**PROTOCOL #: LCI-LUN-ABR-001**

**TITLE:** A PILOT STUDY OF CARBOPLATIN WITH NAB-PACLITAXEL IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER OF SQUAMOUS HISTOLOGY

**LAY TITLE:** A STUDY OF THE DRUGS CARBOPLATIN AND ABRAXANE FOR PATIENTS WITH LUNG CANCER

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The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

**Confidential**

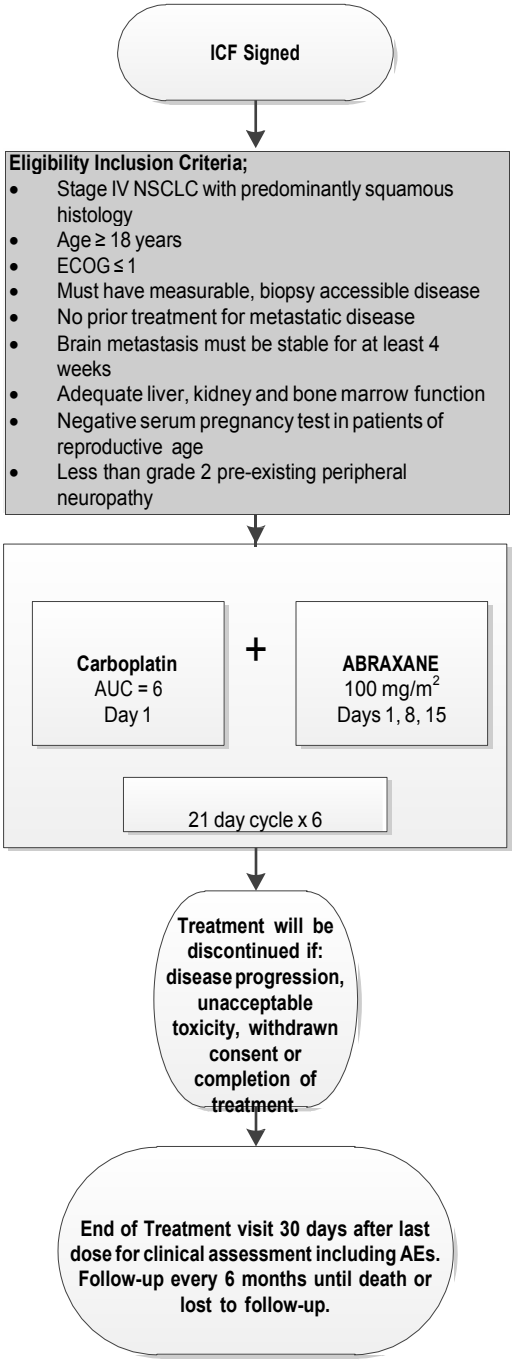
**Commercial agents: Carboplatin & Nab-Paclitaxel**
***Original Phase 2 / Version 2/ November 11, 2015***

| PROTOCOL SUMMARY | |
|---|---|
| **A. Study Title** | A Pilot Study of Carboplatin with Nab-Paclitaxel in Patients with Advanced Non-Small Cell Lung Cancer of Squamous Histology |
| **B. Indication** | Stage IV non-small cell lung cancer of squamous histology |
| **C. Clinical Phase** | 2 |
| **D. Summary of Rationale** | ABRAXANE, based on results from prior studies, is a promising drug in squamous cell carcinoma of the lung. This study will help to explore the combination of ABRAXANE and carboplatin more thoroughly in the subgroup of patients who had the best response in prior studies as well as determine whether there are any biomarkers which can predict for response. |
| **E. Study Objectives** | The primary objective of this study is to assess the response rate of the combination of carboplatin with ABRAXANE in patients with advanced non-small cell lung cancer (NSCLC) with squamous cell histology. Secondary objectives are to assess the disease control rate, duration of response, duration of disease control, overall survival, progression-free survival, and the safety and toxicity profile with this regimen. The exploratory objective is to assess broad molecular profiling. |
| **F. Sample** | Approximately 50 subjects |
| **G. Inclusion/ Exclusion** | • Stage IV NSCLC with predominantly squamous histology<br>• Age ≥ 18 years with ECOG ≤ 1<br>• Measurable, biopsy accessible disease<br>• Subjects with brain metastases must be stable for at least 4 weeks<br>• Adequate liver, kidney, and bone marrow function<br>• Negative serum pregnancy test if female of child-bearing potential<br>• Pre-existing peripheral neuropathy < grade 2 |
| **H. Dosage/Dosage Form, Route, and Dose Regimen** | Carboplatin will be dosed on day 1 and ABRAXANE will be dosed (dose level 0 = 100 mg/m$^2$) on days 1, 8, and 15 of a 21 day cycle for a total of 6 cycles. |

| | |
|---|---|
| **I. Statistical Analysis** | Overall response rate will be calculated as the percent of subjects who achieve CR or PR and the 95% confidence interval will be estimated using the Clopper Pearson method. Disease control rate will be analyzed in a similar manner. For both overall response rate, and disease control rate, the correlation with baseline subject and disease characteristics, and biomarkers will be evaluated using logistic regression.<br><br>Time-to-event variables will be analyzed using survival analysis methods. Survival rates will be estimated using Kaplan-Meier techniques. The correlation with baseline subject and disease characteristics, and biomarkers will be assessed using Cox multiple regression models.<br><br>Correlation among biomarkers in tissue, blood and between tissue and blood will be assessed. The association among various continuous and discrete biomarkers will be assessed first by the exploratory data analysis using graphical techniques such as the scatter plot matrix, box plots, and BLiP plot[17] . Correlation among continuous biomarkers will be examined by Pearson or Spearman rank correlation coefficients. The association on discrete biomarkers will be tested by Fisher's exact test. |

# SCHEMA

## LCI-LUN-ABR-001: Pilot Study of Carboplatin with Nab-Paclitaxel in Patients with Advanced Non-Small Cell Lung Cancer of Squamous Histology



# ABBREVIATIONS

| | |
|---|---|
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| AST | Asparate aminotransferase |
| AUC | Area under curve |
| BSA | Body surface area |
| BRR | Best response rate |
| CI | Confidence interval |
| CPT | Cell preparation tube |
| CR | Complete response |
| cCR | Clinical complete response |
| CTCAE | Common Terminology Criteria for Adverse Events |
| eCRF | Electronic case report form |
| ECOG | Eastern Cooperative Oncology Group |
| EDTA | Ethylene diamine tetraacetic acid |
| FEC | Fluorouracil- epirubicin hydrochloride-cyclophosphamide |
| FDA | Food and Drug Administration |
| GFR | Glomerular filtration rate |
| HER-2 | Human epidermal growth factor receptor 2 |
| IDS | Investigational Drug Services |
| IRB | Institutional Review Board |
| IV | Intravenous |
| LCI | Levine Cancer Institute |
| MTD | Maximum tolerated dose |
| NSCLC | Non-small cell lung cancer |
| ORR | Overall response rate |
| OS | Overall survival |
| PD | Progressive disease |
| PR | Partial response |
| PFS | Progression-free survival |
| PVC | Polyvinyl chloride |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| SAE | Serious adverse event |
| SAR | Suspected adverse reaction |
| SCC | Squamous cell cancer |
| SD | Stable disease |
| SI | Sponsor-investigator |
| SOP | Standard operating procedure |
| TTP | Time-to-progression |
| UAP | Unanticipated adverse problem |
| VEGF | Vascular endothelial growth factor |
| VEGFR-2 | Vascular endothelial growth factor receptor-2 |

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# 1. OBJECTIVES

## 1.1. Primary Objectives

The primary objective of this study is to assess the response rate of the combination of carboplatin with ABRAXANE in patients with advanced non- small cell lung cancer (NSCLC) with squamous cell histology.

## 1.2. Secondary Objectives

Secondary objectives are to assess the disease control rate, duration of response, duration of disease control, overall survival, progression-free survival, and the safety and toxicity profile with this regimen.

## 1.3. Exploratory Objectives

Exploratory objectives are to assess broad molecular profiling.

# 2. BACKGROUND

## 2.1. Non-Small Cell Lung Cancer

Lung cancer is the most common cause of cancer death, both in the United States and worldwide [1]. In the United States, in the year 2012, over 226,000 new cases of lung cancer were projected to be diagnosed and over 160,000 to die of the disease.[1] Once lung cancer is diagnosed, outcomes are poor, with only 15.9% of patients surviving five years after diagnosis (http://seer.cancer.gov/statfacts/html/lungb.html).

Squamous cell carcinoma (SCC) accounts for about 30% of new cases of lung cancer in the United States. Until recently, patients with SCC and adenocarcinoma had very similar overall survival; however, more recent studies have shown improved outcomes for adenocarcinoma relative to SCC.[2] This is potentially due to new treatment options for adenocarcinoma. Several drugs known to be effective in adenocarcinoma, like pemetrexed and bevacizumab, should not be used in SCC, secondary to increased toxicity or lack of efficacy. The standard front-line chemotherapy for SCC is a platinum-based doublet,[3] frequently carboplatin combined with a taxane, but overall survival in clinical trials is usually less than one year.[3] New treatment options for SCC are needed.

## 2.2. ABRAXANE

ABRAXANE for Injectable Suspension (also known as ABI-007, nab-paclitaxel, paclitaxel protein-bound particles for injectable suspension) is an albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers. Paclitaxel exists in the particles in a non-crystalline, amorphous state. ABRAXANE is supplied as a white to yellow, sterile, lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous infusion. Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel. ABRAXANE is free of solvents. The active agent in ABRAXANE is paclitaxel.

### 2.2.1. Indication

In the United States, ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) is indicated 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.

On October 11, 2012, the U.S. Food and Drug Administration (FDA) approved ABRAXANE for use in combination with carboplatin for initial treatment of patients with locally advanced or metastatic non-small cell lung cancer who are not candidates for curative surgery or radiation therapy.

ABRAXANE is also indicated for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.

### 2.2.2. Introduction

ABRAXANE is a biologically interactive albumin-bound paclitaxel combining a protein with a chemotherapeutic agent in the particle form. This composition provides a novel approach of increasing intra-tumoral concentrations of the drug by a receptor-mediated transport process allowing transcytosis across the endothelial cell. This albumin-specific receptor mediated process involves the binding of albumin to a specific receptor (gp60) on the intraluminal endothelial cell membrane, resulting in activation of a protein (caveolin-1), which initiates an internalization process in the endothelial cell through the formation of caveolae, with transport of the intact albumin-bound chemotherapeutic complex via these caveolae to the underlying tumor interstitium. A protein specifically secreted by the tumor (SPARC) binds albumin, allowing release of the hydrophobic drug to the tumor cell membrane[18]. ABRAXANE is the first biologically interactive nanoparticle product leveraging this gp- 60/caveolin-1/caveolae/SPARC pathway to increase intra-tumoral concentration of the drug and reducing toxic effects in normal tissue.

### 2.2.3. Preclinical Studies with ABRAXANE

Preclinical studies comparing ABRAXANE to Taxol® (paclitaxel Cremophor® EL solvent-based, BMS) demonstrated lower toxicities, with a maximum tolerated dose (MTD) approximately 50% higher for ABRAXANE compared to Taxol. At equal doses there was less myelosuppression and improved efficacy in a xenograft tumor model of human mammary adenocarcinoma. At equitoxic doses of paclitaxel, ABRAXANE treated groups showed more complete regressions, longer time to recurrence, longer doubling time, and prolonged survival. At equal dose, tumor paclitaxel area under the curve was 33% higher for ABRAXANE versus solvent based paclitaxel, indicating more effective intratumoral accumulation of ABRAXANE[18].

### 2.2.4. Clinical Studies with ABRAXANE

***Every-Three-Week (Q3W) Schedule in Metastatic Breast Cancer***
In a phase I study, the MTD of ABRAXANE was determined to be 300 mg/m$^2$ by 30 minute infusion Q3W, without premedication or G-CSF support.[4] No severe hypersensitivity reactions occurred with ABRAXANE despite the absence of premedication. Dose-limiting toxicities included sensory neuropathy, stomatitis, and superficial keratopathy, which occurred at a dose of 375 mg/m$^2$.

Two multicenter phase II studies have evaluated 2 dose levels of ABRAXANE (300 mg/m$^2$, n=63, and 175 mg/m$^2$, n=43) in patients with metastatic breast cancer (Ibrahim et al 2005 and Investigator's Brochure, respectively). The overall response rates in these 2 phase II trials were 40% (95% CI 25-54%) for the 175 mg/m$^2$ dose, and 48% (95% CI 35-60%) for the 300 mg/m$^2$ dose. Of 39 patients receiving 300 mg/m$^2$ as first-line therapy for metastatic breast cancer, 64% (95% CI 49-79%) responded. This was contrasted with a 45% response rate in similar patients at the lower dose level. Grade 4 neutropenia was noted in 24% of patients at the higher dose level, occurred primarily during the first cycle and resolved rapidly.

A Phase III trial in patients with metastatic breast cancer compared ABRAXANE 260 mg/m$^2$ (n=229) to Taxol 175 mg/m$^2$ (n=225) given Q3W.[5] Efficacy analyses were based on the ITT population. The ORR was significantly greater for ABRAXANE than for Taxol for all patients (33% *v* 19%, respectively; $P = 0.001$), patients who received first-line therapy (42% *v* 27%, respectively; $P = 0.029$), patients who received second-line or greater therapy (27% *v* 13%, respectively; $P = 0.006$), and patients who had received prior anthracycline therapy in either the adjuvant/metastatic setting (34% *v* 18%, respectively; $P = 0.002$) or the metastatic setting only (27% *v* 14%, respectively; $P = 0.010$). Tumor response rate was also significantly higher for ABRAXANE than for Taxol in patients with visceral dominant lesions (34% *v* 19%, respectively; $P = 0.002$) and in patients aged younger than 65 years (34% *v* 19%, respectively; $P < 0.001$). ORR also was greater for ABRAXANE compared with standard paclitaxel in patients with

nonvisceral dominant lesions (34% *v* 19%, respectively) and in patients ≥ 65 years old (27% *v* 19%, respectively), but the results did not reach statistical significance because of the small number of patients in these subsets.

Median time to progression (TTP) was significantly longer with ABRAXANE than with Taxol for all patients (23.0 *v* 16.9 weeks, respectively; hazard ratio [HR] = 0.75; *P* = 0.006).

There was a trend for greater median survival for all patients treated with ABRAXANE than with Taxol (65.0 *v* 55.7 weeks, respectively; *P* = 0.374). Although no difference in survival was observed in first-line patients, the difference was statistically significant in patients who received ABRAXANE, compared to Taxol, as second-line or greater therapy (56.4 *v* 46.7 weeks, respectively; HR = 0.73; *P* = .024).[5]

The incidence of hypersensitivity reactions (any grade) was low for both arms (1% for ABRAXANE and 2% for Taxol). No severe (grade 3 or 4) treatment-related hypersensitivity reactions occurred in any of the patients in the ABRAXANE group despite the absence of premedication. In contrast, grade 3 hypersensitivity reactions occurred in the Taxol group despite standard premedication (chest pain, two patients; allergic reaction, three patients). Per protocol, corticosteroids and antihistamines were not administered routinely to patients in the ABRAXANE group; however, premedication was administered for emesis, myalgia/arthralgia, or anorexia in 18 patients (8%) in the ABRAXANE group in 2% of the treatment cycles, whereas 224 patients (> 99%) in the Taxol group received premedication in 95% of the cycles.

Although the patients in the ABRAXANE group received an average paclitaxel dose-intensity 49% greater than that received by patients in the Taxol group, the incidence of treatment-related grade 4 neutropenia was significantly lower in the ABRAXANE group than in the Taxol group (9% *v* 22%, respectively; *P* < 0.001), with a higher mean neutrophil nadir (1.67 *v* 1.31x$10^9$/L, respectively; *P* = 0.046), suggesting that polyethylated castor oil may have contributed to this toxicity in patients who received standard (solvent-based) paclitaxel[19].

As expected with a higher dose of paclitaxel, treatment-related grade 3 sensory neuropathy occurred more frequently in the ABRAXANE arm than in the Taxol arm (10% *v* 2%, respectively; *P* < 0.001); however, these episodes improved with interruption of treatment to grade 2 or 1 in a median 22 days and were easily managed with treatment interruption and dose reduction. By day 28 after its first occurrence, the number of patients with persistent grade 3 sensory neuropathy was the same (n = 4) in both study arms. No episodes of motor neuropathy or grade 4 sensory neuropathy were reported in either group.

The only clinical chemistry value that was notably different between the two treatment arms was higher serum glucose levels in the Taxol–treated patients, who also had a

higher incidence of hyperglycemia reported as an AE compared with ABRAXANE–treated patients (7% *v* 1% respectively; $P = 0.003$).

Subgroup analyses revealed that the safety profiles of ABRAXANE (n=97) and Taxol (n=30) in patients who received the drugs as first-line therapy were similar to those in the overall study population. In subgroup analyses by age, the reported AEs were similar in patients < 65 years old and patients ≥ 65 years old in both groups. Of the patients ≥ 65 years old, the incidences of the following AEs were notably lower in the ABRAXANE group (n=30) than in the Taxol group (n=32): neutropenia (23% *v* 59%, respectively), leukopenia (10% *v* 31%, respectively), nausea (20% *v* 38%, respectively), hyperglycemia (0% *v* 19%, respectively), and flushing (0% *v* 16%, respectively). These data indicate no additional safety concerns for ABRAXANE in patients ≥ 65 years old compared with younger patients.

Six patients (3%) in the ABRAXANE group and eight patients (4%) in the standard paclitaxel group died during the study, all as a result of disease progression. No treatment-related deaths occurred in the ABRAXANE group; one patient (< 1%) in the Taxol group died of multi-organ failure, which was considered by the investigator to be possibly related to treatment but may also have been a result of sepsis and/or progressive disease.

***Weekly (QW) for 3 Weeks, Every 4 Weeks Schedule in Metastatic Breast Cancer***

Thirty-nine patients were enrolled into a Phase I study of ABRAXANE administered QW for 3 weeks followed by a 1 week rest in patients with advanced solid tumors.[6] The MTDs for heavily and lightly pre-treated patients were 100 and 150 mg/m$^2$ respectively. Dose limiting toxicities included grade 4 neutropenia and grade 3 sensory neuropathy. Premedication was not required, and unexpected, non-taxane associated toxicities were not observed.

In a Phase II trial in heavily pretreated patients with taxane-refractory metastatic breast cancer, objective antitumor responses occurred in 14% of women treated with ABRAXANE 100 mg/m$^2$ QW schedule. ABRAXANE weekly regimen was well tolerated; 91% of 106 patients were treated at the full dose of 100 mg/m$^2$ of ABRAXANE without dose reductions. Based on the activity and low toxicity documented with this schedule, the study was expanded to evaluate the efficacy and safety/tolerability of a higher dose of ABRAXANE 125 mg/m$^2$ weekly regimen in 75 additional patients. Results of this dose-finding study confirm the dose of ABRAXANE 100 mg/m$^2$ as the appropriate dose for further study in this patient population.[7]

In an open-label, randomized, multicenter phase II study comparing the antitumor response and toxicity of two QW dosing regimens, ABRAXANE dosed Q3W, and Taxotere® (polysorbate solvent-based docetaxel Sanofi-Aventis] Q3W for the first-line treatment of metastatic breast cancer.[5] A total of 300 patients were randomized to one of four treatment arms: (A) ABRAXANE 300 mg/m$^2$ IV Q3W, (n=76); (B)

ABRAXANE 100 mg/m$^2$ IV Day 1,8,15 every 28 days (n=76); (C) ABRAXANE 150 mg/m$^2$ IV Day 1,8,15 every 28 days (n=74); or (D) Taxotere 100 mg/m$^2$ Q3W (n=74). The primary objective of the trial was to evaluate the antitumor activity and safety of three different ABRAXANE regimens to determine the optimal dose and frequency to be used. Secondary objectives included the comparisons of each treatment group with respect to efficacy and safety, specifically: ABRAXANE to Taxotere; ABRAXANE QW regimens to ABRAXANE Q3W regimen; and the two dose levels of QW ABRAXANE. Patients received ABRAXANE as a 30-minute IV infusion without premedication; Taxotere was administered as a 60-minute infusion with corticosteroid premedication. The primary efficacy endpoint was ORR assessed every 8 weeks in all treatment arms by using the RECIST guidelines. The secondary efficacy endpoints included total response (ORR + SD $\geq$16 weeks) and PFS. Tumor response results underwent an evaluation by the investigators, as well as an Independent Radiology Review (IRR). If a pre-set level of congruence was observed between the tumor responses described by the investigators and the IRR, only the tumor response assessed by investigators was reported. Total of 75% of all patients were post-menopausal with a mean age of 53.9 years at randomization.

Both ORRs and total response rates were higher in all ABRAXANE arms compared to the Taxotere arm. The investigator-reported ORRs were 46%, 63%, 74%, and 39%, for arms A, B, C, and D, respectively. This difference was statistically significant for both QW dosing arms of ABRAXANE compared with Taxotere, ($P$ = 0.002 for arm B *v* D, and $P$ <0.001 for arm C *v* D). The corresponding investigator-reported total response rates were 72%, 83%, 91% and 69% for the four arms, respectively. This difference reached statistical significance for arms B and C compared to Taxotere ($P$ = 0.009 for arm B *v* D, and p=0.005 for arm C *v*. D). No significant difference in ORR was noted between the two weekly dosing arms (arm B *v* C, $P$ = 0.24). A significant increase in PFS was observed in the 150 mg/m$^2$ QW arm compared to the Taxotere arm (14.6 *v* 7.8 months, respectively, $P$ = 0.012, hazard ratio 0.57). No significant difference in PFS was found between the ABRAXANE 300 mg/m$^2$ Q3W arm and Taxotere arm (A and D). Similarly, PFS was not significantly different between arms A and C, or arms B and D.

All three ABRAXANE arms demonstrated a favorable safety profile when compared with the Taxotere arm. Toxicity data occurring in >25% of patients is summarized in Table II. The most frequent hematologic adverse event was neutropenia, with significantly lower rates of Grade 3/4 neutropenia in all ABRAXANE arms (Grade 4, 5%, 5%, 9%, 75% for arms A, B, C, D, respectively). ABRAXANE also had lower rates of febrile neutropenia (1%, 1%, 1%, 8% for arms A, B, C, D, respectively) and fatigue (Grade 3, 5%, 0%, 3%, 19% for arms A, B, C, D, respectively) compared to Taxotere. While the incidence of sensory neuropathy was similar in the ABRAXANE and Taxotere arms, the median time to improvement in patients with Grade 3 neuropathy was shorter in all three ABRAXANE arms (22, 22, 19 and 37 days in arms A, B, C and D, respectively).The ABRAXANE arms demonstrated improved safety and

increased efficacy compared with Taxotere. All three ABRAXANE regimens produced lower rates of neutropenia, febrile neutropenia, and fatigue than Taxotere.

***Continuous Weekly (QW) Schedule in Neoadjuvant Breast Cancer***

The NSABP studied the administration of ABRAXANE in a neoadjuvant setting to patients with locally advanced breast cancer at a dose of 100 mg/m$^2$ QW for 12 weeks, with no break.[8] Four cycles of flurouracil- epirubric hydrochloride-cyclophosphamide (FEC) were administered sequentially based on patients' human epidermal growth factor receptor (HER2) status: HER2 negative patients received FEC-100 (F: 500 mg/m$^2$, E: 100 mg/m$^2$, C: 500 mg/m$^2$ Q3 weeks) and HER2 positive patients received weekly trastuzumab in addition to FEC-75 (F: 500 mg/m$^2$, E: 75 mg/m$^2$, C: 500 mg/m$^2$ Q3 weeks). Weekly trastuzumab was permitted during ABRAXANE and FEC-75 treatment at the discretion of the investigator. The primary objective of the trial was to determine the pathologic complete response rate (pCR) in the breast. Secondary endpoints included pCR in breast and nodes, clinical complete response rate (cCR), 2-year progression free survival, and overall survival. Sixty- five patients were evaluable for analyses. The therapy was well tolerated, as 63 of 65 patients received 4 cycles of ABRAXANE with 1 to 3 of the 12 doses omitted in 4 patients. Of the 774 planned doses of ABRAXANE, only 14 (2%) required dose reductions or omissions. The mean duration of ABRAXANE treatment was 12.3 weeks (range 9 to 14 weeks). The mean dose intensity was 94.8 mg/m2/week (range 72.5 to 100 mg/m2/week). A total of 62 patients went on to receive at least one dose of FEC with 58 completing 4 cycles, which resulted in 88% of patients who were initiated on therapy completing all planned chemotherapy. No grade 4 or 5 adverse events were reported during the ABRAXANE therapy. The most frequent grade 2 toxicities were fatigue, nausea, sensory neuropathy, joint pain, and diarrhea. The incidences of grades 2 and 3 sensory neuropathy were 11% and 5%, respectively. The incidences of grades 2 and 3 neutropenia were 6% and 3%, respectively. Following 12 weeks of ABRAXANE, a cCR of 34% was noted. The pCR in breast was 29%, and for the HER2+ subset, the pCR was 58%. The authors concluded that the administration of ABRAXANE 100 mg/m$^2$ QW x 12 was both effective and tolerable.

At the time of this update, more than 20 abstracts and publications have been presented at major oncology conferences or published in medical journals related to ABRAXANE QW schedule in breast cancer, including completed and ongoing studies.

***In Metastatic Non-Small Cell Lung Cancer***

Phase II trials of ABRAXANE in lung cancer as monotherapy [9] and in combination with carboplatin[10] have shown response rates as high as 39%. These studies suggested that the clinical outcomes were improved with weekly ABRAXANE (at 100 mg/m$^2$) versus every 3 week ABRAXANE in combination with carboplatin every three weeks.[10] A phase III trial randomized patients with NSCLC to receive either carboplatin/ ABRAXANE or carboplatin/paclitaxel. Carboplatin was administered at

an AUC of 6 every 3 weeks, and patients received either ABRAXANE 100 mg/m$^2$ weekly without premedication (n=521) or paclitaxel 200 mg/m$^2$ every three weeks with premedication (n=531). The primary endpoint was overall response rate, and secondary endpoints included progression free survival and overall survival. The response rates were significantly higher in the carboplatin/ABRAXANE arm, 33% vs. 25% (p- 0.005). These differences were more pronounced in the subset of patients with squamous cell carcinoma: a 41% response rate with ABRAXANE in combination with carboplatin vs. 24% in the paclitaxel arm. Toxicities were similar between the two arms, with higher rates of grade 3 neutropenia, neuropathy, myalgias, and arthralgias on the paclitaxel arm, and higher rates of grade 3 anemia and thrombocytopenia on the ABRAXANE arm. Median progression free survival was 6.3 months in the ABRAXANE group versus 5.8 months in the control group (p=0.214). Median overall survival was 12.1 months in the ABRAXANE arm versus 11.2 months in the solvent-based paclitaxel group (p=0.271).[12] Based on this trial, ABRAXANE is FDA approved in combination with carboplatin for front-line treatment of patients with advanced non-small cell lung cancer.

## 2.3. Carboplatin

Carboplatin is a commonly used agent in metastatic non-small cell lung cancer.[3] It is frequently used in combination with other chemotherapeutic agents, including paclitaxel,[3] docetaxel,[13] and gemcitabine.[14] It will be dosed according to standards based on ABRAXANE dosing at an AUC of 6, as calculated according to institutional standards.

## 2.4. Rationale

ABRAXANE, based on results from prior studies discussed above, appears to be a promising drug in squamous cell carcinoma of the lung. In a phase II trial, carboplatin (AUC of 6 every three weeks) combined with weekly ABRAXANE at 100 mg/m$^2$ had improved response rates versus a group receiving carboplatin with every three week ABRAXANE (47% vs. 30%).[10] Based on this data, a dosing schedule of carboplatin at an AUC of 6 on day 1 of a three week cycle in combination with ABRAXANE at 100 mg/m$^2$ on days 1, 8, and 15 was selected for further study. In the phase III study with this combination, combination therapy with ABRAXANE and carboplatin produced higher response rates than paclitaxel and carboplatin in metastatic non-small cell lung cancer (33% vs. 25%, p=0.005). The difference in response rate was even more dramatic for patients with squamous cell carcinoma, with 41% responding to the ABRAXANE/carboplatin combination, and only 24% responding to the standard therapy of paclitaxel/carboplatin. Progression free and overall survival were non-inferior with ABRAXANE and carboplatin.[12]

This study will help to explore this combination more thoroughly in the subgroup of patients who had the best response in prior studies (i.e., patients with squamous cell

carcinoma), as well as determine whether there are any biomarkers which can predict for response.

# 3. SUBJECT SELECTION

## 3.1. Accrual

Approximately 50 subjects will be enrolled over an enrollment period of 24 months in order to accrue 45 evaluable subjects (Section 13.3). Interim analyses will be conducted after the enrollment of subject 15, and 30 evaluable subjects.

## 3.2. Inclusion Criteria

**Subjects must meet all the following criteria:**

- Histologically confirmed stage IV non-small cell lung cancer with predominantly squamous histology.
- No prior systemic treatment for metastatic disease. Patients who have received prior adjuvant chemotherapy for early-stage lung cancer are eligible if at least 12 months have elapsed between the date of final chemotherapy administration and the date of consent.
- Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be

recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm with conventional techniques or as ≥10 mm with CT scan, MRI, or calipers by clinical exam. RECIST 1.1 will be used to measure disease per Section 12.

- Biopsy accessible disease.
- Patients with previous radiotherapy as definitive therapy for locally advanced non-small cell lung cancer are eligible, as long as the recurrence is outside the original radiation therapy port. Definitive radiation therapy must have been completed >4 weeks prior to the date the informed consent is signed.
- Age ≥18 years.
- ECOG performance status ≤1.
- If patient has brain metastasis, the disease must be stable (treated and/or asymptomatic), for at least 4 weeks prior to the first dose of study treatment.
- Bilirubin ≤ 1.5 mg/dL.
- Adequate liver function: AST and ALT ≤ 2.5x upper limit of normal, alkaline phosphatase ≤ 2.5x upper limit of normal, unless bone metastasis is present (<5X upper limit of normal) in the absence of liver metastasis.
- Adequate bone marrow function: Platelets >100,000 cells/$mm^3$ (transfusion independent, defined as not receiving platelet transfusions within 7 days prior to laboratory sample).
- Hemoglobin > 9.0g/dL, and ANC ≥ 1,500 cells/$mm.^3$
- Adequate renal function with creatinine ≤1.5 mg/dL is recommended.
- Females of childbearing potential (defined as a sexually mature woman who (1) has not undergone hysterectomy [the surgical removal of the uterus] or bilateral oophorectomy [the surgical removal of both ovaries] or (2) has not been naturally postmenopausal for at least 24 consecutive months [i.e., has had menses at any time during the preceding 24 consecutive months]) must:
  - Either commit to true abstinence* from heterosexual contact (which must be reviewed on a monthly basis), or agree to use, and be able to comply with, effective contraception without interruption, 28 days prior to starting IP therapy (including dose interruptions), and while on study medication or for a longer period if required by local regulations following the last dose of IP and
  - Negative serum or urine β-hCG pregnancy test at screening for patients of childbearing potential and agree to ongoing pregnancy testing after the end of study therapy. This applies even if the subject practices true abstinence* from heterosexual contact.
- Sexually active males must practice true abstinence* or use an effective contraception method during treatment, during dose interruptions and for six months after completing treatment even if he has undergone a successful vasectomy.Patients must have < Grade 2 pre-existing peripheral neuropathy (per CTCAE).
- Ability to understand and the willingness to sign a written informed consent

document.

**True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception].*

### 3.3. Exclusion Criteria

**Subjects must not meet any of the following criteria:**

- Received prior systemic therapy for metastatic disease.
- Receiving any other investigational agents.
- Known hypersensitivity to either carboplatin or ABRAXANE.
- Uncontrolled and current illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
- Pregnant or breast feeding.
- Other active malignancies.
- Neuropathy ≥ grade 2.
- Subject has received limited field radiation for palliation ≤ 2 weeks prior to starting study treatment and/or from whom ≥ 30% of the bone marrow was irradiated.

## 4. INVESTIGATIONAL PLAN

### 4.1. Milestone Date Definitions

**Eligibility date**: the date of the last documented criterion that confirmed subject eligibility.
**Enrollment date**: the date of initiation of carboplatin + abraxane treatment.
**Treatment Discontinuation date**: the date the investigator decided to discontinue subject from carboplatin + abraxane treatment.
**Off Study date**: the date on which the subject is determined to have completed the study (see Section 5.5).

### 4.2. Overall Study Design and Plan

This is a single center, single arm phase II study. Following informed consent and eligibility check, all subjects will receive therapy with carboplatin and ABRAXANE. In the first stage of this study, 15 evaluable (as defined in Section 13.3) patients will be enrolled. All enrolled subjects will continue with study treatment for six cycles, or until progression (radiographic/clinical), unacceptable toxicity, investigator discretion, or consent withdrawal. If 3 or more responses are

observed in the first stage, an additional 15 evaluable subjects will be enrolled. If a total of 7 or more responses are observed in the second stage (of 30 total subjects), a final 15 evaluable subjects will be enrolled.

Data from this study will be collected on electronic case report forms (eCRFs) and stored in the CTMS.

### 4.3. Registration/Enrollment

Subjects will be registered in the CTMS and assigned a Study ID. The Study ID number will begin with "LCI" and include a two digit number sequentially assigned to the subject. (e.g. "LCI01" will be the Study ID assigned to the first subject.)

## 5. TREATMENT PLAN

### 5.1. Pre-Treatment

No protocol-related assessments may be performed prior to obtaining informed consent. Baseline assessments will be conducted according to the Study Calendar in Section 6.12 and Section 7.1.

### 5.2. Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 10. Appropriate dose modifications are described in Section 8. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the subject's malignancy.

#### 5.2.1. ABRAXANE

Subjects will receive ABRAXANE intravenously at a dose of 100 mg/m$^2$ on days 1, 8 and 15 of a 21 day cycle.

Premedication
Subjects do not require premedication prior to ABRAXANE administration, as hypersensitivity reactions are rare. Corticosteroids for anti-emetic purposes may be used per institutional standards.

Although the solubilizing agents Cremophor® EL and Tween® 80 have long been implicated in adverse events including hypersensitivity reactions due to their

detergent-like nature and known ability to induce histamine release [15], the administration of solvent-based taxanes (Taxol® and Taxotere®) requires premedication with corticosteroids and histamine receptor blocking agents to prevent the occurrence of hypersensitivity reactions. However, the hypersensitizing role of the taxane molecules themselves cannot be ruled out.

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

***Availability***
ABRAXANE will be supplied as commercial drug according to package insert parameters and provided by the institutional pharmacy.

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

Refer to the package insert for additional information.

***Study Medication Administration***

ABRAXANE is injected into a vein [intravenous (I.V.) infusion] over 30 minutes. **The use of an in-line filter is not recommended.** Following administration, the intravenous line should be flushed with sodium chloride 9 mg/ml (0.9%) solution for injection to ensure complete administration of the complete dose, according to local practice.

***Reconstitution and use of ABRAXANE***

1. Calculate the subject's body surface area at the beginning of each cycle and if the weight changes by > 10%, from baseline weight, re-calculate the total dose (in mg) to be administered by:
    - Total Dose (mg) = BSA x (study dose mg/$m^2$)

2. Calculate the total number of vials required by:
    - Total Number of Vials = $\frac{\text{Total Dose (mg)}}{\text{100 (mg/vial)}}$

    Round up the number of vials to be reconstituted to the next higher whole number when a fractional number of vials is obtained by the above formula (e.g., if the total number of vials = 4.05 or 4.5, then 5

vials would be reconstituted).

Using sterile technique, prepare the vials for reconstitution.

3. Swab the rubber stoppers with alcohol.
4. Aseptically, reconstitute each ABRAXANE vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP.
    - Slowly inject the 20 mL of 0.9% Sodium Chloride Injection, USP, over a minimum of 1 minute, using the sterile syringe directing the solution flow onto the inside wall of the vial.
    - DO NOT INJECT the 0.9% Sodium Chloride Injection, USP solution directly onto the lyophilized cake as this will result in foaming.
    - Once the injection is complete, allow the vial to sit for a minimum of 5 (five) minutes to ensure proper wetting of the lyophilized cake/powder.
    - Gently swirl and/or invert the vial slowly for at least 2 minutes until complete dissolution of any cake/powder occurs. Avoid generation of foam. Rapid agitation or shaking will result in foaming.
    - If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides.
    - Each ml of reconstituted product will contain 5 mg of paclitaxel.
5. Calculate the exact total dosing volume of 5 mg/ml suspension required for the subject:
    - Dosing volume (ml) = Total dose (mg) / 5 (mg/ml)
6. The reconstituted suspension should be milky and homogeneous

without visible particulates. If particulates or settling are visible, the vial should be gently inverted again to ensure complete resuspension prior to use. Discard the reconstituted suspension if precipitates are observed.

7. 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.
8. 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.
9. 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.

### 5.2.2. Carboplatin

Subjects will receive carboplatin at an AUC of 6 on day 1 of a 21 day cycle.

Carboplatin is a standard treatment for NSCLC. Carboplatin is administered after ABRAXANE by intravenous infusion over 60 minutes with standard antiemetics per local practice guidelines. The carboplatin dose will be calculated per institutional standards.

## 5.3. Duration of Therapy/Treatment Discontinuation

In the absence of treatment delays due to adverse event(s), treatment may continue for up to six cycles or until one of the following criteria applies:

- Disease progression;
- Intercurrent illness that prevents further administration of treatment;
- Unacceptable adverse event(s);
- Subject decides to withdraw consent for the study therapy;
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the investigator;
- Subject non-compliance

**Subjects who discontinue their treatment early are still considered to be on-study and may continue to participate in study procedures (e.g. labs, scans, follow-up).**

## 5.4. Follow-Up

Subjects will be followed until death, three years of follow-up have occurred or lost to follow-up following cessation of treatment. Subjects (or their family members or designees) may be contacted by telephone or in writing or during clinic visits after treatment discontinuation for collection of follow-up data every six months until death or lost to follow-up. Follow-up clinical information may also be obtained through chart reviews. Subjects who discontinued treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event according to standard of care procedures. Subjects who discontinue treatment for any reason will continue follow-up.

## 5.5. Off-Study

Subjects will be considered off study for any of the following reasons:

- Completion of 3 years of follow-up from enrollment date
- Consent withdrawal
- Determination by Principal Investigator
- Lost to follow up
- Death

Off study subjects will not receive study treatment or participate in any study procedures, including data collection.

### 5.5.1. Subject Withdrawals

Subjects are defined as withdrawn from the study if they revoke consent for both treatment and study procedures or the Investigator withdraws them from the study. Subjects **must be** withdrawn from the trial for the following reasons:

- Subject withdraws consent from study treatment and study procedures. A subject must be removed from the trial at his/her own request. At any time during the trial and without giving reason, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- Subject is lost to follow-up after three consecutive months of attempted contact.

Subjects **may be** withdrawn from the study by the Investigator for the following reasons:

- The subject is non-compliant with study drug, study procedures, or both (as determined by the Investigator); including the use of anti-cancer therapy not prescribed by the study protocol.

- Development of an intercurrent illness or situation which would, in the judgment of the Investigator, significantly affect assessments of clinical status and trial endpoints.

Any subject who withdraws themselves or who is withdrawn from the study by the Investigator will remain under medical supervision until discharge or transfer is medically acceptable.

In all cases, the reason for withdrawal must be documented in the subject's medical records and in the CTMS. Withdrawn subjects are considered to be off-study.

### 5.6 Screen Failures and Subject Replacements

Enrolled subjects who have discontinued treatment or who have withdrawn after receiving their first dose of study drug will not be replaced. A consented subject who, for any reason (e.g. failure to satisfy the selection criteria or withdraws consent), terminates participation in the study before receiving first dose of study drug is regarded as a "screen failure." Screen Failures may be replaced.

All screen failures will be tracked in the CTMS.

Note that enrolled subjects who do not meet all of the criteria to be included in the efficacy population (defined in Section 13.3) will be included in the safety population (defined in Section 13.3). However, these subjects will not contribute to the evaluable population and therefore enrollment of subjects will continue until the total expected accrual of evaluable subjects has been reached.

## 6. STUDY PROCEDURES

### 6.1. Informed Consent

Written informed consent will be obtained from each subject prior to undergoing protocol-specific evaluations and prior to receiving treatment. Women will be counseled regarding risk of teratogenicity and need to use contraception through the course of the study. Men will also be counseled on the need to use contraception for all sexual encounters.

### 6.2. Demographics and Medical/Treatment History

A complete medical history will be obtained at baseline, including smoking history. Any clinically significant pre-existing toxicity will also be documented in the medical record and recorded on the eCRF. Medical history will be obtained within

30 days prior to the first dose of study medication. ECOG performance status will be documented at baseline.

### 6.3. Physical Examination

Evaluation by body system, height (pre-treatment only), weight, and body surface area (BSA) will be documented in the medical record and recorded on the eCRF. Vital signs will be recorded and include temperature, blood pressure, pulse rate, respiratory rate, and oxygen saturation. ECOG performance status will be assessed.

### 6.4. Pregnancy Test

A serum or urine pregnancy test will be performed at eligibility screening, within 72 hours prior to starting study drug treatment, and as clinically indicated for women of childbearing potential.

### 6.5. Symptoms and Toxicities

All adverse and serious adverse events will be documented in the medical record and recorded on the eCRF regardless of attribution on an ongoing basis throughout the study.

### 6.6. Concomitant Medications

Any medications other than ABRAXANE and carboplatin will be considered a concomitant medication and dose, route, frequency, administration and start/stop dates will be documented in the medical record and recorded in the eCRF.

## 6.7. Clinical Laboratory Tests

The blood-based clinical laboratory tests will include a complete blood count with differential and platelets, a complete metabolic panel (including sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, albumin, total protein, total bilirubin, AST, ALT, alkaline phosphatase), magnesium, phosphorus, and LDH. CBC with differential will be obtained at baseline and weekly prior to each dose of ABRAXANE. Additional labs including CMP, LDH, magnesium, and phosphorus will be obtained at baseline and every three weeks prior to each cycle with carboplatin plus ABRAXANE. CBC with differential, CMP, LDH, magnesium, and phosphorus will be repeated at cycle 1, day 1 if baseline labs are not within 7 days prior to start of study treatment. CBC with differential, CMP, LDH, magnesium, and phosphorus will be obtained at end of treatment assessment. Laboratory results will be recorded on the eCRF.

## 6.8. Electrocardiogram

A standard electrocardiogram (EKG/ECG) will be required at baseline.

## 6.9. Radiology and Tumor Measurements

A CT (computed tomography) scan with contrast of the chest, pelvis and abdomen will be performed according to the schedule outlined in Section 6.12. Tumor measurements will be recorded on the eCRF.

## 6.10. Tissue and Blood-based Biomarkers

The rationale for tissue-based biomarker analysis includes the possibility of identifying predictive markers of benefit from carboplatin and/or ABRAXANE. Biopsies of tumors from the primary lesion and/or lymph node and/or metastatic site will be collected for exploratory analyses of biomarkers after subject enrollment, but prior to the first dose of study drug. Archival tumor tissue, for which adequate tissue for biomarker testing on prior biopsies may be acceptable, will be obtained when possible. Archival tumor tissue must have been obtained within the past 60 days and prior to any treatment and will be reviewed by the Investigator. If the archive sample is of insufficient quality or amount, a new core biopsy will be required. New biopsies will be fresh-frozen, collected and stored in the CHS Biospecimen Repository for batch analysis at the end of the study.

A baseline blood sample will be collected with additional blood collected at the subsequent time points according to the Study Calendar in Section 6.12, using one EDTA 10 mL tube and two 9 mL CPT tubes for blood cell separation and storage.

For investigational sites unable to process peripheral blood mononuclear cells (PBMCs), obtain two EDTA 10 mL tubes only. Specimens will be delivered to the CHS Biospecimen Repository to be processed within one hour of collection, and stored for batch analysis at the end of the study.

Levine Cancer Institute will analyze biomarkers in both tissue and blood including those relative to treatment and response (e.g., immunophenotyping, biomarkers related to immune balance, etc.). The immunology biomarker analysis will be performed in the Immune Monitoring Core Laboratory at Cannon Research Center, Carolinas Medical Center in Charlotte, NC (c/o Dr. David Foureau). These studies will be defined in a future related IRB-approved laboratory research protocol.

## 6.11. Subsequent Anti-cancer Therapy and Survival Status

Subject's cancer therapies and survival status following completion of treatment will be recorded in the eCRF.

## 6.12. Study Calendar

| Required Procedures | Baseline | During Treatment | End of Treatment | Follow-Up |
|---|---|---|---|---|
| | Within 30 days prior to treatment initiation unless otherwise specified | Every 3 weeks, ± 7 days, unless otherwise specified | Within 30 days after the last dose of study medication unless otherwise specified | Every 6 months until death or lost to follow-up |
| Informed consent | X | | | |
| Demographics | X | | | |
| Medical and Treatment History | X[f] | | | |
| Physical Exam, Vital Signs, Oxygen Saturation | X | X | X | |
| Pregnancy Test (serum or urine)[a] | X | Within 72 hours prior to starting study drug and if/when clinically indicated | If/when clinically indicated | |
| Symptoms & Toxicities | X | X | X | |
| Concomitant Medications | X | X | X | |
| Laboratory Tests | X[b] | X[b] | X[b] | |
| EKG/ECG | X | | | |
| Radiology & Tumor Measurements | X | X<br>Every 6 weeks, ± 14 days | X | X[c] |
| Biopsy Tissue Collection for Biomarkers | X[d]<br>Prior to treatment initiation | | | |
| Blood-based Biomarkers | X<br>Within 30 days prior to treatment initiation | X[e]<br>Pre-dose on day 1 of treatment cycles 3, and 5. | X | |
| Subsequent Anticancer Therapy | | | | X |
| Survival Status | | | | X |

a: In women of child-bearing potential
b: CBC with differential will be obtained at baseline and weekly prior to each ABRAXANE dose. CMP, LDH, magnesium, and phosphorus will be obtained at baseline and every three weeks prior to each cycle of carboplatin plus ABRAXANE dose. CBC with differential, CMP, LDH, magnesium, and phosphorus will be repeated at cycle 1, day 1 if baseline labs are not within 7 days prior to start of study treatment. CBC/differential, CMP, LDH, magnesium, and phosphorus will be obtained at end of treatment assessment.
c: Per standard surveillance guidelines, as clinically indicated.
d: See Section 6.10 for tissue collection requirements.
e: Pre-dose on day 1 of treatment cycles 3, and 5 and per Section 6.10.
f: includes smoking history at baseline only

# 7. REQUIRED EVALUATIONS

## 7.1. Pre-Treatment Evaluations

Pre-treatment evaluation will include screening (to determine subject eligibility), medical history (including smoking history at baseline), physical examination, vital signs, clinical laboratory tests as described in Section 6, as well as adverse events assessment. Fresh or archived tumor biopsies are required prior to treatment initiation. Blood samples for biomarker testing will be obtained prior to treatment initiation.

Imaging tests, including comprehensive (at least chest, abdomen, and pelvis) contrast-enhanced CT or MRI aimed at defining the extent of existing disease must be performed and documented within 30 days prior to the first dose of study therapy. An EKG/ECG must also be performed and documented prior to treatment initiation.

A negative pregnancy test for all women of childbearing potential must be documented before initiating treatment.

Written informed consent must be obtained prior to any study-specific screening evaluations and prior to receiving treatment.

## 7.2. Treatment Period

Prior to each on-study infusion, vital signs and CBC/differential/platelets will be obtained.

Vital signs, weight measurements, toxicity, concomitant medications and adverse events assessments, physical examination, and laboratory tests (hematology and chemistry profiles) will be performed within 7 days of day 1 of each cycle.

Imaging studies and tumor response assessments will be repeated every 6 weeks (± 2 weeks), or as clinically indicated.

After initiating study treatment (cycle 1 day 1), blood samples for biomarker testing will be obtained every 6 weeks (± 2 weeks).

## 7.3. End of Therapy

Every subject will undergo an end-of-therapy evaluation at the time it is determined that he or she is no longer eligible to receive study therapy. End of

therapy evaluations will include vital signs, weight measurements, toxicity, concomitant medications and adverse events assessments, physical examination, and laboratory tests (hematology and chemistry profiles) as well as imaging studies with tumor measurements and blood for biomarker testing. The end of therapy evaluation must be completed within 30 days after treatment discontinuation.

### 7.4. Follow-Up/Survival Period

All subjects will be followed until all treatment-related toxicities have resolved, returned to baseline, stabilized, or are deemed irreversible according to standard of care procedures.

Subjects may be contacted by telephone or in writing, or during clinic visits after treatment discontinuation for collection of follow-up information approximately every 6 months until death or lost to follow-up. Follow-up clinical information may also be obtained through chart reviews.

Imaging studies and tumor assessments will be attempted per standard surveillance guidelines (which may be as frequently as every 6 weeks ± 2 weeks) until documented progression for subjects who had a complete response, partial response, or stable disease, and/or discontinued study therapy due to toxicity or reasons other than progressive disease.

## 8. DOSING DELAYS/DOSE MODIFICATIONS

NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for grading toxicities. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP homepage (http://ctep.cancer.gov/protocol/Development/electronic_applications/ctc.htm#ctc_40). All adverse clinical experiences, whether observed by the Investigator or reported by the subject, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the study drug, and the subject's outcome. The Investigator must evaluate each toxicity for its relationship to the study drug and severity.

### 8.1. Dose Modifications for ABRAXANE

Management of severe or intolerable adverse reactions may require dose reduction and/or interruption of ABRAXANE. Recommendations of dose reduction, interruption or discontinuation in the management of adverse reactions are summarized in Table 1. Clinical judgment of the Investigator should guide the management plan of each subject based on individual benefit/risk assessments.

**Table 1: Pre-specified dose/schedule modifications for adverse events related to ABRAXANE**

| Dose Level | Dose of ABRAXANE ($mg/m^2$) |
|---|---|
| 0 | 100 |
| -1 | 75 |
| -2 | 50 |

Recommendations for dose reduction, interruption, or discontinuation in the management of ABRAXANE-related adverse events are outlined in Table 2.

**Table 2: Criteria for dose modifications for ABRAXANE-related toxicities**

| Toxicity | Dose Modification |
|---|---|
| Abnormal Hematologic Function | |
| • ANC $\leq$ 1.5 x $10^9$ cells/L and platelets <100 x $10^9$ cells/L<br><br>• ANC $\leq$ 1.0 x $10^9$ cells/L and platelets < 75 x $10^9$ cells/L. | • Level 0 ABRAXANE dose should not be administered at the start of each cycle unless ANC criteria are met.<br>• Subjects must meet ANC and platelet criteria for subsequent ABRAXANE doses (days 8 and 15). If the ANC and platelets are not adequate for treatment on Day 8 and/or 15, the dose will be held and the total cycle length remains the same.<br><br>***Refer to Table 3 for information on dose reductions and guidelines for optimal use of growth factors for hematologic toxicity.*** |
| Abnormal Hepatic Function | |
| • AST and ALT $\leq$ 2.5x upper limit of normal, alkaline phosphatase $\leq$ 2.5x upper limit of normal, unless bone metastasis is present in the absence of liver metastasis. | • Maintain level 0 dose level (see Table 1). Hepatic toxicity from taxanes may occur but is uncommon. Therefore, hepatic dysfunction that occurs while the subject is on study should prompt an evaluation to determine the cause, including the possibility of progressive metastatic disease and hepatotoxicity from concurrent medications. |

| | |
|---|---|
| Sensory Neuropathy | |
| • ≥ Grade 3 | • Withhold ABRAXANE. Treatment may be resumed at the next lower dose level (see Table 1) in subsequent cycles after the sensory neuropathy improves to ≤ Grade 1. The time to resolution to ≤ Grade 1 should be the adverse event duration used for adverse event reporting. *Note: The investigator may elect to dose modify for Grade 3 sensory neuropathy.* |
| • ≥ Grade 4 | • Withhold ABRAXANE. Treatment may be resumed at a reduction of 2 dose levels (Dose Level -2; see Table 1) in subsequent cycles after the sensory neuropathy improves to ≤ Grade 1. |
| Hypersensitivity Reactions | |
| • Minor symptoms such as flushing, skin reactions, dyspnea, lower back pain, hypotension, or tachycardia.<br>• Severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema or generalized urticaria. | • Temporarily interrupt ABRAXANE infusion according to institutional standards.<br>• Immediately discontinue ABRAXANE administration and begin aggressive symptomatic therapy. Subjects who experience severe hypersensitivity reactions to ABRAXANE should not be re-initiate treatment.<br>***It is not recommended to administer ABRAXANE to subjects with prior hypersensitivity to a taxane.*** |
| Other toxicities | |
| • ≥ Grade 3, except for anemia | • Treatment should be withheld until resolution to ≤ grade 1 or baseline if baseline was greater than grade 1, then reinstituted, if medically appropriate, at the next lower dose level (see Table 1). |

***G-CSF Administration***

Administer G-CSF 5 mcg/kg/day (rounded to the nearest vial size per investigator/ institution's standard of care) 24 hours after chemotherapy and hold 48 hours prior to the next dose.

**Table 3: Use of G-CSF and Dose reductions for Hematologic Toxicity**

| Toxicity | Occurrence | Action to be Taken |
|---|---|---|
| ANC < 500 cells/$mm^3$ (nadir count) with neutropenic fever > 38° C<br>OR<br>Delay of next cycle due to persistent neutropenia (ANC < 1500 cells/$mm^3$)<br>OR<br>For subjects on weekly treatment whose next treatment within the cycle (Day 8 or Day 15) is omitted due to persistent neutropenia (ANC < 1000 cells/$mm^3$) (i.e. ANC still <1000 cells/$mm^3$ after previous week's omission)<br>OR<br>Neutropenia < 500 cells/$mm^3$ for > 1 week | Any Occurrence | At the first occurrence of a hematological toxicity (as outlined in the Toxicity column), the same dose is maintained and granulocyte colony-stimulating factor (G-CSF) is given as outlined below. In the event that a hematological toxicity re-occurs in the face of G-CSF, dose reduction to the next lower level will be required for subsequent cycles once ANC is ≥ 1500 cells/$mm^3$.<br><br>If G-CSF is given concurrently with weekly ABRAXANE, administration may begin the day after ABRAXANE is given and should stop at least 48 hours prior to when ABRAXANE is given the following week. |
| • Thrombocytopenia Grade 3 or Grade 4 | 1st Occurrence<br><br>Recurrence | • Dose reduction to next lower level.<br><br>• Dose reduction to next lower level. |

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

Caution should be used when concomitantly administering ABRAXANE with inhibitors (e.g., ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozilm cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) or inducers (e.g., rifampicin, carbamazepine, phenytoin, efavirenz, and nevirapine) of either CYP2C8 or CYP3A4.)

### 8.2. Dose Modifications for Carboplatin

Dose modifications for carboplatin can be made at the Investigator's discretion in accordance with the package insert and institutional standards.

## 9. SAFETY DATA COLLECTION, RECORDING AND REPORTING

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology, blood chemistry values, and regular measurement of vital signs and the performance of physical examinations. These assessments should be performed within ± 7 days of the scheduled day of assessment except for adverse events which will be evaluated continuously through the study. Safety and tolerability will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All adverse events (Grades 1 – 5) will be recorded on the eCRF.

## 9.1. Unanticipated Problem (UAP) Definition

An Unanticipated Problem (UAP) is any incidence, experience or outcome that is unexpected, given the information provided in research-related documentation (e.g. investigator's brochure, informed consent), related or possibly related to participation in the research and the study population characteristics that is related or possibly related to participation in the research study and places the participant at an increased risk.

## 9.2. Adverse Event (AE) Definition

An adverse event or adverse experience is any untoward medical occurrence in a study subject who is administered a study drug that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the study drug, whether or not considered related to the study drug.
Pre-existing conditions that increase in frequency or severity or change in nature during or as a consequence of use of a drug in human clinical trials are also considered adverse events. Adverse events may also include pre or post-treatment complications that occur as a result of protocol-mandated procedures (e.g., invasive procedures such as biopsies).

Any continuing medical condition or clinically significant laboratory abnormality with an onset date before the first date of study drug administration should be considered pre-existing and should be documented.

An AE does not include:

- Relapse or progression of the underlying malignant disease; however, the associated signs, symptoms, or diagnoses should be recorded as adverse events (e.g., "jaundice" due to new or increasing liver metastases, or "tumor pain" or "bone pain" due to progressive disease);
- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion). The condition that leads to the procedure is the adverse event;
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions);
- Overdose of either study drug or concomitant medication without any signs or symptoms unless the subject is hospitalized for observation; and

- Pregnancy. (Must be reported as an SAE.)

Laboratory abnormalities are usually not recorded as adverse events; however, signs and/or symptoms that are associated with laboratory findings requiring study withdrawal, dose modification, or medical intervention (e.g., anemia requiring transfusions or hyperglycemia requiring treatment) or other abnormal assessments (e.g., ECG, radiographs, vital signs) must be recorded as adverse events if they meet the definition of an adverse event. In addition, laboratory abnormalities marked as clinically significant by the investigator should also be recorded as adverse events in the eCRF. The investigator will record the most severe grade of the clinically significant laboratory abnormality and will evaluate its relationship to the study drug and clinical condition if/when a clinically significant laboratory abnormality occurs.

The relationship to study drug therapy should be assessed using the following definitions:

Not Related: Evidence exists that the AE has an etiology other than the study drug (e.g., pre-existing condition, underlying disease, intercurrent illness, or concomitant medication). This includes events that are considered remotely or unlikely related to study drug.

Related: A temporal relationship exists between the event onset and administration of the study drug. It cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies. In the case of cessation or reduction of the dose, the event abates or resolves and reappears upon rechallenge. It should be emphasized that ineffective study drug treatment should not be considered as causally related in the context of AE reporting. This includes events that are considered possibly, probably, or definitely related to study drug.

All adverse events (including event name, grade, start/stop date and attribution) will be documented in the medical record and on the eCRF for this protocol.

The Investigator is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial.

## 9.3. Suspected Adverse Reaction (SAR) Definition

A SAR is an adverse event in which there is reasonable possibility that the study drug caused the adverse event as defined by 21 CFR 312.32. The Investigator is responsible for judging whether it is a reasonable possibility that the study drug caused the adverse event.

## 9.4. "Unexpected" Definition

An AE or SAR is to be considered unexpected if the event is not listed in the investigator brochure or is not listed in the severity or specificity observed.

## 9.5. "Serious" and "Life-Threatening" Definitions

An AE or SAR is to be considered serious if the Investigator or Sponsoring Company deems it as such and the event results in any of the following outcomes:

- Death;
- Life-threatening situation (subject is at immediate risk of death);
- Inpatient hospitalization or prolongation of an existing hospitalization (excluding those for study drug administration, protocol-related procedures, palliative or hospice care, or placement of an indwelling catheter, unless associated with other serious events);
- Persistent or significant disability/incapacity;
- Congenital anomaly/birth defect in the offspring of a subject who received study drug;

Other: Important medical events that may not result in death, be immediately life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are:

- Intensive treatment in an emergency room or at home for allergic bronchospasm;
- Blood dyscrasias or convulsions that do not result in hospitalization;
- Development of drug dependency or drug abuse.

An AE or SAR is to be considered life-threatening if the Investigator or Funding Company deems it as such and the event poses an immediate threat of death.

## 9.6. Serious Adverse Event (SAE) Definition

A serious adverse event is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/ birth defect

SAE will be reported to Celgene Corporation within twenty-four (24) hours of LCI becoming aware of the event or non-serious adverse drug reactions, as may be required. Any correspondence to the FDA related to adverse event reporting will be simultaneously copied to Celgene.

SAEs will be captured from the time the subject is enrolled through 30 days after the date of the last study drug administration. SAEs will be followed until clinical recovery

is complete and laboratory tests have returned to baseline, until progression has been stabilized, or until there has been acceptable resolution of the event. This may at times, cause the follow-up period for SAEs to be greater than 30 days. The above referenced 30-day time period applies even if the subject is taken off study and enrolled onto another protocol during this time period. Similarly, the Investigator is responsible for following the subject during the required follow-up period even if the subject lives elsewhere or has been released from his or her care and is being treated under another service at LCI.

**Laboratory abnormalities:**
Laboratory abnormalities that meet the definition of a serious adverse event will be recorded as such the eCRF and reported appropriately. The Investigator will record the most severe grade of the clinically significant laboratory abnormality and will evaluate its relationship to the study drug and clinical condition if/when a clinically significant laboratory abnormality occurs.

**Planned hospitalizations:**
Elective surgeries that have been planned prior to subject enrollment in the study or for conditions existing prior to study enrollment do not need to be captured as SAEs, unless complications occur or the conditions are worse that the subject's baseline. They should however be clearly documented in the eCRF.

Hospital admission for treatment required by the protocol need not be reported as an SAE, unless a complication results that fits the 21CFR 312.32 definition of a SAE.

**Development of New Cancers:**
Secondary malignancies are defined as *new* cancers, not transformations or progression of original disease.

**Secondary malignancies *during* *30 day time period after treatment discontinuation***
Any secondary malignancy diagnosed within 30 days of the last dose, regardless of attribution, must be reported as an SAE. The pathology report documenting the new malignancy should be retained in the subject's research chart and in the medical record.

**Secondary malignancies *after* *the 30 day time period after treatment discontinuation***
Any secondary malignancy diagnosed greater than 30 days after last day of study drug and thought to be possibly, probably or definitely related to drug must be reported as an SAE. The pathology report documenting the new malignancy should be attached.

**Deaths:**
**Deaths *during* *30 day time period after treatment discontinuation***
Any death, expected or unexpected, occurring within 30 days of the last dose of study drug, regardless of attribution, must be reported as an SAE.

**Deaths *after* *the 30 day time period after treatment discontinuation***
Deaths occurring greater than 30 days after last day of study drug and thought to be possibly, probably or definitely related to drug must be reported within 24 hours of knowledge of the event.

**Pregnancies:**
Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is in treatment, or within 28 days of the subject's last dose of study drug, are considered immediately reportable events. ABRAXANE is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported as an SAE and reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form. The female subject may be referred to an obstetrician-gynecologist (not necessarily one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately 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 Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.**

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 ABRAXANE should also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

**Male Subjects:**
If a female partner of a male subject taking ABRAXANE becomes pregnant, the male subject taking ABRAXANE should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately. Male patients treated with nab-paclitaxel are advised not to father a child and up to 6 months after treatment.

**Overdose:**

Overdose, as defined for this protocol, refers to ABRAXANE dosing only. On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of ABRAXANE assigned to a given patient, regardless of any associated adverse events or sequelae.

PO-any amount over the protocol-specified dose

IV- 10% over the protocol-specified dose

SC-10% over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate. For nab-paclitaxel, an infusion completed in less than 25 minutes may increase Cmax by approximately 20%, therefore a nab-paclitaxel infusion completed in less than 25 minutes will meet the infusion rate criterion for an overdose. Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form.

**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

**Questionable events:**
Any suspected adverse reaction can and should be reported as an SAE if deemed appropriate by the Investigator.

All SAEs (including event name, grade, start/stop date and attribution) will be documented in the medical record and on the eCRF.

The Investigator is responsible for verifying and providing source documentation for all SAEs and assigning the attribution for each event for all subjects enrolled on the trial.

## 9.7. Safety Reporting to the Sponsor (Levine Cancer Institute)

All events occurring during the conduct of the study and meeting the definitions of a UAP or SAE will be reported promptly to the Sponsor, but no later than 2 business days from the time

the Investigator learns of the event. Applicable events must be reported via the CTMS with a notification to the Protocol Coordinator and Sponsor-Investigator.
Deviations involving the informed consent process or subject safety will be reported promptly to the Sponsor, but no later than 5 business days from the time the Investigator learns of the event. Applicable events must be reported via the CTMS with a notification to the Protocol Coordinator and Sponsor-Investigator.

## 9.8. Safety Reporting to the IRB

All events occurring during the conduct of a protocol and meeting the definition of an UAP or SAE will be reported to the IRB promptly, but no later than 2 weeks from the time the Investigator learns of the event.

Deviations involving the informed consent process or subject safety will be reported promptly to Chesapeake IRB but no later than two weeks from the time of identification of the deviation by the Investigator.

## 9.9. Safety Reporting to Celgene Corporation

Non-serious adverse events will be reported to Celgene bi-annually (or upon request by Celgene), in accordance with 21 CRF 312.64.

When the Investigator has determined that a SAE has occurred, the Investigator is responsible for providing information regarding the SAE to 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-004075**) and the institutional protocol number (**LCI-LUN-ABR-001**) 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.

Celgene Corporation
Global Drug Safety and Risk Management Connell
Corporate Park
300 Connell Drive Suite 6000
Berkeley Heights, NJ 07922
Fax number: 908-673-9115
Email: drugsafety@celgene.com

Deviations involving subject safety will be reported to Celgene promptly but no later than two weeks from the time of identification of the deviation by the Investigator.

Protocol deviations that are minor or administrative will be reported to Celgene bi-annually.

# 10. TREATMENT-RELATED ADVERSE EVENTS

Subjects will be closely monitored for treatment-related adverse events. Adverse event monitoring will occur on a continuous basis for the duration that subjects are on study therapy. In addition to the planned evaluations during follow-up visits, subjects will be instructed to call their physician to report any adverse events between visits.

## 10.1. Carboplatin

Anaphylactic reactions have occurred with carboplatin injections. Adequate medical supervision must be present and appropriate intervention must be readily available to diagnose and treat hypersensitivity reactions. Bone marrow suppression is the dose limiting toxicity, and is increased in subjects with impaired renal function. It is dose dependent. Thrombocytopenia with platelet counts below $50 \times 10^9$ cells/L occurs in 25% of subjects and neutropenia with granulocyte counts below $1.0 \times 10^9$ cells/L occurs in 16% of subjects. Anemia is cumulative and transfusions may be necessary in subjects receiving prolonged therapy. Cycles should not be repeated until neutrophils and platelet counts have recovered. Nausea, vomiting, and neurotoxicity are other common drug-related adverse events. Other common side effects of carboplatin include nausea, vomiting, appetite loss, hypokalemia, and hypomagnesemia.

## 10.2. ABRAXANE

The following adverse events have been described with ABRAXANE treatment: myelosuppression, nausea and vomiting, diarrhea, mucositis, infections, hypotension, abnormal ECG changes, cough, dyspnea, edema, sensory neuropathy, bilirubin/liver enzyme elevations, allergic reactions, alopecia, asthenia, arthralgia, and myalgia. During post marketing surveillance, rare cases of severe hypersensitivity reactions have occurred.

**Table 10.2.1: Frequency[a] of Important Treatment Emergent Adverse Events in the Randomized Study on a Q3W Schedule**

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

| | | |
|---|---|---|
| **Asthenia** | | |
| Any Symptoms | 47 | 39 |
| Severe Symptoms[f] | 8 | 3 |
| **Fluid Retention/Edema** | | |
| Any Symptoms | 10 | 8 |
| Severe Symptoms[f] | 0 | <1 |
| **Gastrointestinal** | | |
| Nausea | | |
| Any Symptoms | 30 | 22 |
| Severe Symptoms[f] | 3 | <1 |
| **Vomiting** | | |
| Any symptoms | 18 | 10 |
| Severe Symptoms[f] | 4 | 1 |
| **Diarrhea** | | |
| Any Symptoms | 27 | 15 |
| Severe Symptoms[f] | <1 | 1 |
| **Mucositis** | | |
| Any Symptoms | 7 | 6 |
| Severe Symptoms[f] | <1 | 0 |
| **Alopecia** | 90 | 94 |
| **Hepatic (Subjects with Normal Baseline)** | | |
| Bilirubin Elevations | 7 | 7 |
| Alkaline Phosphatase Elevations | 36 | 31 |
| AST (SGOT) Elevations | 39 | 32 |
| **Injection Site Reaction** | <1 | 1 |

[a] Based on worst grade
[b] ABRAXANE dose in mg/m$^2$/duration in minutes
[c] Paclitaxel injection dose in mg/m$^2$/duration in hours
[d] Paclitaxel-injection subjects received premedication
[e] Includes treatment-related events related to hypersensitivity (e.g., flushing, dyspnea, chest pain, hypotension) that began on a day of dosing
[f] Severe events are defined as at least grade 3 toxicity
[g] During study drug dosing

### 10.3. Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events

(CTCAE) version 4.0 will be utilized for AE reporting. All Levine Cancer Institute staff will have access to a copy of the CTCAE version 4.0.

Attribution of the AE:
Definite – The AE is clearly related to the study treatment.
Probable – The AE is likely related to the study treatment.
Possible – The AE may be related to the study treatment.
Unlikely – The AE is doubtfully related to the study treatment.
Unrelated – The AE is clearly NOT related to the study treatment.

# 11. DATA SAFETY AND MONITORING PLAN

## 11.1. Monitoring

This protocol will be monitored according to the processes in effect for all Levine Cancer Institute investigator- initiated studies and the protocol-specific monitoring plan, and will abide by standard operating procedures set forth by both the Carolinas Healthcare System Office of Clinical and Translational Research and the Levine Cancer Institute Clinical Trials Office. It is the responsibility of the Sponsor-Investigator to monitor the safety data for this study. The Sponsor-Investigator, Statistician, Protocol Coordinator, and other team members as needed will meet regularly to monitor subject consents, enrollment and retention, safety data for all subjects [including adverse events (AE's) for all grades and attributions, serious adverse events (SAE's)], study drug administration, and validity/integrity of the data. Documentation of these meetings will be kept with study records. SAEs will be reported to the Food and Drug Administration (FDA) and the IRB per their requirements. Major protocol deviations that result in a threat to subject safety or the integrity of the study will be reported to the FDA and IRB per their requirements. The Sponsor-Investigator will submit data to the LCI Data and Safety Monitoring Committee according to the overarching LCI Data and Safety Monitoring Plan.

## 11.2. Data Quality Assurance

This trial will be organized, conducted, and reported in compliance with the protocol, standard operating procedures (SOPs) of LCI and Carolinas Healthcare System Office of Clinical and Translational Research, the FDA, and other applicable regulations and guidelines (e.g. GCP).

Subjects will be monitored by LCI Research /Data Monitors per the study-specific monitoring plan and LCI/CHS SOPs for data quality. This monitoring will be done by comparing source documentation to the eCRFs. Any variation between the two data sets will be discussed with the Protocol Coordinator, Sponsor- Investigator and/or other study personnel as appropriate.

The trial database will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification will be generated and addressed as needed by appropriate study personnel. Only authorized personnel will make corrections to the database and all corrections will be documented in an electronic audit trail.

# 12. MEASUREMENT OF EFFECT

## 12.1. Antitumor Effect

Response and progression will be evaluated in this study using the revised response evaluation criteria in solid tumors (RECIST) guideline version 1.1.[16]

### 12.1.1. Definitions

Evaluable for toxicity: All subjects will be evaluable for toxicity from the time of their first treatment with ABRAXANE and carboplatin.

Evaluable for efficacy: Only subjects who have measurable disease present at baseline, have received at least one dose of study therapy, and have had their disease re-evaluated (either clinically or radiologically) will be considered evaluable for efficacy. These subjects will have their objective response classified according to the definitions stated below.

### 12.1.2. Disease Parameters

Target lesions: When more than one measurable lesion is present at baseline all lesions up to a maximum of five 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 longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. *Lymph nodes* merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geq$ 15 mm by CT scan or MRI. Only the *short* axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for

MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. All other pathological nodes (those with short axis ≥ 10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed. 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, then as noted above, only the *short* axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including pathological lymph nodes should be identified as *non-target lesions* and should also be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow).

### 12.1.3. Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment 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 is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment. The Sponsor-Investigator or designee will be responsible for performing tumor measurements. The tumor measurements will be recorded in the eCRF.

### 12.1.4. Response Criteria

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

Non-target lesion: Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).

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

Non-target lesion: Not applicable

Stable Disease (SD):
Target lesion: Neither sufficient shrinkage to qualify for a partial response, nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study.

Non-target lesion: Not applicable.

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

Non-target lesion: *Unequivocal progression* (as described in RECIST version 1.1) of existing non-target lesions. (*Note:* the appearance of one or more new lesions is also considered progression).

Non-Complete Response / Non-Progressive Disease:

Target lesion: Not applicable

Non-target lesion: Persistence of one or more non-target lesion(s).

**Table 12.1.1: Summary of RECIST**

| Target Lesions | Non-target Lesions | New Lesions | Overall Response | Best Response for this Category also requires |
|---|---|---|---|---|
| CR | CR | No | CR | Documented at least once ≥ 4 weeks from baseline |
| CR | Non-CR/Non-PD | No | PR | Documented at least once ≥ 4 weeks from baseline |
| PR | Non-PD | No | PR | |
| SD | Non-PD | No | SD | Documented at least once ≥ 4 weeks from baseline |
| PD | Any | Yes or No | PD | No prior SD, PR or CR |
| Any | PD* | Yes or No | PD | |
| Any | Any | Yes | PD | |

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

If nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), a measurement may still be reported on scans. The measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. This means that subjects with CR may not have a total sum of the diameters of 'zero'.

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is *not* a descriptor of an objective response: it is a reason for stopping study therapy. It is included as part of the criteria for determination of Progression Free Survival. The objective response status of such subjects is to be determined by evaluation of target and non-target disease.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

# 13. STATISTICAL DESIGN

## 13.1. Sample Size Determination

The primary objective of this study is to assess the efficacy in terms of overall tumor response of the combination of carboplatin with nab-paclitaxel in subjects with advanced squamous cell lung cancer. Subjects will receive six 3-week cycles

of treatment. The primary endpoint of this study is a binary variable determined for each patient indicating whether or not they achieved an overall tumor response (defined as either CR or PR).

A Bayesian design based on predictive probability will be implemented. This design allows for early stopping if data indicates that the treatment is ineffective. The stopping boundary is chosen by computing the predictive probability from observed data. Specifically, the trial will stop if the current data indicates that, by the end of the trial, it is highly unlikely the 6-cycle best response rate in treated subjects to be higher than 0.20. The specific description of the methodology is given below. Early treatment discontinuation due to unacceptable toxicity, PD (including clinical progression) or death will be considered as failures. Other subjects not meeting all of the criteria for being included in the efficacy population (Section 13.3) will be considered as in-evaluable and therefore will not contribute to the sample size of evaluable subjects.

The maximum number of evaluable subjects is N=45. The treatment outcomes will be monitored at cohorts of 15, 30 and 45 subjects. If X responses (CR or PR) have been observed in the first n subjects and Y represents possible number of responses in the next (N-n) subjects, the predictive probability (PP) of concluding a positive result by the end of the trial is defined as:

$$PP = \sum_{i=0}^{N-n} \{Prob(Y=i) \times [Prob\ (response\ rate > 0.20 \mid X, N, Y=i) > P_T]\}.$$

The trial will be stopped early if PP < PL, where PT and PL are the parameters to be determined to yield desirable operating characteristics. The assumption is that the number of subjects that achieve best response of CR or PR follows a binomial distribution with a probability of p, and p has a prior distribution of Beta (0.2, 0.8). In addition, the probability of accepting the new treatment be no larger than 0.10 when the true best response rate is 0.20. A search algorithm is implemented to find that PT =0.91 and PL =0.04 satisfy the constraint and at the same time minimize the expected sample size when the true best response rate is 0.20.

The following table lists the cumulative number of subjects (n) and the rejection region in the number of best responses of CR or PR in n subjects. The trial will be stopped and the treatment will be considered ineffective when the number of responses first falls into the rejection region.

**Table 13.1.1: Rejection Region**

| N | Rejection Region in Number of Responses (CR or PR) |
|---|---|
| 15 | 0 – 2 |
| 30 | 3 – 6 |
| 45 | 7-12 |

From a frequentist perspective, the statistical operating characteristics of the trial are given as follows. Assuming the true overall response rate is 0.20 under the null hypothesis (i.e. the trial is ineffective), then this design will provide 81% power to detect a difference of 0.15, or a true best response rate is 0.35 under the alternative hypothesis, assuming an alpha = 0.09 significance level. The probabilities of terminating the trial early assuming the true best response rate is 0.20 are 0.40 and 0.65 after Stage 1 and Stage 2, respectively.

To account for about 10% of enrolled patients not meeting the criteria to be included in the efficacy population, we will accrue about 50 subjects.

## 13.2. Analysis Endpoints

### 13.2.1. Primary Efficacy Endpoint

The primary endpoint is a binary variable determined for each patient indicating whether or not they achieved a CR or PR as defined in Section 12.1.4. As per RECIST 1.1, because overall response is the primary endpoint for this study, best responses of CR or PR must be confirmed by a subsequent radiologic assessment.

### 13.2.2. Secondary Efficacy Endpoints

**Table 13.2.1: Efficacy Endpoint Definitions**

| | |
|---|---|
| Disease control | Disease control is calculated for each subject indicating whether or not they achieved an overall response of stable disease or better. |
| Duration of response | For subjects who achieve a CR or PR, response duration will be measured from the first day of the response until the day on which progressive disease (PD) or death occurred. The censoring method will be the same as that described for PFS. |
| Duration of disease control | For subjects who achieve SD or better, duration of disease control will be measured from the treatment start date until the day on which progressive disease (PD) or death occurred. The censoring method will be the same as that described for PFS. |
| Progress-free survival (PFS) | PFS is defined as the duration of time from treatment start date to time of progression or death. Disease progression may be determined objectively as |

| | |
|---|---|
| | in Section 12.1.4 or subjectively as determined by the investigator. Evidence for subjective progressions must be documented in the medical records. For objective disease progression, the date of PD is the date of the radiologic assessment that identified RECIST-defined progressive disease. For subjective disease progression, the date of PD is the date that the clinician makes the determination of disease progression. If the subject died without documented disease progression, the date of progression will be the date of death. For surviving subjects who do not have objectively documented disease progression, PFS will be censored at the date of last radiologic assessment. For subjects who receive subsequent anti-cancer therapy prior to documented disease progression, PFS will be censored at the date of last radiologic assessment prior to the commencement of subsequent therapy. Subjects who experience an initial PFS event immediately following 2 or more consecutive missed assessments will be censored at the date of the last assessment prior to those missed assessments. For participants with only one missed assessment, the documented progressive disease status and assessment date will be used. |
| Overall survival (OS) | OS is defined as the duration of time from treatment start date to the date of death from any cause. Subjects who are alive or lost to follow-up at the time of the analysis will be censored at the last known date they were alive. |

### 13.2.3. Safety Endpoints

Safety endpoints will include data for treatment administration, adverse events (AEs), serious adverse events (SAEs), deaths during study treatment, and laboratory determinations. AEs and SAEs will be assessed according to CTCAE v4.0.

## 13.3. Analysis Populations

The efficacy population (or evaluable population) is defined as all subjects who have measurable disease present at baseline, have received at least one dose of study therapy, and have had their disease re-evaluated (either clinically or radiographically). The

efficacy population will be used to analyze the primary and secondary efficacy endpoints.

The safety population is defined as all subjects who have received at least one cycle of therapy and will be used to analyze the safety endpoints.

## 13.4. Timing of Analysis

The first interim futility analysis will occur after the overall response status has been determined for 15 evaluable patients, and then a second interim futility analysis will occur for 30 evaluable patients, given that the study is not stopped after Stage 1 for futility. The primary analysis will be conducted after the overall response has been determined for all 45 evaluable patients, given the study is not stopped after Stage 2 futility analyses. An updated analysis will be conducted after the overall PFS censoring rate reaches 30% or after all surviving patients have at least one year of follow up. A final analysis will be conducted after the overall survival censoring rate reaches 30% or after all surviving patients have at least 3 years of follow up.

## 13.5. Analysis Plan

For the purposes of the primary analysis, the frequency and proportion of responders (those who achieve CR or PR) will be calculated after the best overall response has been determined for all patients enrolled in the efficacy population. A corresponding 95% confidence interval will be estimated using the Clopper Pearson method. Hypothesis testing will be done using the rejection regions described in Section 13.1, testing the null hypothesis that the ORR is less than 20%. Given the study is not stopped early for futility with the interim analyses at 15 and 30 subjects, if there are at least 13 responders in 45 evaluable subjects, the null hypothesis can be rejected.
For the purposes of the secondary analyses, the frequency and proportion of subjects achieving disease control (SD, PR, or CR) will also be calculated along with corresponding 95% Clopper Pearson interval. For both best response rate, and disease control rate, the correlation with baseline subject and disease characteristics and biomarkers will be evaluated using logistic regression.
Time-to-event variables will be analyzed using survival analysis methods. Survival rates will be estimated using Kaplan-Meier techniques. The correlation with baseline subject and disease characteristics, and biomarkers will be assessed using Cox multiple regression models.
The logistic regression and Cox proportional hazards models described above will involve univariate models to identify individual predictive markers and multivariate models (including backward elimination and forward selection) to identify independent predictive markers.
Biomarkers in both tissue and blood will be analyzed. Correlation among biomarkers in tissue, blood and between tissue and blood will be assessed. The association among various continuous and discrete biomarkers will be assessed first by the exploratory data

analysis using graphical techniques such as the scatter plot matrix, box plots, and BliP plot[17]. Correlation among continuous biomarkers will be examined by Pearson or Spearman rank correlation coefficients. The association on discrete biomarkers will be tested by Fisher's exact test.

# 14. DRUG DISTRIBUTION

## 14.1. Supply and Dispensing

ABRAXANE and carboplatin are commercially available and will be locally sourced, prepared, and dispensed per institutional standards. Storage and handling will comply with the respective package inserts.

## 14.2. Drug Accountability

All study medications will be stored at the investigational site in accordance with Good Clinical Practice (GCP) and Good Manufacturing Practices (GMP) requirements and will be inaccessible to unauthorized personnel.
An adequate record of the dispensing of study drug, and the return of all unused study drugs must be kept in the form of a Drug Accountability Form. The Sponsor-Investigator, or responsible party designated by the Sponsor-Investigator, will maintain a careful record of the inventory using the Drug Accountability Form.

# 15. STUDY COMPLETION

## 15.1. Completion

The study will be considered complete when one or more of the following conditions is met:

- All subjects have completed all study visits including follow-up.
- All subjects have discontinued from the study.
- The IRB, Celgene Corporation, LCI DSMC, or Sponsor-Investigator discontinues the study because of safety considerations.
- The Sponsor-Investigator defines an administrative or clinical cut-off date.

## 15.2. Termination

The study will be terminated when one or more of the following conditions occur:

- If the risk-benefit ratio becomes unacceptable owing to, for example:
- Safety findings from this study (e.g. SAEs)
- Results of any interim analysis
- Results of parallel clinical studies

- Results of parallel animal studies (e.g. toxicity, teratogenicity, carcinogenicity, or reproduction toxicity)
- If the study conduct (e.g. recruitment rate; dropout rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame

The Sponsor-Investigator has the right to close the trial at any time. For any of the above closures, the following apply:

- Closures should occur only after consultation between involved parties.
- All affected institutions must be informed as applicable according to local law.
- In case of a partial study closure, ongoing subjects, including those in follow-up, must be cared for in an ethical manner.

Details for individual subject withdrawals can be found in Section 5.3.

## 16. RETENTION OF RECORDS

Documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence should be retained for at least 2 years after the investigation is completed.

## 17. ETHICAL AND LEGAL ISSUES

### 17.1. Ethical and Legal Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Investigator abide by Good Clinical Practice (GCP) guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate agencies (e.g. DSMC, IRB) will be obtained for all participating centers before start of the study, according to GCP, local laws, regulations and organizations.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the Investigators may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by the Sponsor- Investigator without discussion and agreement by Celgene. However, the Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior approval from applicable agencies. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the appropriate agencies. Any deviations from the

protocol must be explained and documented by the Investigator.
The Sponsor-Investigator is responsible for the conduct of the clinical trial at the sites in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki.
The Sponsor-Investigator is responsible for personally overseeing the treatment of all study subjects. The Sponsor-Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all applicable regulations and guidelines regarding clinical trials both during and after study completion.
The Sponsor-Investigator will be responsible for assuring that all the required data will be collected and properly documented.

### 17.2. Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

## 18. PUBLICATION POLICY

The Sponsor-Investigator must send a draft manuscript of the publication or abstract to Celgene Corporation prior to submission of the final version for publication or presentation. All relevant aspects regarding data reporting and publication will be part of the contract between Celgene Corporation and the Sponsor-Investigator.

The Sponsor-Investigator will ensure that the information regarding the study be publicly available on the internet at www.clinicaltrials.gov.

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# APPENDICES

## APPENDIX A: Performance Status Criteria

| ECOG Performance Status Scale | |
|---|---|
| Grade | Descriptions |
| 0 | Normal activity. Fully active, able to carry on all pre-disease performance without restriction. |
| 1 | Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work). |
| 2 | In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. |
| 3 | In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. |
| 5 | Dead. |

## APPENDIX B: Forms Submission Schedule

*Complete all electronic case report forms in the CTMS within 10 business days of the visit.*

| Required Forms | Baseline | During Treatment | End of Treatment | Follow-Up |
|---|---|---|---|---|
| LCI-LUN-ABR-001: Registration/On Study Form[g] | X | | | |
| LCI-LUN-ABR-001: Medical History eCRF | X | | | |
| Template: Prior Treatment (All) eCRF | X | | | |
| LCI-LUN-ABR-001: Adverse Events eCRF | X | X[a] | X | |
| Template: Concomitant Medications eCRF | X | X[a] | X | |
| Template: Radiology eCRF[f] | X | X | X | X |
| LCI-LUN-ABR-001: Office Visit eCRF | | X[a] | | |
| LCI-LUN-ABR-001: Off Treatment eCRF | | | X[b] | |
| Template: Subsequent Treatment (All) eCRF | | | | X[e] |
| Template: Follow-Up eCRF | | | | X[c] |
| Template: Death eCRF[d] | | | | |

[a] Every 3 weeks, ± 7 days.
[b] Within 30 days after last dose of study drug.
[c] Every 6 months until death or lost to follow-up.
[d] At death, regardless of time point.
[e] When a subsequent anti-cancer therapy is administered.
[f] Every 6 weeks during treatment, and whenever a scan is done thereafter.
[g] See Appendix C for hard copy form.

LCI-LUN-ABR-001

## Registration/On Study Form

*Instructions: Complete this form after the patient signs consent and file it in the research chart. Ensure the subject is registered in the CTMS with the same information.*

1) Subject's Last Name: _____

2) Subject's First Name: _____

3) MRN: _____

4) Enrolling Physician: _____

5) Enrolling Site Name: _____

6) Date Subject Signed Consent: _____
MM DD YYYY

7) Date Subject Found to be Eligible: _____
MM DD YYYY

8) On Study Date (Enrollment Date): _____
MM DD YYYY

**On Study Date (Enrollment Date) = Treatment Start Date*

9) Study ID # (Assigned by Protocol Coordinator): _____

_____

Name of person completing form (please print)

_____

Signature of person completing form Date of signature

V1: 7/9/2014
Registration/On Study Form