer Committee Chair, and the statistician will review the AE data and make appropriate recommendations to the RTOG Executive Committee and Research Strategy Committee about the study. Also, if 2 or more treatment-related grade 5 AEs occur in Arm 1 or 4 or more treatment-related grade 5 AEs occur in Arm 2, then the study will be closed to accrual (if it is applicable), and the above action will be followed.

### 13.4.2 Secondary Endpoints

#### Overall Survival

The time to overall mortality will be measured from the date of randomization to the date of death due to any cause. The time-to-event distribution of overall mortality will be estimated using the Kaplan-Meier method (1958). The Cox proportional hazards regression (1972) will
be used to adjust for the possibly important covariates as age or race (and other factors as appropriate).

Patterns of First Failure
The failure events for progressive disease (PD), marginal failure (MF), regional failure (RF) and distant metastases (DM) are defined in Section 11.2. The first failure event of these secondary endpoints (LP, RF, and DM) will be tabulated by failure sites and failure event. The time to failure for these secondary endpoints (LP, RF, and DM) also will be measured from the date of randomization to the date of the failure event.

The cumulative incidence method (Gray 1988) will be used to estimate the rates of each endpoint. The treatment effect on these failures may impact the observable measures of outcomes, and other competing risks may dilute the sensitivity. Therefore, Fine and Gray's proportional hazards regression (1999) will be used to adjust for covariates, such as age or race (or other factors as appropriate).

Acute and Late Adverse Events
Adverse events are evaluated by the NCI Common Terminology Criteria for Adverse Event (CTCAE), v. 4.0. An acute adverse event is defined as any grade 3 or worse toxicity occurring during protocol treatment and within 30 days from the end of protocol treatment that is possibly, probably, or definitely related to treatment. A late adverse event is defined as any grade 3 or worse toxicity after 30 days from the end of protocol treatment that is possibly, probably, or definitely related to treatment.

Acute and late adverse events in each arm will be tabulated by type, grade, and attribution of adverse event. Multivariate logistic regression (Agresti 1990) will be used to model the distribution of acute treatment-related adverse events by arm. Both unadjusted and adjusted odds ratios and the respective 95% confidence interval will be computed. Appropriate covariates, such as age or race (or other factors as appropriate) will be adjusted for in this analysis.

Surgical Morbidities Among Resectable Patients at Reassessment
Patients will be reassessed to determine whether they remain surgical candidates after completion of chemoradiotherapy and panitumumab. If the patient is felt to be resectable, then surgery will be performed within 4-6 weeks of completion of chemoradiotherapy and panitumumab. The rate of surgical morbidities which occur within 30 days of surgery and are associated with surgical resection will be monitored in those patients undergoing resection. Major morbidities are scored as any adverse event greater than grade 1 from the list in Section 8.3.2. If the rate of major morbidities within the first 30 postoperative days is estimated to be greater than 40% at any time (a minimum of 8 resected patients), the study chairs, the RTOG Lung Cancer Committee Chair, and if appropriate, the RTOG Executive Committee will be notified. The study results will be reviewed and a determination made about continuing the study.

Correlation Between Biomarkers in Pre- and Post-Therapy and Outcomes
At the time of data maturity of this study, we will propose specific details of the markers (at least EGFR and ras mutation status) to be investigated. We will address the assays that will be used at the time of analysis because there might be a more advanced technology available. However, at this time, IHC and FISH are being considered. The following is a general guideline for the statistical consideration for this analysis.

A biomarker will be categorized into two subgroups based upon previously defined (or hypothesized) cut-off points and these two groups will be referred to as favorable and unfavorable risk groups. The patients with biomarkers will be compared with the patients without a value for that biomarker to determine if there are any differences with respect to distribution of important baseline variables (e.g., age). We want to know if there is a difference in mediastinal nodal clearance rate and overall survival rate between these two groups. Tests will be performed to see if one group is statistically significantly better than the other in mediastinal nodal clearance rate and overall survival rate. However, the selection of the cut-off point for each biomarker is not established. If the hypothesized cut-off points do not yield statistical significance, other cut-off points may be evaluated. Therefore, various cut-off points are evaluated for their statistical significance. To correct the problem from the multiple testing, the Bonferroni correction will be used. Two-sample t-test will be used to test
the mediastinal nodal clearance rates of the two groups. Multivariate logistic regression will be used to model the association of factors with the occurrence of a mediastinal nodal clearance. Appropriate covariates, such as age or race (other factors as appropriate) will be adjusted for in this analysis. The overall survival functions will be estimated by the Kaplan-Meier method and will be tested for the overall survival difference between the favorable and unfavorable groups using the log-rank test. The multivariate analysis will be performed using the Cox proportional hazards model for both groups. A stepwise procedure will be used to develop the base model for each outcome endpoint prior to evaluating the prognostic impact of the biomarkers. This approach will be employed to account for as much variation as possible for each outcome before it is tested. It is entirely possible that factors shown to be prognostic in other published series may not be found prognostic here.

Estimation of Response Rate
The response rate will be calculated as the number of patients who have a complete response or partia response (see section 11.2) divided by the total number of analyzable patients at completion of induction chemoradiation +/- panitumumab and prior to anticipated surgery in each arm. Analyzable patients are defined as eligible patients who received any protocol treatment.
13.4.3 Interim Reports
Interim reports will be prepared every 6 months until the final analysis. In general, the interim reports will include information about:
- Patient accrual rate with projected completion date;
- Pretreatment characteristics of patients accrued;
- The frequencies and grade of adverse events due to protocol treatment.

13.4.4 Data Safety Monitoring Board Review
To monitor the safety of this study, the NRG Oncology Data Safety Monitoring Board (DSMB) will officially review this study twice per year in conjunction with the NRG Oncology semi-annual meeting and on an “as needed” basis in between meetings.

13.4.5 CDUS Reporting
This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

13.5 Gender and Minorities
In conformance with the National Institute of Health Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we also have considered the possible interaction between race and treatments. 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 (Graham 1992). Furthermore, an analysis of race did not indicate an association with outcome (Scott 1997). The projected gender and minority accruals are provided in table below.

### Projected Distribution of Gender and Minorities

<table>
<thead>
<tr>
<th>Ethnic Category</th>
<th>Females</th>
<th>Males</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hispanic or Latino</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>40</td>
<td>52</td>
<td>92</td>
</tr>
<tr>
<td><strong>Ethnic Category: Total of all subjects</strong></td>
<td>42</td>
<td>55</td>
<td>97</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Racial Category</th>
<th>Females</th>
<th>Males</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Indian or Alaskan Native</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Asian</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Black or African American</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>White</td>
<td>37</td>
<td>47</td>
<td>84</td>
</tr>
<tr>
<td><strong>Racial Category: Total of all subjects</strong></td>
<td>42</td>
<td>55</td>
<td>97</td>
</tr>
</tbody>
</table>
REFERENCES


REFERENCES (Continued) [3/21/13]


REFERENCES (Continued)


Mitchell EP, LaCouture ME, Shearer H, et al. Updated results from of STEPP, a phase 2, open-label study of preemptive versus reactive skin toxicity treatment in metastatic colorectal cancer (mCRC) patients receiving panitumumab + FOLFIRI or irinotecan-only chemotherapy as second-line treatment. World GI. 2008.


REFERENCES (Continued) (2/9/12)


<table>
<thead>
<tr>
<th>Assessments</th>
<th>Pre-Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pathological proof of tumor:</strong> biopsy, needle aspiration, or sputum</td>
<td>Within 12 weeks</td>
</tr>
<tr>
<td>Mediastinal staging* (node biopsy; see Section 3.1.3)</td>
<td>Within 12 weeks</td>
</tr>
<tr>
<td>History/physical*</td>
<td>Within 8 weeks</td>
</tr>
<tr>
<td>Zubrod</td>
<td></td>
</tr>
<tr>
<td>EKG</td>
<td></td>
</tr>
<tr>
<td>FVC, FEV-1, DLCO</td>
<td></td>
</tr>
<tr>
<td>Thoracic surgeon evaluation</td>
<td>Within 4 weeks</td>
</tr>
<tr>
<td>Tumor location, type, and size</td>
<td>Within 6 weeks</td>
</tr>
<tr>
<td>Whole body FDG-PET or PET/CT</td>
<td>Within 6 weeks</td>
</tr>
<tr>
<td>MRI or CT with contrast (or *PET/CT) of Brain</td>
<td>Within 5 weeks</td>
</tr>
<tr>
<td>CT scan (or *PET/CT) with contrast of lungs &amp; upper abdomen +/- optional chest x-ray</td>
<td>Within 5 weeks</td>
</tr>
<tr>
<td>CBC w/ diff &amp; platelets</td>
<td>Within 2 weeks</td>
</tr>
<tr>
<td>Total bilirubin, ALT, AST, alk phos, creatinine clearance, serum albumin, Mg++</td>
<td>Within 2 weeks</td>
</tr>
<tr>
<td>Serum pregnancy test (if applicable)</td>
<td>Within 2 weeks</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>Recommended, not required</td>
</tr>
<tr>
<td>Lung ventilation/perfusion scan</td>
<td></td>
</tr>
<tr>
<td>Nutrition consult</td>
<td></td>
</tr>
<tr>
<td>*Tissue for banking &amp; translational research (if patient consents)</td>
<td>X</td>
</tr>
<tr>
<td>Blood and urine for translational research (if patient consents)</td>
<td>X</td>
</tr>
<tr>
<td>Assessments</td>
<td>During Treatment</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Pathological proof of tumor: biopsy, needle aspiration, or sputum</td>
<td></td>
</tr>
<tr>
<td>Mediastinal staging* (node biopsy; see Section 3.1.3)</td>
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</tr>
<tr>
<td>History/physical*</td>
<td></td>
</tr>
<tr>
<td>Zubrod</td>
<td>Weekly</td>
</tr>
<tr>
<td>EKG</td>
<td>X</td>
</tr>
<tr>
<td>FVC, FEV-1, DLCO</td>
<td>X</td>
</tr>
<tr>
<td>Thoracic surgeon evaluation</td>
<td>X</td>
</tr>
<tr>
<td>Whole body FDG-PET or PET/CT</td>
<td>X*</td>
</tr>
<tr>
<td>MRI or CT with contrast (or PET/CT) of Brain</td>
<td></td>
</tr>
<tr>
<td>CT scan (or PET/CT) with contrast of lungs &amp; upper abdomen +/- optional chest x-ray</td>
<td></td>
</tr>
<tr>
<td>Bone scan</td>
<td></td>
</tr>
<tr>
<td>CBC w/ diff &amp; platelets</td>
<td>Weekly</td>
</tr>
<tr>
<td>Total bilirubin, ALT, AST, alk phos, creatinine clearance, serum albumin, Mg++</td>
<td>Weekly renal function</td>
</tr>
<tr>
<td>Toxicity Assessment</td>
<td>q 2 wks</td>
</tr>
<tr>
<td>*Tissue for banking &amp; translational research (if patient consents)</td>
<td></td>
</tr>
<tr>
<td>Blood and urine for translational research (if patient consents)</td>
<td></td>
</tr>
<tr>
<td>Assessments</td>
<td>Follow Up</td>
</tr>
<tr>
<td>-------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>History/physical*</td>
<td>X 6 wks after end of all treatment X Every 3 mos. from start of treatment (beginning with 6 mo. visit) for 1 year; every 6 mos. for years 2-3; then annually</td>
</tr>
<tr>
<td>Zubrod</td>
<td>X Every 3 mos. from start of treatment (beginning with 6 mo. visit) for 1 year; every 6 mos. for years 2-3; then annually</td>
</tr>
<tr>
<td>EKG</td>
<td>X* Every 3 mos. from start of treatment (beginning with 6 mo. visit) for 1 year; every 6 mos. for years 2-3; then annually</td>
</tr>
<tr>
<td>FVC, FEV-1, DLCO</td>
<td>X* Every 3 mos. from start of treatment (beginning with 6 mo. visit) for 1 year; every 6 mos. for years 2-3; then annually</td>
</tr>
<tr>
<td>Whole body FDG-PET or PET/CT</td>
<td>X* Every 3 mos. from start of treatment (beginning with 6 mo. visit) for 1 year; every 6 mos. for years 2-3; then annually</td>
</tr>
<tr>
<td>MRI or CT with contrast (or *PET/CT) of Brain</td>
<td>If clinically indicated Every 3 mos. from start of treatment (beginning with 6 mo. visit) for 1 year; every 6 mos. for years 2-3; then annually</td>
</tr>
<tr>
<td>CT scan (or *PET/CT) with contrast of lungs &amp; upper abdomen +/- optional chest x-ray</td>
<td>X Every 3 mos. from start of treatment (beginning with 6 mo. visit) for 1 year; every 6 mos. for years 2-3; then annually</td>
</tr>
<tr>
<td>CBC w/ diff &amp; platelets</td>
<td>X Every 3 mos. from start of treatment (beginning with 6 mo. visit) for 1 year; every 6 mos. for years 2-3; then annually</td>
</tr>
<tr>
<td>Total bilirubin, ALT, AST, alk phos, creatinine clearance, serum albumin, Mg++</td>
<td>X Every 3 mos. from start of treatment (beginning with 6 mo. visit) for 1 year; every 6 mos. for years 2-3; then annually</td>
</tr>
<tr>
<td>Toxicity Assessment</td>
<td>X Every 3 mos. from start of treatment (beginning with 6 mo. visit) for 1 year; every 6 mos. for years 2-3; then annually</td>
</tr>
</tbody>
</table>
## APPENDIX II

### 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</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work</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</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair 50% or more of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on self-care. Totally confined to bed or</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
</tr>
</tbody>
</table>
### APPENDIX III

**AJCC STAGING SYSTEM**


#### LUNG

**Primary Tumor (T)**

<table>
<thead>
<tr>
<th>Stage</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 (i.e., not in the main bronchus)*</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor 2 cm or less in greatest dimension</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor more than 2 cm but 3 cm or less in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor more than 3 cm but 7 cm or less with any of the following features (T2 tumors with these features are classified T2a if 5 cm or less): Involves main bronchus, 2 cm or more distal to the carina; Invades the visceral pleura PL1 or PL2; Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung</td>
</tr>
<tr>
<td>T2a</td>
<td>Tumor more than 3 cm but 5 cm or less in greatest dimension</td>
</tr>
<tr>
<td>T2b</td>
<td>Tumor more than 5 but 7 cm or less in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor more than 7 cm or one that directly invades any of the following: parietal (PL3), chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, 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 or separate tumor nodule(s) in the same lobe</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumor nodules in a different ipsilateral lobe</td>
</tr>
</tbody>
</table>

*The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1a.

**Regional Lymph Nodes (N)**

<table>
<thead>
<tr>
<th>Stage</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</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 in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)</td>
</tr>
</tbody>
</table>

**Distant Metastasis (M)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td>M1a</td>
<td>Separate tumor nodule(s) in a contralateral lobe tumor with pleural nodules or malignant pleural (or pericardial) effusion*</td>
</tr>
<tr>
<td>M1b</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

* Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody 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 classified as M0.
<table>
<thead>
<tr>
<th>STAGE GROUPING</th>
<th>Tumor T-Stage</th>
<th>Node N-Stage</th>
<th>Metastatic M-Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occult Carcinoma</td>
<td>TX, N0, M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 0</td>
<td>Tis, N0, M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IA</td>
<td>T1a-b, N0, M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IB</td>
<td>T2a, N0, M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T2b, N0, M0</td>
<td>T1a-b, N1, M0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>T2a, N1, M0</td>
<td></td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T2b, N1, M0</td>
<td>T3, N0, M0</td>
<td></td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T1a-b, N2, M0</td>
<td>T2a-b, N2, M0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>T3, N1-2, M0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>T4, N0-1, M0</td>
<td></td>
</tr>
<tr>
<td>Stage IIIIB</td>
<td>T1a-b, N3, M0</td>
<td>T2a-b, N3, M0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>T3, N3, M0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>T4, N2-3, M0</td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T, Any N, M1a-b</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX IV
American Thoracic Society Nodal Stations
Lymph Node Map Definitions

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

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

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

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

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

Researchers may wish to designate the lower paratracheal nodes as No. 4s (superior) and No. 4i (inferior) subsets for study purposes; the No. 4s nodes may be defined by a horizontal line extending across the trachea and drawn tangential to the cephalic border of the azygos vein; the No. 4i nodes may be defined by the lower boundary of No. 4s, as described above

5. Subaortic (aorto-pulmonary window)
   Subaortic nodes are lateral to the ligamentum arteriosum or the aorta or left pulmonary artery and proximal to the first branch of the left pulmonary artery and lie within the mediastinal pleural envelope

6. Para-aortic nodes (ascending aorta or phrenic)
   Nodes lying anterior and lateral to the ascending aorta and aortic arch or the innominate artery, beneath a line tangential to the upper margin of the aortic arch

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

8. Paraesophageal nodes (below carina)
   Nodes lying adjacent to the wall of the esophagus and to the right or left of the midline, excluding subcarinal nodes

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

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

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

11. Interlobar nodes
    Nodes lying between the lobar bronchi

12. Lobar nodes
    Nodes adjacent to the lobar bronchi

13. Segmental nodes
    Nodes adjacent to the segmental bronchi

14. Subsegmental nodes
    Nodes around the subsegmental bronchi
Shipping Instructions:
U.S. Postal Service Mailing Address: For FFPE or Non-frozen Specimens Only
NRG Oncology Biospecimen Bank
University of California San Francisco
Campus Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For All Frozen or Trackable Specimens
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

- Include all NRG Oncology paperwork in pocket of biohazard bag.
- Check that the Specimen Transmittal Form (ST) has the consent boxes checked off.
- Check that all samples are labeled with the NRG Oncology study and case number, and include date of collection as well as collection time point (e.g., pretreatment, post-treatment).

- FFPE Specimens:
  o Slides should be shipped in a plastic slide holder/slide box. Place a small wad of padding in top of the container. If you can hear the slides shaking it is likely that they will break during shipping.
  o FFPE Blocks can be wrapped with paper towel, or placed in a cardboard box with padding. Do not wrap blocks with bubble wrap or gauze. Place padding in top of container so that if you shake the container the blocks are not shaking. If you can hear the block shaking it might break during shipping.
  o Slides, Blocks, or Plugs can be shipped ambient or with a cold pack either by United States Postal Service (USPS) to the USPS address (94143) or by Courier to the Street Address (94115). Do NOT ship on Dry Ice.

- Frozen Specimens:
  o Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and clearly identified. If possible, keep serum, plasma, and whole blood in separate bags.
  o Place specimens and absorbent shipping material in Styrofoam cooler filled with dry ice (at least 7 lbs). There should be plenty of dry ice under and above the specimens. If the volume of specimens is greater than the volume of dry ice then ship in a larger Styrofoam box, or two separate boxes. Any Styrofoam box can be used, as long as it is big enough.
  o Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified.
  o Send frozen specimens on dry ice via overnight courier to the address above. Specimens should only be shipped Monday through Wednesday (Monday-Tuesday for Canada) to prevent thawing due to delivery delays. Saturday or holiday deliveries cannot be accepted. Samples can be stored frozen at -80°C until ready to ship.

- For Questions regarding collection/shipping please contact the NRG Oncology Biospecimen Bank by e-mail: RTOG@ucsf.edu or phone: 415-476-7864 or Fax: 415-476-5271.
NRG Oncology FFPE SPECIMEN PLUG KIT INSTRUCTIONS

This Kit allows sub-sampling of an FFPE block for submission to the NRG Oncology Biospecimen Bank. The plug kit contains a shipping tube and a punch tool.

**Step 1**
If the block is stored cold, allow it to equilibrate for 30 minutes at room temperature. Place the punch tool on the paraffin block over the selected tumor area. (Ask a pathologist to select area with tumor.) Push the punch into the paraffin block. Twist the punch tool once around to separate the plug from the block. Then pull the punch tool out of the block. The punch should be filled with tissue sample.

**Step 2**
Label the punch tool with the proper specimen ID. DON’T remove specimen from the punch.

Use a separate punch tool for every specimen. Call or e-mail us if you have any questions or need additional specimen plug kits.

**Step 3**
Once punch tool is labeled, place in shipping tube and mail to address below. Please do not mix specimens in the same tube.

We will remove core specimen from the punch, embed in a paraffin block, and label with specimen ID.

*NOTE:* If your facility is uncomfortable obtaining the plug but wants to retain the tissue block, please send the entire block to the NRG Oncology Biospecimen Bank and we will sample a plug from the block and return the remaining block to your facility. Please indicate on the submission form the request to perform the plug procedure and return of the block.

Ship specimen plug kit, specimen in punch tool, and all paperwork to the address below. For Questions regarding collection/shipping or to order an FFPE Specimen Plug Kit, please contact the NRG Oncology Biospecimen Bank by e-mail: RTOG@ucsf.edu or call 415-476-7864/Fax 415-476-5271.

**U.S. Postal Service Mailing Address:** For Non-frozen Specimens Only
NRG Oncology Biospecimen Bank
University of California San Francisco
Campus Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

**Courier Address (FedEx, UPS, etc.):** For All Frozen Specimens or Trackable shipments
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115
NRG ONCOLOGY BLOOD COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of serum, plasma, or whole blood (as specified by the protocol):

Kit contents:
- One Red Top tube for serum (A)
- One Purple Top EDTA tube for plasma (B)
- One Purple Top EDTA tube for Whole Blood (C)
- Twenty-five (25) 1 ml cryovials
- Biohazard bags (3) and Absorbent shipping material (3)
- Styrofoam container (inner) and Cardboard shipping (outer) box
- UN1845 DRY Ice Sticker and UN3373 Biological Substance Category B Stickers
- Specimen Transmittal Form (ST) and Kit Instructions

PREPARATION AND PROCESSING OF SERUM, PLASMA AND WHOLE BLOOD:

(A) Serum (if requested): Red Top Tube
- Label as many 1ml cryovials (5 to 10) as necessary for the serum collected. Label them with the NRG Oncology study and case number, collection date/time, and time point, and clearly mark cryovials “serum”.

Process:
1. Allow one red top tube to clot for 30 minutes at room temperature.
2. Spin in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the ST Form.
3. Aliquot 0.5 mL serum into as many cryovials as are necessary for the serum collected (5 to 10) labeled with NRG Oncology study and case numbers, collection date/time, protocol time-point collected (e.g. pretreatment, post-treatment), and clearly mark specimen as “serum”.
4. Place cryovials into biohazard bag and immediately freeze at -70 to -90°C, and store frozen until ready to ship. See below for storage conditions.
5. Store serum at -70 to -90°C until ready to ship on dry ice. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on the ST Form.

(B) Plasma (if requested): Purple Top EDTA tube #1
- Label as many 1ml cryovials (5 to 10) as necessary for the plasma collected. Label them with the RTOG study and case number, collection date/time, and time point, and clearly mark cryovials “plasma”.

Process:
1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the ST Form.
3. If the interval between specimen collection and processing is anticipated to be more than one hour, keep specimen on ice until centrifuging is performed.
4. Carefully pipette and aliquot 0.5 mL plasma into as many cryovials as are necessary for the plasma collected (5 to 10) labeled with NRG Oncology study and case numbers, collection date/time, time point collected and clearly mark specimen as “plasma”. Avoid pipetting up the buffy coat layer.
5. Place cryovials into biohazard bag and immediately freeze at -70 to -90°C.
6. Store frozen plasma until ready to ship on dry ice.
7. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on the ST Form.

(continued on next page)
NRG ONCOLOGY BLOOD COLLECTION KIT INSTRUCTIONS (continued)

(C) Whole Blood for DNA (if requested): Purple Top EDTA tube #2

- Label as many 1ml cryovials (3 to 5) as necessary for the whole blood collected. Label them with the RTOG study and case number, collection date/time, and time point, and clearly mark cryovials “blood”.

Process:
1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA. Blood can also be mixed for 5 minutes on a mixer at room temperature.
2. Carefully pipette and aliquot **1.0 mL blood** into as many cryovials as are necessary for the blood collected (3 to 5) labeled with NRG Oncology study and case numbers, collection date/time, time point collected and clearly mark specimen as “blood”.
3. Place cryovials into biohazard bag and freeze immediately at -70 to -80°C Celsius.
4. Store blood samples frozen until ready to ship on dry ice.
5. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on ST Form.

Freezing and Storage:
- Freeze Blood samples in a -80°C Freezer or on Dry Ice or snap freeze in liquid nitrogen.
- Store at -80°C (-70°C to -90°C) until ready to ship.
  - If a -80°C Freezer is not available,
    - Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
    - OR: Samples can be stored in plenty of dry ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only; Canada: Monday-Tuesday only).
    - OR: Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
- Please indicate on Specimen Transmittal (ST) Form the storage conditions used and time stored.

Shipping/Mailing:
- Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- Include all NRG Oncology paperwork in a sealed plastic bag and tape to the outside top of the Styrofoam box.
- Wrap frozen specimens of same type (i.e., all serum together, plasma together and whole bloods together) in absorbent shipping material and place each specimen type in a separate biohazard bag. Place specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum).
  - **Add padding to avoid the dry ice from breaking the tubes.**
- Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.

(continued on next page)
RTOG BLOOD COLLECTION KIT INSTRUCTIONS (continued)

- Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice. Add padding to avoid the dry ice from breaking the tubes.
- For questions regarding collection, shipping or to order a Blood Collection Kit, please e-mail RTOG@ucsf.edu or call (415)476-7864.

Shipping Address:
Courier Address (FedEx, UPS, etc.): For all Frozen Specimens
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115
For questions, call 415-476-7864 or e-mail: RTOG@ucsf.edu
NRG ONCOLOGY URINE COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of urine specimens.

Kit Contents:
- One (1) Sterile Urine collection cup
- Two 7 ml disposable pipettes
- Absorbent paper towel
- Two 15 ml polypropylene centrifuge tubes
- Biohazard bags
- Parafilm for sealing outside of tubes

Preparation and Processing of Urine Specimens:

Process:
- A clean catch urine specimen will be collected. To collect the specimen, use the following instructions:
  - Males should wipe clean the head of the penis and females need to wipe between the labia with soapy water/cleansing wipes to remove any contaminants.
  - After urinating a small amount into the toilet bowl to clear the urethra of contaminants, collect a sample of urine in the collection cup.
  - After 10-25 mL urine has been collected, remove the container from the urine stream without stopping the flow of urine.
  - Finish voiding the bladder into the toilet bowl.
- Aliquot 5-10 mls of Urine into each of two 15 ml polypropylene centrifuge tubes (disposable pipets are provided in the kit). Do not fill with more than 10 mls to avoid cracking of tubes due to expansion during freezing. Replace the cap and tighten on the tubes. Make sure the cap is not cross-threaded or placed on incorrectly or leaking will occur.
- Use parafilm to seal the cap around the outside rim of the urine tube to prevent leakage.
- Discard remaining Urine and collection cup.
- Label the specimen with the NRG Oncology study and case number, collection date and time, time point of collection, and clearly mark specimens as “urine”.
- Wrap Urine Tubes with absorbent material (paper towels) and place into biohazard bag and seal the bag. Freeze and store Urine samples in a -20°C or -80°C freezer until ready to ship.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED with RTOG study and case numbers, collection date/time, and time point collected (e.g. pretreatment, post-treatment).

Storage and Shipping:

Freezing and Storage:
- Urine specimens may be sent in batches or with other frozen biospecimens, if within 30-60 days of collection. Store at -20°C or -80°C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:
  - Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).

OR:
  - Samples can be stored in plenty of Dry Ice for up to one week, replenishing daily (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
  - Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

Shipping/Mailing:
- Ship specimens on Dry Ice overnight Monday-Wednesday (Monday-Tuesday from Canada) to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- Include all NRG Oncology paperwork in a sealed plastic bag and tape to the outside top of the Styrofoam box.
- Place sealed specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). Add padding to avoid the dry ice from breaking the tubes.
- Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.
- Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice. Add padding to avoid the dry ice from breaking the tubes.
- Samples received thawed will be discarded, and a notification will be sent immediately to the Principal Investigator and Clinical Research Assistant of the submitting institution. The institution should send a subsequent sample, collected as close as possible to the original planned collection date.
- For questions regarding ordering, collection, or shipping of a Urine Collection Kit, please e-mail RTOG@ucsf.edu or call (415) 476-7864 or fax (415) 476-5271.

Shipping Address: FedEx/UPS/Courier address (For all frozen samples)

NRG Oncology Biospecimen Bank at UCSF
2340 Sutter Street, Room S341, San Francisco, CA 94115
Contact Phone: (415) 476-7864

79 RTOG 0839, Version Date: 10/9/14
APPENDIX VI (3/10/14)

Panitumumab Clinical Safety Experience

The studies referenced below reflect the reported adverse events at the time of the last Panitumumab Investigator’s Brochure (Version 8.0, 17 November 2009). Please refer to the current version of the Panitumumab Investigator’s Brochure as well as the updated safety information contained in the Investigational New Drug safety letters for further updates.

Panitumumab Monotherapy Studies
An integrated analysis of the safety of panitumumab has been conducted for 1052 subjects with mCRC receiving panitumumab monotherapy (mCRC Monotherapy Set). Subjects primarily received panitumumab doses of 2.5 mg/kg once weekly (15%) or 6.0 mg/kg every 2 weeks (82%).

Consistent with the published data on subjects treated with EGFr inhibitors (i.e., class/target effect) [Perez-Soler 2005], the most commonly reported treatment-related adverse events in subjects treated with panitumumab were associated with the skin, including pruritus (52%), acneiform dermatitis (51%), erythema (50%), and rash (38%). Most subjects (833 of 1052 subjects, 79%) with any dermatologic toxicity had events that were considered to be mild or moderate. Only 3% of subjects permanently discontinued panitumumab administration for dermatologic toxicities. Dermatologic toxicities typically were observed after initiation of panitumumab, with a median time to first integument toxicity (of any severity) of 10 days (95% CI: 8, 11).

Rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis (≥ 1/10,000 patients and < 1/1000 patients, respectively) have been reported with patients treated with panitumumab.

Other common treatment-related adverse events (i.e., subject incidence ≥ 10%) included fatigue (15%) and diarrhea (13%).

Subjects in the wild-type KRAS subset received a higher number of panitumumab infusions compared with subjects in the mutant subset (mean [median] 10.0 [8.0] and 4.9 [4.0], respectively). More treatment-related adverse events occurred in the wild-type KRAS subset compared with the mutant KRAS subset, presumably due to the greater number of panitumumab infusions received. These adverse events were mainly skin toxicities (erythema, pruritus, dermatitis acniform) likely reflecting the increased duration of exposure to panitumumab. No qualitative differences in overall adverse events were observed between the wild-type KRAS subset and the overall population, however, treatment related grade 3 adverse events were reported for 25% of subjects in the wild-type KRAS subset compared with 12% of subjects in the mutant KRAS subset. Two percent of wild-type KRAS subjects and 1% of mutant KRAS subjects withdrew for panitumumab-related events. Infusion reactions to panitumumab were infrequent even though premedication was not mandated in the panitumumab clinical program. Overall, 1% of subjects had an infusion reaction reported by the investigator as an adverse event. Using a definition consistent with the Vectibix USPI (2007), 3% of panitumumab-treated subjects had a potential infusion reaction; < 1% of subjects had a potential infusion reaction by this definition ≥ grade 3.

Panitumumab Combination Chemotherapy Studies
To date, panitumumab has been evaluated in combination with chemotherapy in subjects with CRC, NSCLC, and SCCHN.

In the mCRC setting in combination with IFL (Study 20025409), the incidence of grade 3 or 4 diarrhea (58%) was notably higher than that historically expected for this already highly GI-toxic chemotherapy regimen, and 1 subject had an episode of grade 4 diarrhea that was also considered serious. Of note, panitumumab in combination with the FOLFIRI regimen using the same agents but different doses/infusion times was better tolerated with an incidence of grade 3 or 4 diarrhea similar to that expected from the literature for this chemotherapy regimen alone (25%) [Andre 1999; Saltz 2000]. These data suggest that the potential for additive toxicities in the gastrointestinal tract exists when panitumumab is administered in combination with GI toxic chemotherapy. However, these toxicities could be managed by appropriate selection of the concomitant chemotherapy regimen.
No clear additive effects were observed in the NSCLC setting where panitumumab was combined with carboplatin/paclitaxel (Study 20025404). One case of pulmonary fibrosis was reported in a subject treated with this combination. Although subjects with evidence of interstitial pneumonitis or pulmonary fibrosis were excluded from clinical studies (from 2004 onward), this subject, who had a previous history of underlying idiopathic pulmonary fibrosis, was enrolled before the protocol exclusions were implemented.

Acute renal failure has been observed in patients who develop severe diarrhea and dehydration.

Infusion reactions, including anaphylactic reactions, bronchospasm, and hypotension, have been reported in the clinical trials and post-marketing experience. Across all clinical studies, severe infusion reactions (NCI-CTC grade 3 and grade 4) occurred with the administration of panitumumab in < 1% of patients. In the postmarketing setting, serious infusion reactions have also been reported in n < 1% of patients, very rarely with a fatal outcome (less than 1 in 10,000). Fatal reactions have been observed in patients with a history of prior hypersensitivity reaction to panitumumab. Stop infusion if a severe infusion reaction occurs. Depending on the severity and/or persistence of the reaction, consider permanently discontinuing panitumumab.

Amgen study 20040249 (PACCE) is an open-label, controlled study of bevacizumab and chemotherapy administered with and without panitumumab as first-line treatment of subjects with mCRC. Chemotherapy included oxaliplatin-or irinotecan-based regimens. Based on the results of a planned interim analysis (conducted after 257 progression or death events had occurred), adding panitumumab to bevacizumab and oxaliplatin-based chemotherapy did not prolong progression-free survival and contributed increased toxicity to the multi-agent regimens. Panitumumab treatment was discontinued from the study at that time (22 March 2007).

A final analysis of on-treatment efficacy and safety was performed based on available data as of 31 May 2007. The addition of panitumumab to bevacizumab and oxaliplatin-based chemotherapy showed an unfavorable benefit-risk profile with shorter progression-free survival time and increased toxicity. Although panitumumab treatment in the irinotecan-based chemotherapy stratum was also prematurely discontinued, there was no evidence of significant benefit with the addition of panitumumab to bevacizumab and irinotecan-based chemotherapy in first-line treatment of mCRC. Given the unfavorable benefit-risk outcome, the PACCE study as designed did not support the use of panitumumab with bevacizumab and oxaliplatin- or irinotecan-based chemotherapy as first-line treatment of metastatic colorectal cancer.

Please refer to the current Panitumumab Investigator’s Brochure for further details.

**Panitumumab Combination Radiotherapy With or Without Chemoradiotherapy Studies**

An open-label, dose-finding study (Study 20040235) of AMG 706 or panitumumab when administered with induction chemotherapy (IC) and/or chemo-radiotherapy (CRT) in the treatment of subjects with loco-regionally advanced squamous cell carcinoma of the head and neck is ongoing. Five dose cohorts are currently planned for this study. As of the data cut-off date (18 May 2007), 5 subjects were enrolled in cohort A [TPF (T – docetaxel 75 mg/m2; P cisplatin 75 mg/m2; F – 5-fluorouracil 750 mg/m2 days 1 to 5) induction chemotherapy followed by chemoradiotherapy + panitumumab 1.5 mg/kg QW (n = 7) and 2.5 mg/kg (n = 3), and 4 subjects were enrolled in cohort B (TPF induction chemotherapy followed by chemoradiotherapy + AMG 706). Of the 9 subjects enrolled in cohorts A and B, 8 had completed study and 1 had treatment ongoing (data on file at Amgen Inc). Safety data was available for all 9 subjects.

At least 1 treatment-emergent adverse event was reported for all 9 subjects (100%) in cohorts A and B. Two subjects in cohort A1 experienced a DLT (one each grade 3 and 4 mucositis). Subsequently, the protocol was amended to modify the DLT definition for mucositis to limit it to grade ≥ 3 toxicity that occurred in the first 5 weeks of radiotherapy or led to a 5-day radiotherapy delay. There were no further DLTS. The most common grade ≥ 3 AE during the panitumumab + chemoradiotherapy phase was mucositis (n = 6). There was 1 event each of grade 3 esophagitis, dysphagia, and odynophagia, all reported as unrelated to panitumumab. One subject also experienced grade 3 radiation dermatitis that was considered related but did not meet the criteria of a DLT. The most common grade ≥ 3 adverse events during induction chemotherapy were febrile neutropenia (n = 5) and mucositis (N = 4). No subjects in cohort A have died within 30 days of last dose of investigational product (data on file at Amgen Inc)

Please refer to the current Panitumumab Investigator’s Brochure for further details.
APPENDIX VII (3/21/13)
RTOG 0839
Thoracic Surgeon’s Questionnaire

Please complete this questionnaire following a careful review of the eligibility (Section 3.0) and surgical (Section 8.0) sections of RTOG 0839 and return this form to your Research Associate. Surgeon credentialing is a pre-registration requirement (Section 5.4).

1. This study requires careful documentation of stage of disease prior to registration. CT and PET scan findings are not accepted as sole criteria of nodal status. Pre-treatment mediastinal sampling is required for most patients. Is this a procedure that you perform routinely and would you agree to do for this protocol?
   YES ______ NO _______
   Comments:

2. This protocol requires systematic nodal sampling or dissection at thoracotomy at all levels of hilar and mediastinal nodes according to the American Thoracic Society Lymph Node Map.
   Are you familiar with this nodal mapping system?
   YES ______ NO _______
   Comments:

   Do you routinely perform systemic mediastinal nodal sampling or dissection at the time of pulmonary resection?
   YES ______ NO _______
   Comments:

   Do you agree to perform systematic nodal sampling or dissection as specified in the protocol? Including removal of lymph nodes from stations 2R, 4R, 7, 9R and 10R for right sided resections and from stations 5, 6, 7 9L, and 10L for left sided resections?
   YES ______ NO _______
   Comments:

3. This study requires an operation for all patients after chemoradiotherapy except those who have progressive disease or pathologic conformation of persistent mediastinal disease. Do you agree to attempt resection of all patients if no medical contraindication exists, including those patients who achieved only stable disease on CT and PET scan re-evaluation?
   YES ______ NO _______
   Comments:

4. Please check the item that best describes the scope of your practice:

   _____ General Surgery plus Thoracic Surgery
   _____ Primarily Thoracic Surgery; some Cardiac Surgery
   _____ Primarily Cardiac Surgery; some Thoracic Surgery
   _____ Equal mix of Thoracic and Cardiac Surgery
   _____ Only Thoracic Surgery

(Continued on the next page)
5. This study requires the placement of autologous soft tissue flap to the bronchial stump following resection. An intercostal muscle from the fifth intercostal space, pericardial fat pad or thymic flap is to be used for a lobectomy and a serratus anterior or fifth intercostal muscle flap is to be used for pneumonectomies to buttress the stump. Are you familiar with these procedures?
   YES_______ NO_______
   Comments:

Do you routinely buttress you bronchial stumps with autologous soft tissue in patient who have received pre-operative chemoradiotherapy?
   YES_______ NO_______
   Comments:

Do you agree to buttress the bronchial stump with autologous soft tissue as specified in the protocol?
   YES_______ NO_______
   Comments:

6. The primary endpoint of this trial is the extent of clearance of mediastinal lymph node disease at the time of resection. Residual lymph node involvement will be quantified into one of six categories: a) positive with extra capsular extension; b) positive with 100% replacement with viable tumor; c) positive with < 100% and > 50% replacement with viable tumor; d) positive with < 50% and > 25% viable tumor; e) positive with < 25% viable tumor; or f) negative. It is necessary that the surgeon adequately report the amount of residual disease based upon the pathologic evaluation of the lymph nodes. This may require consultation with the pathologist to adequately quantify the extent of disease involvement if it is not clearly stated in the pathology report.

Do you agree to take the steps required to quantify residual lymph node involvement?
   YES_______ NO_______
   Comments:

7. Please estimate the number of lobectomies and/or pneumonectomies you perform per year. _______

8. Please estimate the number of post-chemoradiotherapy lobectomies and/or pneumonectomies you perform per year. _______
   
   NOTE: Surgeons must have performed a minimum of 10 lobectomies/pneumonectomies per year in order to participate in RTOG 0839.

9. If there are other surgeons at your institution who will be participating in this program, have they also completed one of these forms?
   YES_______ NO_______
If you have any specific questions about this form or other aspects of the trial, please contact:

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Signature of Surgeon completing this form

Institution Name

Printed Name of Surgeon

Telephone number of Surgeon

Physician’s Fax Number

Site RTOG Institution Number/CTEP ID Number

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Return this form to your Research Associate

RTOG Research Associates: E-mail the completed form to Dr. Donington: jessica.donington@nyumc.org

Dr. Donington will e-mail the reviewed form, indicating her decision (via the box below) to CTSU, CTSURegOffice@ecogchair.org and to RTOG HQ, rtog0839@acr.org.

Reviewed and approved

Reviewed and not approved: Dr. Donington also will contact the site.

Jessica Donington, MD, Thoracic Surgery Co-Chair

Date

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