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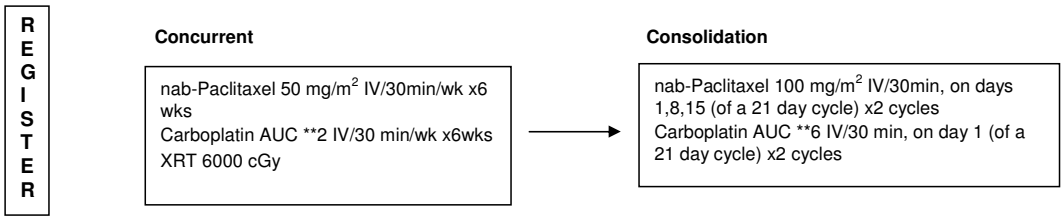
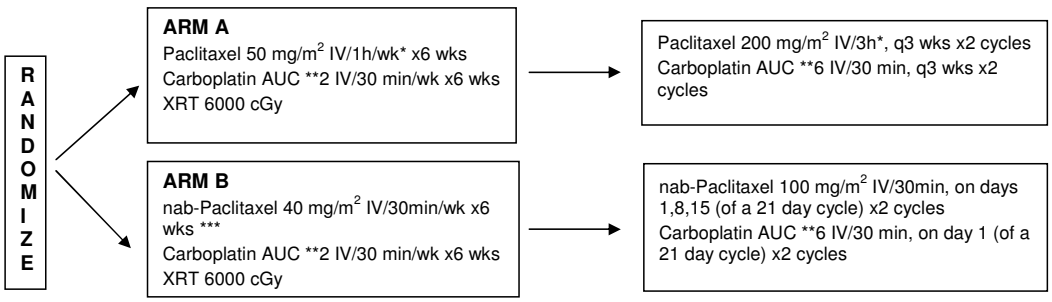
SCHEMA

A RANDOMIZED PHASE I/II STUDY OF NAB-PACLITAXEL, OR PACLITAXEL, PLUS CARBOPLATIN WITH CONCURRENT RADIATION THERAPY FOLLOWED BY CONSOLIDATION IN PATIENTS WITH FAVORABLE PROGNOSIS INOPERABLE STAGE IIIA/B NON-SMALL CELL LUNG CANCER (NSCLC)

Phase 1 (Feasibility Testing)



Phase 2



See Sections 6.0 and 7.0 for details.

* **Premedication (before each cycle of paclitaxel)**
- Dexamethasone 20 mg PO on the evening prior to and morning of paclitaxel infusion, or IV 30 minutes prior to paclitaxel
- Diphenhydramine 50 mg IV (or equivalent) 30 minutes prior to paclitaxel
- Cimetidine 300 mg IV (or equivalent, ranitidine 50 mg or famotidine 20 mg) 30 minutes prior to paclitaxel

** **Dose of Carboplatin using Calvert Formula** = AUC x (CrCl + 25)**:**

***** Based on Phase I data, 40 mg/m^2 of Nab-Paclitaxel will be given during concurrent Phase.**

Patient Population (See Section 3.0 for Eligibility)
Histologically or cytologically documented NSCLC; Patients must be M0. Patients with T1-T2 with N2 or T3N1-2 are eligible, if inoperable. Patients with T4 with any N or any T with N2 or N3 disease are eligible if unresectable.

Required Sample Size: 6 total during the Phase 1 (Feasibility Testing)
92 during the Phase 2 (46 in Arm A, 46 in Arm B): total patient accrual is 98.

Institution # _____ **Patient Initials** _____ **Patient #**_____

ELIGIBILITY CHECKLIST

(page 1 of 2)

_____(Y)	1.	Does the patient have histologically or cytologically documented NSCLC?
_____(N)	2.	Has the tumor been totally resected?
_____(Y)	3.	Is the patient stage IIIA/B with no evidence of metastasis (M0)?
_____ (Y)	4.	Is disease measurable, as defined in Section 10.4?
_____(Y)	5.	Is the patient ≥ 18 years of age?
_____(Y)	6.	Is the Zubrod performance status 0-1?
_____(Y)	7.	Are the pre-treatment laboratory values within the parameter of eligibility per section 3.1.5?
_____(Y)	8.	Is the FEV1 ≥ 1200 cc or ≥ 50% predicted?
_____(N)	9.	Has the patient had weight loss > 10% over the past 3 months?
_____(Y)	10.	Has the patient recovered from exploratory thoracotomy?
_____(Y)	11.	Were required pretreatment evaluations administered as specified in Section 3.1.11?
_____(N)	12.	Has the patient had prior systemic chemotherapy, targeted therapy and/or thoracic/neck radiotherapy for any reason and/or surgical resection of present cancer?
_____(N)	13.	Does the patient have a > grade 1 neuropathy?
_____ (N)	14.	Is there evidence of other malignancy within the past two years other than those stated in Section 3.2.7?
_____ (N)	15.	If female, is the patient pregnant or nursing?
_____ (Y)	16.	Is the patient (male or female) willing and able to practice effective contraception throughout the study and for four weeks after completion of treatment?
_____ (Y/N)	17.	Is there evidence of pleural effusion on CT scan?
_____ (Y)		If yes, is the pleural effusion transudate, cytologically negative, and non-bloody; or determined to be too small to tap?

(Continued on next page)

Institution # _____ **Patient Initials** _____ **Patient #**_____

ELIGIBILITY CHECKLIST

(page 2 of 2)

The following questions will be asked at Study Registration:

_____ 1. Name of institutional person registering this case?

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

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

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

_____ 5. Patient's Initials (First Middle Last) (If no middle initial, use hyphen)

_____ 6. Name of Verifying Physician

_____ 7. Patient's ID Number

_____ 8. Date of Birth

_____ 9. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; African American; Unknown)

_____ 10. Race

_____ 11. Gender

_____ 12. Smoking History

____Never, ____Quit:____Yrs ago, ____yr Smoking Hx, ____Still Smoking

_____ 13. Treatment Start Date

_____ 14. Name of Medical Oncologist

_____(Y/N) 15. Tissue/Blood kept for current study?

_____ (Y/N) 16. Tissue/Blood kept for cancer research?

_____(Y/N) 17. Tissue/Blood kept for medical research?

_____(Y/N) 18. Allow contact for future research?

_____(Y/N) 19. Was a PET scan performed on this patient?

_____(NA/Y/N) 20. Was the PET scan used in staging?

_____(NA/Y/N) 21. Was the PET scan used in treatment planning for radiation therapy?

Completed by _____ Date _____

1.0 INTRODUCTION

1.1 Non-small Cell Lung Cancer

1.1.1 *Background on Non-small Cell Lung Cancer (NSCLC) Therapy*

Lung cancer is the second most common cancer diagnosed for both sexes in the United States, second to prostate cancer for men and breast cancer for women. Approximately 226,160 new cases are estimated for 2012, accounting for about 14% of cancer diagnoses It is the leading cause of cancer deaths in both men and women, with approximately 160,340 deaths estimated for 2012.[1]

Upon initial presentation, less than one-half of patients will have surgically resectable lung cancer with the potential for cure. Approximately one-quarter of patients will present with locally advanced disease involving either the ipsilateral mediastinal or subcarinal lymph nodes (American Joint Committee on Cancer [AJCC] Tl-3 N2 M0, Stage IIIA) or contralateral mediastinal, hilar or ipsilateral or contralateral scalene or supraclavicular nodes (AJCC Tl-2 N3 M0, Stage IIIB) without evidence of extrathoracic metastases. A smaller number of patients will have a centrally located primary tumor involving mediastinal structures (AJCC T4 Nx M0, Stage IIIB). These patients are generally not considered candidates for surgical resection.

Since the 1970's, a number of investigators sought to improve the survival results of stage III NSCLC patients by combining chemotherapy with thoracic RT. There now have been four randomized trials published that demonstrate a statistically significant survival advantage of a cisplatin-containing regimen with thoracic RT over thoracic RT alone.[2-6]

Two of these trials, CALGB 8433 and RTOG 88-08, used two cycles of pre-RT full dose cisplatin and vinblastine.[2,4] One alternated chemotherapy with RT and the other delivered low dose daily and weekly single agent cisplatin during thoracic RT.[6] Based on somewhat incomplete analyses of patterns of tumor failure location, it appears that sequential chemoradiation reduces or delays the development of extra-thoracic metastases, while low dose concurrent cisplatin appeared to improve the control rate of intra-thoracic tumor, i.e., acted as a potentiator of the radiation effect. The goal of many investigators in recent years has been to take advantage of both the benefits of full dose chemotherapy and the sensitizing effects of concurrent chemoradiation.

RTOG 94-10 was a three-arm phase III trial that compared: 1) an established sequential chemoradiation regimen of vinblastine and cisplatin followed by once-daily RT to a dose of 60Gy on Day 50, 2) concurrent chemoradiation regimen in which once-daily RT to a dose of 60Gy (with cisplatin/vinblastine) or 3) concurrent chemoradiation regimen in which twice-daily RT to a dose of 69.6Gy (with cisplatin/etoposide). Median survival times were 14.6 months for the sequential arm and 17 and 15.6 months for the concurrent arms with once-daily and twice-daily RT, respectively. 5-year overall survival was 10% for Arm 1, 16% for Arm 2 and 13% for Arm 3 (P=0.046).[7]

The West Japan Lung Cancer Group compared sequential to concurrent chemoradiation using mitomycin, vindesine, and cisplatin, (MVC) chemotherapy among 320 patients with stage III NSCLC and demonstrated a survival advantage

favoring the concurrent arm, with median survival times of 16.5 versus 13.3 months, respectively (P=0.047).[8]

1.1.2 *Paclitaxel, Carboplatin, and RT in NSCLC*

Paclitaxel acts as a mitotic inhibitor, blocking cells in G_2 and M phases of the cell cycle. The inhibition is unique in that the drug enhances the rate and yield of microtubular assembly and prevents microtubular depolymerization.[9,10] It is well known that cells in the G_2 and M phase of the cell cycle are particularly sensitive to radiation.[11] Tishler et al. showed that 24-hour treatment with 10 nM paclitaxel resulted in a radiosensitivity enhancement in a radio-resistant astrocytoma cell line.[12] The enhanced level of cell kill was consistent with the greater radiosensitivity of G_2 /M cells. A radiation sensitizing effect of paclitaxel was also observed with only one hour of treatment with 300 nM Taxol, in human leukemia cell line (HL-60) and human lung cancer cell line (Calu-3).[13]

Carboplatin also can be used as a radiation sensitizer. The mechanism of radiation sensitization with carboplatin is different from that of paclitaxel. Carboplatin potentially interferes with repair of sublethal radiation injury while paclitaxel recruits cells in the radiosensitive G_2/M phase. Laboratory data have suggested a possible synergistic relationship of paclitaxel and carboplatin.[14]

A number of phase I-II single arm trials have been performed evaluating paclitaxel and paclitaxel/carboplatin concurrent with radiation. Many of these have also incorporated induction or consolidation full-dose paclitaxel/carboplatin.[15-19] Two recent randomized trials evaluating this general approach have been reported. The LAMP trial was a randomized phase II trial for patients with unresected stages IIIA and IIIB NSCLC with Karnofsky performance status ≥ 70% and weight loss ≤ 10%. The three arms were: 1) paclitaxel (200mg/m^2)/carboplatin (AUC 6) followed by radiation (sequential), 2) paclitaxel(200mg/m^2)/carboplatin (AUC 6) followed by chemoradiation with paclitaxel(45mg/m^2)/carboplatin (AUC 2) (weekly) (induction/concurrent), and 3) chemoradiation with paclitaxel(45mg/m^2)/carboplatin (AUC 2) (weekly) followed by consolidation paclitaxel(200mg/m^2)/carboplatin (AUC 6) (concurrent/consolidation). Accrual to arm 2 was discontinued early for low feasibility in that only 46% of patients completed chemoradiation. Analysis showed median overall survival rates of 13, 12.7, and 16.3 months in arms 1, 2, 3 respectively.[20]

CALGB 39801 is a phase III randomized trial that tested induction chemotherapy with paclitaxel and carboplatin followed by concurrent radiation with paclitaxel/ carboplatin versus chemoradiation with paclitaxel/carboplatin alone. Patients with unresectable stage III NSCLC were enrolled onto the study and received either induction therapy consisting of two cycles of paclitaxel (200 mg/m^2) and carboplatin (AUC 6) administered every 3 weeks followed by weekly paclitaxel (50 mg/m^2) and carboplatin (AUC 2) with RT (2.0 Gy/day for 66.0 Gy) (arm 1) or the same chemoradiation without induction or consolidation paclitaxel/carboplatin (arm 2). Three hundred thirty-one patients were evaluable. Response rates, median and two year failure-free and overall survival rates were not significantly different between the two arms. Median survival was 14 and 12 months (p = .10) in arms 1 and 2, respectively.[21]

Results from the LAMP trial and CALGB 39801 suggest that induction paclitaxel/carboplatin followed by chemoradiation has low feasibility and is not more effective than chemoradiation alone. This may be related, in part, to poor tolerance and limited delivery of chemoradiation following chemotherapy. However, additional systemic chemotherapy beyond what is delivered with

chemoradiation is theoretically important given the high rate of distant metastases observed in patients so treated. Thus, using paclitaxel/carboplatin as a base regimen, the study proposed herein utilizes concurrent chemoradiation followed by consolidation with additional chemotherapy, similar to arm 3 of the LAMP trial. In order to further improve on the outcome of treating patients with unresectable NSCLC, we propose to use weekly nab-paclitaxel (Abraxane) and carboplatin with concurrent radiation followed by consolidaton with nab-paclitaxel (Abraxane) and carboplatin.

1.2 Radiation Therapy for Stage III NSCLC

A significant radiation therapy trial begun more than 30 years ago (RTOG 73-01) established 60 Gy as the optimal standard radiation dose for locally advanced NSCLC.[22] Based on this trial, doses from 55-66 Gy are still used in most studies. It is important to realize that the dose of 60 Gy was established as optimal before the advent of modern imaging. The first computed tomography scanner in the U.S. was installed in 1973 at the Mayo Clinic. Before the widespread use of computed tomography (CT), radiation planning was two-dimensional (2-D) based on plain X-ray. Most of the published phase III studies to date for lung cancer have used 2-D treatment planning. There have been many advances since RTOG 73-01 established 60 Gy as the standard of care. These include CT-based treatment planning, conformal radiation therapy, positron emission tomography (PET), and knowledge of tumor motion during radiation delivery. One major shift in treatment strategy was the irradiation of gross disease without prophylactic/elective nodal irradiation. There were several reasons for this philosophy. The dose of radiation commonly employed (60 Gy/30 fractions) was not enough to sterilize bulky epithelial tumors. Simply increasing the dose delivered to the large volumes of the chest included when irradiating lymph nodes prophylactically was believed to cause unacceptable toxicity. Additionally, irradiating clinically uninvolved nodal areas prophylactically did not appear rational when the gross tumor was infrequently controlled.

The currently accepted standard of care for patients with inoperable stage III NSCLC is concurrent chemoradiation therapy. The accepted standard radiation dose is 60-66 Gy. Three separately run phase I dose escalation trials using concurrent chemoradiation therapy have demonstrated a maximum tolerated dose of 74 Gy (RTOG, NCCTG, and North Carolina).[23-25] Current phase II data from these series estimate a median survival of 24 months, which is higher than the expected median survival time for the RTOG 94-10 control arm (17 months). However, results of an early analysis of RTOG 06-17, a randomized phase III trial examining whether treatment with a higher radiation dose (74 Gy) improves overall survival compared with the current standard dose (60 Gy) (scheduled to take place upon 90 participant deaths being reported) demonstrated that the higher dose of radiation did not improve overall survival, at which time the two high-dose radiation therapy arms were closed to further participant enrollment. It was also reported that there was no significant difference in treatment-related toxicity between the high-dose and standard radiation treatment arms. Therefore, the current standard dose of 60Gy will be used in this regimen.

1.3 Nab-Paclitaxel

Paclitaxel and docetaxel are highly hydrophobic, and have to be delivered in synthetic vehicles. For paclitaxel, the vehicle is polyoxyethylated castor oil (Cremophor EL) and ethanol, and for docetaxel, the vehicle is polysorbate 80 and ethanol. These vehicles are both biologically and pharmacologically active. They are known to cause hypersensitivity reactions characterized by dyspnea,

flushing, angioedema, rash and generalized urticaria. It requires premedication with moderate to high doses of corticosteroids and antihistamines. (Cremophor EL) also contributes to peripheral neurotoxicity caused by paclitaxel administration. These vehicles also alter the pharmacokinetics by drug entrapment, leading to decreased drug clearance, decreased volume of distribution, and nonlinear pharmacokinetics.

Nab-Paclitaxel (Abraxane) is a novel, solvent-free, albumin-bound, 130 nm particle form of paclitaxel designed to avoid the problems caused by the solvent used in (Cremophor EL) based paclitaxel.[26] Nab-Paclitaxel (Abraxane) can be administrated intravenously over 30 minutes without premedication. A higher concentration of intratumor paclitaxel can be achieved with Nab-Paclitaxel (Abraxane) due to the utilization of albumin receptor-mediated endothelial transport, thus leading to increased antitumor activity.[27]

Nab-Paclitaxel (Abraxane) has been tested extensively in metastatic breast cancer. A phase III study randomized 460 patients to receive Nab-Paclitaxel (Abraxane) 260 mg/m^2 or CrEL-paclitaxel 175 mg/m^2 every 3 weeks.[28] Nab-Paclitaxel (Abraxane) demonstrated significantly higher response rate compared with CrEL-paclitaxel (33% versus 19%, p=0.001) and significantly longer time to tumor progression (23.0 weeks versus 16.9 weeks, p=0.006). Although higher dose was given, the incidence of grade 4 neutropenia was significantly lower for Nab-Paclitaxel (Abraxane) compared with CrEL-paclitaxel and febrile neutropenia was uncommon. Grade 3 sensory neuropathy was more common in the Nab-Paclitaxel (Abraxane) arm than in the CrEL-paclitaxel arm (10% versus 2%), but was easily managed and improved rapidly. Based on the results of this study, Nab-Paclitaxel (Abraxane) is approved by the U.S. Food and Drug Administration (FDA) for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy.

Randomized study comparing Nab-Paclitaxel (Abraxane) to docetaxel in metastatic breast cancer has completed.[29] In this study, patients were randomized into four arms: Nab-Paclitaxel (Abraxane) 300 mg/m^2 every 3 weeks, Nab-Paclitaxel (Abraxane) 100 mg/m^2 weekly for 3 out of 4 weeks, Nab-Paclitaxel (Abraxane)150 mg/m^2 weekly for 3 out of 4 weeks, or docetaxel 100 mg/m^2 every 3 weeks. Report of interim analysis showed that the response rate of both weekly Nab-Paclitaxel (Abraxane) schedules were significantly better than 3-weekly Nab-Paclitaxel (Abraxane) and docetaxel and the progression-free survival was significantly better for Nab-Paclitaxel (Abraxane) regardless of schedule. All doses of Nab-Paclitaxel (Abraxane) were better tolerated than docetaxel. The difference between Nab-Paclitaxel (Abraxane) and docetaxel toxicity was most striking in the incidence of neutropenia: grade 3-4 neutropenia occurred in 95% of docetaxel patients compared with only 22% of those on Nab-Paclitaxel (Abraxane) arms.

Nab-Paclitaxel (Abraxane) is also active in head and neck cancer.[30] In a phase I/II study, 31 patients with advanced head and neck cancer were treated with Nab-Paclitaxel (Abraxane) by intraarterial administration. The maximal tolerance dose (MTD) was determined to be 270 mg/m^2. Of 29 patients with assessable diseases, 3 had complete response and 19 partial responses, with a total response rate of 76% (10% complete response and 66% partial response). No human trials using Nab-Paclitaxel (Abraxane) with radiation have been reported; however, preclinical data has also shown that Nab-Paclitaxel (Abraxane) has tumor radiosensitizing effects, while not increasing normal tissue sensitivity. A

dose of 90 mg/m^2 (150% of the MTD of paclitaxel) demonstrated no treatment related animal toxicity, and tumor progression was significantly delayed.[31]

Nab-Paclitaxel (Abraxane) has also demonstrated activity in NSCLC.[32-37] Green et. al. evaluated Nab-Paclitaxel (Abraxane) 260mg/m^2 in 43 patient who had not previously received therapy for advanced NSCLC.[33] The overall response rate of 16% and median time to progression (TTP) of 6 months were comparable with reports of phase II trials of single agent paclitaxel but without the need for premedication. The median OS was 11 months and 1-year survival rate was 45%. Virtually identical results were seen in a phase I/II trial at a dose of 125mg/m^2 on days 1, 8 and 15 of a 28-day cycle conducted by Rizvi et al.[36] Stinchcombe and colleagues have evaluated Nab-Paclitaxel (Abraxane) in combination with carboplatin in advance solid tumors, including NSCLC, and found that the combination demonstrates level of activity comparable with paclitaxel/carboplatin, with less toxicity.[37] The study enrolled 41 patients and evaluated escalating doses of Nab-Paclitaxel (Abraxane) with 3 different schedules of drug administration (weekly for 3 out of 4 weeks, on days 1 and 8 every 21 days, and on days 1 every 21 days) in combination with a fixed dose of carboplatin area under the curve (AUC) of 6. The primary toxicity of the combination was myelosuppression. The maximum tolerated dose (MTD) for Nab-Paclitaxel (Abraxane) were 100 mg/m^2, 125 mg/m^2 and 300 mg/m^2 for the weekly, days 1 and 8, and every 21-day schedules respectively. Allerton et al also evaluated weekly Nab-Paclitaxel (Abraxane) 100mg/m^2 combined with carboplatin AUC of 6 in 56 patients.[32] They compared the toxicity and outcomes with a similar regimen of carboplatin/paclitaxel and found a comparable level of benefit with less neurotoxicity (0% vs 5%). A large phase I/II study by Hawkins et al evaluated 4 cohorts of patients with previously untreated NSCLC.[34] Nab-Paclitaxel (Abraxane) was administered to cohorts of 25 patients at doses of 225 mg/m^2, 260 mg/m^2, 300 mg/m^2 and 340 mg/m^2 in combination with carboplatin AUC of 6. The response rate was 27% overall, without a clear dose response. More recently, initial results of a randomized phase III trial of Nab-Paclitaxel (Abraxane) and carboplatin compared with paclitaxel and carboplatin as first-line therapy in advanced NSCLC were presented.[38] Patients received carboplatin AUC of 6 every 3 weeks and either Nab-Paclitaxel (Abraxane) at 100 mg/m^2 every week or paclitaxel 200 mg/m^2 every 3 weeks. The primary endpoint of overall response rate was met with a rate of 33% for the Nab-Paclitaxel (Abraxane) group verus 25% for the paclitaxel group. Additionally, Nab-Paclitaxel (Abraxane) was well tolerated with significantly improved safety profile compared to paclitaxel, with decreased rates of neutropenia, neuropathy, myalgia and arthralgias.

In an attempt to further decrease rates of adverse effects, Paik et al has shown that infusion of 125 mg/m^2 of Nab-Paclitaxel (Abraxane) over 2 hours (compared to the standard 30 minutes) on days 1, 8, and 15 of a 28-day cycle for the treatment of advanced NSCLC lead to decreased rates of peripheral neuropathy and neutropenia with similar rates of median overall survival of 11 months.[39]

1.4 Rationale

Unresectable and/or metastatic NSCLC is a cancer with few successful therapeutic options. Since taxanes have been widely used in treating locally advanced non-small cell lung cancer, Nab-Paclitaxel (Abraxane) has demonstrated activity in non-small cell lung cancer and has better side effect profile as compared to Cremophor EL-based paclitaxel and docetaxel as demonstrated in the breast cancer trials and phase I/II NSCLC trials, and potentially better antitumor activity, it is of interest to further explore the use of

Nab-Paclitaxel (Abraxane) in concurrent chemoradiotherapy for treating non-small cell lung cancer.

The investigators at the Vanderbilt University just completed a Phase I trial evaluating weekly nab-paclitaxel/carboplatin with concurrent radiation therapy (66 Gy) in patients with unresectable stage III NSCLC.[40] In that trial, eleven patients were enrolled. Ten patients were treated at 2 dose levels of nab-paclitaxel, 40mg/m^2 (6 pts) and 60mg/m^2 (4 pts). One patient signed consent and then withdrew. Six patients were treated at 40mg/m^2 with no dose limiting toxicities (DLT). Four patients were treated at 60mg/m^2 with 2 DLT of radiation dermatitis and esophagitis. During concurrent treatment, Grade 2 toxicities were fatigue, dehydration, nausea, dysphagia, esophagitis, mucositis, hypoxia, neutropenia, anemia, and thrombocytopenia, and Grade 3 toxicities were neutropenia, mucositis, esophagitis, and dermatitis. No grade 4 toxicities were seen during concurrent treatment. Ten patients were evaluable for response with 9 partial responses and 1 stable disease. Based on these results, the investigators recommended a Phase II dose of weekly nab-paclitaxel to be 40mg/m^2. However we will explore 50 mg/m^2 of nab-paclitaxel as a lead in dose during the initial phase.

We propose this phase I/II study to use weekly Nab-Paclitaxel (Abraxane) and carboplatin with concurrent radiation in local-regionally advanced lung cancer. There are no published human studies combining Nab-Paclitaxel (Abraxane) with radiation. We will first confirm the tolerated dose (TD) of concurrent Nab-Paclitaxel (Abraxane) at 50mg/m^2, and then will begin enrolling patients into the phase II component using either Nab-Paclitaxel (Abraxane) at the TD with carboplatin concurrent with daily radiation or paclitaxel with with carboplatin concurrent with daily radiation.

2.0 OBJECTIVES

2.1 Primary Objective

To determine the 2-year overall survival from randomization for patients receiving carboplatin/paclitaxel or carboplatin/nab-paclitaxel with radiation therapy

2.2 Secondary Objectives

2.2.1 To determine the feasibility of concurrent carboplatin/nab-paclitaxel and radiation therapy as measured by safety and compliance. Safety is measured by the rate of grade 3 or higher radiation related esophagitis or pulmonary toxicity or chemotherapy related grade 4 hematological or other non-hematological toxicities occurring within 60 days of the start of treatment; compliance is defined as the completion of the treatment regimen with no more than minor variations.

2.2.2 To determine the overall response rate for patients receiving carboplatin/paclitaxel or carboplatin/nab-paclitaxel with radiation therapy

2.2.3 To determine the progression-free survival for patients receiving carboplatin/paclitaxel or carboplatin/nab-paclitaxel with radiation therapy

2.2.4 To determine the median overall survival for patients receiving carboplatin/paclitaxel or carboplatin/nab-paclitaxel with radiation therapy

2.2.5 To assess quality of life (QOL) of patients receiving either nab-paclitaxel or paclitaxel when given with concurrent radiotherapy

2.2.6 To correlate outcomes (survival, toxicity, QOL) with biological parameters (future analysis under UTSW tissue bank protocol – see Section 11.0).

3.0 PATIENT SELECTION

3.1 Eligibility

3.1.1 Histologically or cytologically documented NSCLC, including squamous cell carcinoma, adenocarcinoma (including bronchioloalveolar carcinoma), and large cell anaplastic carcinoma (including giant and clear cell carcinomas) and poorly differentiated (not otherwise specified, NOS) non-small cell lung cancer; totally resected tumors are excluded.

- Patients must be M0;
- Patients with T1 or T2 disease with N2 or T3N1-2 disease (Stage IIIA) are eligible.
- Patients with T4 with any N or any T with N3 disease are eligible (Stage IIIB).
- Measurable disease is required. See Section 10.4 for RECIST definitions of measurable disease.

3.1.2 Patients with tumors adjacent to a vertebral body are eligible as long as all gross disease can be encompassed in the radiation boost field. The boost volume must be limited to < 50% of the ipsilateral lung volume.

3.1.3 Patients must be ≥18 years of age

3.1.4 Patients with Zubrod performance status 0-1 (See Appendix A)

3.1.5 Adequate hematologic function defined as: ANC ≥ 1,000/mm^3, platelets ≥ 100,000/mm^3, and hemoglobin ≥ 9 g/dL (prior to transfusions); adequate hepatic function defined as: total bilirubin ≤ 1.5 x upper limit of normal (ULN), AST/SGOT and ALT/SGPT ≤ 2.5 x ULN, adequate renal function defined as Creatinine clearance ≥ 30 mL/minute (calculated by Cockcroft-Gault formula), a serum creatinine level ≤ 1.5 mg/dL alkaline phosphatase ≤ 2.5 x ULN, glucose ≤ 2 x ULN

3.1.6 FEV1 with ≥ 1200 cc or ≥ 50% predicted

3.1.7 Patients with weight loss ≤ 10% over the past 3 months

3.1.8 Patients with a pleural effusion that is a transudate, cytologically negative and non-bloody are eligible if the radiation oncologists feel the tumor can still be encompassed within a reasonable field of radiotherapy (See Sections 6.4 and 6.5). If a pleural effusion can be seen on the chest CT but is too small to tap, the patient is eligible.

3.1.9 Patients who have recovered from exploratory thoracotomy

3.1.10 Women of childbearing potential must have a negative serum pregnancy test performed within 7 days prior to registration

3.1.11 Pretreatment evaluations required for eligibility include:

- A medical history, physical examination, assessment of Zubrod performance status within 4 weeks prior to study entry;
- CBC with differential and platelet count, and laboratory profile must be completed within 4 weeks prior to study entry;
- FEV1, CT scan or MRI of the chest, a bone scan (or PET or PET/CT), and a CT scan or MRI of the brain (to rule out brain metastasis) within 6 weeks prior to study entry;
- Medical Oncology and Radiation Oncology consults and approval.

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

3.2 Conditions for Patient Ineligibility

3.2.1 Prior systemic chemotherapy (for lung cancer) and/or thoracic/neck radiotherapy for any reason and/or surgical resection of present cancer;
3.2.2 Exudative, bloody, or cytologically malignant effusions;
3.2.3 Prior therapy with any molecular targeted drugs (for lung cancer)
3.2.4 Active pulmonary infection not responsive to conventional antibiotics;
3.2.5 Active cardiac disease defined as unstable angina, uncontrolled hypertension, myocardial infarction in the last six months (unless successfully treated with CABG or PTCA), uncontrolled arrhythmia, or congestive heart failure; $\geq$ 3 heart-related hospitalization in the past year.
3.2.6 Patients with > grade 1 neuropathy;
3.2.7 Evidence of malignancy in the past 2 years except for adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, or other *in situ* cancers;
3.2.8 Women who are pregnant or breast feeding, as treatment involves unforeseeable risks to the participant, embryo, fetus, or nursing infant; women with a positive pregnancy test on enrollment or prior to study drug administration;
3.2.9 Women of childbearing potential and male participants who are unwilling or unable to use an acceptable method of contraception throughout the study and for four weeks after completion of treatment or those who are using a prohibited contraceptive method.
3.2.10 Patients who currently are participating in other phase III therapeutic clinical trials and/or who have participated in other phase III therapeutic clinical trials in the previous 30 days.
3.2.11 Uncontrolled hypertension defined as systolic blood pressure > 150 mmHg or diastolic pressure > 90 mmHg, despite optimal medical management
3.2.12 Known human immunodeficiency virus (HIV) infection or chronic Hepatitis B or
3.2.13 Active clinically serious infection > CTCAE Grade 2.
3.2.14 Thrombolic or embolic events such as a cerebrovascular accident including transient ischemic attacks within the past 6 months.
3.2.15 Pulmonary hemorrhage/bleeding event ≥CTCAE Grade 2 within 4 weeks of study registration.
3.2.16 Any other hemorrhage/bleeding event ≥CTCAE Grade 3 within 4 weeks of study registration.
3.2.17 Serious non-healing wound, ulcer, or bone fracture.
3.2.18 Evidence or history of bleeding diathesis or coagulopathy.
3.2.19 Major surgery, open biopsy or significant traumatic injury within 4 weeks of first study drug.
3.2.20 Known or suspected allergy to any agent given in the course of this trial.
3.2.21 Total bilirubin > 1.5x the upper limit of reference range (ULRR)
3.2.22 Creatinine clearance < 30 mL/minute (calculated by Cockcroft-Gault formula).
3.2.23 CTCAE V4.0 grade 3-4 electrolyte abnormalities:
- Calcium < 7 mg/dl or > 12.5 mg/dl;
- Glucose < 40 mg/dl or > 250 mg/dl;
- Magnesium < 0.9 mg/dl or > 3 mg/dl;
- Potassium < 3 mmol/L or > 6 mmol/L;
- Sodium < 130 mmol/L or > 155 mmol/L

3.2.24 Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 × ULRR or alkaline phosphatase (ALP) >2.5 x ULRR.
3.2.25 Evidence of severe or uncontrolled systemic disease or any concurrent condition which in the Investigator's opinion makes it undesirable for the patient to participate in the trial or which could jeopardize compliance with the protocol.
3.2.26 Any unresolved toxicity greater than CTC grade 1 from previous anti-cancer therapy

3.3 Restrictions

Patients who are blood donors should not donate blood during the trial and for 3 months following their last dose of trial treatment.

4.0 RECOMMENDED PRETREATMENT EVALUATIONS

(In addition to required evaluations in Section 3.1.11)

4.1 **PET scan of chest at pretreatment: Highly recommended**.

4.2 **Post-treatment PET scan**

The post-treatment PET scan is also highly recommended on the same scanner (or, if this is not feasible, on the same model PET scanner). The post-treatment PET scan will be done approximately 12-16 weeks after the completion of **all** radiotherapy/chemotherapy that the participant has received. This includes any adjuvant, post-radiotherapy chemotherapy. It will be done no sooner than 12 weeks after the completion of radiotherapy in order to allow for partial resolution of post-treatment inflammatory effects that can cause false positive PET scan results.

4.3 **Patient-Reported Outcomes:** Trial Outcome Index of the Functional Assessment of Cancer Therapy-Lung (FACT-L), FACT-Taxane and EQ-5D

5.0 REGISTRATION PROCEDURES

5.1 **Pre-Registration Requirements**

See study parameters (section 10.1) for a complete list of required pre-registration procedures.

5.2 **Registration**

The coordinating center for this trial will be UT Southwestern. Patients can be registered only after eligibility criteria are met and approved by UTSW. For patients who pass screening, a completed patient registration form, which can be found in your forms binder, and a copy of the signed patient consent will need to be faxed with the provided cover sheet to: **Radiation Oncology Clinical Research, UT Southwestern, fax 214-645-8913.** UTSW will review the eligibility criteria to ensure eligibility and will fax back page 3 of the form which will contain signature and patient study number. If a patient is ineligible or if a waiver is granted, the enrolling institution will be notified of such decision which will include a brief explanation. Any waiver granted for patient eligibility is at the discretion of the principal investigator, Dr. Choy.

5.3 **Written Informed Consent**

Provision of written Informed Consent must be obtained prior to any study-related procedures. The principal investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The principal investigator must store the original, signed written Informed Consent Form. A copy of the signed written Informed Consent Form must be given to the subject. Where genetic analyses are included, special account of these will be made in the consent form, as it is recognized that special provisions need to be made to retain confidentiality of medical information. These factors have been taken into account in the design of the consent form. Consent forms specific for the collection of genotyping samples will be used; the format depends on the design of the study. The subject's signed and dated informed consent(s) must be obtained before conducting any procedure specifically for the study. The principal investigator(s) must store the original, signed written Informed Consent Form(s). A copy of the signed written Informed Consent Form(s) must be given to the subject. If modifications are made according to local requirements, the new version has to be approved by Celgene.

5.4 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), the written Informed Consent Form must include a subject authorization to release medical information to Celgene and/or allow Celgene, a regulatory authority, or Institutional Review Board access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

6.0 RADIATION THERAPY [NOTE: INTENSITY MODULATED RADIOTHERAPY (IMRT) IS ALLOWED]

Questions regarding Radiation Therapy should be directed to Dr. Choy, (preferably by email or alternatively by phone).

Protocol treatment must begin within 4 weeks after patient registration to the trial.

6.1 Dose Specifications

6.1.1 Patients will receive treatment 5 days per week, in once daily fractions, 2 Gy per fraction. **The total dose will be 60 Gy in 30 fractions.** There are no field reductions. All fields must be treated daily and the entire PTV must be treated daily. Radiation therapy (RT) commences within 48 hours of chemotherapy. On days when chemotherapy is given concurrently with RT, chemotherapy is not necessarily administered prior to RT.

6.1.2 Normalization of the treatment plan will cover 95% of the PTV with the prescription dose. The minimum PTV dose must not fall below 95% of the prescription dose. All radiation doses will be calculated with inhomogeneity corrections that take into account the density differences within the irradiated volume (i.e., air in the lung and bone). The MTD will be quoted as the PTV minimum target dose. The maximum and minimum point doses *(within the PTV)* will be reported.

6.1.3 Variations of dose prescription:

6.1.3.1 No deviation: ≥ 95% of the PTV receives the prescribed dose; ≥ 99% of the PTV receives ≥ 93% of the prescribed dose, and no more than 20% of the PTV receives ≥110% of the prescribed dose.

6.1.3.2 Minor deviation: Deviations of this magnitude are not desirable, but are acceptable. Coverage for the dose that is equal to 93% of the prescribed dose falls below 99% of the PTV but not below 95% of this volume. Or, between 20 and 25% of the PTV receives >110% of the prescribed dose.

6.1.3.3 Major deviation: Doses in this region are not acceptable. More than 1 cm^3 of tissue outside the PTV receives ≥ 110% of the prescribed dose. Or, coverage for the dose that is equal to 93% of the prescribed dose falls below 95% of the PTV. Or, > 25% of the PTV receives ≥ 110% of the prescribed dose.

6.1.4 Heterogeneous dose calculations: For the purposes of this protocol, superposition/convolution dose calculation algorithms demonstrate agreement between planned versus delivered dose.

6.2 Technical Factors

6.2.1 Beam Energy: 6 - 18 MV are to be used.
6.2.2 Beam Shaping: Multi-leaf collimation (MLC) or individually-shaped custom blocks should be used to protect normal tissues outside of the target volume.

6.3 Localization, Simulation, and Immobilization

6.3.1 A volumetric treatment planning CT study will be required to define gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV) (see definitions below). Each patient will be positioned in an immobilization device in the treatment position on a flat table. Contiguous CT slices, having 3 mm thickness through the regions harboring gross tumor and grossly enlarged lymph nodes and 8-10 mm thickness of the remaining regions are to be obtained starting from the level of the cricoid cartilage and extending inferiorly through the entire liver volume. The GTV, CTV, and PTV and normal organs will be outlined on all appropriate CT slices.

6.3.2 A treatment planning FDG PET/CT scan (or FDG-PET alone) with the patient in the treatment position is encouraged for treatment planning. In the case where the PET/CT is obtained in the treatment position, the CT from this study may be used as the planning CT scan.

6.3.3 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 can be overridden or the contrast scan must be registered to a non-contrast scan for planning purposes.

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

6.3.5 The use of four-dimensional radiation treatment planning is highly encouraged. Acceptable methods of accounting for tumor motion include: design of the PTV to cover the excursion of the lung primary cancer and nodes during breathing such as an ITV approach, a maximum intensity projection (MIP) approach, automatic breath-hold (i.e., Elekta ABC device) or a gating approach (e.g., Varian RPM system).

6.4 Treatment Planning/Target Volumes

6.4.1 Target Volumes: The definitions of volumes will be in accordance with the 1993 ICRU Report #62

6.4.1.1 Definition of the GTV: The primary tumor and clinically positive lymph nodes seen either on the planning CT (> 1 cm short axis diameter) or pretreatment PET scan (SUV > 3) will constitute the GTV. This volume(s) may be disjointed. In the event of a collapsed lobe or lung segment, the use of PET to distinguish tumor from fluid/atelectasis is encouraged. The ITV includes the envelope that encompasses the tumor motion for a complete respiratory cycle.

6.4.1.2 Definition of the CTV: The CTV is defined to be the GTV plus a 0.5 cm to 1 cm margin as appropriate to account for microscopic tumor extension. If an ITV approach is used then the ITV plus 0.5 cm to 1 cm is added to the ITV to form the CTV. Elective treatment of the mediastinum and supraclavicular fossae will not be done.

6.4.1.3 Definition of the PTV:

Non-ITV approach:

There are two components to the PTV expansion if the ITV approach is not used. The first is a margin to account for motion (IM margin) which should be at least 1 cm in the inferior-superior direction, and 0.5 cm in the axial plane. An additional 0.5 – 1.0 cm margin should be added to account for setup uncertainty (SU margin). If the ITV approach is NOT used then the total PTV includes the CTV plus a total margin of 1.5 to 2.0 cm to the superior-inferior dimensions and 1.0 to 1.5 cm in the axial plane. If daily imaging is used to align vertebrae on a daily basis we recommend using the smaller of these margins.

ITV approach:

If the ITV approach is used, then the PTV margin should account for setup uncertainties and may be individualized but should not be less than 1.0 cm. If daily imaging is used to align the vertebral bodies, then the margins for setup margins may be reduced to 0.5 cm.

For institutions not using 4DCT, the use of fluoroscopy to determine the margin for motion in the inferior superior direction is encouraged.

For institutions with gating technology, the use of respiratory gating is encouraged.

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

6.4.2 Treatment Planning:

6.4.2.1 3D Conformal Therapy The PTV is to be treated with any combination of coplanar or noncoplanar 3-dimensional conformal fields shaped to deliver the specified dose while restricting the dose to the normal tissues. Field arrangements will be determined by 3D planning to produce the optimal conformal plan in accordance with volume definitions. The treatment plan used for each patient will be based on an analysis of the

volumetric dose including DVH analyses of the PTV and critical normal structures. Each field is to be treated daily.

6.4.2.2 Intensity Modulated Radiation Therapy (IMRT): IMRT is allowed for intra-thoracic IMRT treatments.

6.5 Critical Structures

Normal tissue constraints shall be prioritized in the following order for treatment planning: 1=spinal cord, 2=lungs, 3=esophagus, 4=brachial plexus, and 5=heart.

6.5.1 **Spinal Cord:** The spinal cord dose limitation is the highest priority dose constraint and thus must be met irrespective of other constraints. Total "direct" dose to the spinal cord must not exceed 48 Gy, and total dose must not exceed 50.5 Gy (counting scatter dose).

6.5.2 **Lungs:** The dose-volume constraint to the lungs is the second highest priority and must be met, except if it conflicts with the cord dose constraints. The volume of *both* lungs that receive more than 20 Gy (the V_{20}) should not exceed 37% of the total. Alternatively, the mean lung dose should optimally be $\leq$ 20 Gy. (By total lung volume we mean the total lung minus the CTV).

6.5.2.1 If either of these constraints is exceeded, several solutions can be entertained.
First, one might increase the weighting of AP/PA treatments by one and reduce the obliques. This can be done as long as the cord dose (above), which takes precedence, is not exceeded.
Second, one can reduce the CTV to the minimum range suggested above.
Third, one can try to reduce the PTV by using respiratory gating techniques.
If after all attempts to decrease the V_{20} to below 37%, the V_{20} value still exceeds this limit, the patient should be treated to the dose specified

6.5.3 **Esophagus:** The mean dose to the esophagus is optimally kept below 34 Gy.[41,42] 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.

6.5.4 **Brachial Plexus:** Brachial plexus doses should be kept <66 Gy.

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

6.5.6 **Skin:** Care should be taken to minimize the volume of skin receiving the full dose. No "hot spot" (except within pure tumor) should exceed 120%.

6.6 Documentation Requirements

6.6.1 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.

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

6.6.3 Isodose plans for 3-D radiotherapy and IMRT and DVHs of GTV, CTVs, and critical normal structures for IMRT.

6.7 Compliance Criteria

See Section 6.1.3 for radiation dose compliance criteria.

6.8 R.T. Quality Assurance Review

The Radiation Oncology Principal Investigator, Hak Choy, M.D., will perform an RT Quality Assurance Remote Review after complete data for the first 20 cases enrolled have been received at the UTSW. Dr. Choy will perform the next remote review after complete data for the next 20 cases enrolled have been received at the UTSW. 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 have been received at UTSW, whichever occurs first.

The Radiation Therapy Quality Assurance (RTQA) Review will be performed by Hak Choy, M.D. All of the materials listed below should be forwarded to:

Jean Wu
Clinical Research Manager
Department of Radiation Oncology
5641 Southwestern Medical Ave.
Dallas, Texas 75235-8808
214-648-1892
Fax: 214-645-8913
Jean.Wu@UTSouthwestern.edu

6.9 Radiation Therapy Adverse Events

6.9.1 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 occur 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 six months after initiation of treatment. It is essential to spare as much normal lung as possible in order to avoid symptomatic lung injury.

6.9.2 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 Xylocaine, Carafate, or other medications should be used for symptomatic relief. Occasionally, 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, and a treatment interruption is being considered, every effort should be made to limit it to 3 treatment days or less. Patients requiring hospitalization because of esophagitis may have their treatment interrupted. In this event, please notify Dr. Choy.

Esophagitis should be graded according to the CTCAE v.4.0

Table 1: Esophagitis grading system

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

Treatment should be interrupted for grade 4 or greater dysphagia or odynophagia. Acute esophageal toxicity, which typically can occur within two weeks of the initiation of treatment and manifests as dysphagia, odynophagia, reflux symptoms, etc. should be pharmacologically managed with the following approach and should be initiated at the first signs or symptoms of esophageal toxicity. Recommended treatments are in Table 2.

Table 2: Suggestions for management of radiation esophagitis

1) Ketoconazole 200 mg PO q day **OR**
2) Fluconazole 100 mg PO q day until the completion of radiation
3) Mixture of: 2% viscous lidocaine: 60 cc
   Mylanta: 30 cc
   Sucralfate (1 gm/ 10cc): 10 cc
   Take 15-30 cc of mixture PO q3-4 hrs prn.
   (*Contraindications: pts on Dilantin, Cipro, Digoxin*)
4) Ranitidine 150 mg PO BID (or other H2 blocker or a proton pump inhibitor such as omeprazole)until the completion of radiation
5) Grade 4 esophagitis: hold RT + chemotherapy until grade 2 or less. We expect a significant portion of patients will experience grade 3 esophagitis.

6.10 Functional Imaging

FDG-PET functional imaging is not a required component of this protocol, but is strongly encouraged for cancer staging.

6.10.1 Adverse Events

Adverse events from FDG-PET are exceedingly rare. If an adverse event from functional imaging is to occur, it would most likely be related to the intravenous catheter infusion site, consisting of erythema and discomfort from the IV. An allergic reaction to the FDG is possible as well.

6.11 Radiation Adverse Event Reporting

See Section 9.0 for Adverse Event Reporting.

7.0 DRUG THERAPY

7.1 Treatment Plan

This is a multi-center randomized phase I/II study evaluating 60 Gy chemoradiation therapy with carboplatin/paclitaxel or carboplatin/nab-paclitaxel in patients with locally advanced NSCLC. Nab-paclitaxel will be administered (in conjunction with carboplatin) to the patients at a planned dose run-in of 50 mg/m^2 during the initial feasibility testing phase followed by 50 mg/m^2 during the phase II stage intravenously in a weekly manner if no more than 1 dose limiting toxicities (DLT) are observed. If more than 1 DLTs are observed in the phase I stage, then a dose level of 40 mg/m^2 will be used in the phase II stage. During the consolidation phase, a 100mg/m^2 weekly dose of nab-paclitaxel (in conjunction with carboplatin) will be administered.

Phase 1 (Feasibility Testing): Nab-paclitaxel dose during the concurrent phase (in conjunction with weekly carboplatin AUC=2)

Level	Dose	# of patients
1	50 mg/m^2	initially 3, then if there are < or = 1 DLT increase to 6
-1	40 mg/m^2	

(continue to phase 2 using dose level 1 if < or = 1 DLT total out of the 6 patients; if > 1 DLT, use dose level -1 in phase 2 stage)

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for grading of all adverse events. A copy of the CTCAE v4.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov). A DLT will be considered if it is deemed to be definitely or probably related to treatment.

We define dose-limiting toxicity (DLT) as:

- **Any ≥ grade 4 hematologic toxicity that lasted ≥ 7 days**
- **Any ≥ grade 3 other non-hematologic toxicity that lasted ≥ 7 days (excluding esophagitis, nausea, vomiting, and alopecia)**
- **Grade 3 or 4 febrile neutropenia**

Based on the Phase I stage, 40mg/m2 of nab-paclitaxel will be administered during the concurrent chemoradiation phase.

7.1.1 Concurrent Chemoradiation (Weeks 1-6)

During the concurrent phase of treatment patients will receive paclitaxel 50 mg/m² over 60 minutes and carboplatin AUC=2 over 30 minutes administered weekly for 6 weeks (6doses) or will receive nab-paclitaxel 40 mg/m^2 based on phase I stage over 30 minutes and carboplatin AUC=2 over 30 minutes administered weekly for 6 weeks (6doses). Weekly administration of nab-paclitaxel or paclitaxel with carboplatin will be considered as one cycle for a total of 6 cycles administered. Patients need to be pre-medicated prior to paclitaxel infusion (see section 7.3.4).

7.1.2 Consolidation Therapy (Weeks 10-16)

Beginning on week 10 (3 weeks post concurrent therapy), paclitaxel will be administered at 200 mg/m² over 3 hours and carboplatin at AUC=6 *IV* over 30 minutes or nab-paclitaxel will be administered at 100 mg/m² over 30 minutes and carboplatin at AUC=6 *IV* over 30 minutes. Paclitaxel and carboplatin will be delivered every 3 weeks for 2 cycles or nab-paclitaxel will be delivered on days 1, 8 and 15 (of a 21 day cycle) and carboplatin will be delivered on day 1 (of a 21 day cycle) for 2 cycles. Patients need to be pre-medicated prior to paclitaxel infusion (see section 7.3.4).

7.2 Nab-Paclitaxel (ABI-007, Abraxane, albumin-bound paclitaxel)

7.2.1 Description: NAB-PACLITAXEL (ABRAXANE) for Injectable Suspension (also known as ABI-007, nab-paclitaxel, paclitaxel protein-bound particles for injectable suspension) is an albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers. Paclitaxel exists in the particles in a non-crystalline, amorphous state. NAB-PACLITAXEL (ABRAXANE) is supplied as a

white to yellow, sterile, lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous infusion. Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel. NAB-PACLITAXEL (ABRAXANE) is free of solvents. The active agent in NAB-PACLITAXEL (ABRAXANE) is paclitaxel.

7.2.2 Potential Risks of NAB-PACLITAXEL (ABRAXANE) Toxicities

Myelosuppression, nausea and vomiting, diarrhea, mucositis, infections, hypotension, abnormal ECG changes, cough, dyspnea, edema, sensory neuropathy, bilirubin/liver enzyme elevations, allergic reactions, alopecia, asthenia, arthralgia, and myalgia. During post marketing surveillance, rare cases of severe hypersensitivity reactions have occurred.

Table 3: Frequency[a] of Important Treatment Emergent Adverse Events in the Randomized Study on an Q3W Schedule

	Percent of Patients	
	NAB-PACLITAXEL (ABRAXANE) 260/30min[b] (n=229)	**Paclitaxel Injection 175/3h[c,d] (n=225)**
Bone Marrow		
Neutropenia $< 2.0 \times 10^9$/L $< 0.5 \times 10^9$/L	80 9	82 22
Thrombocytopenia $< 100 \times 10^9$/L $< 50 \times 10^9$/L	2 <1	3 <1
Anemia < 11 g/dL < 8 g/dL	33 1	25 <1
Infections	24	20
Febrile Neutropenia	2	1
Bleeding	2	2
Hypersensitivity Reaction[e]		
All	4	12
Severe[f]	0	2
Cardiovascular		
Vital Sign Changes[g]		
Bradycardia	<1	<1
Hypotension	5	5
Severe Cardiovascular Events[f]	3	4
Abnormal ECG		
All patients	60	52
Patients with Normal Baseline	35	30
Respiratory		
Cough	7	6
Dyspnea	12	9
Sensory Neuropathy		
Any Symptoms	71	56
Severe Symptoms[f]	10	2
Myalgia / Arthralgia		
Any Symptoms	44	49
Severe Symptoms[f]	8	4

Table 3 (continued): Frequency[a] of Important Treatment Emergent Adverse Events in the Randomized Study on an Every-3-Weeks Schedule

Percent of Patients		
	NAB-PACLITAXEL (ABRAXANE)® 260/30min[b] (n=229)	**Paclitaxel Injection 175/3h[c,d] (n=225)**
Asthenia		
Any Symptoms	47	39
Severe Symptoms[f]	8	3
Fluid Retention/Edema		
Any Symptoms	10	8
Severe Symptoms[f]	0	<1
Gastrointestinal		
Nausea		
Any symptoms	30	22
Severe symptoms[f]	3	<1
Vomiting		
Any symptoms	18	10
Severe Symptoms[f]	4	1
Diarrhea		
Any Symptoms	27	15
Severe Symptoms[f]	<1	1
Mucositis		
Any Symptoms	7	6
Severe Symptoms[f]	<1	0
Alopecia	90	94
Hepatic (Patients with Normal Baseline)		
Bilirubin Elevations	7	7
Alkaline Phosphatase Elevations	36	31
AST (SGOT) Elevations	39	32
Injection Site Reaction	<1	1

[a] Based on worst grade

[b] NAB-PACLITAXEL (ABRAXANE) dose in mg/m^2/duration in minutes

[c] paclitaxel injection dose in mg/m^2/duration in hours

[d] paclitaxel injection pts received premedication

[e] Includes treatment-related events related to hypersensitivity (e.g., flushing, dyspnea, chest pain, hypotension) that
began on a day of dosing.

[f] Severe events are defined as at least grade 3 toxicity

[g] During study drug dosing.

7.2.3 Nab-Paclitaxel (Abraxane) Premedication

Patients do not require premedication prior to NAB-PACLITAXEL (ABRAXANE) administration, as hypersensitivity reactions are rare.

Although the solubilizing agents Cremophor® EL and Tween® 80 have long been implicated in adverse events including hypersensitivity reactions due to their detergent-like nature and known ability to induce histamine release,[43] the administration of solvent-based taxanes (Taxol® and Taxotere®) requires premedication with corticosteroids and histamine receptor blocking agents to prevent the occurrence of hypersensitivity reactions. However, the hypersensitizing role of the taxane molecules themselves cannot be ruled out.

In the unlikely event of a mild hypersensitivity reaction, premedication may be administered using the premedication regimen the institution typically uses for solvent based paclitaxel.

In the rare event of a severe hypersensitivity reaction, discontinue NAB-PACLITAXEL (ABRAXANE).

7.2.4 Study Medication Administration

Nab-paclitaxel will be administered over 30 minutes for both the concurrent and consolidative phases.

NOTE: For NAB Paclitaxel (ABRAXANE) the use of inline filters is not recommended because the reconstituted solution may clog the filter.

7.2.5 Dose Modifications/Reductions

Administration of Study Drug to Patients with Abnormal Hematologic Function

NAB-PACLITAXEL (ABRAXANE) dosing should not be administered at the start of each cycle (day 1 of q weekly cycle during the concurrent phase and day 1 of a 21 day cycle during the consolidation phase) until the absolute neutrophil count returns to $\geq 1.0 \times 10^9$ cells/L and the platelet count returns to $\geq 75 \times 10^9$ cells/L. For patients receiving weekly NAB-PACLITAXEL (ABRAXANE) for a 21 day cycle, for each subsequent dose of NAB-PACLITAXEL (ABRAXANE) within a cycle (Days 8 and 15), patients must have an ANC $\geq 1.0 \times 10^9$ cells/L and platelets $\geq 75 \times 10^9$ cells/L. If the ANC and platelets are not adequate for treatment on Day 8 and/or 15, the dose will be omitted and the total cycle length remains the same (21 days).

Administration of Study Drug to Patients with Abnormal Hepatic Function

Study drug should only be administered if hepatic function is within the parameters established in the eligibility criteria. Hepatic toxicity from taxanes may occur but it is uncommon. Therefore, hepatic dysfunction that occurs while the patient is on study should prompt an evaluation to determine the cause, including the possibility of progressive metastatic disease and hepatotoxicity from concurrent medications.

Sensory Neuropathy

NAB-PACLITAXEL (ABRAXANE) should be withheld in patients who experience ≥ Grade 3 sensory neuropathy. Treatment may be resumed at the next lower dose level (see Table 5) in subsequent cycles after the sensory neuropathy improves to ≤ Grade 1. The time to resolution to Grade ≤ 1 should be the adverse event duration used for adverse event reporting. In those patients who

experience Grade 4 sensory neuropathy, study drug should be withheld, and treatment resumed at a reduction of 2 dose levels (Dose Level -1; see Table 5) in subsequent cycles after the sensory neuropathy improves to ≤ Grade 1. Note: the investigator may elect to dose modify for Grade 3 sensory neuropathy.

Hypersensitivity Reactions

Hypersensitivity reactions rarely occur. If they do occur, minor symptoms such as flushing, skin reactions, dyspnea, lower back pain, hypotension, or tachycardia may require temporary interruption of the infusion. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema or generalized urticaria require immediate discontinuation of study drug administration and aggressive symptomatic therapy. Patients who experience a severe hypersensitivity reactions to NAB-PACLITAXEL (ABRAXANE) should not be re-challenged. It is not recommended to administer NAB-PACLITAXEL (ABRAXANE) to patients with prior hypersensitivity to a taxane.

Other Toxicities

If toxicities are ≥ grade 3, except for anemia, treatment should be withheld until resolution to ≤ grade 1 or baseline if baseline was greater than grade 1, then reinstituted, if medically appropriate, at the next lower dose level (see Table 5).

Concomitant Medications

Supportive care, including but not limited to anti-emetic medications, may be administered at the discretion of the Investigator. Concurrent treatment with bisphosphonates is allowed. Erythropoietin may be administered at the discretion of the investigator, consistent with institutional guidelines.

7.2.6 Packaging, Labeling, and Storage of Study Drug

Availability

NAB-PACLITAXEL (ABRAXANE) will be supplied by Celgene Corporation. Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel.

Storage and Stability

Storage: Store the vials in original cartons at 20º C to 25º C (68º F to 77ºF). Retain in the original package to protect from bright light.
Stability: Unopened vials of NAB-PACLITAXEL (ABRAXANE) are stable until the date indicated on the package when stored between 20ºC to 25ºC (68ºF to 77ºF), in the original package. Neither freezing nor refrigeration adversely affects the stability of the product.

Stability of Reconstituted Suspension in the Vial

Reconstituted NAB-PACLITAXEL (ABRAXANE) should be used immediately, but may be refrigerated at 2ºC to 8ºC (36ºF to 46ºF) for a maximum of 8 hours if necessary. If not used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from bright light. Discard any unused portion.

Stability of Reconstituted Suspension in the Infusion Bag

The suspension for infusion prepared as recommended in an infusion bag should be used immediately, but may be stored at ambient temperature (approximately 25º C) and lighting conditions for up to 8 hours.

Study Medication Administration

NAB-PACLITAXEL (ABRAXANE) is injected into a vein [intravenous (I.V.) infusion] over 30 minutes. The use of an in-line filter is not recommended.

Reconstitution and use of NAB-PACLITAXEL (ABRAXANE)

1. Calculate the patient's body surface area at the beginning of the study and if the weight changes by > 10% by using the formula provided in the study manual.
2. Calculate the total dose (in mg) to be administered by:
   - **Total Dose (mg) = BSA x (study dose mg/m2)**
3. Calculate the total number of vials required by:

   Total Number of Vials = $\frac{\text{Total Dose (mg)}}{\text{100 (mg/vial)}}$

   Round up the number of vials to be reconstituted to the next higher whole number when a fractional number of vials is obtained by the above formula (eg, if the total number of vials = 4.05 or 4.5, then 5 vials would be reconstituted).
4. Using sterile technique, prepare the vials for reconstitution.
5. Swab the rubber stoppers with alcohol.
6. Aseptically, reconstitute each NAB-PACLITAXEL (ABRAXANE) vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP.
   - **Slowly** inject the 20 mL of 0.9% Sodium Chloride Injection, USP, over a minimum of **1 minute**, using the sterile syringe directing the solution flow onto the **inside wall** of the vial.
   - **DO NOT INJECT** the 0.9% Sodium Chloride Injection, USP solution directly onto the lyophilized cake as this will result in foaming.
   - Once the injection is complete, allow the vial to sit for a **minimum of 5 (five) minutes** to ensure proper wetting of the lyophilized cake/powder.
   - **Gently** swirl and/or invert the vial **slowly** for at least **2 minutes** until complete dissolution of any cake/powder occurs. Avoid generation of foam. Rapid agitation or shaking will result in foaming.
   - If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides.
   - Each ml of reconstituted product will contain 5 mg of paclitaxel.
7. Calculate the exact total dosing volume of 5 mg/ml suspension required for the patient:
   - **Dosing volume (ml) = Total dose (mg) / 5 (mg/ml)**
8. The reconstituted suspension should be milky and homogeneous without visible particulates. If particulates or settling are visible, the vial should be **gently** inverted again to ensure complete resuspension prior to use. Discard the reconstituted suspension if precipitates are observed.
9. Once the exact volume of reconstituted NAB-PACLITAXEL (ABRAXANE) has been withdrawn from the vials, discard any excess solution left over in accordance with standard operating procedures.
10. Further dilution is not necessary. Draw up the calculated dosing volume of the

reconstituted NAB-PACLITAXEL (ABRAXANE) suspension into a syringe and administer via a syringe pump or inject the dose into an emptysterile, standard PVC IV bag using an injection port if the dose volume is large enough to infuse the entire dose through a standard infusion pump. If a standard PVC IV bag is used, inject perpendicularly into the center of the injection port to avoid dislodging plastic material into the IV bag.

11. Administer the calculated dosing volume of reconstituted NAB-PACLITAXEL (ABRAXANE) suspension by IV infusion over 30 minutes. The use of in-line filters is not recommended because the reconstituted solution may clog the filter.

7.2.7 Drug Distribution and Destruction

- Supplier

Celgene Corporation
86 Morris Avenue
Summit, NJ 07901

Industry Contact:

Norma Powers
Director, Medical Operations
Celgene Corporation
86 Morris Avenue
Summit, NJ 07901
Mobile: 267-337-2720
Fax: 908-673-2779
Email: npowers@celgene.com

- Drug Distribution

  NAB-PACLITAXEL (ABRAXANE) will be distributed by Celgene Corporation. No supplies will be shipped to any site until regulatory approval has been obtained. Investigational sites will be supplied with NAB-PACLITAXEL (ABRAXANE) upon identification and screening of a potential trial subject.

  Upon identification of a potential subject, sites must fax a completed Drug Request Form to Celgene Corporation. Allow at least 5 working days for drug shipment. There are no shipments on Fridays or holidays.
  For re-supply of drug, please complete and fax the Drug Request Form to Celgene Corporation at 908-673-2779

- Drug Return and Destruction

  If the investigational site does not have a policy, procedure or SOP detailing the process to follow for study drug destruction, the study drug must then be returned to Celgene using the Drug Return Form provided in the package containing the study drug. The following information must be recorded on the site's pharmacy drug accountability log: quantity of vials to be returned, expiration date and lot number. A copy of the Drug Return Form and the study drug should be returned to Celgene Clinical Supplies Dept. using the mailing address on the packaging slip that came with the original study drug order. A copy of the Drug Return Form should be retained at the clinical site. In the event of study completion or termination, a copy of all pharmacy

records (drug dispensing log, drug accountability log and any destruction memos) must be mailed to Celgene Medical Operations.

If the investigational site has a policy, procedure or SOP detailing the process to follow for study drug destruction, the pharmacist or designee can choose to destroy the study drug on site. The following information must be recorded on the site's pharmacy drug accountability log: quantity of vials destroyed, expiration date and lot number. The pharmacist must document that the study drug was destroyed in accordance with their institution's drug destruction policy or SOP. A drug destruction memo and the site's drug destruction SOP/policy should be sent to Celgene Medical Operations Dept. A copy of the drug destruction memo should be retained at the clinical site. In the event of study completion or termination, a copy of all pharmacy records (drug dispensing log, drug accountability log and any destruction memos) must be mailed to Celgene Medical Operations.

7.3 Paclitaxel

7.3.1 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.

7.3.2 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 USP 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.

7.3.3 Administration*:* Paclitaxel will be administered as a 60 minute IV infusion for the concurrent phase and as a 3 hours IV infusion for the consolidation phase 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. A 0.22 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.

7.3.4 Patients will receive prophylactic antiallergy premedication prior to paclitaxel administration as follows:
Dexamethasone: 20 mg *IV* approximately 30 minutes prior to paclitaxel
Diphenhydramine: 50 mg *IV* x 1 dose 30 min prior to paclitaxel
Ranitidine: 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.

7.3.4 Storage*:* Paclitaxel vials should be stored between 2°- 25°C (36°-77°F).

7.3.5 Adverse Effects:
- Hematologic: Myelosuppression
- Gastrointestinal: Nausea and vomiting; diarrhea, stomatitis, mucositis, pharyngitis, typhlitis, 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.

7.3.6 Supply: Paclitaxel is commercially available.

7.4 Carboplatin

7.4.1 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.

7.4.2 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:

Vial Strength	Diluent Volume
50 mg	5 ml
150 mg	15 ml
450 mg	45 ml

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.

7.4.3 Administration: Carboplatin will be administered after paclitaxel/nab-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.

The dose of carboplatin is calculated (in mg, not mg/m^2) as follows, using the modified Calvert formula based on creatinine clearance:

AUC dose = Target AUC* x (creatinine clearance + 25)

The *Target AUC for carboplatin treatment is AUC=2 (concurrent therapy) or AUC=6 (consolidation therapy).

The creatinine clearance used to calculate the carboplatin dose will be estimated, based on serum creatinine, using the Cockroft-Gault formula (In the Calvert Formula to calculate AUC based dosing using the Cockcroft Gault equation to calculate CrCl, the CrCl should not exceed 125mL/min):

Table 4

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:

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

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

7.4.5 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

7.4.6 Supply: Carboplatin is commercially available.

7.5 Dose Modifications

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

Table 5:

Dose Levels of Paclitaxel and Carboplatin

	Starting Dose	Dose Level -1	Dose Level -2
Concurrent Therapy[a]			
Paclitaxel	50 mg/m^2	NA	NA
Nab-Paclitaxel	50 mg/m^2	40 mg/m^2	NA
Carboplatin	AUC=2	NA	NA
Consolidation Therapy[b]			
Paclitaxel	200 mg/m^2	150 mg/m^2	NA
Nab-Paclitaxel	100 mg/m^2	80 mg/m^2	NA
Carboplatin	AUC=6	AUC=4.5	NA

[a] For concurrent therapy, paclitaxel and carboplatin doses will not be adjusted.

[b] For consolidation therapy, dose reductions of paclitaxel, nab-paclitaxel and carboplatin below the -1 dose level will not be allowed.

7.5.2 Dose Modifications During Concurrent Therapy

7.5.2.1 Paclitaxel/nab-Paclitaxel/Carboplatin Dose Modifications for Hematologic Toxicity

Table 6:

Toxicity NCI CTCAE Grade (CTCAE v4.0)	**Paclitaxel Dose At Start of Subsequent Cycles of Therapy** [a]	**Nab-Paclitaxel Dose at Start of Subsequent Cycles of Therapy** [a]	**Carboplatin Dose at Start of Subsequent Cycles of Therapy** [a]
Neutropenia			
1 (1500-1999/mm^3)	Maintain dose level	Maintain dose level	Maintain dose level
2 (1000-1499/mm^3)	Maintain dose level	Maintain dose level	Maintain dose level
3 (500-999/mm^3)	Hold therapy[b]	Hold therapy [b]	Hold therapy [b]
4 (< 500/mm^3)	Hold therapy[b]	Hold therapy [b]	Hold therapy [b]
Neutropenic fever	Hold therapy[b]	Hold therapy[b]	Hold therapy[b]
Thrombocytopenia			
1 (< LLN-75,000/mm^3)	Maintain dose level	Maintain dose level	Maintain dose level
2 (50,000-74,999/mm^3)	Hold therapy [b]	Hold therapy [b]	Hold therapy [b]
3 (25,000-49,999/mm^3)	Hold therapy[b]	Hold therapy [b]	Hold therapy [b]
4 (< 25,000/mm^3)	Hold therapy [b]	Hold therapy [b]	Hold therapy [b]

[a]Dose levels are relative to the starting dose in the previous cycle. For concurrent therapy, paclitaxel and carboplatin doses will not be adjusted.

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

7.5.2.2 If paclitaxel, nab-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 concurrent therapy.

7.5.2.3 Paclitaxel/nab-Paclitaxel/Carboplatin Dose Modifications for Non-Hematologic Toxicity During Concurrent Therapy

Table 7:

Worst Toxicity NCI CTCAE Grade (CTCAE v4.0) [a, c]	**Paclitaxel Dose At Start of Subsequent Cycles Of Therapy** [b]	**Nab-Paclitaxel Dose At Start of Subsequent Cycles of Therapy** [b]	**Carboplatin Dose At Start of Subsequent Cycles of Therapy** [b]
Neuropathy			
≤ Grade 1	Maintain dose level	Maintain dose level	Maintain dose level
Grade 2	Hold therapy until Grade ≤ 1; restart at full dose[d]	Hold therapy until Grade ≤ 1; restart at full dose[d]	Maintain dose level
Grade 3	Discontinue therapy	Discontinue therapy	Maintain dose level
Other non-hematologic toxicities			
Grade 4	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2

[a] For ≤ CTCAE Grade 2 non-hematologic toxicity not described above, excluding neuropathy, maintain dose level of all study. For neuropathy, follow the guidelines listed above.

[b] Dose levels are relative to the starting dose in the previous cycle. For concurrent therapy, paclitaxel and carboplatin doses will not be adjusted.

[c] 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.

[d] See Section 7.5.2.5 for further neuropathy details.

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7.5.2.4 *Carboplatin Dose Modifications for Renal Toxicity*

A > 25% change in the renal function, based on weekly calculated creatinine clearance, will warrant a recalculation of the carboplatin dose.

7.5.2.5 *Paclitaxel/nab-paclitaxel Dose Modifications for Neuropathy*

If paclitaxel/nab-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 7.5.2.2).

7.5.2.6 If there is a decline in Zubrod performance status to ≥ 2 for greater than 2 weeks while under treatment, radiotherapy should be held with no further chemotherapy administered. Re-evaluate patient after one week for resumption of radiotherapy.

7.5.2.7 Paclitaxel/Nab-paclitaxel/Carboplatin/RT Dose Modifications for In RT Field, Non-Hematologic Toxicity During Concurrent Therapy.

Table 8:

Treatment Modification for In-field Non-Hematologic Toxicity					
In-field	**CTCAE Toxicity Grade**	**XRT**	**Paclitaxel**	**Nab-Paclitaxel**	**Carboplatin**
Esophagus/pharynx *(on day of XRT)*	4	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2
Esophagus/pharynx *(on day of chemo)*	3	No change or hold ≤ 5 days	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2
Esophagus/pharynx *(on day of chemo)*	2	No change	No change	No change	No change
Pulmonary	4	Discontinue	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2
Pulmonary	3	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2
Skin	4	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2
Skin	3	No change	No change	No change	No change

7.5.2.8 For infield esophagitis, see the table 8 in section 7.5.2.7. and table 2 in Section 6.9.2 for treatment recommendations. Re-evaluate patient weekly.

7.5.2.9 For dermatitis or other in-field radiotherapy-related toxicity, see the table 8 in section 7.5.2.7. On day of chemotherapy administration during any treatment week, omit paclitaxel/nab-paclitaxel and carboplatin until toxicity resolves to grade ≤ 2 as detailed in table 8.

7.5.2.10 Radiotherapy should be interrupted for Grade 4 toxicity, including Grade 4 esophagitis or pulmonary toxicity and resumed according to the table 8 in Section 7.5.2.7. If treatment is interrupted for > 2 weeks, protocol treatment should be discontinued. Follow up and data collection will continue as specified in the protocol. Further treatment off protocol is at the discretion of the treating physician. If the patient experiences esophagitis so that *IV* fluid support is needed, insertion of a feeding tube should be considered.

7.5.3 Dose Modifications During Consolidation Therapy

7.5.3.1 Paclitaxel/Nab-paclitaxel/Carboplatin Dose Modifications for Hematologic Toxicity

Table 9:

Toxicity NCI CTCAE Grade (CTCAE v4.0)	**Paclitaxel Dose At Start of Subsequent Cycles of Therapy** [a, c]	**Nab-Paclitaxel Dose at Start of Subsequent Cycles of Therapy** [a, c]	**Carboplatin Dose at Start of Subsequent Cycles of Therapy** [a, c]
Neutropenia			
1 (1500-1999/mm^3)	Maintain dose level	Maintain dose level	Maintain dose level
2 (1000-1499/mm^3)	. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 1,000 mm^3	. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 1,000 mm^3	. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 1,000 mm^3
3 (500-999/mm^3)	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 1,000 mm^3	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 1,000 mm^3	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 1,000 mm^3
4 (< 500/mm^3)	Hold therapy[b] and decrease by 1 dose level when ≥ 1,000 mm^3	Hold therapy[b] and decrease by 1 dose level when ≥ 1,000 mm^3	Hold therapy[b] and decrease by 1 dose level when ≥ 1,000 mm^3
Neutropenic fever	Hold therapy[b] and decrease by 1 dose level when ≥ 1,000 mm^3	Hold therapy[b] and decrease by 1 dose level when ≥ 1,000 mm^3	Hold therapy[b] and decrease by 1 dose level when ≥ 1,000 mm^3
Thrombocytopenia			
1 (≥ 75,000/mm^3)	Maintain dose level	Maintain dose level	Maintain dose level
2 (50,000 - 74,999/ mm^3)	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 75,000 mm^3	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 75,000 mm^3	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 75,000 mm^3
3 (25,000- 49,999/ mm^3)	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 75,000 mm^3	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 75,000 mm^3	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 75,000 mm^3
4 (< 25,000/mm^3)	Hold therapy[b] and decrease by 1 dose level when ≥ 75,000 mm^3	Hold therapy[b] and decrease by 1 dose level when ≥ 75,000 mm^3	Hold therapy[b] and decrease by 1 dose level when ≥ 75,000 mm^3

[a] Dose levels are relative to the worst toxicities in the previous cycle. For consolidation therapy, dose reductions of paclitaxel/nab-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.

7.5.3.2 Paclitaxel/Nab-paclitaxel/Carboplatin Dose Modifications for Non-Hematologic Toxicity During Consolidation Therapy

Table 10:

Worst Toxicity NCI CTCAE Grade (CTCAE v4.0) [a]	**Paclitaxel Dose At Start of Subsequent Cycles of Therapy** [b]	**Nab-Paclitaxel Dose At Start of Subsequent Cycles of Therapy** [b]	**Carboplatin Dose At Start of Subsequent Cycles of Therapy** [b]
Neuropathy			
≤ Grade 1	Maintain dose level	Maintain dose level	Maintain dose level
Grade 2	Hold therapy until Grade ≤ 1; restart at full dose	Hold therapy until Grade ≤ 1; restart at full dose	Maintain dose level
≥ Grade 3	Discontinue therapy	Hold therapy until Grade ≤ 1 then resume at next lowest dose level	Maintain dose level
Other non-hematologic toxicities			
≥ Grade 3	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade ≤ 1 then resume at next lowest dose level	Hold treatment until ≤ Grade 2

[a] For ≤ CTCAE Grade 2 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. Dose reductions of nab-paclitaxel below the -1 dose level will not be allowed. For concurrent therapy, paclitaxel and carboplatin doses will not be adjusted.

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.**

7.5.3.3 Carboplatin Dose Modifications for Renal Toxicity

A > 25% change in the renal function, based on weekly calculated creatinine clearance for the concurrent phase and every 3 weeks calculated creatinine clearance for the consolidation phase prior to chemo infusion, will warrant a recalculation of the carboplatin dose.

7.5.3.4 Paclitaxel/nab-paclitaxel Dose Modifications for Neuropathy

If paclitaxel/nab-paclitaxel doses must be withheld for greater than two consecutive weeks, the drug will be held permanently for the duration of concurrent therapy.

7.6 Duration of Treatment

7.6.1 Discontinuation from Protocol Treatment*:* Study therapy MUST be immediately discontinued for the following reasons:

- Withdrawal of consent (patient's decision to withdraw for any reason);
- 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;
- Pregnancy;

- Progressive disease (Further treatment will be at the discretion of the treating physician).

The reason(s) for discontinuation from protocol treatment should be documented in the patient's medical record and Case Report Form (CRF). All patients should be followed as specified in Sections 10.2.

7.6.2 Treatment Compliance*:* Trained medical personnel will administer study therapy. Treatment compliance will be monitored by drug accountability, as well as recording treatment administration in the patient's medical record and Case Report Forms.

7.6.3 Modality Review*:* The Medical Oncology Co-Chair, David Gerber, M.D., will perform a Chemotherapy Assurance Review of all patients who receive or are to receive chemotherapy in this trial. The goal of the review is to evaluate protocol compliance. The scoring mechanism is: per protocol; variation acceptable; deviation unacceptable; not evaluable for chemotherapy review, or, incomplete chemotherapy. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

7.7 Procedures in Case of Pregnancy

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study. Should pregnancy occur during a subject's trial participation, the subject will immediately be discontinued from the trial and followed-up per protocol.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All outcomes of pregnancy must be followed-up, documented and reported to Celgene. The site will complete and forward to Celgene their site-specific pregnancy form. The following information must be reported to Celgene.

8.0 OTHER THERAPY

8.1 Prohibited Therapies

Patients should not receive any other anti-cancer drugs while receiving paclitaxel, carboplatin, or nab-paclitaxel, including hormonal and immunotherapy agents. Treatment with hormones or other chemotherapeutic agents will result in the patient's removal from the study. Exceptions are steroids administered for acute symptom management, adrenal failure, septic shock, or as antiemetics; or hormones administered for non-disease related conditions (e.g., insulin for diabetes). Colony stimulating factors (i.e., G-CSF, GM-CSF, etc.) should not be administered. In case of myelotoxicity, dose reductions will be made. In addition, treatment with amifostine is not allowed during radiation or within 3 months of completion of radiation therapy

8.2 Supportive Therapy

Patients should receive full supportive care (except for colony stimulating factors) including transfusions of blood and blood products, antibiotics, antiemetics, etc., when appropriate. Electrolytes should be maintained within the normal range using supplements if necessary. The use of erythropoietin (i.e., Epogen®, Procrit®) is permitted. Sucralfate slurries may provide symptomatic relief of mucositis and esophagitis. Post-treatment pneumonitis attributed to radiation should be treated with prednisone after excluding microbial causes.

9.0 SAFETY REPORTING

9.1 Definitions and Reporting:

The definitions of Adverse Events (AEs) and Serious Adverse Events (SAEs) are given below. It is of the utmost importance that all staff involved in the study be familiar with the content of this section. The principal investigator is responsible for ensuring this.

9.1.1 Adverse Event

An Adverse Event (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

Any detrimental change in a patient's condition subsequent to them entering the study and during the follow-up period should be considered an AE. When there is a deterioration in the condition for which the study treatment is being used, there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless the reporting physician considers that study treatment contributed to the deterioration or local regulations state to the contrary, the deterioration should be considered a lack of efficacy. Signs and symptoms of disease progression are therefore not considered AEs.

The development of a new cancer should be regarded as an AE. New cancers are those that are not the primary reason for administration of study treatment and have been identified after inclusion of the patient into the clinical study.

9.1.2 Serious Adverse Event

A Serious Adverse Event (SAE) is an AE occurring during any study phase (e.g., run-in, treatment, washout, and follow-up), and at any dose of the investigational product, comparator or placebo, that fulfills one or more of the following criteria:

-Results in death

-Is immediately life-threatening

-Requires inpatient hospitalization or prolongation of existing hospitalization

-Results in persistent or significant disability or incapacity

-Is a congenital abnormality or birth defect

-Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

The investigator or his team should report Local Adverse Event (Occurring to a subject enrolled on a protocol under the UT Southwestern IRB jurisdiction) that are Not Serious but Unexpected (in terms of nature, severity or frequency) and Definitely, Probably or Possibly related within 10 working days.

The investigator or his team will report all local Serious Adverse Events that are reportable to the IRB regardless of whether they are expected or related to research participation within 24 hours of discovery of the event.

All local SAEs are required to be reported to the DSMC.

Celgene will be communicating all non-local adverse events to the investigator or his research team. The investigator or his team will in turn report within 10 working days non-Local Serious Adverse Event (Occurring in the same multi-site study as is conducted by the PI at UT Southwestern but at a different site), that is unexpected (in terms of nature, severity or frequency) and definitely, Probably or Possibly related and serious or otherwise places subjects or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized.

Any event or hospitalization that is unequivocally due to progression of disease, as determined by the investigator, must not be reported to the sponsor (Celgene) as an SAE, however should be communicated to Celgene.

The causality of SAEs (their relationship to all study treatment) will be assessed by the investigator(s) and communicated to Celgene.

All non-serious adverse events will be reported to Celgene at the conclusion of the study.

9.1.3 Reporting of Serious Adverse Events

UTSW IRB: SAEs will be collected from the time consent is given, throughout the treatment period, and until subject's participation in the trial has ended or participants death.

Celgene; Investigators and other site personnel must inform the FDA, via a MedWatch form, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32, and will concurrently forward all such reports to Celgene. A copy of the MedWatch report must be faxed to Celgene at the time the event is reported to the FDA. It is the responsibility of the investigator to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to Celgene at the same time.

***** A ***cover page*** from Celgene should accompany the ***MedWatch*** form indicating the following:

- The investigator ***IND number*** assigned by the FDA
- The ***investigator's name*** and ***address***
- The ***trial name/title*** and ***Celgene reference number***

***** Investigative site must also indicate, either in the SAE report or the cover page, the ***causality*** of events ***in relation to all study medications*** and if the SAE is ***related to disease progression***, as determined by the principal investigator.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to Celgene and the FDA.
Serious adverse events that do not require expedited reporting to the FDA need to be reported to Celgene preferably using the MedDRA coding language for serious adverse events. This information should be reported on a monthly basis and under no circumstance less frequently than quarterly

All SAEs have to be reported to Celgene, whether or not considered causally related to the investigational product. All SAEs will be documented. The investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

Non-serious adverse events will be collected from the time consent is given, throughout the treatment period and up to and including the *30 day follow-up* period. After withdrawal from treatment, subjects must be followed-up for all existing and new AEs for *30 calendar days after the last dose of trial drug and/or until event resolution.* All new AEs occurring during that period must be recorded (if SAEs they must be reported to the FDA and Celgene per Section 3.6.1.3). All study-related toxicities/ SAEs must be followed until resolution, unless in the Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease.

All serious adverse events must be reported to the UT Southwestern TELEPHONE LINE: (214) 633-1753 within 24 hours of the investigator's awareness of the occurrence of the event. All safety reports shall be faxed to (214) 645-8913 or e-mail to the attention of the project manager.

9.1.4 The principal investigator will respond promptly to any query from UT Southwestern regarding adverse event reports.

9.2 Audits and Inspections

Authorized representatives of Celgene, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the center to perform audits or inspections, including source data verification. The purpose of an Celgene audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. The investigator should contact Celgene immediately if contacted by a regulatory agency about an inspection at his or her centre.

10.0 PATIENT ASSESSMENTS

10.1 Study Parameters

Table 11:

Procedure	Pre-Treatment	During Protocol Therapy	End of Concurrent Therapy	End of all Protocol Therapy	Post Treatment Follow-up (See Section 10.2)
Medical History	X[a]			X	X
Physical Examination, Zubrod performance status, concomitant medications	X[a]	X[c]	X	X	X
RT and Med Onc Consults	X[l]				
Vital Signs	X[a]	X[c]		X	X
Height and Weight and BSA	X[a]	X[c, d]	X[d]	X[d]	X[d]
FEV1	X[b]				X[j]
Toxicity Assessment/Adverse Events		X	X	X	X
Quality of Life Assessments	X		X		X[o]
CBC with differential platelet count	X[a]	X[c]	X	X	X[e]
Bilirubin, alk. Phos., glucose, sodium, potassium, calcium, magnesium, BUN, albumin, total bilirubin, AST, ALT, total protein	X[a]	X[c]	X	X	X[e]
Serum creatinine	X[a]	X[c]	X	X	X[e]
Amylase, Lipase	X[a]		X	X	
Pregnancy Test (serum)	X[g]				
Tissue Assessment	X[h]				
Serum samples for correlative studies	X[h]				
CT Scan or MRI of Chest OR PET, PET/CT	X[b,m]			X[n]	X[f]
CT Scan or MRI of Brain	X[b,m]				X[e]
PET, PET/CT or Bone scan	X[k]				X[k]

a. Within 4 weeks prior to study entry;
b. Within 6 weeks prior to study entry;
c. Weekly during concurrent, q3 weeks during consolidation prior to chemo infusion (paclitaxel/carboplatin arm or nab-paclitaxel/carboplatin arm)
d. Assess weight only; recalculate the BSA if there has been > 10% weight loss/gain;
e. At relapse;
f. Recommended every 6 months for 2 years, then annually;
g. For women of childbearing potential; within 7 days prior to registration
h. See 11.0 TISSUE/SPECIMEN SUBMISSION

i. Approval to proceed must be received prior to initiation of study treatment.
j. At 6 months after completion of consolidation therapy, then at 1 year
k. Highly recommended at pretreatment and at 12-16 weeks after completion of therapy, but not required. Refer to section 4.0
m. Perform CT scan or MRI at a minimum of 1 cm slice thickness to include the lung apices through the adrenals. It is recommended that a consistent evaluation (CT or MRI) be used throughout the study.
n. Within Six weeks on completion of consolidation treatment.
o. On 3, 12 and 24 months follow up.

10.2 Post-treatment Follow-up

A follow-up evaluation will be performed approximately 30 days following completion of all protocol treatment. In addition, all patients will be followed for a minimum of 30 days after the last dose of study therapy or every 4 weeks until all study drug related toxicities have resolved, returned to baseline, or are deemed irreversible, whichever is longer. Thereafter, patients will be seen for follow up every 3 months following protocol treatments for 2 years, every 6 months for years 3 and 4, then annually for life.

10.3 Prospective Health-Related Quality of Life (HRQOL) Analysis

Note: Patients must be offered the opportunity to participate in the correlative components of the study. If the patient consents to participate in the quality of life component of the study, sites are required to administer the baseline assessments prior to the start of protocol treatment. Sites are not permitted to delete the quality of life component from the protocol or sample consent.

The study design is to prospectively analyze the QOL among patients with stage III NSCLC randomized between paclitaxel/carboplatin versus nab-paclitaxel/carboplatin with concurrent radiotherapy followed by consolidation chemotherapy. The primary normal tissue toxicities in patients receiving chemoradiation for lung cancer are esophagitis and pneumonitis. Prior studies have demonstrated that the most sensitive and clinically meaningful method for accurately capturing the normal tissue toxicities is via patients reported outcomes (PROs), such as HRQOL.

In this randomized trial, we plan to assess the FACT-L, FACT-Taxane and the EQ-5D in all arms at 5 specific time points to minimize patient burden: baseline (pretreatment), at the end of chemoradiation (week 7), at the first follow-up (3 months), and at 12 months and 24 months from baseline.

In order to analyze the difference in QOL between all arms, we plan to use a brief, validated instrument that is user friendly and has clinical relevance (the Lung Cancer Subscale of the FACT-TOI (the FACT-L)). FACT-TOI is a measure that sums the functional well being (FWB), physical well being (PWB), and the lung cancer subscale (LCS) of the Functional Assessment of Cancer Therapy - Lung (FACT-L) QOL instrument, which has been extensively used for measuring QOL in patients with lung cancer.[44] In a review of the literature reported that the FACT-L scale has been used in more than 5,000 patients and has been found to be sensitive to changes in performance status and treatment response.[45] FACT has been translated into 26 languages and is available free of charge to institutions with the completion of an agreement to share data, accessible at http://www.facit.org/translation/licensure.aspx. The full FACT-L questionnaire can be completed in less than 10 minutes.[46] This instrument has not only been shown to be prognostic for survival, but also sensitive to changes in QOL on serial

evaluations throughout treatment.[45] Importantly, the FACT-TOI has been associated with clinically meaningful changes in patients with lung cancer.[47] The lung cancer sub-scale (LCS) consists of 9 items, involving lung cancer specific symptoms. All items are rated on a 5 item (point) Likert Scale, from 0 (not at all) to 4 (very much). It has been determined that a 3-point difference on the FACT-G subscales is associated with a meaningful difference in clinical and subjective indicators.[47] Thus, a difference of 3 LCS points will be considered clinically significant. As the LCS focuses on lung cancer symptoms, this will be used for the primary endpoint; however, the more general subscales of physical and functional well-being (on the brief FACT-TOI) will also be collected. In addition, we will utilize the FACT-Taxane instrument to ascertain for differences in neuropathic symptoms and overall effect on well being.

In order to analyze the potential benefits of nab-paclitaxel (in terms of survival, decreased toxicity), a quality-adjusted survival analysis can be performed. The EQ-5D is a method for obtaining valuations of health-related QOL which also can be used for quality-adjusted survival and cost-utility analyses.[48-51] It is a two-part questionnaire that takes approximately 5 minutes to complete.[52] The first part of the EQ-5D consists of five items addressing five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension can be graded on three levels: 1-no problems, 2-moderate problems, and 3-extreme problems. Health states are defined by the combination of the response levels for each of the five dimensions, generating 243 health states to which unconsciousness and death are added.[53] The second part of the EQ-5D is a visual analogue scale (VAS) valuing current health state, measured on a 20-cm 10-point-interval scale. Worst imaginable health state is scored as 0 at the bottom of the scale, and best imaginable health state is scored as 100 at the top. Both the five-item index score and the VAS score are transformed into a utility score between 0-"worst health state" and 1-"best health state." Either the index score or the VAS score can be used in the quality-adjusted survival analysis, or the cost-utility equation can be entered, depending on the health state(s) of interest.[54]

Although developed in Europe, the EQ-5D has been used in the United States and Canada.[48-51] The EQ-5D web site, http://www.euroqol.org/, lists multiple languages in which the instrument has been validated. There have been few studies published reporting on the incorporation of the EQ-5D into the evaluation of patients with NSCLC. Trippoli et. al. used the EQ-5D in the evaluation of 95 patients with NSCLC treated at 15 Italian hospitals.[55] The mean utility score was 0.58 in the self-classifier version and 0.58 in the VAS version. Both the self-classifier version and the VAS version showed statistically significant correlation with each of the eight domains of the Short Form-36 (SF-36).

The patients will be given the FACT-L, FACT-Taxane and EQ5D instruments to be completed in the clinic at specified visits. A research assistant will be available to answer any questions that the patients have and review the questionnaire for completeness. If the questionnaires are not complete, patients will be asked if they left out answering the question by mistake or because they did not wish to answer the question. If the former, patient will be asked to answer those questions; if the latter, patients would not be asked anything further. If a patient does not come in to clinic (and/or if requested), the questionnaires will be mailed to the patient. If the questionnaires have not been received in two weeks after the due date, another set will be sent to the patients, reminding them to complete the questionnaire. If the patient prefers, he or she will be interviewed by the research assistant over the telephone at that time. Reminder notices will be routinely sent to the clinical research associates whose institutions are accruing to the trial that

the HRQOL instruments need to be distributed to the patients at the prescribed time frames.

10.4 Response Assessment (RECIST Criteria)

10.4.1 Measurement of Response

Response will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee.[56] See http://ctep.info.nih.gov/guidelines/recist.html for further details.

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

- **Measurable disease -** the presence of at least one measurable lesion; if the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

- **Measurable lesions** - lesions that can be accurately measured in at least one dimension with longest diameter (LD) ≥ 20 mm using conventional techniques or ≥ 10 mm with spiral CT scan.

- **Non-measurable lesions** - all other lesions, including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques

Table 12: Response Criteria: Evaluation of target lesions

Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

10.4.2 Target lesion assessment guidelines

The longest diameter (LD) for the target lesion (or lesions) will be calculated from the treatment planning CT scan using pulmonary and/or mediastinal windowing and reported as the baseline LD. The baseline LD will be used as a reference by which to characterize the objective tumor.

Local treatment effects in the vicinity of the tumor target may make determination of tumor dimensions difficult. For example, bronchial or bronchiolar damage may cause patchy consolidation around the tumor that over time may coalesce with the residual tumor. In cases in which it is indeterminate whether consolidation represents residual tumor or treatment effect, it should be assumed that abnormalities are residual tumor.

11.0 TISSUE/SPECIMEN SUBMISSION

This study does not involve genetic analysis. Patients will be offered the Radiation Oncology Tissue Procurement study which is a separate UTSW IRB approved study.

12.0 DATA MANAGEMENT

12.1 Data Collection

All data will be collected and entered into the Case Report Form (CRF). The CRF must be completed legibly in ink and submitted within the timelines listed below. Participants are to be identified by initials, date of birth, and subject number. All information entered on the CRFs must also be reflected in the source documents. The CRFs will be faxed to (214) 648-5923 or e-mailed to Project Manager in a PDF format.

UTSWMC Radiation Oncology Clinical Research department will review CRFs for completeness. Audits will be performs for randomly selected cases to ensure the accuracy of CRFs. Data queries will be generated as needed for quality purposes.

For patients enrolled at participating institutions, data will be collected and stored according to their institutional policies. The data will be kept in a secure location in accordance with prevailing HIPAA regulations. The investigator must maintain adequate and accurate records to enable the conduct of the study and monitoring. The investigator must contact UTSWMC Radiation Oncology Clinical Research department prior to destroying any records associated with the study.

12.2 Summary of Data Submission

Table 13:

Item	Due
Demographic Form	Within 2 weeks of study entry
Initial Evaluation Form	Within 2 weeks of study entry
Pathology Report	Within 2 weeks of study entry
Preliminary Dosimetry Information:	Within 1 week of start of RT
RT Prescription (Protocol Treatment Form)	
Films (simulation and portal)	
Calculations	
Treatment Planning CT Scan [if done]	
Final Dosimetry Information:	Within 1 week of RT end
Daily Treatment Record	
Isodose Distribution	
Radiotherapy Form	Within 1 week of RT end
Treatment Summary Form	At 8, 12, and 17 weeks
QOL Forms (FACT-L, FACT-Taxane, EQ-5D)	Within 2 weeks of study entry, at week 8 and after 3, 12, 24 month follow up
Follow-up Form	Within 2 weeks of completion of each

	follow-up visit
Adverse Event Form	Within 48 hours of investigator's awareness
Autopsy Report as Applicable	Within 4 weeks of completion of autopsy

12.3 Data Safety Monitoring Board

Adverse events will be reviewed and discussed at the monthly UTSW Department of Radiation Oncology Clinical Research meetings and meeting minutes will be made available to participating institutions. The data quality and patient safety will also be monitored by the UT Southwestern Simmons Cancer Center Data Safety Monitoring Committee in accordance with UTSW cancer center guidelines and meeting minutes will be made available to participating institutions.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Design and Primary Endpoint

The primary goal of this randomized phase I/II study is to evaluate the efficacy of two treatment regimens involving radiation treatment for patients with inoperable stage III non-small cell lung cancer. Arm A includes concurrent chemotherapy consisting of paclitaxel and carboplatin with radiation therapy followed by additional consolidation chemotherapy of paclitaxel and carboplatin. Arm B consists of nab-paclitaxel and carboplatin with radiation therapy followed by additional consolidation chemotherapy of nab-paclitaxel and carboplatin. **This study is not a comparative trial between these two arms; its purpose is to determine the efficacy and toxicity profile of each of the treatment regimens to guide further investigation**. Therefore the primary endpoint question of 2-year survival rate will be analyzed in each treatment arm alone compared to historical controls.

Randomization will be 1:1, with 1 patient accrued to Arm B for every 1 patient accrued to Arm A.

The primary endpoint of this phase I/II study is 2-year overall survival from randomization.

Based on previous regimens utilizing concomitant chemoradiation plus consolidation (LAMP), which derived a 2-year survival rate of 31%, the threshold of interest for pursuing a Phase 3 trial for these regimens will be 50%. A 2-year survival of 30% or lower will be of no interest. It would be of interest for further investigation if the addition of nab-paclitaxel produced a 2-year survival rate of 50% or higher.

Because there is limited information about the toxicity of adding nab-paclitaxel to this chemoradiation regimen concurrently, an initial toxicity assessment and compliance phase will be conducted only for the Arm B treatment.

Secondary endpoints are toxicity/feasibility (as described in previous paragraph), overall response rate, progression-free survival, median overall survival, and quality of life measurements.

13.2 Sample Size Justification

We are planning the study with an accrual interval of 24 months, and additional follow-up after the accrual interval of 24 months. Prior data indicate that the two-year survival rate of historical treatment is around 31%. If the true two-year survival rate of our new treatment is 50% or higher, we will need to study 43

patients to be able to reject the null hypothesis that the new treatment and the historical treatment survival curves are equal with probability (power) of 0.80. The two-sided Type I error probability associated with this test of this null hypothesis is 0.05. This calculation was based on log-rank test assuming exponential survival function. The exponential parameter (lamda) was derived from the expected two year survival rate. Assuming ineligibility or lack of data rate of up to 5%, an additional 3 patients per arm should be accrued. This would then lead to a sample size of 46 patients for each of the two arms, respectively.

13.3 Initial Toxicity and Compliance Phase

Before randomization between the two treatment arms begins, an initial 6 patients will be treated with radiation treatment concurrently with weekly treatment of nab-paclitaxel/carboplatin followed by nab-paclitaxel and carboplatin. The design is a simple 3-6 patient initial run-in. Three patients will be treated, if there are zero or one dose limiting toxicities (DLT) an additional 3 will be treated. If there are zero or one DLT (of the 6 patients) then the study will proceed to phase 2 at dose level 1. If there are more than one DLT out of the first three or out of the total six patients, then dose level -1 will be used in the phase II stage. Patients must be followed for one complete treatment cycle (concurrent and consolidation) from the start of treatment (including time for treatment breaks or delays) to the end of the consolidation phase before proceeding to the next step.

If more than one of the first three patients or more than one of the total 6 patients experiences grade 3 or greater non-hematological toxicities or grade 4 or greater hematological toxicities, then the study will be temporarily suspended and re-evaluated at a lower dose level of 40mg/m^2 of nab-paclitaxel. DLT will be defined as occurring whenever any one of the following are determined to be definitely or probably treatment related:

- **Any $\geq$ grade 4 hematologic toxicity that lasted $\geq$ 7 days**
- **Any $\geq$ grade 3 other non-hematologic toxicity that lasted $\geq$ 7 days (excluding esophagitis, nausea, vomiting, and alopecia)**
- **Grade 3 or 4 febrile neutropenia**

The UT Southwestern Data Safety Monitoring Committee (DSMC) will be asked to review the toxicity and compliance data and patient information and make appropriate recommendations about continuing the study.

13.4 Patient Accrual

Initially, during the phase I portion of the study, 6 patients will be accrued. The eventual accrual goal during the phase II portion of the study is a total of 92 patients, 46 in Arm #A and 46 in Arm #B. Therefore, the overall accrual goal for this randomized phase I/phase II study is 98 patients.

We expect that the study will accrue at the rate of 7 patients per month. With an accrual rate of 7 patients per months, patient accrual should be completed within 14 months. Allowing an initial 4 months for institutions to complete IRB paperwork before beginning patient accrual, it is expected that 18 months will be needed to complete patient accrual on this study. A minimum of 24 months of follow-up will be needed to test the primary study endpoint hypotheses

13.4.1 Definition of an evaluable patient

Any patient who enrolls on the study and begins therapy will be counted as an evaluable patient. If a patient discontinues therapy or there is a modification to protocol therapy this will be noted as a protocol deviation and will be reported to the principal investigator, Dr. Choy. Patients with deviations will still be followed as specified in section 10.0 and no replacement subjects will be enrolled.

13.5 Fatal Treatment-Related Toxicity

Accrual to this study will be suspended if any patient experiences a fatal treatment-related toxicity. In the event that a patient has a fatal treatment-related toxicity at any time, the UT Southwestern data safety monitoring committee (DSMC) will be asked to review the data and patient information to make appropriate recommendations about continuing the study.

13.6 Interim Analyses of Accrual and Toxicity Data

Interim reports will be prepared every 6 months until the primary endpoint analysis. The usual components of this report are:

a) The patient accrual rate with a projected completion date for the accrual phase;
b) Accrual by institution;
c) The distribution of pretreatment characteristics;
d) The quality of submitted data with respect to timeliness, completeness, and accuracy;
e) The frequency and severity of the toxicities.

Copies of Interim reports will be provided to the SCC-DSMC on an ongoing basis during the course of the trial.

The statistician will report any problems identified to the study chairs and UT Southwestern DSMC.

13.7 Analysis for Reporting Initial Treatment Results

This analysis will be done when all the patients accrued to the study have been potentially followed for a minimum of 24 months. It will include:

a) Tabulation of all cases entered into the trial;
b) Institutional accrual;
c) Distribution of important prognostic baseline variables;
d) Treatment compliance per study chair assessment.
e) Observed results for the endpoints listed in Section 13.1.

The primary objective of this study is to determine whether using Nab-paclitaxel (Abraxane) in concurrent radiation therapy and chemotherapy regimens will significantly increase the 2-year overall survival from historical 31%

All eligible patients randomized will be included in the comparison and will be grouped by assigned treatment in the analysis. The primary hypothesis of treatment benefit for the primary endpoint question will be tested using the log-rank statistic with a 2-sided significance level of 0.05. Comparison will be performed between the new treatment and historical controls. Additional exploratory analyses of treatment effect will be performed using the Cox proportional hazard model with the stratification factors included as fixed covariates, as well as other possible modifying factors, such as age, gender, race, and other patient characteristics that are imbalanced between the treatment arms.

Estimates of overall survival and progression free survival (calculated using the Kaplan-Meier method[62]) at one and two years will be calculated along with 95%

confidence intervals. Survival time is defined as the time beginning at randomization until death or last known follow-up. Progression-free survival is computed as the time between randomization and local or regional progression, distant metastases, death, or last known follow-up.

Response (determined two months after completion of consolidation chemotherapy and for each additional post-treatment imaging study) is taken to be complete response (CR) or partial response (PR) using the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (Section 10.4).[63] Overall response rate (ORR) will be defined as the percentage of people who experience a decrease in the size of treated measurable disease (this will be the sum of the complete and partial response rates). Point and interval estimates of the proportion of patients with PR, CR, or either CR or PR, and ORR, using an exact 95% confidence interval will be calculated.

For both the concurrent chemoradiation and the consolidation treatment periods, the frequency of toxicity occurrence will be tabulated by the most severe occurrence. CTCAE v 4.0 will be used to assess and grade toxicities. Results will be presented for each arm by attribution (definitely, probably, or possibly related to treatment and unlikely or unrelated to treatment).

Within each treatment group, the pattern of treatment failure (local, distant, regional) will be summarized.

13.8 Analysis for Reporting Long-Term Results

This analysis, if necessary, will be done when all the patients accrued to the study have been potentially followed for a minimum of 36 months or when all patients are dead. It will include all items found in section 13.7.

13.9 Health-Related Quality of Life (HRQOL) and Health Utility Analysis

These HRQOL and health utility analyses will be carried out with respect to the use of nab-paclitaxel. We will use three instruments to measure HRQOL: FACT-TOI, including the lung cancer subscale (LCS), FACT-Taxane and EQ-5D. FACT-TOI is a measure that sums the functional well being (FWB – 7 items), physical well being (PWB – 7), and the lung cancer subscale (LCS – 9 items) of the Functional Assessment of Cancer Therapy - Lung (FACT-L). Patients eligible for the treatment comparison will be included in the QOL analysis only if they have provided baseline and at least one subsequent measurement. The difference in the LCS, the FACT-TOI and FACT-Taxane score between the baseline and each follow-up evaluation will be computed for each patient. These differences of the means will be calculated at 3, 12 and 24 months and the point and interval estimates using an exact 95% confidence intervals will be presented.

The primary QOL hypothesis is that patients receiving nab-paclitaxel will have clinically meaningfully higher QOL as measured by the LCS subscale of the FACT-L and FACT-Taxane instruments at 3 months post completion of treatment. Secondarily, this higher QOL score will be maintained at longer follow up as well (at twelve and 24 months from the start of treatment). Since the study is not powered for formal statistical testing on this, results will be tabulated and summarized by treatment arms for examination.

Quality-adjusted survival is the sum of the products generated by multiplying a patient's health utility score for each specific time period by the length of that time period. The quality-adjusted survival time estimates need to account for the presence of censoring. Due to the induced informative censoring problem, the ordinary survival method (e.g., Kaplan-Meier estimator) cannot be applied in this

case. Accordingly, we will use the inverse-probability weighted method of Zhao and Tsiatis to carry out the survival time analysis.[57,58] To estimate quality adjusted survival time, data from EQ-5D will first be translated into utility measures. These measures are obtained at discrete time points, so they will be interpolated into the time intervals between the visits. The quality-adjusted survival time is just an integration of the utility measures over a patient's overall survival time. The point and interval estimates of mean quality-adjusted survival for each arm using exact 95% confidence intervals will be calculated.

We will describe the distributions of QOL data collection patterns over all collection points in each treatment arm. The distribution of pretreatment characteristics, such as performance score and treatment assignment, will be compared between the patients with available QOL data and the patients without QOL data.

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Appendix A

ZUBROD PERFORMANCE SCALE

0	**Fully active, able to carry on all predisease activities without restriction**
1	**Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work**
2	**Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours**
3	**Capable of only limited self-care, confined to bed or chair 50% or more of waking hours**
4	**Completely disabled. Cannot carry on self-care. Totally confined to bed**
5	**Death**

Appendix B

NEW YORK HEART ASSOCIATION (NYHA) CARDIAC CLASSIFICATION

The NYHA classification system relates symptoms to everyday activities and the patient's quality of life.

Class	Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.