LINEBERGER COMPREHENSIVE CANCER CENTER
CLINICAL ONCOLOGY RESEARCH PROGRAM
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

PROTOCOL AMENDMENT # 4

LCCC 1210: A Phase II, multicenter, single arm study of the tolerability of weekly nab-paclitaxel as second line treatment for elderly patients with advanced lung cancer

AMENDMENT INCORPORATES (check all that apply):

Editorial, administrative changes

X Scientific changes (IRB approval)

__ Therapy changes (IRB approval)

__ Eligibility Changes (IRB approval)

AMENDMENT RATIONALE AND SUMMARY:

The study has been amended to include a plan to evaluate sarcopenia by CT scans.

1. New Section (1.5.4) added to explain the rationale for evaluating sarcopenia in this trial.

2. Correlative objective (2.3.4) added to account for sarcopenia evaluation.

3. New section 6.11.6 added to efficacy assessments to account for sarcopenia evaluations.

THE ATTACHED VERSION DATED 5/26/17 INCORPORATES THE ABOVE REVISIONS

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PROTOCOL AMENDMENT # 3

LCCC 1210: A Phase II, multicenter, single arm study of the tolerability of weekly nab-paclitaxel as second line treatment for elderly patients with advanced lung cancer

AMENDMENT INCORPORATES (check all that apply):

Editorial, administrative changes

X Scientific changes (IRB approval)

__ Therapy changes (IRB approval)

X Eligibility Changes (IRB approval)

AMENDMENT RATIONALE AND SUMMARY:

Study inclusion criteria have been revised to account for recent changes in the standard of care for advanced lung cancer due to the recent approval of nivolumab as second-line therapy for NSCLC after failure on platinum-based chemotherapy. Hence inclusion criterion 3.1.6 has been revised to ensure continued accrual on this study.

Other changes

The Time and Events Table (Section 6.1) has been revised to reduce the number of times blood is collected for analysis of $p16^{ink4}$. The Time and Events Table (Section 6.1) has been revised so that blood collection for $p16^{ink4}$ analyses occur at screening , on cycle 3 D1, cycle 5 D1, and at the end of treatment rather than at screening , on Day 1 of odd numbered cycles, before chemotherapy beginning with cycle 3, and at the end of treatment.

THE ATTACHED VERSION DATED 7/24/15 INCORPORATES THE ABOVE REVISIONS

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PROTOCOL AMENDMENT # 2

LCCC 1210: A Phase II, multicenter, single arm study of the tolerability of weekly nab-paclitaxel as second line treatment for elderly patients with advanced lung cancer

AMENDMENT INCORPORATES (check all that apply):

X Editorial, administrative changes
Scientific changes (IRB approval)
___ Therapy changes (IRB approval)
X Eligibility Changes (IRB approval)

AMENDMENT RATIONALE AND SUMMARY:

The driver for this amendment was the need to make inclusion and exclusion criteria consistent with regards to amount of time that should lapse between radiation therapy and study treatment. As such, exclusion criterion 3.2.5 has been changed to "no radiation within 2 weeks' prior to study start." In addition, the primary endpoint (≥Grade 3 treatment related toxicity) was slightly revised to clarify that we will focus on clinically significant toxicities and that those of doubtful importance, such as asymptomatic grade 3 lymphopenia will not be included. This change was made in sections 1.1, 2.4.1, 6.10 and 8.1.

Other changes:

Deleted Appendix B. Abraxane® in Metastatic Breast Cancer, as more recent information is available in the package insert, which is referenced in the protocol.

Section 4.4.1 clarified that D8 and D15 CBCs are not required, however, if they are done, the dosing table provides guidance for investigators

Updated industry contact for drug shipments (section 5.1.5)

Clarified in table heading that assessments listed are to occur on day 1 of every treatment cycle (section 6.1) Added windows (+/- 24 hours) for each study visit.

Added Celgene tracking number for this study to section 7.3.4.

Minor edits throughout protocol.

THE ATTACHED VERSION DATED 8/21/14 INCORPORATES THE ABOVE REVISIONS

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LINEBERGER COMPREHENSIVE CANCER CENTER
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UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

PROTOCOL AMENDMENT # 1

LCCC 1210: A Phase II, multicenter, single arm study of the tolerability of weekly nab-paclitaxel as second line treatment for elderly patients with advanced lung cancer

AMENDMENT INCORPORATES (check all that apply):

X Editorial, administrative changes
X Scientific changes (IRB approval)
___ Therapy changes (IRB approval)
___ Eligibility Changes (IRB approval)

AMENDMENT RATIONALE AND SUMMARY:

The driver for this amendment is a change in the frequency of protocol-mandated patient evaluations on days 8 and 15 of each 28 day cycle. Standard of care patient evaluation for NSCLC patients undergoing chemotherapy occurs on day 1 of each cycle. As the primary objective of LCCC1210 is evaluation of tolerability, mandating collection of toxicity data on days 8 and 15 would inappropriately bias results when compared to historical controls. If clinically indicated, patients will be evaluated on days 8 and 15 at discretion of investigator. This change is reflected in sections 6.0 and 6.3.

Other changes

Nab-paclitaxel is now indicated (as of October 2012) for the treatment of first line treatment of locally advanced or metastatic NSCLC in combination with carboplatin. This is reflected throughout the protocol, and section 5.1.6 now includes clinical safety information on the use of nab-paclitaxel for this indication.

The text from Section 4.3.2 (Permitted Medications) was moved to section 4.3 (Supportive Care Guidelines); section 4.3.2 was deleted as it was redundant with section 4.5 (Concomitant Medications/Treatments).

Section 6.11.5-removed reference to required confirmation of response rate as this is appropriate only when primary endpoint is response.

Sections 4.6, 6.11.1, 6.11.3, and 9.4 were slightly revised to match updated LCCC protocol template. Section 4.9 (Study Withdrawal) was added to match updated LCCC protocol template.

THE ATTACHED VERSION DATED 2/1913 INCORPORATES THE ABOVE REVISIONS

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LCCC 1210: A Phase II, multicenter, single arm study of the tolerability of weekly nab-paclitaxel as second line treatment for elderly patients with advanced lung cancer

Principal Investigator
Jared Weiss, MD
170 Manning Drive, Room 3115
Campus box 7305
Chapel Hill, NC 27599
919-966-3856 (OFFICE)
919-843-7718 (ADMIN)
919-966-6735 (FAX)
Email: jared_weiss@med.unc.edu

Co-Investigators
Thomas Stinchcombe, MD
Carrie Lee, MD, MPH
Juneko Grilley-Olson, MD
Hyman Muss, MD

Biostatistician
Allison Deal, MS
Lineberger Comprehensive Cancer Center, Room 20-024
Chapel Hill, NC 27599
Phone: 919-966-1387
Fax: 919-966-4244

Clinical Protocol Office
Lineberger Comprehensive Cancer Center
The University of North Carolina at Chapel Hill
450 West Drive, 3rd Floor, CB# 7295
Chapel Hill, NC 27599-7295

University of North Carolina Cancer Network (UNCCN) Study Coordinator:
Phone: 919-966-7359
Fax: 919-966-4300

Sponsor: Lineberger Comprehensive Cancer Center

Funding Source: Celgene Corporation

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August 21, 2014 Amendment #2; July 24, 2015 Amendment #3, May 26, 2017 Ammendment #4

LCCC 1210: A Phase II, multicenter, single arm study of the tolerability of weekly nab-paclitaxel as second line treatment for elderly patients with advanced lung cancer

Principal Investigator
Jared Weiss, MD
170 Manning Drive, Room 3115
Campus box 7305
Chapel Hill, NC 27599
919-966-3856 (OFFICE)
919-843-7718 (ADMIN)
919-966-6735 (FAX)
Email: jared_weiss@med.unc.edu

Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name:_____

PI Signature: _____

Date:_____

TABLE OF CONTENTS

1.0 BACKGROUND AND RATIONALE

1.1 Study Synopsis

This will be a non-randomized phase II study evaluating the safety and efficacy of weekly nab-paclitaxel for second-line treatment in 42 elderly (≥ 70 years of age) patients with non-small cell lung cancer (NSCLC). Patients will be required to have progressed on a single prior regimen. Nab-paclitaxel 100mg/m^2 will be administered intravenously, weekly for 3 weeks of every 4-week cycle. After every two cycles of therapy, imaging will be performed to assess for response. Patients will be eligible to continue receiving therapy until the time of disease progression.

The primary endpoint will be occurrence of clinically significant ≥Grade 3 nab-paclitaxel-related toxicities (specifically neuropathy, myalgia, arthralgia, neutropenia, thrombocytopenia and anemia) as well as any ≥Grade 3 unexpected toxicities deemed clinically significant and considered related to nab-paclitaxel by the treating physician. Secondary endpoints include overall survival; progression-free survival; response rate; quality of life (QoL); and correlation of component scores of the Geriatric Assessment and p16 ^{INK4a} levels with treatment outcomes and toxicity.

1.2 Lung Cancer in the Elderly

Lung cancer remains the leading cause of cancer mortality in the United States and throughout the world.[1] The majority of patients with lung cancer will have NSCLC subtype, and will present with advanced stage disease.[2, 3] The goals of treatment for patients with advanced stage disease are to extend overall survival (OS), improve quality of life (QoL) and reduce disease related symptoms. Cytotoxic chemotherapy is the primary therapy for the majority of patients. The median age of patients with advanced NSCLC in the United States is 71 years.[4] The number of elderly patients with advanced NSCLC is expected to increase as the size of the elderly population increases reflecting improvements in life expectancy and demographic trends.[5]

1.2.1 First-line Treatment of the Elderly Patient with Advanced NSCLC

A variety of subgroup analyses and population-based studies provided evidence that the fit elderly patient should be treated with doublet chemotherapy, but this remained unproven until the 2010 presentation of the Quiox study of patients aged 70-89 with advanced NSCLC. This phase III trial compared carboplatin monthly combined with weekly paclitaxel to single agent therapy (gemcitabine or vinorelbine); the primary end-point was OS.[6, 7] Patients assigned to the double-agent arm experienced an improvement in progression-free (6.3 vs. 3.2 months, HR=0.55, p<0.001) and OS (10.4 vs. 6.2 months, HR=0.6, p = 0.0001). Patients in the double agent arm compared to the single agent arm experienced a statistically significant higher rate of grade ≥ 3 neutropenia, febrile neutropenia, thrombocytopenia, and sensory neuropathy. The rate of treatment-related deaths

was significantly higher in the double agent compared to the single agent arm (6.62% vs. 1.83%, p=0.035).

1.2.2 Histology-based Therapy in First- Line Treatment

The regimen of carboplatin plus paclitaxel has been the standard of care for first line chemotherapy for NSCLC for many years, regardless of age. Other doublet regimens have been evaluated in NSCLC, and shown similar survival benefits to carboplatin/paclitaxel. The recently published Scagliotti [8] trial was designed to show and confirmed non-inferiority for the combination of cisplatin plus pemetrexed as compared to cisplatin plus gemcitabine. Similar to the carboplatin/paclitaxel doublet, median OS for both regimens was 10.3 months. However, based on a planned subset analysis, the combination of cisplatin plus pemetrexed improved OS among patients with non-squamous histology; conversely the combination of cisplatin plus gemcitabine was more effective in patients with squamous histology.

Given the high tolerability and efficacy of both pemetrexed and gemcitabine, many clinicians consider the potential improvement of the therapeutic index with histology-directed therapy particularly applicable to the elderly patient. Thus, many clinicians routinely treat fit elderly patients in the first line with squamous cell NSCLC with gemcitabine plus carboplatin and non-squamous NSCLC with pemetrexed plus carboplatin.

1.2.3 Second-Line Treatment of the Elderly Patient with Advanced NSCLC

There are currently two cytotoxic agents, pemetrexed and docetaxel, and one epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI: erlotinib) that are available for use in U.S. patients with NSCLC who have experienced disease progression during or after initial chemotherapy.[9-13] No prospective, elderly-specific trials have been performed to define either the merits of second line therapy in the elderly, or choice of agent. A limited number of subset analyses have been performed.

A subset analysis of elderly patients (n=86, 15% of patients enrolled) in a phase III trial comparing docetaxel to pemetrexed was performed. Elderly patients assigned to pemetrexed (n=47) compared to the docetaxel arm (n=39) experienced a numerically longer OS (HR=0.66, 95% CI, 0.53 to 1.42; median 9.5 and 7.7 months, respectively).[14] This analysis was performed before it was known that the efficacy of pemetrexed was restricted to tumors with non-squamous histology and the number of elderly patients in each treatment arm was small. The rate of grade ≥ 3 febrile neutropenia among elderly patients was substantially lower in patients in the pemetrexed arm compared to the docetaxel arm, 2.5% and 19% (p=0.025). While pemetrexed appeared more effective, and is better tolerated, most patients with non-squamous histology will have received pemetrexed for their first line treatment, thus reducing the choices of tolerable therapy for second-line.

Another subset analysis was performed of elderly (≥ 70 years) patients enrolled in a phase III trial of erlotinib compared to placebo in patients who progressed after first-line chemotherapy.[15] Of the 731 patients enrolled, 163 patients were elderly (112 in the erlotinib arm and 51 in the placebo arm). Elderly patients compared to younger patients experienced more grade 3 or 4 toxicity (35% vs. 18%; p< 0.001), were more likely to discontinue treatment (12% vs. 3%; p<0.0001), and had a lower relative dose intensity (64% vs. 82% received >90% of the planned dose; p<0.001). Elderly patients receiving erlotinib compared to placebo experienced numerically longer OS (HR=0.92; 95% CI, 0.64 to 1.34; p=0.67; median OS 7.6 and 5.0 months, respectively). Therefore despite improved survival with erlotinib, there was a significant increase in Grade 3/4 toxicity and increased likelihood for discontinuation of treatment. Additional, more easily tolerated options are needed for second-line treatment of NSCLC in the elderly.

1.3 Nab-Paclitaxel (Abraxane®)

The active cytotoxic agent in nanoalbumin bound paclitaxel (henceforth nab-paclitaxel) is paclitaxel, an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This agent is currently indicated for the treatment of previously treated metastatic breast cancer, or disease that has relapsed within 6 months of adjuvant chemotherapy. As of October 2012, this agent is also indicated for the treatment of locally advanced or metastatic NSCLC as first-line treatment in combination with carboplatin.

Nab-paclitaxel delivers the paclitaxel bound to albumin and has several theoretical advantages over paclitaxel [16]. First, the cremophor solvent is not needed. Cremophor requires special glass or non-PVC infusion systems, premedication with histamine 1 and 2 blockers, can cause infusion reactions and may contribute to peripheral neuropathy. As albumin facilitates the administration of the water-insoluble compounds, effective active dose-delivery is higher, by as much as 49%. Infusion time with nab-paclitaxel is faster than with paclitaxel. Finally, binding of the active drug to albumin may increase tumor-specificity.

Lung cancer

Results were recently presented from a randomized international Phase III trial that compared four cycles of first-line carboplatin plus paclitaxel to four cycles of carboplatin plus nab-paclitaxel in NSCLC. The nab-paclitaxel arm showed improved response rates (RR 33%) compared to standard paclitaxel when combined with carboplatin (25%) [17, 18]. Importantly, most of this improvement was a result of improved response in patients with squamous cell histology, where the RR improved from 24% to 41%. Although effective dose delivery was higher with nab-paclitaxel (82 mg/m^2/week) compared to standard paclitaxel (65 mg/m^2/week) the overall toxicity profile, with the exception of anemia and thrombocytopenia, favored nab-paclitaxel as shown in Table 1.

Table 1. Grade 3/4 toxicity following nab-paclitaxel plus carboplatin (ab-P/C) vs. paclitaxel plus carboplatin (P/C) in advanced NSCLC [18]

Toxicity	Nab-paclitaxel + carboplatin (n=514) %		Paclitaxel + carboplatin (n=524) %		p value
	Grade 3	Grade 4	Grade 3	Grade 4	
Nonhematologic					
Neuropathy	3	0	11	<1	<.001
Myalgia	<1	0	2	0	.011
Arthralgia	0	0	2	0	.008
Hematologic					
Neutropenia	33	14	32	26	<.001
Thrombocytopenia	13	5	7	2	<.001
Anemia	22	5	6	<1	<.001

Exploratory subgroup analyses revealed that overall response rate (ORR) was improved with nab-paclitaxel in patients with squamous histology and in the elderly) ≥70 years old) population (Figure 1)[17, 19].

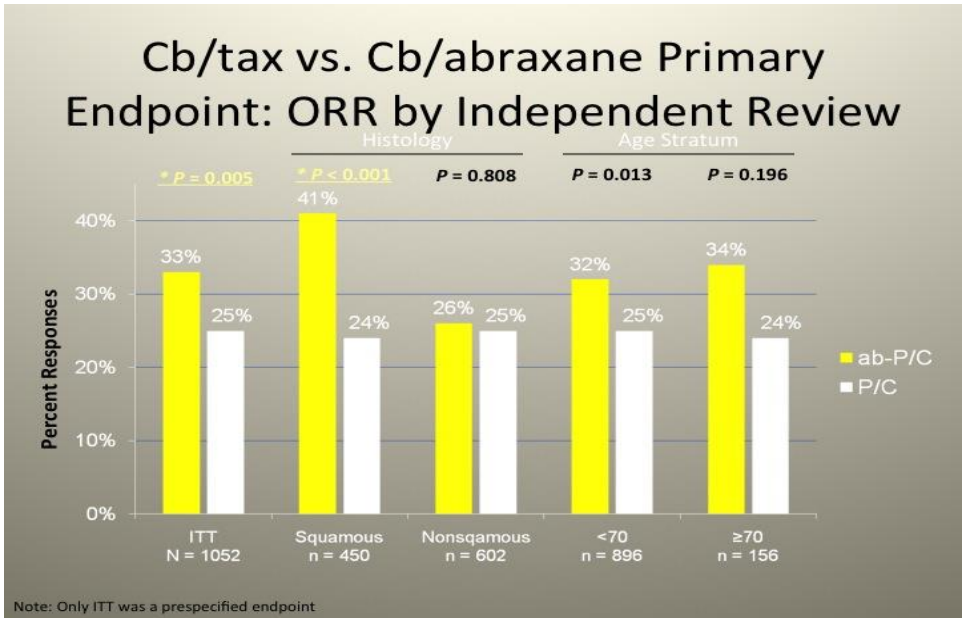


Figure 1. Comparison of overall response rate (ORR) following nab-paclitaxel plus carboplatin (ab-P/C) vs. paclitaxel plus carboplatin (P/C) in advanced NSCLC REF. ITT = intent to treat analysis [17, 19]

Overall survival results also favored the nab-paclitaxel group in the elderly exploratory subgroup analysis as shown in Figure 2:

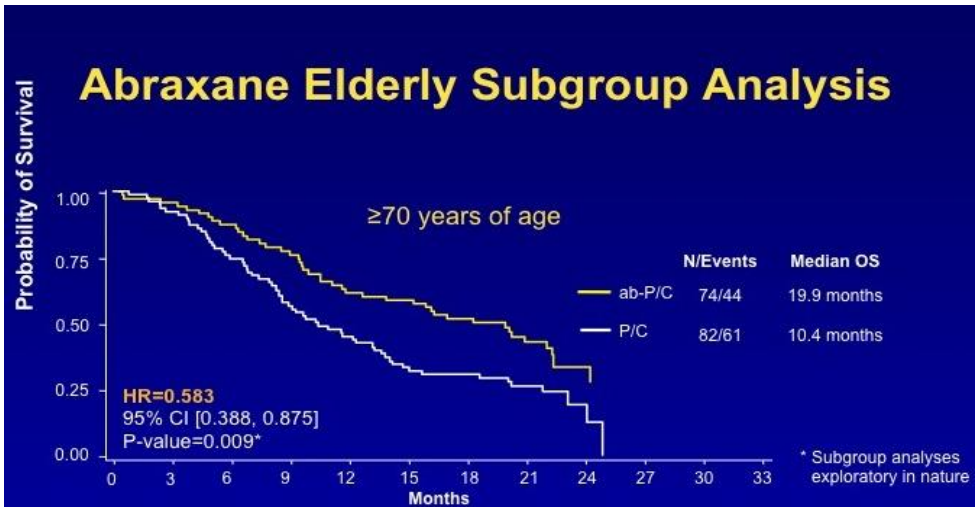


Figure 2. Comparison of overall survival following nab-paclitaxel plus carboplatin (ab-P/C) vs. paclitaxel plus carboplatin (P/C) in advanced NSCLC [17, 19]

1.4 Study Rationale

Platinum-based doublets are the standard of care in first line with choice of partner drug based on patient characteristics. For the elderly population, partner agents for first-line typically include gemcitabine for squamous cell NSCLC, and pemetrexed for non-squamous NSCLC. Some elderly patients are treated with paclitaxel in combination with a platinum.

The fit elderly are often not offered second-line treatment based on concern for toxicity. When elderly patients with advanced NSCLC are offered second-line therapy, the choice of therapy is frequently based on avoidance of toxicity rather than on disease-related endpoints. In particular, the one taxane that is FDA approved for second-line use, docetaxel, is widely considered too toxic for use in the elderly.

We hypothesize that treatment with single-agent, weekly administration of nab-paclitaxel will be tolerable and associated with a favorable clinical response (as compared to a historical control) in elderly patients undergoing second-line therapy for advanced NSCLC.

Data suggest that weekly taxane administration improves tolerability over an every 3 week schedule, and does not appear to compromise clinical effectiveness. Taxanes have been extensively studied as weekly regimens in the breast and lung cancer populations. A phase III study compared carboplatin plus paclitaxel on a standard every three week regimen (with both drugs given on day one) to a four week cycle (with carboplatin given on day 1 and paclitaxel given weekly for weeks one to three) [20]. Survival was similar between the two arms, but non-hematologic toxicity favored the weekly taxane arm. A dose finding study conducted at this institution showed a favorable benefit to risk ratio with weekly

nab-paclitaxel at a dose of 100mg/m^2 when administered in combination with carboplatin [21].

Taxanes on a weekly schedule have been shown to be particularly effective as first-line therapy in the elderly. The superiority of doublet chemotherapy over single-agent chemotherapy in the elderly was recently demonstrated using a regimen of carboplatin at an AUC of 6, combined with paclitaxel at 90mg/m^2 weekly[7]. A recent phase III study compared carboplatin plus paclitaxel on an every three week schedule to carboplatin plus nab-paclitaxel at 100mg/m^2 given weekly—the subgroup analysis of elderly patients was particularly favorable towards the weekly regimen[17].

Based on these data, we propose a single arm phase II study of weekly nab-paclitaxel in the elderly second-line NSCLC population. Nab-paclitaxel will be dosed at 100mg/m^2 weekly, for 3 weeks of every 4-week cycle, with cycles repeated until progressive disease.

1.5 Correlative Studies

1.5.1 Comprehensive Geriatric Assessment

While the Eastern Cooperative Oncology Group (ECOG) and Karnofsky Performance Status (PS) tools are easy and quick to use, they measure only one domain of functioning and thus lack sensitivity for frailty. More comprehensive evaluation with a geriatric assessment (GA) tool can provide more complete information regarding functional status, co-morbid medical conditions, psychological state, social support, nutritional status, cognition, and medications. This information can potentially improve the therapeutic index of therapy by aiding in clinical selection of appropriate patients. Comprehensive GA is well accepted by patients.[22] Baseline GAs will be performed in all patients enrolled into this trial, and components of the GA will be explored as predictors of chemotherapy tolerance and overall survival.

1.5.2 Biologic Assessment of Physiologic Age and p16^{INK4a}

The protein, p16^{INK4a}, is a tumor suppressor which originates from the INK4/ARF locus on chromosome 9p21. Recently, p16^{INK4a} expression has been proposed as a marker of physiologic aging. Levels of p^{16INK4a} increase nearly tenfold over sixty years.[23] In addition to correlating with age, p16^{INK4a} is associated with tobacco use and physical inactivity, two factors positively associated with an increased risk of age-related diseases. This suggests that p16^{INK4a} may be a marker not simply of chronologic age, but rather physiologic age. In patients over 65 years of age, treatment with chemotherapy increases p16^{INK4a} to a similar extent as ten years of aging.[24] Levels of p^{16INK4a} will be drawn serially across the trial, and results explored as predictors of chemotherapy tolerance and overall survival. Based on the previously reported correlation between p16^{INK4a} and factors associated with age-related disease (e.g., tobacco use, physical inactivity), we will also include a brief health behaviors questionnaire, to capture the baseline level of physical activity, smoking habits and alcohol consumption. These data will be used to explore correlations with changes in *p16^{INK4a}* expression.

1.5.3 Quality of Life

Lung Cancer Symptom Scale (LCSS)[25]

The LCSS is designed as a site-specific measure of quality of life (QoL), particularly for use in clinical trials. The LCSS is designed for use in patients with lung cancer, capturing QoL factors most related to treatment and changes in the disease state. It evaluates six major symptoms associated with lung malignancies and their effect on overall symptomatic distress, functional activities, and global QoL. The LCSS consists of a nine-item patient-rating scale and a six-item observer rating scale.

Functional Assessment of Cancer Therapy-Lung (FACT-L) Scale

The FACT-L is a validated, multidimensional, self-report QoL instrument specifically designed for use with lung cancer patients [26]. It consists of 27 core items which assess patient function in four domains: Physical, Social/Family, Emotional, and Functional well-being, which is further supplemented by 9 site specific items to assess for lung cancer related symptoms. Each item is rated on a 5-point Likert type scale, and then combined to produce subscale scores for each domain, as well as a global QoL score.

1.5.4 Sarcopenia assessment

Sarcopenia has been shown to be associated with poor survival in older cancer patients (PMID: 26882087). Sarcopenia, as measured by CT imaging was shown to predict taxane toxicity, hospitalization and survival in 40 breast cancer patients treated with various taxanes; a weakness of the work was heterogeneity in taxane treatment (PMID: 27489287). While abdominal imaging is preferred, chest CT has been previously used to evaluate sarcopenia in lung cancer patients (PMID: 27364150) and it correlates with lumbar results obtained from abdominal imaging.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

2.1.1 To evaluate the tolerability of weekly nab-paclitaxel in older adults with advanced lung cancer who have progressed on at least 1 prior regimen after 6 cycles or 3 weeks after discontinuation of treatment, for those who come off treatment earlier.

2.2 Secondary Objectives

2.2.1 To estimate overall survival (OS)

2.2.2 To estimate progression-free survival (PFS)

2.2.3 To estimate the response rate (RR)

2.3 Correlative Objectives

2.3.1 To explore baseline components of the GA as predictors of chemotherapy tolerance and overall survival

2.3.2 To explore the use of p16 measurements in the elderly as predictors of chemotherapy tolerance and overall survival

2.3.3 To explore the impact of weekly nab-paclitaxel treatment on quality of life, as measured by LCSS and FACT-L

2.3.4 To explore the impact of sarcopenia on toxicity, RR, PFS, OS and changes in quality of life.

2.4 Endpoints

2.4.1 Primary Endpoint

- Occurrence of clinically important ≥grade 3 treatment-related toxicity (such as neuropathy, myalgia, arthralgia, neutropenia, thrombocytopenia and anemia) and any ≥Grade 3 unexpected toxicities deemed clinically significant and considered related to nab-paclitaxel by the treating physician associated with 6 cycles of treatment, or 3 weeks after discontinuation of treatment, for those who come off treatment earlier, as assessed via NCI CTCAE version 4.0

2.4.2 Secondary Endpoints

- OS is defined as the time from day 1 (D1) of treatment until death as a result of any cause
- PFS is defined as the time from D1 of treatment until progression or death as a result of any cause
- OR rate (CR + PR) as defined via RECIST 1.1

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

The patient must meet all of the inclusion criteria listed below to participate in this study:

3.1.1 Signed, written informed consent

3.1.2 Male or female patient

3.1.3 ≥ 70 years of age

3.1.4 Diagnosis of NSCLC, histologically or cytologically confirmed

3.1.5 International Association for the Study of Lung Cancer (IASLC) Version 7, Stage IV disease; or recurrence after prior surgery or radiotherapy

3.1.6 Progression following a single line of prior cytotoxic therapy including a platinum agent plus a standard cytotoxic partner other than a taxane (typically pemetrexed, gemcitabine or vinorelbine):

- Previous treatment with targeted therapy will not count as a prior line of therapy if the patient's tumor has the relevant molecular change (eg, EGFR mutation for erlotinib and EML4/ALK or ROS1 for crizotinib).

- Previous treatment with immune-oncologic agents (such as nivolumab) will not count as a prior line of therapy.

3.1.7 Eastern Cooperative Oncology Group (ECOG) performance status 0 – 2; see Appendices, Section 11.0

3.1.8 Adequate organ and bone marrow function as defined by:

- Absolute neutrophil count (ANC) $\geq$ 1,500 cells/mm^3
- Hemoglobin $\geq$ 9 g/dL (it is acceptable to reach this through transfusion)
- Platelets >100,000 cells/mm^3
- Creatinine $\leq$ 1.5mg/dL
- Total bilirubin $\leq$ 1.5 mg/dL
- Alkaline phosphatase $\leq$ 2.5 x upper limit of normal (ULN)
- Alanine aminotransferase (ALT, SGPT) $\leq$ 2.5 x ULN
- Aspartate aminotransferase (AST, SGOT) $\leq$ 2.5 x ULN

3.1.9 Recovered from all reversible toxicities related to their previous treatment (other than alopecia) to $\leq$grade 1 or baseline

3.1.10 Patients must have < Grade 2 pre-existing peripheral neuropathy (per CTCAE)

3.1.11 Women of childbearing potential and sexually active men must agree to use effective contraception prior to study entry, for the duration of study participation and for three months after completing treatment. Adequate contraception is defined as any medically recommended method (or combination of methods) as per standard of care.

3.1.12 Negative serum or urine β-hCG pregnancy test at screening for patients of childbearing potential

3.1.13 Patients with brain metastases may participate if they have undergone appropriate treatment for the lesion(s), are at least two weeks post treatment without evidence for post-treatment progression, have no significant neurologic symptoms, and no longer require steroids for the reason of brain metastases. Patients with symptoms suggestive of CNS metastases should be evaluated with imaging prior to study participation.

3.2 Exclusion Criteria

Subjects meeting any of the following exclusion criteria at baseline will be excluded from study participation:

3.2.1 Prior taxane therapy for any indication

3.2.2 Less than 3 weeks elapsed since prior exposure to chemotherapy

3.2.3 Pre-existing neuropathy greater than grade 1

3.2.4 Other active, invasive malignancy requiring ongoing therapy or expected to require systemic therapy within two years; localized squamous cell carcinoma of the skin, basal-cell carcinoma of the skin, carcinoma in-situ of the cervix, or other malignancies requiring locally ablative therapy only will not result in exclusion.

3.2.5 Concomitant anticancer therapy, immunotherapy, or radiation therapy (no radiation within prior 2 weeks)

3.2.6 Have received treatment within the last 30 days prior to study entry with any drug that has not received regulatory approval for an indication at the time of study entry

3.2.7 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection requiring IV antibiotics, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements

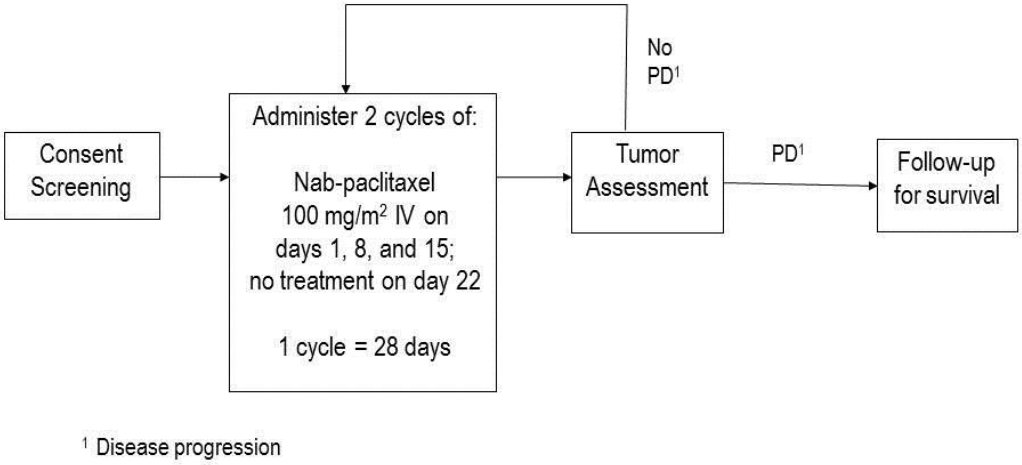
3.2.8 Pregnant women are excluded due to the potential for teratogenic or abortifacient effects of nab-paclitaxel. Because there is a potential risk for adverse events in nursing infants secondary to treatment of the mother with these agents, breastfeeding should be discontinued prior to participation of the mother on study.

3.2.9 Known hypersensitivity to protein bound paclitaxel

3.2.10 Any other concurrent condition that in the investigator's opinion would jeopardize compliance with the protocol

4.0 TREATMENT PLAN

4.1 Schema



This is a single arm, non-randomized, Phase II study evaluating the tolerability of weekly nab-paclitaxel as second line treatment in 42 elderly patients with advanced lung cancer. Patients will receive nab-paclitaxel once weekly (days 1, 8 and 15) for 3 weeks of every 4-week cycle. After every 2 cycles, tumor measurements will be assessed for response. Patients will continue treatment until disease progression. Following discontinuation of treatment, patients will be followed for up to 2 years. Section 6.0 (time and events table) outlines the study assessments and correlative studies, including the GA (baseline and end of treatment), Health Behaviors questionnaire (baseline), QoL questionnaires (serially across the trial), and blood levels for evaluation of $p16^{INK4a}$ (serially across the trial). See sections 6.6, 6.7, 6.8, and 6.9 for additional information on these correlative studies.

The average duration of active patient participation in this study is expected to be approximately 3- 4 cycles (i.e., 3 to 4 months). This is based on median time to progression of 2.9 months following second-line treatment with docetaxel in elderly patients with advanced NSCLC [14]. Accrual to this study is expected to occur within 14 months.

4.2 Treatment Dosage and Administration

See Section 5.0 for more detailed information on nab-paclitaxel. Refer to the Full Prescribing Information for nab-paclitaxel for complete safety information: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/(in addition to that already provided in sections 1.3, 5.0 and . Dose modifications are described in section 4.4.1.

Nab-paclitaxel 100mg/m^2 will be infused over 30 minutes on Days 1, 8 and 15 of every 28-day cycle (see Table 2). Actual body weight will be used for the dose calculation. It is not a requirement to use in-line filters during the administration of nab-paclitaxel. In any event, filters of pore-size less than 15 micrometers must not be used. If patient body weight changes by >10%, recalculate the body surface area and dose of nab-paclitaxel. Note: Dose changes will apply for the next cycle; doses will not be changed mid- cycle.

Nab-paclitaxel should be prepared for intravenous administration according to instructions provided in the manufacturers' Prescribing Information.

Table 2

Drug	Dose	Route	Schedule	Cycle Length
Nab-paclitaxel	100 mg/m^2	Intravenous infusion over 30 minutes	Days 1, 8, 15 of each cycle	4 weeks (28 days)

4.3 Supportive Care Guidelines

All concomitant medications taken during the study will be recorded in the electronic case report form (eCRF) with indication, dose information, and dates of administration. Subjects should receive full supportive care during the study, including transfusion of blood and blood products, and treatment with antibiotics, antiemetics, and analgesics, as appropriate.

4.3.1 Nab-paclitaxel Premedication

Patients do not require premedication prior to nab-paclitaxel administration, as hypersensitivity reactions are rare.

Administration of solvent-based taxanes (Taxol® and Taxotere®) requires premedication with corticosteroids and histamine receptor blocking agents to prevent the occurrence of hypersensitivity reactions. 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. [27] 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 event of a severe hypersensitivity reaction, discontinue nab-paclitaxel.

4.3.2 Anti-emetic Medications

The recommended regimen will include Zofran 16 mg by oral, or 8 mg by IV route, or an alternative 5HT-3 antagonist. Aprepitant and dexamethasone use are not recommended as nab-paclitaxel is not sufficiently emetogenic as to require aprepitant and without cremophor, dexamethasone is not required to prevent infusion reactions. While not recommended, neither medicine is prohibited--clinicians may adjust the antiemetic regimen as needed for individual patients.

4.3.3 Hematopoietic Growth Factors

Use of erythropoiesis- stimulating agents (ESAs) will neither be recommended nor prohibited. If the clinician elects to utilize ESAs, they must be used within FDA-approved guidelines. The use of peg-filgrastim is not allowed in this study. The use of prophylactic filgrastim during chemotherapy is permitted at the discretion of the treating physician; it is recommended in patients with low blood counts that threaten treatment continuity. It is strongly advised in patients who have previous febrile neutropenia or who have treatment delays due to neutropenia.

When filgrastim is used, administer filgrastim 5 mcg/kg/day (rounded to the nearest vial size per investigator/institution's standard of care). The number of days of filgrastim is up to the discretion of the treating MD; however, the patient must start at least 24 hours after the dose of chemotherapy and be held at least 48 hours prior to the next dose. The dose of filgrastim can be adjusted based on the investigator's discretion. The delivery of G-CSF following week #3 of any cycle is per investigator discretion (since the patient will have a 2 week break prior to the next dose).

4.4 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives any treatment on this protocol will be evaluable for toxicity. Each patient will be assessed periodically for the development of any toxicity according to the Time and Events table (Section 6.0). Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Dose adjustments should be made according to the system showing the greatest degree of toxicity. See Section 4.4.1 for suggested dose modifications and dose delays due to toxicity.

If more than 2 dose reductions of nab-paclitaxel are required, protocol therapy is to be discontinued, response assessed, and the patient should proceed to optimal definitive therapy outside the constraints of the clinical trial. Once a patient's dose has been reduced, the dose reduction will be permanent. Dose re-escalation will not be permitted.

If a patient misses more than 28 consecutive days of treatment or more than 2 cycles of treatment due to toxicity, the patient will be removed from the study. If the treating clinician feels that the patient has been benefitting from treatment with nab-paclitaxel and would benefit more from ongoing study therapy than another treatment, he/she may request an exemption from these requirements by the PI and these may be granted on a case-by-case basis.

For AEs that require dose reductions of nab-paclitaxel, please refer to the dose reductions described in Table 3:

Table 3

Dose Level	Nab-paclitaxel dose (mg/m^2)
0 (starting dose)	100
-1	80
-2	60

Hypersensitivity reactions to nab-paclitaxel 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 nab-paclitaxel administration and aggressive symptomatic therapy. Patients who experience a severe hypersensitivity reaction to nab-paclitaxel should not be re-challenged.

4.4.1 Dose Delays and Dose Modifications for nab-paclitaxel

Hematological Toxicity	Toxicity grade	Dose Level for Subsequent Administration
Neutropenia or Febrile neutropenia If ANC <1,000/mm^3, hold treatment. Resume per table once ANC ≥1,000/mm^3	Grade 2 (ANC <1,500/mm^3 to 1,000/mm^3)	Maintain dose; Consider G-CSF [1]
	Grade 3 (ANC < 1,000/mm^3)	↓ 1 dose level and strongly consider G-CSF [1]
	Febrile neutropenia	↓ 1 dose level and administer G-CSF[1]
Thrombocytopenia **Day 1**: If platelets <100,000/mm^3 hold treatment. Initiate cycle once platelets ≥100,000/mm^3 **Days 8, 15**[3]: If platelets <75,000/mm^3 hold treatment. Resume per table once platelets ≥75,000/mm^3	Grade 1 (<LLN to 75,000/mm^3)	Maintain dose. If recurrent or early in treatment, ↓1 dose level
	Grade 2 (<75,000/mm^3 to 50,000/mm^3)	↓1 dose level (when treatment resumes)
	Grade 3 (<50,000/mm^3 to 25,000/mm^3)	↓2 dose levels (when treatment resumes)
Anemia If Hgb<8 g/dL, transfuse PRBCs. Once Hgb is ≥ 8 g/dL, therapy may resume.	≥Grade 3 (Hgb <8 g/dL)	For Hgb <8 g/dL, consider ↓1 dose level (when treatment resumes)
Non-hematological Toxicity		
Sensory neuropathy If ≥ grade 3, hold treatment. Resume per table once ≤grade 1	Grade 1	Maintain dose
	Grade 2	↓1 dose level
	Grade 3 - 4	↓2 dose levels (when treatment resumes)
Hyperbilirubinemia If bilirubin >2mg/dL, hold treatment. . Resume per table once bilirubin ≤2mg/dL	Bili >2 mg/dL	↓1 dose level (when treatment resumes)
	Bili >3 mg/dL	↓2 dose levels (when treatment resumes)
Transaminase elevation (ALT or AST) If ≥ Grade 2 (>3 x ULN) hold treatments. Resume per table once transaminases ≤ 3 x ULN	Grade 1 (>ULN – 3x ULN)	Maintain dose
	Grade 2 (>3 – 5 x ULN)	↓1 dose level (when treatment resumes)
	≥Grade 3 (>5 x ULN)	↓2 dose levels (when treatment resumes)
Renal toxicity If serum Cr >2 mg/dL, hold treatment. Resume per table once serum Cr<2 mg/dL	≤Grade 2 (≤ 3 x ULN)	Maintain dose
	≥Grade 3 (>3 x ULN)	↓1 dose level (when treatment resumes)
Other non-specified[2] Hold treatment until toxicity resolves to ≤Grade 1. Resume treatment with dose adjusted per table.	≥ Grade 3	↓1 dose level (when treatment resumes)

[1] If G-CSF (filgrastim) is given concurrently with weekly *nab*-paclitaxel, administration may begin 24 hours after nab-paclitaxel is given and should stop at least 48 hours prior to when *nab*-paclitaxel is given the following week. The dose is 5mcg/kg/day rounded to the nearest vial size per investigator/institution's standard of care. See section 4.3.3. Note: peg-filgrastim is not permitted during the study.
[2]Excludes alopecia and non-refractory nausea/vomiting
[3]D8 and D15 CBCs are not required, however, if they are obtained, please follow the guidance provided in this table

4.5 Concomitant Medications/Treatments

No drug interactions studies have been conducted with nab-paclitaxel, a drug metabolized by CYP2C8 and CYP3A4. Caution should be used when administering nab-paclitaxel with medications known to inhibit or induce either CYP2C8 or CYP3A4. Use of peg-filgrastim (Neulasta®) is not permitted during this trial.

4.6 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue until:

- Disease progression
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from study treatment, **OR**
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

4.7 Duration of Follow-up

Patients will be followed for 24 months after completion of treatment or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event and followed up per protocol.

4.8 Removal of Patients from Protocol Therapy

The following indications will result in discontinuation from protocol therapy (patient will be followed-up per protocol):

- The investigator decides that the patient should be withdrawn from the study because of toxicity or other factors. If this decision is made because of a serious adverse event or clinically significant laboratory value, the study drug is to be discontinued and appropriate measures are to be taken.
- The patient requests to be withdrawn from the study. Patient to be followed-up per protocol unless patient refuses
- The patient for any reason requires treatment with another therapeutic agent (other than that specified by the protocol) for their disease. In this case discontinuation from the study occurs immediately upon introduction of the new agent.
- Evidence of progressive disease
- Unacceptable toxicity.
- The patient becomes pregnant or fails to use adequate birth control (for those patients able to conceive).
- The patient is lost to follow-up; in this case patient will be removed from study.
- General or specific changes in the patient's condition or co-morbidity renders the patient unacceptable for further treatment in the judgment of the investigator

If a patient is removed from study treatment, the Principal Investigator will be notified, and the reason for study removal and the date the patient was removed will be documented in the electronic Case Report Form (e-CRF). The patient should be followed-up per protocol.

4.9 Study Withdrawal

If a patient decides to withdraw from the study (and not just from protocol therapy) all efforts should be made to complete and report study assessments as thoroughly as possible. The investigator should contact the patient or a responsible relative by telephone or through a personal visit to establish as completely as possible the reason for the study withdrawal. A complete final evaluation at the time of the patient's study withdrawal should be made with an explanation of why the patient is withdrawing from the study. If the reason for removal of a patient from the study is an adverse event, the principal specific event will be recorded on the eCRF.

5.0 DRUG INFORMATION

5.1 Nab-paclitaxel (Abraxane®; ABI-007)

Nab-paclitaxel is a protein-bound form of paclitaxel indicated in the United States for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated. It is also indicated for locally advanced or metastatic NSCLC as first-line treatment in combination with carboplatin in patients who are not candidates for curative surgery or radiation therapy. See:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
for additional information, and the nab-paclitaxel investigator's brochure for complete information.

5.1.1 Packaging, Labeling, Storage and Supply of nab-paclitaxel

Nab-paclitaxel (Abraxane®) will be supplied by Celgene Corporation, in single-use vials. Each single-use 50 mL vial will contain paclitaxel (100 mg) and human albumin (HA; approximately 900 mg). Commercial drug will be supplied. Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel. Un-reconstituted nab-paclitaxel (Abraxane®) should be stored at controlled room temperature (20° to 25°C or 68° to 77°F) in its original carton to protect from bright light. Unopened vials are stable until the date indicated on the package when stored between 20°C to 25°C (68°F to 77°F), in the original package. Neither freezing nor refrigeration adversely affects the stability of the product.

Reconstituted nab-paclitaxel (Abraxane®) should be used immediately. If not used immediately, the vial of reconstituted nab-paclitaxel (Abraxane®) must be placed in its carton in a refrigerator at 2° to 8°C (36° to 46°F) for a maximum of 8

hours. 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. Both forms should be stored in an area free of environmental extremes and must be accessible only to study personnel.

Temperature records for nab-paclitaxel (Abraxane®) must be kept for verification of proper study drug storage.

If storing reconstituted nab-paclitaxel (Abraxane®), some settling may occur. Ensure complete re-suspension by mild agitation prior to use.

The suspension for infusion prepared as recommended in an infusion bag should be used immediately, but may be stored at ambient temperature (approximately 25°C) and lighting conditions for up to 4 hours.

5.1.2 Reconstitution of nab-paclitaxel

Nab-paclitaxel will be reconstituted by appropriate study personnel and administered to the patient in the study site setting at weekly intervals. The investigator will calculate the body surface area (BSA) of the patient in order to determine the total amount of nab-paclitaxel to be administered.

Reconstitution and use of nab-paclitaxel:

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

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

   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 (e.g., 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. Reconstitute each nab-paclitaxel (Abraxane®) vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP or equivalent into each vial over a period of not less than 1 minute (Note: change the syringes after reconstituting every 3 vials).
   - **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 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 sample 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 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. Inject the calculated dosing volume of reconstituted Abraxane® suspension into an empty sterile, standard PVC IV bag using an injection port. 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 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.

5.1.3 Dose and Schedule of nab-paclitaxel

See section 4.2.

5.1.4 Administration

Nab-paclitaxel will be infused intravenously over 30 minutes. Actual body weight will be used for the calculation.

NOTE: It is not a requirement to use filter needles in the preparation of, or in-line filters during the administration of nab-paclitaxel. In any event, filters of pore-size less than 15 micrometers must **not** be used.

5.1.5 Receipt and Return of nab-paclitaxel

Upon receipt of the study drug supplies from Celgene Corporation

Celgene Corporation
86 Morris Avenue
Summit, NJ 07901

The investigator or designee will conduct an inventory and sign both copies of the study drug receipt form and forward one copy to the address indicated on the

form. One copy of the receipt and the packing slip must be retained in the investigational drug services (IDS) records.

No supplies will be shipped to any site until regulatory approval has been obtained. Investigational sites will be supplied with 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.

Industry Contact:

Martha Kennedy
Senior Manager, Medical Operations
Celgene Corporation
86 Morris Avenue
Summit, NJ 07901
Mobile: 908-723-6919
Fax: 908-673-2779
Email: mkennedy@celgene.com

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.

5.1.6 Clinical Safety Summary

See prescribing information for information on nab-paclitaxel when used according to its FDA indication in the treatment of metastatic breast cancer and dosed every 3 weeks or when used in NSCLC dosed days 1, 8 and 15 of every 21 day cycle in combination with carboplatin on day 1: http://www.accessdata.fda.gov/scripts/cder/drugsatfda

When used in combination with carboplatin in NSCLC, the most common reactions (≥10%) included anemia (98%), neutropenia (85%), thrombocytopenia (68%), alopecia (56%), peripheral neuropathy (48%), nausea (27%), fatigue (25%), decreased appetite (17%), asthenia (16%), constipation (16%), diarrhea (15%), vomiting (12%), dyspnea (12%), peripheral edema (10%), arthralgia (13%), rash (10%), and myalgia (10%).

When administered weekly as a single agent at 100mg/m^2 in 65 patients with locally advanced breast cancer for 12 doses, no grade 4 nab-paclitaxel adverse events were reported. The most common (% of patients) nab-paclitaxel-related adverse events included neutropenia (grade 2: 6%, grade 3: 3%), febrile neutropenia (grade 3: 2%), fatigue (grade 2: 26%, grade 3:6%) neuropathy (grade 2: 11%, grade 3: 5%), nausea (grade 2: 10%), vomiting (grade 2: 8% , grade 3: 2%), and diarrhea (grade 2: 9%, grade 3: 5%). Dose reductions or omissions were required in 14 (2%) of doses [28].

The following adverse events are associated with nab-paclitaxel when studied in metastatic breast cancer:

Hematologic: Myelosuppression, primarily neutropenia, is dose dependent and reversible, but dose limiting. Thrombocytopenia is uncommon, while anemia occurred in 33% (severe in <1%) of patients in the randomized trial.

Infections: Infectious episodes were reported in 24% of patients in the randomized phase III trial in metastatic breast cancer.

Hypersensitivity: Hypersensitivity reactions (Grade 1 or 2) occurred on the day of nab-paclitaxel administration in the randomized phase III trial in metastatic breast cancer and consisted of dyspnea (1%) and flushing, hypotension, chest pain, and arrhythmias (all <1%).

Cardiovascular: Hypotension occurred in 5% and bradycardia (during the infusion) in <1% of patients in the randomized Phase III trial. Severe cardiovascular events possibly related to nab-paclitaxel occurred in approximately 3%, and included cardiac ischemia/infarction, chest pain, cardiac arrest, supraventricular tachycardia, edema, thrombosis, pulmonary thromboembolism, pulmonary emboli, and hypertension. Strokes and TIAs have been reported.

ECG abnormalities: occurred in 35% of patients who had a normal ECG at baseline in the randomized Phase III trial in metastatic breast cancer.

Respiratory: Following treatment with nab-paclitaxel, dyspnea (12%), cough (7%) and pneumothorax (<1%) were reported in the randomized Phase III trial in metastatic breast cancer.

Neurologic: Sensory neuropathy occurs frequently with nab-paclitaxel (71% in the randomized clinical trial, 10% severe). It is dose-dependent, and increases with cumulative dose.

Vision: Ocular/visual disturbances occurred in 13%; 1% were severe and included keratitis and blurred vision.

Arthralgia/Myalgia: Symptoms occurred in 44% of patients in the randomized clinical trial (8% of patients experienced severe symptoms).

Hepatic: Exposure and toxicity of paclitaxel can be increased with hepatic impairment. Grade 3 or 4 elevations in GGT occurred in 14% of patients in the randomized Phase III trial.

Renal: Elevated serum creatinine occurred in 11% (1% severe) of patients in the randomized Phase III trial.

General Toxicity Information

Drug Interactions: No drug interactions studies have been conducted with nab-paclitaxel, a drug metabolized by CYP2C8 and CYP3A4. Caution should be used when administering nab-paclitaxel with medications known to inhibit or induce either CYP2C8 or CYP3A4.

Injection site reactions: These reactions occur infrequently with nab-paclitaxel and were mild in the randomized clinical trial.

Use in patients with hepatic impairment: The starting dose of nab-paclitaxel should be reduced for patients with moderate and severe hepatic impairment.

Use in pregnancy: Nab-paclitaxel is pregnancy category D. Men should also be advised not to father a child while receiving treatment with nab-paclitaxel.

Albumin: Nab-paclitaxel contains human albumin, and thus carries an extremely remote risk for transmission of viral diseases, and Creutzfeldt-Jakob Disease.

Other potential risks associated with nab-paclitaxel include mucositis, bilirubin/liver enzyme elevations, edema, alopecia, asthenia, nail changes, dehydration and pyrexia.

See the nab-paclitaxel prescribing information and investigator's brochure for additional information on post-marketing toxicities reported with nab-paclitaxel.

6.0 EVALUATIONS AND ASSESSMENTS

6.1 Time and Events Table

Assessments	Screening[1]	Day 1 of every cycle[1a]	Day 1 of odd numbered cycles, before chemotherapy (begin with Cycle 3)	Day 1 of Cycle 3 and Cycle 5	End of Treatment[2]	Follow-up[3]
Informed Consent	X					
Medical History	X[4]	X[4]			X[4]	
Physical Exam[5]	X[5]	X[5]			X[5]	
ECOG Performance Status	X	X			X	
Weight	X	X[6]			X	
Pregnancy test (serum or urine β-hCG)	X					
CBC w/differential	X	X[8]			X[7]	
Serum chemistries[8]	X	X[8]			X[7]	
Whole blood for $p16^{INK4a}$	X[9]			X[9]	X[9]	
Geriatric Assessment	X				X	
HBQ[10]	X					
LCSS[11]	X		X		X	
Fact-L[12]	X		X		X	
Tumor imaging evaluation[13]	X[1,13]		X[13]		X[2,13]	X[3, 13]
Concomitant medications	X	X			X	
Toxicity assessment		Continuous during study				
Survival assessment						X[3]

[1]Screening evaluations to take place within 2 weeks of day 1 of study. Screening tumor imaging may take place within 4 weeks of treatment initiation.
[1a]Patients may be evaluated more frequently during cycle when clinically indicated, and at investigator discretion. Each study visit should take place within 24 hours +/- of originally scheduled date.
[2]End of treatment visit to occur 21 to 30 days after last treatment; radiographic evaluation of tumor at discretion of physician
[3]Follow-up will take place every 2-3 months after end of treatment visit for 2 years or until death (whichever is first), and may be conducted via telephone. Evaluations limited to survival status, any follow-up of toxicity that is necessary, and tumor evaluation at discretion of physician.
[4]Complete medical history at baseline (including history of prior treatment of NSCLC); symptom-directed history thereafter
[5] Physical exam to include vital signs and height (the latter at baseline only)
[6]If weight changes >10%, recalculate the body surface area for dosing of nab-paclitaxel.
[7]These are necessary if last assessment was >3 weeks prior
[8]Serum chemistries to include sodium, potassium, chloride, bicarbonate, BUN, serum creatinine, glucose, calcium, phosphorus, magnesium, liver function tests (LFTs; total bilirubin, alkaline phosphatase, AST, ALT), total protein, albumin. (NOTE: If screening labs are drawn within 7 days prior to D1, they do not need to be repeated on D1 of cycle 1).
[9]For evaluation of $p16^{INK4a}$, CBC with differential must be drawn on the same day
[10] Health Behaviors Questionnaire; see section 6.8
[11]Lung Cancer Symptom Scale; see section 6.9.
[12]Functional Assessment of Cancer Therapy-Lung; see section 6.9
[13] To include CT of chest, abdomen and pelvis. CNS imaging only required if felt clinically indicated by treating physician. Imaging during study to occur within 1 week prior to Day 1 of odd-numbered cycles.

6.2 Pre-Study Assessments

Baseline evaluations are to be conducted within 2 weeks prior to start of protocol therapy. Tumor imaging must be done within 4 weeks prior to start of therapy. Baseline assessments include:

- Complete medical history and physical examination, including height measurement.
- Weight
- ECOG Performance Status; see Appendices section 11.0
- Geriatric Assessment (Version 5); see section 6.7; Appendices, section 11.1
- Health Behaviors questionnaire; see section 6.8; Appendices, section 11.2
- LCSS; see section 6.9; Appendices, section 11.3
- FACT-L (Version 4); see section 6.9; Appendices, section 11.4
- Pregnancy test (serum or urine β-hCG) for female patients of childbearing potential
- Laboratory evaluations: CBC with differential; serum chemistries (sodium, potassium, chloride, bicarbonate, BUN, serum creatinine, glucose, calcium, phosphorus, magnesium, liver function tests (LFTs: total bilirubin, alkaline phosphatase, AST, ALT), total protein, albumin)
- Blood sample for $p16^{INK4a}$ (confirm drawn on same day as CBC with differential) ; see section 6.6.
- Concomitant medication(s)
- Tumor evaluation: to include CT of chest, abdomen and pelvis. CNS imaging only required if felt clinically indicated by treating physician.
- Toxicity assessment: record any non-serious and serious AEs and assign appropriate toxicity grade (NCI CTCAE, Version 4).

6.3 Treatment Assessments

Day 1 each chemotherapy cycle (NOTE: If screening labs* are drawn within 7 days prior to D1, they do not need to be repeated on D1 of cycle 1; patients may be evaluated more frequently during cycle when clinically indicated, and at investigator discretion.).

- Physical examination and limited medical history
- Weight
- ECOG Performance Status (see Appendices section 11.0)
- Laboratory evaluations: CBC with differential; serum chemistries (sodium, potassium, chloride, bicarbonate, BUN, serum creatinine, glucose, calcium, phosphorus, magnesium, liver function tests (LFTs; total bilirubin, alkaline phosphatase, AST, ALT), total protein, albumin)
- Concomitant medication(s) – record all medication(s) added, changed or discontinued.
- Toxicity assessment: record any non-serious and serious AEs and assign appropriate toxicity grade (NCI CTCAE, Version 4).

Day 1 of odd-numbered chemotherapy cycles (beginning with Cycle 3), prior to chemotherapy treatment

- Tumor evaluation (to include CT of chest, abdomen and pelvis) CNS imaging only required if felt clinically indicated by treating physician.
- Imaging will occur within 1 week prior to Day 1 of odd-numbered cycles; results to be reviewed prior to treatment on Day 1.
- Blood sample for $p16^{INK4a}$ (confirm drawn on same day as CBC with differential) ; see section 6.6.
- LCSS; see section 6.9 and Appendices, section 11.3
- FACT-L (Version 4); see section 6.9 and Appendices, section 11.4

6.4 End-of-Treatment Visit

This visit should occur in patients when they stop treatment, whether due to disease progression or unmanageable toxicity.

The end of treatment visit will occur 21 to 30 days following completion of chemotherapy treatment:

- Limited medical history and physical examination
- Weight
- ECOG Performance Status (see Appendices section 11.0)
- LCSS; see section 6.9 and Appendices, section 11.3
- FACT-L (Version 4); see section 6.9 and Appendices, section 11.4
- Geriatric Assessment (Version 5); See section 6.7 and Appendices, section 11.1
- Laboratory evaluations will be performed if last assessment was more than 3 weeks prior to end-of-treatment visit: CBC with differential; serum chemistries (sodium, potassium, chloride, bicarbonate, BUN, serum creatinine, glucose, calcium, phosphorus, magnesium, liver function tests (LFTs; total bilirubin, alkaline phosphatase, AST, ALT), total protein, albumin)
- Blood sample for $p16^{INK4a}$ (confirm drawn on same day as CBC with differential) ; see section 6.6.
- Concomitant medication(s)
- Tumor evaluation (to include CT of chest, abdomen and pelvis) CNS imaging only required if felt clinically indicated by treating physician.
- Toxicity assessment: record any non-serious and serious AEs and assign appropriate toxicity grade (NCI CTCAE, Version 4).

6.5 Follow-up

Follow-up will take place every 2 to 3 months after the end of treatment visit, for 2 years or until death (whichever is first), and may be conducted via telephone.

Follow-up will focus on survival status, follow-up of toxicity as necessary, any subsequent anti-cancer medication taken by the patient, and tumor evaluation at discretion of the physician.

6.6 Whole blood for CBC and p16INK4a

A whole blood sample will be taken for $p16^{INK4a}$ (confirm drawn on same day as CBC with differential). The CBC with differential is necessary to normalize biomarker expression to the total lymphocyte count. If CBC with differential already scheduled per standard of care on same day as blood draw for biomarker is scheduled, there is no need to repeat the CBC with differential.

Processing of p16 blood samples:
At the UNC site, after phlebotomy, the tube will be well-mixed and transported immediately to the Sharpless laboratory in the Lineberger Cancer Center for storage and processing.
At external study sites, blood processing will be performed after phlebotomy, to yield a frozen T cell pellet. The pellet will be stored at -80 degrees C until ready for shipment to the Sharpless laboratory for analysis. Additional processing and shipping details will be provided in a study laboratory manual.

Expression of $p16^{INK4a}$ is measured by quantitative Taqman RT-PCR.

Blood samples for CBC and $p16^{INK4a}$ will be collected at baseline, on Day 1 of every odd numbered cycle beginning with cycle 3, and at the end of treatment visit.

We are currently examining how expression of other senescence markers change with age in our study of normal adults. Should we find changes in any other senescence effectors we may perform exploratory analyses of these DNA markers (e.g. telomere length) and serum proteins in the future. Thus, excess serum and non-lymphoid cells remaining after assaying for $p16^{INK4a}$ expression will be stored in the Sharpless laboratory (Room #21-225, Lineberger Comprehensive Cancer Center, CB #7295, University of North Carolina) for potential future use.

6.7 Geriatric Assessment (GA) (Version 5)

After completing some initial demographic information, the first 3 formal items within the GA will be completed with the assistance of the study staff. These include the Blessed Orientation-Memory-Concentration (BOMC) test, the Karnofsky Performance Status tool (KPS), and the Timed "Up and Go" test. The BOMC consists of six questions designed to screen for macroscopic cognitive impairment[29]. The KPS is a general measure of patient independence in carrying out normal activities and self-care needs[29]. The Timed Up and Go is a performance test of physical mobility, and measures how long it takes the patient, in seconds, to stand up from a standard arm chair, walk a distance of approximately 10 feet, turn, walk back to the chair, and sit down again. Together, these 3 items should take approximately 10 minutes to complete on average.

Following completion of the external evaluation, the patient will complete the patient questionnaire. After answering 7 questions on their background (additional demographic information, see section I of patient questionnaire), patients will complete section II which includes a number of assessments

designed to evaluate their functional status. The first tool is the Instrumental Activities of Daily Living (IADL, 7 questions), a subscale of the Multidimensional Functional Assessment Questionnaire (MFAQ): Older American Resources and Services (OARS). Each question is scored from 0 (completely unable) to 2 (without help) and sums to a score of 0-14. This is followed by the Activities of Daily Living (ADL, 10 items) subscale of the Medical Outcomes Study (MOS) Physical Health. Both the IADL questions and the ADL items are rated using a 3-point Likert scale measuring the degree to which an activity can be performed independently (see Section II). Also included in section II is a self-reporting version of the KPS, developed to assess the patient's perception of their own performance status. This involves patient selection of 1 of 8 phrases that the patient believes best describes their functional status. Section II ends by asking patients to report the number of times they've fallen in the last 6 months.

Sections III & IV of the questionnaire include a co-morbidity scale (the Physical Health Section of the OARS) that contains a list of current illnesses and conditions an individual might have and the degree to which they impair daily activities, as well as a request for the patient to list all current medications they are taking. A brief section on nutrition follows, comprised of 3 brief questions. Section VI involves an assessment of psychological distress and well-being and includes 17 questions from The Mental Health Index (MHI-17).

The formal GA finishes with separate evaluations of social functioning (via the 4 question MOS Social Activity Limitations Measure) and social support (via the 12 item MOS Social Support Survey: Emotional/Information and Tangible subscales).

Once the GA is completed, the evaluation ends with 4 questions evaluating patient satisfaction with the self-administered portion of the GA.

The Geriatric Assessment will be administered prior to treatment and at the end of treatment visit. (See Appendices, Section 11.1 below)

6.8 Health Behaviors Questionnaire

Patients will be asked to complete a brief health behaviors questionnaire at study entry, regarding their smoking and exercise habits, and weekly alcohol consumption (see Appendices, section 11.2).

6.9 Assessment of Quality of Life

Quality of life will be evaluated using the lung cancer symptom scale (LCSS) and the Functional Assessment of Cancer Therapy-Lung (FACT-L, Version 4) scale.

LCSS and FACT-L will be administered prior to treatment, before each odd-numbered treatment cycle (beginning with Cycle 3), and at the End of Treatment visit. (See Appendices, sections 11.3 and 11.4)

For the LCSS, both a patient and observer rating scale will be completed. Additional documentation regarding the administration and scoring of the LCSS will be provided in the study manual.

6.10 Assessment of Safety

The primary objective of this study will be tolerability of weekly nab-paclitaxel, as measured by occurrence of Grade 3 or worse toxicity after 6 cycles or 3 weeks after discontinuation of treatment, for those who come off treatment earlier. Grade 3 and 4 toxicities of interest include those of clinical significance, such as neuropathy, myalgia, arthralgia, neutropenia, thrombocytopenia and anemia and those that are deemed clinically significant and considered related to nab-paclitaxel by the treating physician.

Any patient who receives treatment on this protocol will be evaluable for toxicity. The criteria used to assess toxicity are the National Cancer Institute (NCI), Common Terminology Criteria for Adverse Events (CTCAE), version 4.

Further information on assessment for toxicity is provided in the time and events table (Section 6.0). See section 4.4.1 for description of dose limiting toxicity and dose modifications.

6.11 Assessment of Efficacy

Efficacy outcomes are secondary objectives for this study, and include OS, ORR, and PFS. All patients who receive at least one dose of nab-paclitaxel will be evaluable for OS. Patients who have received at least 2 cycles of therapy and have at least one post-baseline efficacy assessment after Cycle 2 will be evaluable for assessment of the secondary response objectives (ORR and PFS). Patients who drop out of the study prior to the first formal tumor assessment for the reason of progression will be assessable and counted as having progressive disease. Patients who drop out of the study prior to the first formal tumor assessment for reasons other than progression will not be evaluable for ORR or PFS. ORR and PFS will be assessed via RECIST1.1.

6.11.1 Assessment of Disease-Tumor Measurement Based on RECIST 1.1

See the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1 (Eur J Cancer 45;2009:228-247) for additional details on RECIST1.1.

Measurable disease will be defined as the presence of at least one measurable lesion that can be accurately measured in at least one dimension with the longest diameter a minimum size of:

- $\geq$10mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest x-ray.

For malignant lymph nodes to be considered pathologically enlarged and measurable, a lymph node must be ≥15mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5mm). At baseline and in follow-up, only the short axis will be measured and followed.

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

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam. Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesions is recommended.

6.11.2 Baseline Documentation of Target and Non-Target Lesions

All measurable lesions up to a maximum of 5 lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longer diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as “present” or “absent,” or in rare cases “unequivocal progression.”

6.11.3 Evaluation of Target Lesions using RECIST 1.1 Criteria

NOTE: In addition to the information below, also see section 4.3.2 in the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1 (Eur J Cancer 45;2009:228-247) for special notes on the assessment of target lesions.

Complete response (CR)−Disappearance of all target lesions. Any pathological lymph node (LN) target or no must have decreased in short axis to <10mm.

Partial response (PR)−At least a 30% decrease in the sum of the LD of the target lesions taking as reference the baseline sum LD.

Progressive Disease (PD)−At least a 20% increase in the sum of the LD of the target lesions taking as reference the smallest sum LD recorded since the treatment started including baseline if that is the smallest on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm. The appearance of one or more new lesions also constitutes PD.

Stable disease (SD)−Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum LD since the treatment started.

6.11.4 Evaluation of Non-Target Lesions using RECIST 1.1 Criteria

Complete response (CR)−Disappearance of all non-target lesions and normalization of tumor marker levels. All LN must be non-pathological in size (<10mm short axis).

Non-complete response (non-CR)/non-progression (non-PD)−Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.

Progressive disease (PD)−Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

6.11.5 Evaluation of Best Overall Response using RECIST 1.1 Criteria

The best overall response is the best response recorded from the start of the study treatment until the end of treatment. The best overall response will be defined according to the following table:

Overall Response First Time Point	Overall Response Subsequent Time Point	BEST Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR[1]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE[2]	SD provided minimum criteria for SD duration met, otherwise, NE[2]
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE[2]	SD provided minimum criteria for SD duration met, otherwise, NE[2]
NE	NE[2]	NE[2]

[1] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

[2] NE=not evaluable

6.11.6 Sarcopenia: CTs of the chest, and, when available, abdomen, will be obtained at baseline and at the first disease assessment. Exploratory analyses will be conducted evaluating the L3 muscle index if an adequate number of samples (abdominal CTs) are available or at L1 if an adequate number of samples are not. Baseline muscle indexes and their change at first disease assessment will be reported. Both baseline measures and the change will be explored for association with toxicity, RR, PFS, OS and changes in quality of life.

7.0 ADVERSE EVENTS

7.1 Definitions

7.1.1 Adverse Event (AE)

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria below), regardless of etiology. Any worsening

(i.e., any clinically significant adverse change in the frequency or intensity of a preexisting condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the electronic case report from (e-CRF) rather than the individual signs or symptoms of the diagnosis or syndrome. An overdose, accidental or intentional, whether or not it is associated with an AE, or abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. If an overdose is associated with an AE, the overdose and adverse event should be reported as separate terms.

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/interruption of the dose of the drug, or any therapeutic intervention; or
- is judged to be of significant clinical importance.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the electronic case report form (eCRF). If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE.

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) need not be considered AEs and should not be recorded as an AE. Disease progression should not be recorded as an AE, unless it is attributable by the investigator to the study therapy.

In this study, toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

7.1.2 Suspected Adverse Reaction (SAR)

A suspected adverse reaction (SAR) is any AE for which there is a *reasonable possibility* that the drug is the cause. *Reasonable possibility* means that there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Causality assessment to a study drug is a medical judgment made in consideration of the following factors: temporal relationship of the AE to study drug exposure, known mechanism of action or side effect profile of study treatment, other recent or concomitant drug exposures, normal clinical course of the disease under investigation, and any other underlying or concurrent medical conditions. Other factors to consider in considering drug as the cause of the AE:

- Single occurrence of an uncommon event known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event not commonly associated with drug exposure, but otherwise uncommon in the population (e.g., tendon rupture); often more than once occurrence from one or multiple studies would be needed before the sponsor could determine that there is *reasonable possibility* that the drug caused the event.
- An aggregate analysis of specific events observed in a clinical trial that indicates the events occur more frequently in the drug treatment group than in a concurrent or historical control group

7.1.3 Unexpected AE or SAR

An AE or SAR is considered unexpected if the specificity or severity of it is not consistent with the applicable product information (e.g., Investigator's Brochure (IB) for an unapproved investigational product or package insert/summary of product characteristics for an approved product). Unexpected also refers to AEs or SARs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.1.4 Serious AE or SAR (or Pregnancy)

An AE or SAR is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Requires inpatient hospitalization (>24 hours) or prolongation of existing hospitalization;*
- Results in congenital anomaly/birth defect;
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. For reporting purposes, also consider the occurrences of pregnancy as an event which must be reported as an important medical event.

*Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.

Pregnancy

For females of childbearing potential: Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on nab-paclitaxel, or within 30 days of the last dose of nab-paclitaxel, are considered immediately reportable events. See Reporting requirements below. Nab-paclitaxel is to be discontinued immediately.

The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

Male subjects: If a female partner of a male subject taking nab-paclitaxel becomes pregnant, the male subject taking nab-paclitaxel should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

7.2 Documentation of non-serious AEs or SARs

For non-serious AEs or SARs, documentation must begin from day 1 of study treatment and continue through the 30 day follow-up period after treatment is discontinued.

Collected information should be recorded in the Case Report Forms (CRF) for that patient. Please include a description of the event, its severity or toxicity grade, onset and resolved dates (if applicable), and the relationship to the study drug. Documentation should occur at least monthly.

7.3 SAEs or Serious SARs (or Pregnancy-suspected or positive)

7.3.1 Timing

After informed consent but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g. SAEs related to invasive procedures such as biopsies, medication washout, etc).

For any other experience or condition that meets the definition of an SAE or a serious SAR, recording of the event must begin from day 1 of study treatment and continue through the 30 day follow-up period after treatment is discontinued.

7.3.2 Documentation and Notification

These events (SAEs or Serious SARs) must be recorded in the SAE console within Oncore™ for that patient within 24 hours of learning of its occurrence. To meet the requirements of Celgene (see section 7.3.4 below), all SAEs must also be recorded on a MedWatch3500A form and faxed to Celgene.

7.3.3 Reporting

IRB Reporting Requirements:

UNC**:**

- UNC will submit an aggregated list of all SAEs to the UNC IRB annually at the time of study renewal according to the UNC IRB policies and procedures.
- The UNC-IRB will be notified of all SAEs that qualify as an Unanticipated Problem as per the UNC IRB Policies using the IRB's web-based reporting system (see section 9.5.3) within 7 days of the Investigator becoming aware of the problem.

Affiliate sites:

- For affiliate sites using a local IRB of record, please submit adverse events per local IRB policy.
- For affiliate sites relying on the UNC-IRB, an aggregated list of all SAEs will be submitted to the UNC IRB annually at the time of study renewal according to the UNC IRB policies and procedures. In addition, any SAEs that qualify as an Unanticipated Problem will be entered into Oncore and reported to the UNC IRB by the UNCCN Study Coordinator using the IRB's web-based reporting system (see section 9.5.3) within 7 days of the Investigator becoming aware of the problem.

7.3.4 Expedited Reporting by Investigator to Celgene

Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours/1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number (AX-CL-NSCLC-PI-004513) and the institutional protocol number (LCCC1210) should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

Within 24 hours of being made aware of any SAE or pregnancy (suspected or positive), the UNC Study Coordinator (for events at UNC), or the Affiliate Study Coordinator (for events at Affiliate sites) is responsible for informing Celgene by faxing the MedWatch form 3500A and any copies of relevant source documentation (e.g., hospital admission or discharge summary, laboratory or other test results) that pertain to the event to Celgene. *For Affiliate sites, the 3500A form should be faxed simultaneously to the UNCCN Study Coordinator.

7.3.5 Celgene Drug Safety Contact Information:

Celgene Corporation
Global Drug Safety and Risk Management

Connell Corporate Park
300 Connell Dr.
Suite 6000
Berkeley Heights, NJ 07922
Fax: (908) 673-9115
E-mail: drugsafety@celgene.com

SAEs brought to the attention of the investigator at any time after cessation of study drug medication and considered by the investigator to be related or possibly related to study drug medication must be reported to Celgene if and when they occur.

Pregnancy Follow-Up

The Investigator will follow the female subject until completion of the pregnancy, and must notify the UNC Study Coordinator (for events at UNC), or the UNCCN Study Coordinator (for events at Affiliate sites) about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form. If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene within 24 hours of the Investigator's knowledge of the event (follow reporting requirements above).

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the nab-paclitaxel should also be reported to Celgene within 24 hours of the Investigator's knowledge of the event.

7.4 Data and Safety Monitoring Plan

The Principal Investigator will provide continuous monitoring of patient safety in this trial with periodic reporting to the Data and Safety Monitoring Committee (DSMC).

Meetings/teleconferences will be held at a frequency dependent on study accrual, and in consultation with the study Biostatistician. These meetings will include the investigators as well as protocol nurses, clinical research associates, regulatory associates, data managers, biostatisticians, and any other relevant personnel the principal investigators may deem appropriate. At these meetings, the research team will discuss all issues relevant to study progress, including enrollment, safety, regulatory, and data collection.

The team will produce summaries or minutes of these meetings. These summaries will be available for inspection when requested by any of the regulatory bodies charged with the safety of human subjects and the integrity of data including, but not limited to, the oversight (Office of Human Research Ethics (OHRE)

Biomedical IRB, the Oncology Protocol Review Committee (PRC) or the North Carolina TraCS Institute Data and Safety Monitoring Board (DSMB).

The UNC LCCC Data and Safety Monitoring Committee (DSMC) will review the study on a regular (quarterly to annually) basis, with the frequency of review based on risk and complexity as determined by the UNC Protocol Review Committee. The UNC PI will be responsible for submitting the following information for review: 1) safety and accrual data including the number of patients treated; 2) significant developments reported in the literature that may affect the safety of participants or the ethics of the study; 3) preliminary response data; and 4) summaries of team meetings that have occurred since the last report. Findings of the DSMC review will be disseminated by memo to the UNC PI, PRC, and the UNC IRB and DSMB.

8.0 STATISTICAL CONSIDERATIONS

8.1 Study Design/Study Endpoints

This is a multicenter, single arm, phase II trial of 42 patients evaluating the tolerability of treatment with weekly nab-paclitaxel in elderly patients with advanced NSCLC who have progressed on at least one prior regimen.

The primary study endpoint is clinically significant Grade 3 or higher toxicity associated with 6 cycles or 3 weeks after discontinuation of treatment, for those who come off treatment earlier. Secondary endpoints include overall survival, progression-free survival, response rate, quality of life and correlation of Geriatric Assessment measures and p16 levels with treatment outcomes, overall grade 3 or higher toxicity, and specific toxicities.

8.2 Sample Size and Accrual

The null hypothesis that the rate of grade 3/4/5 toxicity after 6 cycles (or 3 weeks after discontinuation of treatment, for those who come off treatment earlier) is 60% will be tested against the one-sided alternative that the grade 3/4/5 toxicity rate is lower. (Alternatively written, the null hypothesis that the toxicity-free rate is 40% will be tested against the one-sided alternative that the toxicity-free rate is higher than 40%.) A Simon's two-stage design with a relaxed futility stopping rule will be used. In the first stage, toxicity will be assessed after the second cycle, or 3 weeks after discontinuation of treatment, for those who come off treatment earlier. In the second stage, toxicity will be determined after 6 cycles, or 3 weeks after discontinuation of treatment, for those who come off treatment earlier.

In the first stage, 25 patients will be accrued. If there are 10 or fewer patients that are grade 3/4/5 toxicity-free in these 25, the study will be stopped for futility. Otherwise, 17 additional patients will be accrued for a total of 42. The null hypothesis will be rejected if 23 or more patients are grade 3/4/5 toxicity-free

after 6 cycles, or 3 weeks after discontinuation of treatment, for those who come off treatment earlier. Assuming that the toxicity-free rate after 2 cycles has a uniform distribution, uniform (0, 0.3) under the null hypothesis, and can be at most 40% under the alternative, this design yields a type I error rate of at most 0.0375 and power of at least 80% when the true toxicity-free rate is 60%.

The total accrual for this study is 42 patients; the expected accrual rate is 3 patients per month, and is expected to occur within 14 months.

8.3 Data Analysis Plans

The percentage of patients with a grade 3 or higher toxicity after 6 cycles (or 3 weeks after discontinuation of treatment, for those who come off treatment earlier) and overall response rate (as measured by standard RECIST1.1 criteria) will be reported with an exact 95% confidence interval (CI). Progression-free survival and overall survival will be evaluated by the Kaplan-Meier method and median with 95% CIs will be reported.

The association of baseline components of the GA and p16 with the occurrence of a grade 3 or higher toxicity will be evaluated using the Wilcoxon Rank Sum tests for continuous variables and Fisher's Exact tests for categorical variables. Cox regression and the Kaplan-Meier Method will be used to evaluate associations with time to event analyses. Longitudinal analyses will be used to explore the changes in LCSS over the course of the study.

9.0 STUDY MANAGEMENT

9.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

9.2 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Protocol Office (CPO) at the University of North Carolina.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the principal investigator and any sub-investigators who will be involved in the study.
- Form FDA 1572 appropriately filled out and signed with appropriate documentation (NOTE: this is required if UNC holds the IND. Otherwise, the Investigator's signature documenting understanding of the protocol and providing commitment that this trial will be conducted according to all stipulations of the protocol is sufficient to ensure compliance)
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

9.3 Registration Procedures

All patients must be registered with the CPO at the University of North Carolina before enrollment to study. For UNC patients, prior to registration, eligibility criteria must be confirmed with the UNC Study Coordinator. To register a patient, call the Oncology Protocol Office at 919-966-4432 Monday through Friday, 9:00AM-5:00PM.

For Affiliate patients, please contact the UNCCN Study Coordinator to ensure there is an opening available on the study for the potential subject (direct line 919-966-7359), Monday through Friday, 9:00AM-5:00PM. To register a patient, please fax registration forms and eligibility documents to 919-966-4300.

9.4 Data Management and Monitoring/Auditing

The UNCCN of the UNC LCCC will serve as the coordinating center for this trial. Data will be collected through a web based clinical research platform, OnCore®. Other study institutions will be given a password to directly enter their own data onto the web site via electronic case report forms (eCRFs). UNCCN personnel will coordinate and manage data for quality control assurance and integrity.

All data will be collected and entered into OnCore® by Clinical Research Associates (CRAs) from UNC LCCC and participating institutions. The investigators at each site will allow monitors to review all source documents

supporting data entered into OnCore®. The UNCCN Data Coordinator can be reached at 919-843-2742 or 1-877-668-0683.

As an investigator initiated study, this trial will also be audited by the Lineberger Cancer Center audit committee every six to twelve months, depending on participation of Affiliate sites.

9.5 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

9.5.1 Emergency Modifications

UNC and Affiliate investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior UNC or their respective institution's IRB/IEC approval/favorable opinion.

For Institutions Relying on UNC's IRB:
For any such emergency modification implemented, a UNC IRB modification form must be completed by UNC Research Personnel within five (5) business days of making the change.

For Institutions Relying on Their Own IRB:
For Affiliate investigators relying on their own institution's IRB, as soon as possible after the modification has been made, the implemented deviation or change and the reasons for it should be submitted to:

- To UNC Principal Investigator for agreement
- The Affiliate institution's IRB for review and approval.

(Once IRB's response is received, this should be forwarded to the UNCCN Regulatory Associate).

9.5.2 Single Patient/Subject Exceptions

For Institutions Relying on UNC's IRB:
Any request to enroll a single subject who does not meet all the eligibility criteria of this study requires the approval of the UNC Principal Investigator and the UNC IRB.

For Institutions Relying on Their Own IRB:
Any request to enroll a single subject who does not meet all the eligibility criteria of this study requires the approval of the UNC Principal Investigator and the participating institution's IRB, per its policy. Please forward the IRB response to the UNCCN Regulatory Associate by facsimile or via email within 10 business days after the original submission.

9.5.3 Other Protocol Deviations/Violations

According to UNC's IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance meets any of the following criteria:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs please follow the guidelines below:

For Institutions Relying on UNC's IRB:
Protocol Deviations: UNC or Affiliate personnel will record the deviation in OnCore®, and report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Violations should be reported by UNC personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

For Institutions Relying on Their Own IRB:
In addition to adhering to the policies regarding protocol compliance set forth by your institution's IRB, the following is also required:

Protocol Deviations: In the event a deviation from protocol procedures is identified, record the deviation in OnCore®.

Protocol Violations: Any protocol violation that occurs must be reported to your IRB per institutional policies and reported to the UNCCN Study Coordinator within 5 days. UNC-CH will determine if the violation affects the safety of the patient and integrity of the data. Once your institution's IRB response is received, please forward to the UNCCN Regulatory Associate.

Unanticipated Problems:
Affiliate Sites:

Any events that meet the criteria for "Unanticipated Problems (UPs)" as defined by UNC's IRB must also be reported to the UNCCN Study Coordinator. The UNCCN Study Coordinator will report the event to the UNC IRB using the IRB's web-based reporting system. Examples of such UPs include a lost or stolen laptop computer that contains sensitive study information.

UNC
Any events that meet the criteria for "Unanticipated Problems" as defined by UNC's IRB must be reported by the Study Coordinator using the IRB's web-based reporting system.

9.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator at UNC. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

For Institutions Relying on UNC's IRB:
The written amendment, and if required the amended consent form, must be sent to UNC's IRB for approval prior to implementation.

For Institutions Relying on Their Own IRB:
Investigators must submit the UNC IRB approved amendment to their institution's IRB for approval. For multi-center studies, any affiliate site must submit their informed consent revisions to the UNCCN Regulatory Associate prior to submission to their IRB.

9.7 Record Retention

Study documentation includes all eCRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

9.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered into the eCRFs. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all eCRFs will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

10.0 REFERENCES

1. Jemal, A., et al., *Global cancer statistics.* CA Cancer J Clin. 61(2): p. 69-90.
2. Govindan, R., et al., *Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database.* J Clin Oncol, 2006. 24(28): p. 4539-44.
3. Yang, P., et al., *Clinical features of 5,628 primary lung cancer patients: experience at Mayo Clinic from 1997 to 2003.* Chest, 2005. 128(1): p. 452-62.
4. Howlader, N., et al., *SEER Cancer Statistics Review, 1975-2008*. 2010, Bethesda, MD: National Cancer Institute http://seer.cancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to the SEER web site, 2011.
5. Owonikoko, T.K., et al., *Lung cancer in elderly patients: an analysis of the surveillance, epidemiology, and end results database.* J Clin Oncol, 2007. 25(35): p. 5570-7.
6. Quoix, E.A., et al., *Weekly paclitaxel combined with monthly carboplatin versus single-agent therapy in patients age 70 to 89: IFCT-0501 randomized phase III study in advanced non-small cell lung cancer (NSCLC).* Journal of Clinical Oncology, 2010. 28(15s): p. 2.
7. Quoix, E., et al., *Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: IFCT-0501 randomised, phase 3 trial.* Lancet., 2011. 378(9796): p. 1079-88. Epub 2011 Aug 8.
8. Scagliotti, G.V., et al., *Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer.* J Clin Oncol, 2008. 26(21): p. 3543-51.
9. Kim, E.S., et al., *Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial.* Lancet, 2008. 372(9652): p. 1809-18.
10. Hanna, N., et al., *Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy.* J Clin Oncol, 2004. 22(9): p. 1589-97.
11. Shepherd, F.A., et al., *Erlotinib in previously treated non-small-cell lung cancer.* N Engl J Med, 2005. 353(2): p. 123-32.
12. Shepherd, F.A., et al., *Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy.* J Clin Oncol, 2000. 18(10): p. 2095-103.
13. Fossella, F.V., et al., *Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group.* J Clin Oncol, 2000. 18(12): p. 2354-62.
14. Weiss, G.J., et al., *Elderly patients benefit from second-line cytotoxic chemotherapy: a subset analysis of a randomized phase III trial of pemetrexed compared with docetaxel in patients with previously treated advanced non-small-cell lung cancer.* J Clin Oncol, 2006. 24(27): p. 4405-11.
15. Wheatley-Price, P., et al., *Erlotinib for advanced non-small-cell lung cancer in the elderly: an analysis of the National Cancer Institute of Canada Clinical Trials Group Study BR.21.* J Clin Oncol, 2008. 26(14): p. 2350-7.

16. Ibrahim, N.K., et al., *Phase I and pharmacokinetic study of ABI-007, a Cremophor-free, protein-stabilized, nanoparticle formulation of paclitaxel.* Clin Cancer Res, 2002. 8(5): p. 1038-44.
17. M. A. Socinski, I.N.B., N. A. Karaseva, A. Makhson, I. Vynnychenko, I. Okamoto, J. K. Hon, V. Hirsh, P. Bhar, J. Iglesias, *Results of a randomized, phase III trial of nab-paclitaxel (nab-P) and carboplatin (C) compared with cremophor-based paclitaxel (P) and carboplatin as first-line therapy in advanced non-small cell lung cancer (NSCLC).* J Clin Oncol 28:18s, 2010 (suppl; abstr LBA7511), 2010.
18. Socinski, M.A., et al., *Weekly nab-Paclitaxel in Combination With Carboplatin Versus Solvent-Based Paclitaxel Plus Carboplatin as First-Line Therapy in Patients With Advanced Non-Small-Cell Lung Cancer: Final Results of a Phase III Trial.* J Clin Oncol, 2012. 30(17): p. 2055-62.
19. Socinski, M.A., I. N. Bondarenko, N. A. Karaseva, A. Makhson, I. Vynnychenko, I. Okamoto, J. K. Hon, V. Hirsh, P. Bhar, G. I. Berk, J. L. Iglesias, *Survival results of a randomized, phase III trial of nab-paclitaxel and carboplatin compared with cremophor-based paclitaxel and carboplatin as first-line therapy in advanced non-small cell lung cancer.* J Clin Oncol 29: 2011 (suppl; abstr 7551)
20. Belani, C.P., et al., *Randomized, phase III study of weekly paclitaxel in combination with carboplatin versus standard every-3-weeks administration of carboplatin and paclitaxel for patients with previously untreated advanced non-small-cell lung cancer.* J Clin Oncol, 2008. 26(3): p. 468-73.
21. Socinski, M.A., et al., *A dose finding study of weekly and every-3-week nab-Paclitaxel followed by carboplatin as first-line therapy in patients with advanced non-small cell lung cancer.* J Thorac Oncol., 2010. 5(6): p. 852-61.
22. Hurria, A., et al., *Implementing a geriatric assessment in cooperative group clinical cancer trials: CALGB 360401.* J Clin Oncol. 29(10): p. 1290-6.
23. Liu, Y., et al., *Expression of p16(INK4a) in peripheral blood T-cells is a biomarker of human aging.* Aging Cell, 2009. 8(4): p. 439-48.
24. Muss, H.B., et al., *$P16^{INK4a}$ expression after chemotherapy in older women with early-stage breast cancer.* Journal of Clinical Oncology, 2011. 29 (suppl; abstr 9002).
25. Hollen, P.J., et al., *Measurement of quality of life in patients with lung cancer in multicenter trials of new therapies. Psychometric assessment of the Lung Cancer Symptom Scale.* Cancer., 1994. 73(8): p. 2087-98.
26. Cella, D.F., et al., *Reliability and validity of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality of life instrument.* Lung Cancer, 1995. 12(3): p. 199-220.
27. ten Tije, A.J., et al., *Pharmacological effects of formulation vehicles : implications for cancer chemotherapy.* Clin Pharmacokinet, 2003. 42(7): p. 665-85.
28. Robidoux, A., et al., *A phase II neoadjuvant trial of sequential nanoparticle albumin-bound paclitaxel followed by 5-fluorouracil/epirubicin/cyclophosphamide in locally advanced breast cancer.* Clin Breast Cancer, 2010. 10(1): p. 81-6.
29. Hurria, A., et al., *Developing a cancer-specific geriatric assessment: a feasibility study.* Cancer, 2005. 104(9): p. 1998-2005.

11.0 APPENDIX A: ECOG Performance Status

Grade	Activity Level
0	Fully active; no performance restrictions
1	Strenuous physical activity restricted; fully ambulatory and able to carry out light work
2	Capable of all self-care but unable to carry out any work activities. Up and about >50 percent of waking hours
3	Capable of only limited self-care; confined to bed or chair >50 percent of waking hours
4	Completely disabled; cannot carry out any self-care; totally confined to bed or chair
5	Dead

Reference:

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the eastern cooperative oncology group. Am J Clin Oncol 1982; 5: 649-55.

11.1 APPENDIX C: Geriatric Assessment (Version 5)

11.1.1 Geriatric Assessment: Data to be Gathered by the Healthcare Team

V5 (02/01/2011)

Geriatric Assessment Study

APPENDIX I

Data to be Gathered by the Healthcare Team

MRN/Study #

Subject ID/Sequence #

O Male
O Female

O Pre-Treatment
O During Treatment
O Post-Treatment

Protocol ID

Research ID (UNC-CH Only)

Instructions:

PRE-TREATMENT: Biopsy for diagnosis purposes only. No definitive surgery, radiation, chemo, biological or hormonal therapy.

DURING TREATMENT: Within 4 weeks of surgery or while on radiation, chemo or any other therapy for relevant cancer diagnosis.

POST-TREAMENT: After completion of surgery, chemo, radioation or any other prescribed therapy for relevant cancer diagnosis. OK to be on Endocrine therapy.

Page 1 of 5

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II) Karnofsky Performance Status: ☐☐☐ %

DEFINITION	%	CRITERIA
Able to carry on normal activity and able to work. No special care is needed.	100	Normal: no complaints; no evidence of disease
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal Activity with effort; some signs or symptoms of disease.
Unable to work. Able to live at home, and for most personal needs, a varying amount of assistance is needed	70	Cares for self. Unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his needs
	50	Requires considerable assistance and frequent medical care
Unable to care for self. Requires equivalent of institutional or hospital care. Disease may be progressing rapidly.	40	Disabled; requires special care and assistance
	30	Severely disabled; hospitalization is indicated although death is not imminent.
	20	Very sick; hospitalization necessary; active supportive treatment
	10	Moribund; fatal processes progressing rapidly
	0	Dead

Karnofsky Physician-rated Performance Rating Scale: Karnofsky, D.A., et al., 1948

III) Timed "Up and Go": ☐☐.☐☐ Seconds Unable to Complete ☐

Instructions: The timed "Up & Go" measures, in seconds, the time it takes for an individual to stand up from a standard arm chair (approximate seat height of 46 cm), walk a distance of 3 meters (approximately 10 feet), turn, walk back to the chair, and sit down again. The subject wears his/ her regular footwear and uses their customary walking aid (none, cane, walker). No physical assistance is given. The subject starts with his back against the chair, his arm resting on the chair's arm, and his walking aid at hand. He is instructed that, on the word "go," he is to get up and walk at a comfortable and safe pace to a line on the floor 3 meters away (approximately 10 feet), turn, return to the chair, and sit down again. The subject walks through the test once before being timed in order to become familiar with the test. Either a wrist watch with a second hand or a stop-watch can be used to time the performance.

Timed Up and Go: Podsiadlo, D., et al., 1991

IV) Cognition: Orientation-Memory-Concentration Test

	Patient's response	Maximum errors	Score	Weight	Final Score
1. What year is it now? [without looking at a calendar]	☐☐☐☐	1	☐	x 4 =	☐☐
2. What month is it now? [without looking at a calendar]	☐☐	1	☐	x 3 =	☐☐

Memory phrase
Repeat this phrase after me: 'John Brown, 42 Market Street, Chicago .'

3. About what time is it? [within 1 hour - without looking at your watch]	☐☐:☐☐	1	☐	x 3 =	☐☐
4. Count backwards from 20 to 1.		2	☐	x 2 =	☐☐
5. Say the months in reverse order.		2	☐	x 2 =	☐☐
6. Repeat the memory phrase.		5	☐	x 2 =	☐☐

Total Score = ☐☐

Incomplete ☐

Scoring: For items 1 to 3, the response is either correct (score 0) or incorrect (score 1). For items 4 to 6, subtract one point for each error (item 4 and 5 maximum error is 2; for item 6, maximum error is 5); total all scores in "Final Score" column. Total score of 11 or greater indicates cognitive impairment; please notify MD and assist patient in completing questionnaires. Maximum score = 28

Blessed Orientation-Memory-Concentration test: Kawas, C., et al, 1991

V) Nutrition:

a) What is the patient's height? ☐ feet ☐☐ inches (Please round to the nearest whole number.)

b) What is the patient's current weight? ☐☐☐.☐ pounds

c) What is the patient's weight approximately 6 months ago? ☐☐☐.☐ pounds

d) Calculated Body Mass Index: ☐☐.☐

$$\text{Body Mass Index} = \frac{\textbf{weight (kg)}}{\textbf{height}^2\,(m^2)} \quad \textbf{OR} \quad \frac{\textbf{weight (lb) x 703}}{\textbf{height}^2\,(in^2)}$$

e) Percent Unintentional Weight Loss: ☐☐☐.☐ %

$$\%\ \text{unintentional weight loss} = \left(\frac{\textbf{unintentional weight lost in last 6 months}}{\textbf{baseline body weight}} \right) \times 100$$

VI) Scoring:

a) Did the patient score ≥ 11 on the Blessed Orientation-Memory-Concentration Test (see previous page)?

- O No
- O Yes (if yes, notify the patient's treating physician)

VII) Did the patient require assistance with Appendix II (questionnaires to be completed by the study participant)?

- O No
- O Yes

VIII) Time to complete:

a) Appendix I (Data to be gathered by the healthcare team)

Start Time: ☐☐ : ☐☐

End Time: ☐☐ : ☐☐

b) Appendix II (Questionnaires to be completed by the study participant)

Start Time: ☐☐ : ☐☐

End Time: ☐☐ : ☐☐

N/A: Completed at home ☐

Total time to complete Appendix I and II: ☐☐ : ☐☐

Name of person completing this document:

Signature: ______________________________ Date: ☐☐ / ☐☐ / ☐☐☐☐

11.1.2 Geriatric Assessment: Patient Questionnaire

V.5 (02/01/11)

Geriatric Assessment Study

PATIENT QUESTIONNAIRE

I. Your Background:

Instructions: Please answer the following questions about your background. While this information will be helpful to us, you do not have to answer any questions if you do not wish to. If you have any questions or need help in filling out this form, ask the person who gave you the form for help or call (919) 843-1906.

1. **What is the highest grade you finished in school?** (*Fill in one oval completely.*)
   - O 1-8 grades
   - O 9-11 grades
   - O High school graduate
   - O Some college
   - O Junior college degree
   - O College degree (B.A./B.S.)
   - O Some post-college work
   - O Advanced degree

2. **What is your marital status?** (*Fill in one oval completely.*)
   - O Single, never married
   - O Married
   - O Separated
   - O Divorced
   - O Widowed

Office use only

MRN/Study #: Date: / /

Protocol ID | Subject ID/Sequence # | Research ID (UNC-CH Only)

- O Pre-Treatment
- O During Treatment
- O Post-Treatment

3. With whom do you live? (*Mark an X in all that apply.*)

- ☐ Spouse/Partner
- ☐ Parent(s)/Parent(s)-In-Law
- ☐ Live alone
- ☐ Other relative, specify:
- ☐ Children aged 18 years or younger
- ☐ Children aged 19 years or older
- ☐ Other, specify:

4. What is your current employment status? (*Mark an X in all that apply.*)

- ☐ Employed more than 32 hours per week
- ☐ Employed less than 32 hours per week
- ☐ Full-time student
- ☐ Part-time student
- ☐ Homemaker
- ☐ On medical leave
- ☐ Disabled
- ☐ Unemployed
- ☐ Retired
- ☐ Other, specify:

5. How old are you? ☐☐ years old

6. What is your race? (*Fill in one oval completely.*)

- O White
- O Black or African American
- O Native Indian or Alaskan Native
- O Prefer not to answer
- O Asian
- O Native Hawaiian or Other Pacific Islander
- O Unknown

7. What is your ethnicity? (*Fill in one oval completely.*)

- O Hispanic or Latino
- O Non-Hispanic
- O Unknown
- O Prefer not to answer

II. Your Daily Activities:

Instructions: Please fill in one oval for each question.

1. **Can you use the telephone . . .**
   - O without help, including looking up and dialing;
   - O with some help (can answer phone or dial operator in an emergency, but need a special phone or help in getting the number or dialing); or
   - O are you completely unable to use the telephone?

2. **Can you get to places out of walking distance . . .**
   - O without help (drive your own car, or travel alone on buses or taxis);
   - O with some help (need someone to help you or go with you when traveling); or
   - O are you unable to travel unless emergency arrangements are made for a specialized vehicle like an ambulance?

3. **Can you go shopping for groceries or clothes (assuming you have transportation) . . .**
   - O without help (taking care of all shopping needs yourself, assuming you had transportation);
   - O with some help (need someone to go with you on all shopping trips); or
   - O are you completely unable to do any shopping?

4. **Can you prepare your own meals . . .**
   - O without help (plan and cook full meals yourself);
   - O with some help (can prepare some things but unable to cook full meals yourself); or
   - O are you completely unable to prepare any meals?

5. **Can you do your housework . . .**
   - O without help (can clean floors, etc.);
   - O with some help (can do light housework but need help with heavy work); or
   - O are you completely unable to do any housework?

6. **Can you take your own medicines . . .**
   - O without help (in the right doses at the right time);
   - O with some help (able to take medicine if someone prepares it for you and/or reminds you to take it); or
   - O are you completely unable to take your medicines?

7. **Can you handle your own money . . .**
   - O without help (write checks, pay bills, etc.);
   - O with some help (manage day-to-day buying but need help with managing your checkbook and paying your bills); or
   - O are you completely unable to handle money?

Older Americans Resources and Services (OARS) IADL: Fillenbaum GG., et al., 1981

Instructions: The following items are activities that you might do during a typical day.
Does your health limit you in these activities? Please fill in the appropriate oval.

Activities	Limited a lot	Limited a little	Not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	O	O	O
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	O	O	O
c. Lifting or carrying groceries	O	O	O
d. Climbing several flights of stairs	O	O	O
e. Climbing one flight of stairs	O	O	O
f. Bending, kneeling, or stooping	O	O	O
g. Walking more than a mile	O	O	O
h. Walking several blocks	O	O	O
i. Walking one block	O	O	O
j. Bathing or dressing yourself	O	O	O

Medical Outcomes Study (MOS) Physical Health: Stewart AL., et al., 1992

Which of the following phrases best characterizes you at this time? *(Please mark only one response.)*

- O Normal, no complaints, no symptoms of disease
- O Able to carry on normal activity, minor symptoms of disease
- O Normal activity with effort, some symptoms of disease
- O Care for self, unable to carry on normal activity or to do active work
- O Require occasional assistance but able to care for most of personal needs
- O Require considerable assistance for personal care
- O Disabled, require special care and assistance
- O Severely disabled, require continuous nursing care

Karnofsky Self-Reported Performance Rating Scale: Loprinzi, C.L., et al., 1994

How many times have you fallen in the last 6 months?

☐☐☐ times

III. Your Medications:

How many medications do you take on a daily basis?

☐☐ medications

Please list all medications you take (including prescribed medication, over-the-counter medications, herbs, or vitamins). List perscription medications on this page and non-prescription medications on next page.

Name of Prescription Medication	Take Daily or at Regular Interval	Take As Needed
	○	○
	○	○
	○	○
	○	○
	○	○
	○	○
	○	○
	○	○
	○	○
	○	○

Name of Non-Prescription Medication	Take Daily or at Regular Interval	Take As Needed
	○	○
	○	○
	○	○
	○	○
	○	○
	○	○
	○	○
	○	○
	○	○
	○	○

IV. Your Health:

Instructions: We would like to ask you a few questions about any health problems you might have. Do you have any of the following illnesses **at the present time**? Please fill in the appropriate oval (yes or no). If you fill in "yes," please tell us how much the illness intereferes with your activities: Not at All, Somewhat, or A Great Deal. Fill in the appropriate oval.

			IF YOU HAVE THE ILLNESS, how much does it interfere with your activities?		
Illness	**No**	**Yes**	**Not at all**	**Somewhat**	**A Great Deal**
1. Other cancers or leukemia	O	O →	O	O	O
2. Arthritis or rheumatism	O	O →	O	O	O
3. Glaucoma	O	O →	O	O	O
4. Emphysema or chronic bronchitis	O	O →	O	O	O
5. High blood pressure	O	O →	O	O	O
6. Heart disease	O	O →	O	O	O
7. Circulation trouble in arms or legs	O	O →	O	O	O
8. Diabetes	O	O →	O	O	O
9. Stomach or intestinal disorders	O	O →	O	O	O
10. Osteoporosis	O	O →	O	O	O
11. Chronic liver or kidney disease	O	O →	O	O	O
12. Stroke	O	O →	O	O	O
13. Depression	O	O →	O	O	O

14a. How is your eyesight (with glasses or contacts)?

- O Excellent
- O Good
- O Fair
- O Poor
- O Totally blind

If fair, poor, or totally blind:

How much does it interfere with your activities?

- O Not at all
- O Somewhat
- O A great deal

15a. How is your hearing (with a hearing aid, if needed)?

- O Excellent
- O Good
- O Fair
- O Poor
- O Totally deaf

If fair, poor, or totally deaf:

How much does it interfere with your activities?

- O Not at all
- O Somewhat
- O A great deal

Older Americans Resources and Services (OARS) Physical Health Section: Fillenbaum, G.G., et al., 1981

V. Your Nutritional Status:

1. Have you lost weight unintentionally over the past 6 months?

- O No
- O Yes

If yes, how much?

☐☐☐ pounds

2. What is your weight now?

☐☐☐ pounds

3. What was your weight 6 months ago?

☐☐☐ pounds

VI. Your Mood:

These questions are about how you feel, and how things have been with you mostly within the *past two weeks*. Please fill in the bubble with the answer that best corresponds to how you felt for each statement.

How much of the time during the past two weeks:	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
1. has your daily life been full of things that were interesting to you?	O	O	O	O	O	O
2. did you feel depressed?	O	O	O	O	O	O
3. have you felt loved and wanted?	O	O	O	O	O	O
4. have you been a very nervous person?	O	O	O	O	O	O
5. have you been in firm control of your behavior, thoughts, emotions, feelings?	O	O	O	O	O	O
6. have you felt tense or high-strung?	O	O	O	O	O	O
7. have you felt calm or peaceful?	O	O	O	O	O	O
8. have you felt emotionally stable?	O	O	O	O	O	O
9. have you felt downhearted and blue?	O	O	O	O	O	O
10. have you felt restless, fidgety, or impatient?	O	O	O	O	O	O
11. have you been moody, or brooded about things?	O	O	O	O	O	O
12. have you felt cheerful, light-hearted?	O	O	O	O	O	O
13. have you been in low or very low spirits?	O	O	O	O	O	O
14. were you a happy person?	O	O	O	O	O	O
15. did you feel you had nothing to look forward to?	O	O	O	O	O	O
16. have you felt so down in the dumps that nothing could cheer you up?	O	O	O	O	O	O
17. have you been anxious or worried?	O	O	O	O	O	O

MHI-17: Stewart and Ware, 1992

VII. Your Social Activities:

Instructions: Please fill in the appropriate oval completely.

1. **During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?**

   - O All of the time
   - O Most of the time
   - O Some of the time
   - O A little of the time
   - O None of the time

2. **Compared to your usual level of social activity, has your social activity during the past 6 months decreased, stayed the same, or increased because of a change in your physical or emotional condition?**

   - O Much less socially active than before
   - O Somewhat less socially active than before
   - O About as socially active as before
   - O Somewhat more socially than before
   - O Much more socially active than before

3. **Compared to others your age, are your social activities more or less limited because of your physical health or emotional problems?**

   - O Much more limited than others
   - O Somewhat more limited than others
   - O About the same as others
   - O Somewhat less limited than others
   - O Much less limited than others

4. **During the last 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**

   - O Not at all
   - O Slightly
   - O Moderately
   - O Quite a bit
   - O Extremely

Medical Outcomes Study (MOS) Social Activity Limitations Measure: Sherbourne, C.D., et al., 1991

VIII. Your Social Support:

Instructions: Please fill in the appropriate oval completely.

KINDS OF SUPPORT Do you have...	None of the time	A little of the time	Some of the time	Most of the time	All of the time
1. Someone to help if you were confined to bed	O	O	O	O	O
2. Someone you can count on to listen to you when you need to talk	O	O	O	O	O
3. Someone to give you good advice about a crisis	O	O	O	O	O
4. Someone to take you to the doctor if needed	O	O	O	O	O
5. Someone to give you information to help you understand a situation	O	O	O	O	O
6. Someone to confide in or talk to about yourself or your problem	O	O	O	O	O
7. Someone to prepare your meals if you were unable to do it yourself	O	O	O	O	O
8. Someone whose advice you really want	O	O	O	O	O
9. Someone to help you with daily chores if you were sick	O	O	O	O	O
10. Someone to share your most private worries and fears with	O	O	O	O	O
11. Someone to turn to for suggestions about how to deal with a personal problem	O	O	O	O	O
12. Someone who understands your problems	O	O	O	O	O

Medical Outcomes Study (MOS) Social Support Survey: Emotional/ Information and Tangible subscales: Sherbourne, C.D., et al., 1991

IX. Your Feedback on the Questionnaire:

1. Were any of these questions difficult to understand?

O No

O Yes, which questions were they?

2. Was the time it took to answer all the questions too long, just right, or too short?

O Too short. How long would you have liked the interview to be? ☐☐☐ minutes

O Just right

O Too long. How long would you have liked the interview to be? ☐☐☐ minutes

Which items would you remove?

3. Did you require assistance with the questionnaire? O No

O Yes

Date you completed questionnaire: ☐☐ / ☐☐ / ☐☐☐☐

How long did it take you to complete the questionnaire? ☐☐☐ minutes

4. **Do you find any of the questions upsetting?**

   ○ No

   ○ Yes, which questions were they?

Could you tell me why they were upsetting?

5. **Do you think the questionnaire left out any questions that were important to ask?**

THANK YOU VERY MUCH!

11.2 APPENDIX D: Health Behaviors Questionnaire (Version 1)

9350

Version 1 // 11.2010

Health Behaviors Questionnaire

Subject Number ☐☐☐☐☐ Research ID ☐☐☐☐☐☐☐☐ Protocol ID ☐☐☐☐☐☐

1. Which of the following best describes your smoking habits

☐ I have never smoked (skip to #4)
☐ I used to smoke
☐ I smoke

2. How many years have you/did you smoke? ☐☐☐ Years

3. How many packs a day did/do you smoke? ☐☐.☐ Packs

4. How often do you do vigorous physical activities for at least 10 minutes that cause heavy sweating or large increases in heart rate or breathing?

☐ Never (skip to #6)
☐ A few times per month
☐ 1-2 times per week
☐ 3-4 times per week
☐ 5 or more times per week

5. How long do you do these vigorous physical activities each time?

☐☐☐ Minutes

6. Do you drink alcohol?

☐ Yes
☐ Almost never
☐ No (skip to #9)

7. If you drink alcohol, about how many drinks do you have each week?

☐☐☐ Drinks

8. What do you drink most often?

☐ Beer
☐ Red Wine
☐ White and Red Wine
☐ Hard Liquor (such as bourbon, gin, vodka)
☐ All of the above

9. If your parents are still living, how old are they? Or, if either one has passed away, how old was he or she when they died?

Mother ☐☐☐ ☐ Alive ☐ Deceased **(current age, or if deceased age of death)**

Father ☐☐☐ ☐ Alive ☐ Deceased **(current age, or if deceased age of death)**

11.3 APPENDIX E: Lung Cancer Symptom Scale

11.3.1 Lung Cancer Symptom Scale: Observer Form

Name of Subject: _____

Date of Protocol: _____

Name of Observer: _____

Date of Assessment: _____

LUNG CANCER SYMPTOM SCALE (LCSS): OBSERVER FORM

Directions: Direct the interview to assess lung cancer symptoms using the timeframe of

DURING THE PAST DAY (within the last 24 hours).

1. Loss of appetite: (Score: _____)

100 ***None***.
75 ***Mild***; occasional loss of appetite but does not interfere with food intake.
50 ***Moderate***; occasional loss of appetite which occasionally interferes with food intake.
25 ***Marked***; frequent loss of appetite which generally interferes with food intake.
0 ***Severe***; appetite so poor that medical intervention for feeding (intravenously or feeding tube) is needed.

2. Fatigue: (Score: _____)

100 ***None***.
75 ***Mild***; occasionally troubled by modest fatigue.
50 ***Moderate***; usually troubled by modest fatigue.
25 ***Marked***; occasionally troubled by major fatigue.
0 ***Severe***; usually troubled by major fatigue.

3. Cough: (Score: _____)

100 ***None***.
75 ***Mild***; present and increased over a year ago, but not bothersome; no medications needed.
50 ***Moderate***; bothersome; leads to SOB on occasion.
25 ***Marked***; bothersome; disturbs sleep and other normal functioning.
0 ***Severe***; nearly constant; disrupts any normal activities.

4. Dyspnea: (Score: _____)

100 ***None***.
75 ***Mild***; noticed only with major activity (e.g., climbing more than one flight of stairs);
SOB does not limit usual activities.
50 ***Moderate***; present when walking at normal pace; interferes with ability to carry out
some usual activities.
25 ***Marked***; present with minimal activity; supplemental O_2 used only occasionally.
0 ***Severe***; supplemental O_2 required most or all of the time.

5. Hemoptysis: (Score: _____)

100 ***None***.
75 ***Mild***; blood in sputum, less frequently than daily.
50 ***Moderat*e**; blood in sputum at least daily but generally just "flecks" as part of the sputum.
25 ***Marked***; sputum is often purely bloody (not just flecks) on a daily basis.
0 ***Severe***; same as marked but blood loss by hemoptysis measurably lowering hemoglobin.

6. Pain: (Score: _____)

100 ***None***.
75 ***Mild***; present but either no medications required or only non-narcotic, non-codeine type oral agents; pain control satisfactory or reasonable.
50 ***Moderate***; codeine or codeine-containing oral medications needed; pain control satisfactory or reasonable.
25 ***Marked***; narcotic oral agents are required; pain control satisfactory or reasonable.
0 ***Severe***; narcotic oral medications required but pain control not satisfactory, or parenteral narcotics are required.

The Lung Cancer Symptom Scale is reproduced with permission of Quality of Life Research Associates.

11.3.2 Lung Cancer Symptom Scale: Patient Scale

Note: The LCSS Patient Scale will be administered in a cardset format versus single sheet of paper.

Lung Cancer Symptom Scale (LCSS): Patient scale

English Version

Directions: Please place a mark along each line where it would best describe the symptoms of your lung cancer DURING THE PAST DAY (within the last 24 hours).

Example Question:

How good is the weather?

As good as it could be |_____| As bad as it could be

1. How good is your appetite?

As good as it could be |_____| As bad as it could be

2. How much fatigue do you have?

None |_____| As much as it could be

3. How much coughing do you have?

None |_____| As much as it could be

4. How much shortness of breath do you have?

None |_____| As much as it could be

5. How much blood do you see in your sputum?

None |_____| As much as it could be

6. How much pain do you have?

None |_____| As much as it could be

7. How bad are your symptoms from lung cancer?

I have none |_____| As bad as they could be

8. How much has your illness affected your ability to carry out normal activities?

Not at all |_____| So much that I can do nothing for myself

9. How would you rate the quality of your life today?

Very high |_____| Very low

11.4 APPENDIX F: Fact-L (Version 4)

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4

GS 3	I get support from my friends	0	1	2	3	4
GS 4	My family has accepted my illness	0	1	2	3	4
GS 5	I am satisfied with family communication about my illness	0	1	2	3	4
GS 6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box ☐ and go to the next section.*					
GS 7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	<u>EMOTIONAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4

GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
B1	I have been short of breath	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
L1	My thinking is clear	0	1	2	3	4
L2	I have been coughing	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
L3	I feel tightness in my chest	0	1	2	3	4
L4	Breathing is easy for me	0	1	2	3	4
Q3	Have you ever smoked? No ___ Yes ___ If yes:					
L5	I regret my smoking	0	1	2	3	4