PHASE II STUDY OF ABRAXANE AND GEMCITABINE IN PATIENTS WITH ADVANCED ADENOCARCINOMA NON-SMALL CELL LUNG CANCER PROGRESSING AFTER FIRST-LINE PLATINUM-BASED CHEMOTHERAPY

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List of Abbreviations

NSCLC- non-small cell lung cancer

Study Summary

Title	Phase II study of albumin-bound paclitaxel and gemcitabine in patients with advanced adenocarcinoma non-small cell lung cancer progressing after first-line platinum-based chemotherapy
Short Title	Phase II albumin-bound paclitaxel and gemcitabine
Protocol Number	UPCC 21514
Phase	Phase II
Methodology	Single arm, open label
Study Duration	2 - 2.5 years
Study Center(s)	Single-center
Objectives	The primary objective is overall response rate. Secondary objectives include clinical benefit, overall survival, and progression-free survival.
Number of Subjects	37 (12 in stage 1 and 25 in stage 2, in an optimal Simon 2-stage design)
Diagnosis and Main Inclusion Criteria	Patients with stage IV or recurrent adenocarcinoma of the lung, age 18 or older, with an ECOG performance status of 0 to 1, who have progressive disease on or after a first-line, platinum-based chemotherapy
Study Product, Dose, Route, Regimen	albumin-bound paclitaxel (Abraxane) 100 mg/m^2 intravenously days 1 and 8 of a 21 day cycle Gemcitabine 1000 mg/m^2 intravenously, days 1 and 8 of a 21 day cycle
Duration of administration	Drugs will be administered until documented progression of disease or intolerable toxicity
Reference therapy	The study product is being compared to historical controls of second-line treatment of non-small cell lung cancer.
Statistical Methodology	This optimal Simon 2-stage phase II trial will reject the albumin-bound paclitaxel and gemcitabine combination if the objective response rate is <5% and will accept the combination if the objective response rate is >20%, with 10% type I error rate and 90% power. Objective response rate will be examined by *K-ras* mutation status. Median PFS and OS will be estimated by Kaplan-Meier method.

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

Three agents are currently FDA approved for use for non-small cell lung (NSCLC) cancer that has progressed following platinum-based chemotherapy: docetaxel, pemetrexed or erlotinib. However, response rates to second-line treatment are consistently low, and survival benefits remain modest. Better therapeutic strategies are needed. One option to consider is a combination of albumin-bound paclitaxel and gemcitabine.

Platinum-based doublet chemotherapy in the first-line treatment of advanced non-small cell lung cancer has consistently proved superior to single agent chemotherapy in terms of improving overall survival, even in elderly and poor performance status patients [1-3]. While single-agent treatment has shown a survival advantage over best supportive care in the second-line setting [4, 5], outcomes and response rates for single agent therapies remain poor, with response rates for the three approved agents of less than 10% in randomized clinical trials. Cytotoxic doublet therapy in the second-line setting can improve response rates and progression free survival [6], but it has yet to improve overall survival relative to single-agent treatment.

The taxanes are consistently active agents in the treatment of NSCLC and are approved for use with platinum compounds in the first-line treatment of non-small cell lung cancer (paclitaxel, docetaxel, and albumin-bound paclitaxel). In addition, docetaxel is an approved second-line agent with a demonstrated survival benefit. Gemcitabine shows efficacy in the treatment of NSCLC [7, 8] and is approved for use with platinum in the first-line setting, though it lacks formal approval in second-line treatment. Albumin-bound paclitaxel plus gemcitabine is a well-tolerated doublet with important clinical activity in patients with advanced pancreatic cancer [9]. In a preclinical therapeutic study, the combination of albumin-bound paclitaxel and gemcitabine was shown in a mouse model of pancreatic ductal adenocarcinoma to overcome the resistance mechanism of suboptimal intra-tumoral concentrations of gemcitabine, leading to tumor regression [10]. This suggests one possible mechanism for the notable anti-tumor activity of the drug combination. In a pivotal phase III trial, this combination proved superior to single agent gemcitabine in patients with advanced pancreatic cancer with a statistically significant improvement in overall response rate, progression free survival, and overall survival [11].

In addition, in patients with NSCLC, the combination of gemcitabine and docetaxel has previously been shown to have activity in the second-line setting after progression on platinum, with median overall survival exceeding one year [12]. Although albumin-bound paclitaxel has not been formally compared to docetaxel in non-small cell lung cancer, weekly albumin-bound paclitaxel in combination with carboplatin every three weeks yielded a higher response rate compared to standard paclitaxel administered every three weeks in combination with carboplatin [13].

In summary, single chemotherapy agents have remained the standard of care for NSCLC in the second line setting. However, given albumin-bound paclitaxel and gemcitabine's potential ability to overcome important chemotherapy resistance mechanisms, this combination may be more effective than doublets that have been studied in the past. In addition, this combination has been notably well tolerated even in patients with advanced cancer. Therefore, we propose a phase II trial of albumin-bound paclitaxel and gemcitabine in patients with advanced NSCLC progressing after first-line platinum-based chemotherapy. Because there are now treatment distinctions for non-small cell lung cancer patients based on histology, we are limiting our study population to those with adenocarcinoma. The majority of patients with squamous cell histology receive either a taxane or gemcitabine in combination with platinum in the first-

line setting. However, a significant percentage of patients with adenocarcinoma receive pemetrexed with platinum in the first-line setting and are therefore often naïve to both the taxanes and gemcitabine in the second-line setting and are therefore more likely to benefit from the combination.

1.2 Investigational Agent

Albumin-bound paclitaxel (Abraxane, Celgene) 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 [14]. A protein specifically secreted by the tumor (SPARC) binds albumin, allowing release of the hydrophobic drug to the tumor cell membrane [15]. 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.

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.

Gemctabine (GEMZAR, Eli Lilly) is a nucleoside metabolic inhibitor indicated in combination with cisplatin for the treatment of non-small cell lung cancer and as a single agent for the treatment of pancreatic cancer. Gemzar (gemcitabine for injection USP) is a white to off-white lyophilized powder available in sterile single-use vials containing 200 mg or 1 g gemcitabine. Adding 5 mL to the 200-mg vial or 25 mL to the 1-g vial yields a Gemzar concentration of 38 mg/mL. Complete withdrawal of the vial contents will provide 200 mg or 1 g of Gemzar. Prior to administration the appropriate amount of drug must be diluted with 0.9% Sodium Chloride Injection. Final concentrations may be as low as 0.1 mg/mL.

Reconstituted gemcitabine is a clear, colorless to light straw-colored solution. Inspection visually prior to administration allows for discarding for particulate matter or discoloration. Gemzar solutions are stable for 24 hours at controlled room temperature of 20° to 25°C (68° to 77°F) and should not be refrigerated as crystallization can occur. No incompatibilities have been observed with infusion bottles or polyvinyl chloride bags and administration sets.

The combination of gemcitabine and albumin-bound paclitaxel has been administered to patients with advanced pancreatic cancer in phase 1, 2 and 3 clinical trials.

1.3 Preclinical Data

Preclinical studies comparing Abraxane to Taxol® (paclitaxel Cremophor® EL solvent-based, BMS) demonstrated lower toxicities, with an 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 [16].

In a preclinical therapeutic study, the combination of Abraxane and gemcitabine was shown in a mouse model of pancreatic ductal adenocarcinoma to overcome the resistance mechanism of suboptimal intra-tumoral concentrations of gemcitabine, leading to tumor regression [10]. This suggests one possible mechanism for the notable anti-tumor activity of the drug combination.

1.4 Clinical Data to Date

Both albumin-bound paclitaxel and gemcitabine are, in combination with a platinum agent, approved for use in the first-line treatment of advanced non-small cell lung cancer based upon established efficacy and acceptable tolerability. In a direct comparison of carboplatin and paclitaxel versus carboplatin and albumin-bound paclitaxel in the first-line treatment of advanced non-small cell lung cancer, the nab-paclitaxel combination led to an improved response rate and decreased neuropathy and myalgias/arthralgias [13]. The taxanes are a class of cytotoxic agents that function by inhibiting microtubule function. Three taxanes (paclitaxel, docetaxel, and albumin-bound paclitaxel) have demonstrated efficacy in non-small cell lung cancer and are approved for use with platinum in the first-line setting. Docetaxel is approved in the second-line setting based upon demonstrated survival benefit relative to best supportive care.

The combination of two effective agents in the first-line treatment of non-small cell lung cancer (platinum in combination with a taxane, gemcitabine, vinorelbine, or pemetrexed) has established superiority over single-agent treatments [1-3, 17, 18]. However, in the second-line setting, no combination has yet demonstrated clear superiority over single agent treatment. Because both albumin-bound paclitaxel and gemcitabine have activity in non-small cell lung cancer, pre-clinical evidence of synergy, and established tolerability when used in combination, this study proposes to use the combination in the second-line setting.

The most relevant clinical data for this approach are studies evaluating the efficacy of gemcitabine and docetaxel in the second-line treatment of NSCLC [12] as well as studies of gemcitabine and albumin-bound paclitaxel in patients with advanced pancreatic cancer discussed previously [9, 11].

1.5 Dose Rationale and Risk/Benefits

The maximum tolerated dose of Abraxane plus gemcitabine in patients with advanced pancreatic cancer is 125 mg/m^2 of Abraxane plus 1,000 mg/m^2 of gemcitabine once a week for 3 weeks, every 28 days [9]. The doses were tolerable in this population of patients with an advanced solid malignancy. The same dosing was used in the MPACT (Metastatic Pancreatic Adenocarcinoma Clinical Trial) study [11]. Abraxane has been used safely and effectively at 100 mg/m^2 weekly in combination with carboplatin in non-small cell lung cancer patients with advanced disease [13].

Gemcitabine has been safely used at 1000 mg/m^2 on days 1, 8, and 15 of a 28 day cycle in patients with metastatic non-small cell lung cancer as a single agent [19], and when combined with agents such as cisplatin [20].

Given this data, patients will receive Abraxane at 100 mg/m^2 intravenously plus gemcitabine at 1000 mg/m^2 intravenously on days 1 and 8 of each cycle. One cycle will be defined as 3 weeks. The risks to subjects are reasonable in relation to the anticipated benefits and also the knowledge that might reasonably be expected from the results given that this combination has been notably well tolerated in patients with very advanced cancer, and also given the poor response rates to second line treatment of advanced NSCLC.

2 Study Objectives

Primary Objective
To assess the overall response rate in subjects treated with Abraxane and gemcitabine as measured by RECIST 1.1 criteria.

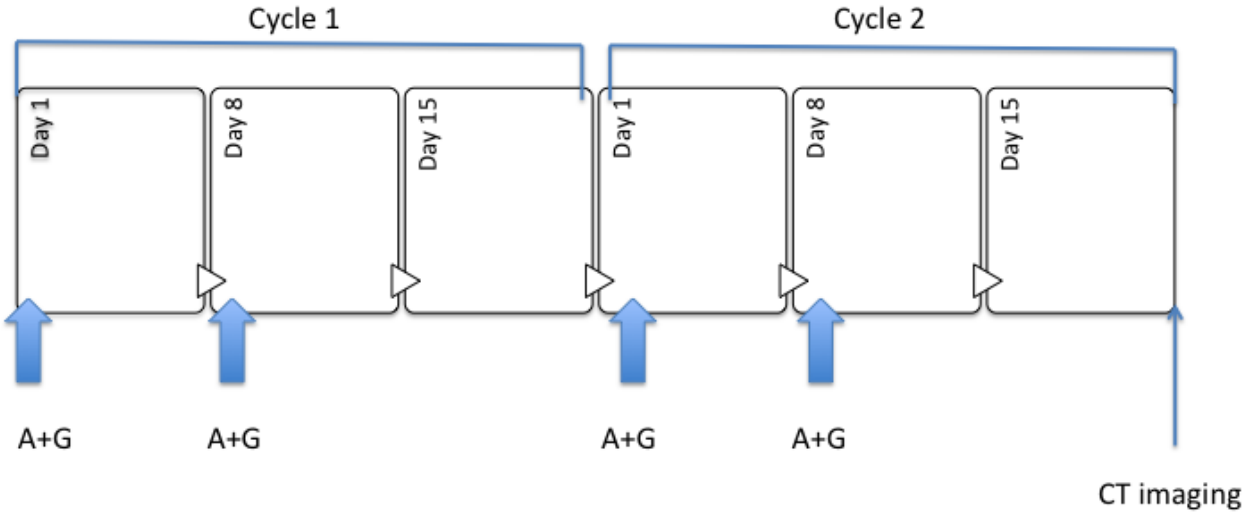
Secondary Objective
To assess progression-free survival, disease control rate (complete response, partial response or stable disease), and overall survival in subjects treated with Abraxane and gemcitabine.

3 Study Design

3.1 General Design

- The design of this study is a phase II non-randomized, single-arm, and single institution study.

Figure 1: Schema of drug schedule.



- Treatment duration: Subjects with remain on the study drugs until they have documented progressive disease or intolerable side effects. Subjects will be followed for progression-free and overall survival following completion of therapy.

3.2 Primary Study Endpoints

The primary endpoint is overall response rate, which is the percentage of patients with a partial response or complete response recorded from the start of the treatment until disease progression/recurrence by RECIST 1.1 criteria.

3.3 Secondary Study Endpoints

Secondary endpoints include the following:
1. Progression-free survival: measures the length of time from the first day of therapy until progressive disease, death from any cause, or last patient contact.
2. Disease control rate: measures the percentage of patients with a partial response, a complete response, or stable disease during the study.
3. Overall survival: measures the length of time from the first day of therapy to death from any cause or last patient contact.

3.4 Primary Safety Endpoints

The safety and tolerability of Abraxane and gemcitabine in patients with adenocarcinoma NSCLC will be evaluated. Clinical assessment and laboratory evaluation of Adverse Events and Dose Limiting Toxicities will be done according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.02 of the National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP).

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

1. Histologic or cytologic diagnosis of adenocarcinoma non-small cell lung cancer
2. Stage IV non-small cell lung cancer or recurrent disease which cannot be approached with curative intent.
3. First-line treatment with a standard platinum doublet chemotherapy regimen (carboplatin or cisplatin at standard dosing plus one of the following drugs at standard dosing: paclitaxel, docetaxel, vinblastine, vinorelbine, pemetrexed, or etoposide). Patients who received platinum-based chemotherapy for localized lung cancer (either adjuvant chemotherapy following surgery or chemotherapy given in conjunction with definitive radiation) are eligible if their cancer has recurred within 6 months of platinum-based chemotherapy.
4. Must have recovered from toxic effects of prior chemotherapy
5. ECOG performance status of 0-1
6. Life expectancy of at least 12 weeks
7. Age 18 or greater
8. 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 as > 20 mm with conventional techniques or > 10 mm with spiral CT scanning).
9. Patients with prior malignancies are allowed, provided they have been treated with curative intent and have no evidence of active disease.
10. Patients must be capable of giving informed consent and be willing and able to comply with scheduled visits, treatment plan and laboratory testing.
11. Bilirubin $\leq$ 1.5 mg/dL
12. Patients must have adequate liver function: AST and ALT $\leq$ 2.5 X upper limit of normal, alkaline phosphatase $\leq$ 2.5 X upper limit of normal, unless bone metastasis is present in the absence of liver metastasis
13. Patients must have adequate bone marrow function: Platelets >100,000 cells/mm3, Hemoglobin > 9.0g/dL and ANC $\geq$ 1,500 cells/mm^3
14. Patients must have adequate renal function: creatinine $\leq$1.5 mg/dL
15. Women of childbearing potential and sexually active males must use an effective contraception method during treatment and for three months after completing treatment
16. Negative serum β-hCG pregnancy test at screening for patients of childbearing potential.
17. Patients must have < Grade 2 pre-existing peripheral neuropathy (per CTCAE)

4.2 Exclusion Criteria

1. Patients with common activating EGFR (deletions in exon 19 and L858R mutation in exon 21) or EML4-ALK mutations
2. Patients previously treated with gemcitabine or Abraxane for metastatic or recurrent disease
3. Uncontrolled intercurrent illness including, but not limited to: uncontrolled ongoing infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
4. Known HIV or Hepatitis C
5. Untreated central nervous system metastases. Patients are eligible if they are clinically stable, off all steroids after cranial irradiation (whole brain radiation therapy, focal radiation therapy, stereotactic radio surgery) ending at least 2 weeks prior to enrollment, or after surgical resection performed at least 2 weeks prior to enrollment.
6. Concurrent treatment with other anticancer therapy, including other chemotherapy, immunotherapy, hormonal therapy, radiotherapy, chemo-embolization, targeted therapy, or an investigational agent
7. Pregnant or breast-feeding patients, as chemotherapy is thought to present substantial risk to the fetus/infant. Men and women of reproductive potential may not participate in this study unless they have agreed to use an effective contraceptive method while in this study. (Postmenopausal woman must have been amenorrheic for at least 12 months to be considered of non-childbearing potential). Patients must agree to continue contraception for 3 months from the date of the last study drug administration

4.3 Subject Recruitment and Screening

Subjects will be recruited for this study from the clinical practices of the Abramson Cancer Center at the University of Pennsylvania. Subjects will be required to give written informed consent to participate in the study before any screening tests or evaluations are conducted that are not part of standard care. Screening laboratories will include a complete blood count and serum comprehensive metabolic panel.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Subjects who do not complete the study protocol will be considered to have prematurely discontinued the study. The reasons for premature discontinuation (for example, voluntary withdrawal, toxicity, death) must be recorded on the case report form (CRF). Final study evaluations will be completed at the time of discontinuation. Reasons for withdrawal include, but are not limited to, the following:

1. Inter-current illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree or require discontinuation of study drugs;
2. Unacceptable toxicity: Patients will be followed until resolution or stabilization;
3. Disease progression;
4. Withdrawal of patient consent;
5. Treatment delay greater than four weeks for any toxicity
6. Non- compliance with study procedures that cannot be resolved;
7. Major protocol violations, including, but not limited to:
    1. failure to meet inclusion/exclusion criteria;
    2. failure to complete evaluations as required by protocol;

3. use of concomitant therapies other than specified above.

The reason(s) for withdrawal should be noted in the case report form and in the patient's medical record. Standard supportive therapy should be maintained for subjects withdrawn from active treatment. Long-term follow-up data, including survival and progression data, will be collected.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Patients taken off study due to toxicity will be followed until resolution or stabilization. All patients will be followed for progression-free and overall survival data.

5 Study Drug

5.1 Description

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.

Gemctabine (GEMZAR, Eli Lilly) is a nucleoside metabolic inhibitor indicated in combination with cisplatin for the treatment of non-small cell lung cancer and as a single agent for the treatment of pancreatic cancer. Gemzar (gemcitabine for injection USP) is a white to off-white lyophilized powder available in sterile single-use vials containing 200 mg or 1 g gemcitabine. Adding 5 mL to the 200-mg vial or 25 mL to the 1-g vial yields a Gemzar concentration of 38 mg/mL. Complete withdrawal of the vial contents will provide 200 mg or 1 g of Gemzar. Prior to administration the appropriate amount of drug must be diluted with 0.9% Sodium Chloride Injection. Final concentrations may be as low as 0.1 mg/mL.

5.2 Treatment Regimen

Patients will receive Abraxane at 100 mg/m^2 intravenously plus gemcitabine at 1000 mg/m^2 intravenously on days 1 and 8 of each 21 day cycle. One cycle will be defined as 3 weeks.

Dose Modifications/Reductions

Dose level reductions, as referenced in Tables 2 and 3, are provided in Table 1.

Table 1: Dose level reductions

Dose level	Abraxane (mg/m^2)	Gemcitabine (mg/m^2)
Full dose	100	1000
1st dose reduction	75	800
2nd dose reduction	Discontinue	600
If additional dose reduction required	Discontinue	Discontinue

Recommended dose modifications for neutropenia and thrombocytopenia are provided in Table 2.

Table 2: Dose Recommendation and Modifications for Neutropenia and/or Thrombocytopenia at the Start of a Cycle or within a Cycle

Cycle day	ANC (cells/mm^3)		Platelet Count (cells/mm^3)	Abraxane/Gemcitabine
Day 1	<1500	OR	<100,000	Delay dose until recovery
Day 8	500 to <1000	OR	50,000 to < 75,000	Reduce 1 dose level
	<500	OR	<50,000	Withhold dose

* If patient counts recover and at the discretion of the investigator Abraxane can be restarted at the lowest dose on Day 1 of the next cycle.

Abbreviations: ANC = Absolute Neutrophil Count
Recommended dose modifications for other adverse drug reactions are provided in Table 3.

Table 3: Dose Modifications for Other Adverse Drug Reactions

Adverse Drug Reaction	Abraxane	Gemcitabine
Febrile Neutropenia: Grade 3 or 4	Withhold until fever resolves and ANC ≥ 1500; resume at next lower dose level	
Peripheral Neuropathy: Grade 3 or 4	Withhold until improves to ≤ Grade 1; resume at next lower dose level	No dose reduction
Cutaneous Toxicity: Grade 3 or 4	Reduce to next lower dose level; discontinue treatment if toxicity persists	
Gastrointestinal Toxicity: Grade 3 mucositis or diarrhea	Withhold until improves to ≤ Grade 1; resume at next lower dose level	

Abraxane and gemcitabine dosing should not be administered at the start of each cycle until the absolute neutrophil count returns to $\geq 1.5 \times 10^9$ cells/L and the platelet count returns to $>100 \times 10^9$ cells/L. If the ANC and platelets are not adequate for treatment on Day 8, the dose will be omitted and the total cycle length remains the same.

Administration of Study Drug to Patients with Abnormal Hepatic Function

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

Hypersensitivity Reactions

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

Other Toxicities

If toxicities are ≥ grade 3, except for anemia, treatment should be withheld until resolution to ≤ grade 1 or baseline if baseline was greater than grade 1, then reinstituted, if medically appropriate, at the next lower dose level (see Table 2).

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 and G-CSF may be administered at the discretion of the investigator, consistent with institutional guidelines.

5.3 Method for Assigning Subjects to Treatment Groups

This trial is not randomized.

5.4 Preparation and Administration of Study Drugs

Abraxane
A research supply of Abraxane will be supplied by Celgene. It will be shipped, stored and dispensed from the Outpatient Clinic Pharmacy in the Perelman Center for Advanced Medicine (2nd floor, West Pavilion) of the Hospital of the University of Pennsylvania as well as to the infusion center of Penn Presbyterian for patients enrolled at that site. The drug preparation will be done in the pharmacy.

Study Medication Administration
Abraxane is injected into a vein (intravenous (I.V.) infusion) over 30 minutes. The use of an in-line liter is not recommended. Abraxane will be administered per institutional guidelines

Reconstitution and use of Abraxane

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

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

   Round up the number of vials to be reconstituted to the next higher whole number when a fractional number of vials is obtained by the above formula (eg, if the total number of vials = 4.05 or 4.5, then 5 vials would be reconstituted).
4. Using sterile technique, prepare the vials for reconstitution.
5. Swab the rubber stoppers with alcohol.
6. Aseptically, reconstitute each Abraxane vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP.
   - **Slowly** inject the 20 mL of 0.9% Sodium Chloride Injection, USP, over a minimum of **1 minute**, using the sterile syringe directing the solution flow onto the **inside wall** of the vial.
   - **DO NOT INJECT** the 0.9% Sodium Chloride Injection, USP solution directly onto the lyophilized cake as this will result in foaming.
   - Once the injection is complete, allow the vial to sit for a **minimum of 5 (five) minutes** to ensure proper wetting of the lyophilized cake/powder.

- **Gently** swirl and/or invert the vial **slowly** for at least **2 minutes** until complete dissolution of any cake/powder occurs. Avoid generation of foam. Rapid agitation or shaking will result in foaming.
- If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides.
- Each ml of reconstituted product will contain 5 mg of paclitaxel.

7. Calculate the exact total dosing volume of 5 mg/ml suspension required for the patient:
   - **Dosing volume (ml) = Total dose (mg) / 5 (mg/ml)**
8. The reconstituted suspension should be milky and homogeneous without visible particulates. If particulates or settling are visible, the vial should be **gently** inverted again to ensure complete resuspension prior to use. Discard the reconstituted suspension if precipitates are observed.
9. Once the exact volume of reconstituted Abraxane has been withdrawn from the vials, discard any excess solution left over in accordance with standard operating procedures.
10. Further dilution is not necessary. Inject the calculated dosing volume of reconstituted Abraxane suspension into an empty sterile, standard PVC IV bag using an injection port. Inject perpendicularly into the center of the injection port to avoid dislodging plastic material into the IV bag.
11. Administer the calculated dosing volume of reconstituted Abraxane suspension by IV infusion over 30 minutes. The use of in-line filters is not recommended because the reconstituted solution may clog the filter.

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

Abraxane Premedication
Patients do not require premedication prior to Abraxane administration, as hypersensitivity reactions are rare.

Although the solubilizing agents Cremophor® EL and Tween® 80 have long been implicated in adverse events including hypersensitivity reactions due to their detergent-like nature and known ability to induce histamine release [21], 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.

Gemcitabine
Gemcitabine will be prepared and administered per institutional guidelines. Gemcitabine wil be obtained commercially.

5.5 Subject Compliance Monitoring

The study team will track subject compliance with the treatment regimen at each visit and note the dose, date, and time of study medication administration on the case report form. If there are any significant irregularities in compliance (in the opinion of the investigator), the subject should be withdrawn from the study.

5.6 Prior and Concomitant Therapy

A reasonable effort will be made to document any medications the subject received within 30 days prior to Day 1. Any medication taken within 7 days of study medication administration must be recorded in the CRF as a prior medication. All concomitant medications taken during the study will be recorded in the CRF with indication, dose information, including any changes in dose, as well as start and stop dates and frequency of administration. The minimum requirement is that drug name, dose, and the dates of administration are to be recorded.

Concomitant Therapy: Growth Factor
Erythropoiesis-stimulating agents (ESAs) are allowed for anemia during the study as per accepted standards. G-CSF is allowed during the study for subjects with severe neutropenia and recurrent infections.

Any change in dosage of any concomitant medication (change in dose or frequency) MUST be recorded in the eCRF, to include: drug name, dose, frequency of administration, start and stop dates and indication.

5.7 Packaging

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

Standard, commercially-availablegemcitabine will be used.

5.8 Blinding of Study Drug

The drugs will not be blinded.

5.9 Receiving, Storage, Dispensing and Return of Abraxane

5.9.1 Receipt of Drug Supplies

Upon receipt of the of the study treatment supplies, an inventory must be performed and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files. The investigator must notify Celgene of any damaged or unusable study treatments that were supplied to the investigator's site.

Drug Distribution and Destruction

Supplier
Celgene Corporation
86 Morris Avenue
Summit, NJ 07901

Industry Contact:
Norma Powers
Director, Medical Operations
Celgene Corporation
86 Morris Avenue
Summit, NJ 07901
Mobile: 267-337-2720

Fax: 908-673-2779
Email: npowers@celgene.com

Drug Distribution
Abraxane® will be distributed by Celgene Corporation. No supplies will be shipped to any site until regulatory approval has been obtained. Investigational sites will be supplied with Abraxane® upon identification and screening of a potential trial subject.
Upon identification of a potential subject, sites must fax a completed Drug Request Form to Celgene Corporation. Allow at least 5 working days for drug shipment. There are no shipments on Fridays or holidays.
For re-supply of drug, please complete and fax the Drug Request Form to Celgene Corporation at 908-673-2779.

5.9.2 Storage

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.

Stability of Reconstituted Suspension in the Vial
Reconstituted Abraxane should be used immediately, but may be refrigerated at 2ºC to 8ºC (36ºF to 46ºF) for a maximum of 4 hours if necessary. If not used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from bright light. Discard any unused portion.

Stability of Reconstituted Suspension in the Infusion Bag
The suspension for infusion prepared as recommended in an infusion bag should be used immediately, but may be stored at ambient temperature (approximately 25º C) and lighting conditions for up to 4hours.

5.9.3 Dispensing of Study Drug

Regular study drug reconciliation will be performed to document drug assigned, drug used, and drug remaining. This reconciliation will be logged on the drug reconciliation form, and signed and dated by the study team.

5.9.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to destruction of unused study drug. Drug destroyed on site will be documented in the study files.

Drug Destruction
The investigational site will follow its internal drug destruction policy. The following information must be recorded on the site's pharmacy drug accountability log: quantity of vials destroyed, expiration date and lot number. The pharmacist must document that the study drug was destroyed in accordance with their institution's drug destruction policy or SOP. A drug destruction memo and the site's drug destruction SOP/policy should be sent to Celgene Medical Operations Dept. A copy of the drug destruction memo should be retained at the clinical site. In the event of study completion or termination, a copy of all pharmacy records

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

6 Study Procedures

Study procedures are detailed below. See Table 4 for complete details

6.1 Pretreatment Evaluation

1. Signed written informed consent before any study procedure.
2. Complete medical history
3. Complete physical examination including, but not limited to, vital signs, height, weight, ECOG Performance Status, and tumor measurements (within 28 days prior to enrollment; tumor measurements will need to be repeated if cycle1/day 1 occurs more than 28 days following tumor measurements).
4. Tumor Evaluation: Confirmation of diagnosis of NSCLC and staging Radiological Evaluation by CT scan should be performed within 28 days prior to cycle 1/day 1 of treatment. MRI abdomen/pelvis is allowed as an alternative modality at the discretion of the treating physician. The same modality should be used throughout to assess disease.
5. Clinical laboratory testing: CBC with differential and platelet count, Serum Chemistries (total serum bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), serum creatinine, serum electrolytes, serum calcium, serum albumin, magnesium), and a pregnancy test for female patients of childbearing potential. Creatinine clearance should be calculated by the Cockroft-Gault formula or directly measured if clinically indicated (within 28 days before enrollment).

6.2 On-Treatment Evaluation

6.2.1 Procedures before each treatment

1. Laboratory assessment: Hematology: CBC with differential and platelet count and Serum chemistries: alkaline phosphatase, total serum bilirubin, SGOT, SGPT, creatinine or creatinine clearance, serum electrolytes, serum albumin, calcium and magnesium.
2. Vital signs and weight
3. Interim history, including documentation of concomitant medications, and solicitation of adverse event (AE) information if not volunteered by the patient, specifically inquiring as to the known AEs attributed in the past to any of the study drugs. Other documentation will include performance status, concomitant medications, and treatment-related toxicity (acute and cumulative),. Mid-level providers, including CRNPsand PAs, will be allowed to see patients and perform history and physical in lieu of the physician.
4. A complete physical examination prior to each study treatment .
5. Any other clinically indicated procedure(s)
6. During any study drug infusion, patients must be carefully checked so that immediate intervention can occur should an adverse event (i.e. hypersensitivity) occur.

6.2.2 Other procedures during the treatment period

1. Patients will be followed with CBC, differential, and serum chemistries (required weekly during Cycle 1 and subsequently as clinically indicated between treatment cycles).
2. Radiologic evaluation with CT Chest, abdomen and pelvis to be performed after every 2 cycles. Patients who stop treatment and/or come off study prior to developing progressive disease will continue to be followed for progression with CT of chest/abdomen/pelvis performed every 6 weeks until disease progression for one year of therapy and then every 9 weeks until disease progression. Patients who remain on treatment longer than a year may also have scans done every 9 weeks to minimize scan burden.

Patients who develop progressive disease and have completed study treatment will be followed for overall survival only. Their follow-up status will be assessed q6 months until death or the study ends.

6.2.3 Evaluations at End of Last Treatment cycle

The following assessments will be completed no less than 30 days after the patient's last study drug infusion:

1. Interim medical history with adverse event evaluation.
2. Complete physical examination with vital signs including temperature, weight and estimated ECOG Performance Status.
3. Laboratory testing: CBC with differential and platelet count, serum chemistries.
4. Following end of treatment/early termination visit, patients will be followed

Table 4: Study procedures by visit

Assessment	Pre-treatment[a]	Cycle 1, Days 1 & 8[e]	Cycle 2 on, Days 1 & 8[e]	Every other cycle, beginning with Cycle 3[be]	End of treatment/early termination[c]
Consent	X				
Serum pregnancy test	X				
PE, including ECOG PS	X	X	X		X
CBC w/ differential and serum chemistries[d]	X	X	X		X
Imaging (CT or MRI)	X			X	
Abraxane and gemcitabine		X	X		
Adverse event assessment		X	X		X
Review of concomitant medications	X	X	X		X

a: Pre-treatment evaluations must be performed within 28 days of first dose of study treatment (cycle 1/day 1)

b: Patients will radiologic assessment of measurable disease (CT chest/abdomen/pelvis) performed every other cycle while undergoing treatment for one year, then every 3 cycles until disease progression. Patients who discontinue treatment/come off study prior to disease progression will have radiographic assessment (CT chest/abdomen/pelvis) performed every 6 weeks until disease progression occurs.

c: Patients who have experienced progression of disease will be followed for overall survival only. Their survival status will be assessed q6 months until death or the study ends.

d: comprehensive metabolic profile including electrolytes (Na, K, bicarconate, chloride), liver function tests, BUN and creatinine, serum albumin and magnesium.

e: Day 8 assessment may occur one day prior or one day after scheduled. Day of subsequent cycles may occur 2 days before or 2 days after scheduled.

PE= physical exam, PS= performance status, w/= with

7 Statistical Plan

7.1 Sample Size Determination

The sample size will be 12- 37 evaluable patients based on a standard optimal Simon 2-stage phase II trial.

7.2 Statistical Methods

This optimal Simon 2-stage phase II trial will reject the Abraxane and gemcitabine combination if the objective response rate is <5% and will accept the combination if the objective response rate is >20%, with 10% type I error rate and 90% power. In stage 1, if no responders are observed in 12 evaluable patients, the trial will be terminated. If >1 responder is observed, 25 evaluable patients will be enrolled in stage 2. At the end of stage 2, if >4 responders are observed in 37 evaluable patients, the combination will be considered promising. The chance of terminating the study after evaluating 12 patients is 54%, if the objective response rate is <5%. Objective response rate will be examined by K-ras mutation status. Median PFS and OS will be estimated by Kaplan-Meier method. The study of 37 evaluable patients will actively enroll patients for 2 - 2.5 years.

7.3 Subject Population(s) for Analysis

Any patient who receives one dose of treatment will be considered evaluable for the primary and secondary endpoints. Patients who are enrolled in study but do not undergo at least one treatment due to failure to meet eligibility or other reason will be considered non-evaluable and will be replaced.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event
An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Non-clinically significant labs as deemed by the investigator will not be captured as adverse events.

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedure to the end of the study treatment follow-up. For this study, adverse event reporting will begin with the initiation of study treatment (cycle 1/day 1) until the end of the study treatment follow-up which is defined as 30 days following the last administration of study treatment.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if <u>any one of the following</u> conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator

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 on IP, or within (insert time-frame which must be at least 3 months of the subject's last dose of IP), are considered immediately reportable events. IP is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be 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.
Al**l neonatal deaths that occur within 3 months of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 3 months that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24** hours of the Investigator's kno**wledge of the event using the SAE Report Form, or approved equivalent form.**

Male Subjects
If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period starting on the day of treatment (cycle 1/day 1) will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any

serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

Investigators must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others (see definitions, section 8.1).

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

8.3.1 Investigator reporting: notifying Celgene

Toxicity will be scored using CTCAE Version 5.0 for toxicity and adverse event reporting. A copy of the CTCAE Version 5.0 can be downloaded from the CTEP homepage (HTTP://CTEP.INFO.NIH.GOV). All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0. All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

The investigator will appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

Any study-related unanticipated problem posing risk of harm to subjects or others, and any type of serious adverse event, must be reported to the Celgene within 24 hours of the event. To report such events, a Serious Adverse Event (SAE) form must be completed by the investigator and faxed to Celgene within 24 hours. The investigator will keep a copy of this SAE form on file at the study site. Report serious adverse events by facsimile to:

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

Within the following 48 hours, the investigator must provide further information on the serious adverse event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the

understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the study sponsor.

8.3.2 Investigator reporting: notifying the Penn IRB

This section describes the requirements for safety reporting by investigators who are Penn faculty, affiliated with a Penn research site, or otherwise responsible for safety reporting to the Penn IRB. The University of Pennsylvania IRB (Penn IRB) requires expedited reporting of those events related to study participation that are unforeseen and indicate that participants or others are at increased risk of harm. The Penn IRB will not acknowledge safety reports or bulk adverse event submissions that do not meet the criteria outlined below. The Penn IRB requires researchers to submit reports of the following problems within 10 working days from the time the investigator becomes aware of the event:

- Any adverse event (regardless of whether the event is serious or non-serious, on-site or off-site) that occurs any time during or after the research study, which in the opinion of the principal investigator is:

  Unexpected (An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.)

  AND

  Related to the research procedures (An event is "related to the research procedures" if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.)

Deaths occurring for subjects on-study and within 30 days of study drug administration that are considered unforeseen and indicates participants or others are at increased risk of harm (i.e. unexpected and probably/definitely related), must be reported to the IRB within 24 hours of notification.

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

Other Reportable events:
For clinical drug trials, the following events are also reportable to the Penn IRB:

- Any adverse experience that, even without detailed analysis, represents a serious unexpected adverse event that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome).
- Any adverse event that would cause the sponsor to modify the investigators brochure, protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects.
- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
  - An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
  - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
  - A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
- Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Breach of confidentiality

- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of subjects.

The IRB will accept other reports when the investigator is unsure whether the event should be reported, and the IRB will review such reports to determine whether the event meets the threshold for an unanticipated event presenting risk to the participant.

Office of Regulatory Affairs, Institutional Review Board
3624 Market Street, Suite 301S, Philadelphia, PA 19104-6006
Phone: 215-573-2540
Fax: 215-573-9438

8.3.3 Investigator reporting: Abramson Cancer Center DSMC

Grade 3 or higher AEs for Penn Subjects, determined to be related to the study drug regardless of expectedness or that affect subject safety, must be submitted to the Abramson Cancer Center's DSMC within 5 days of notification, with the exception of the following. The treating investigator must clearly document the relationship of these events.

- Grade 3 or 4 events that are probably or definitely related to the subjects' underlying disease and/or other co-morbidity.
- Grade 3 or 4 events that are probably or definitely related to an FDA approved drug based on the current labeling. However if the toxicity is more severe or is occurring more frequently than the current labeling, the event would be reportable. If the drug is not being used in accordance with the current FDA approval (i.e. dose, disease, route, as part of a treatment cocktail) then standard reporting is required.
- Grade 3 or 4 events that are obviously unrelated to the study drug (i.e. events related to a standard of care test/procedure).

Other events should be submitted if clinically significant or if a relationship to the study drug cannot be ruled out.

AEs that are related to the subjects' disease and/or other co-morbidity are not reportable to the ACC DSMC. All unexpected deaths or deaths related to the study drug should be reported within 24 hours of notification. All other deaths should be reported within 30 days.

Deaths of subjects off-study for greater than 30 days from the last study treatment/intervention are not reportable with the following exceptions:

a) Deaths on in-house gene or cellular-therapies
b) Deaths on in-house studies utilizing on-campus manufacturing of the study agent(s) or components of the study agent(s)
c) Deaths on first-in-human studies

AE reports should be sent to the DSMC for 90 days following the last date the last subject received study drug, and will not be accepted or processed after that time.

AEs will be submitted to the DSMC through the Velos Clinical Trial Management System.

Data and Safety Monitoring Committee
3400 Spruce Street, 2017 Penn Tower
Philadelphia, PA 19104-4283

8.4 Unblinding Procedures

This study will not be blinded.

8.5 Medical Monitoring

The medical monitor for this study will be Dr. Ursina Teitelbaum from the University of Pennsylvania. Dr. Teitelbaum is an Assistant Professor of Clinical Medicine in the Department of Hematology-Oncology at Penn with extensive oncology and clinical experience. She is not directly involved in the trial and is not collaborating with the Sponsor-Investigator on any other trials.

In the role, Dr. Teitelbaum will review all AEs including grading, toxicity assignments, all other safety data and activity data observed in the ongoing clinical trial. This will include a real-time review of safety data in the event of any unexpected and related SAE regardless of grade, and any on-study deaths. The Medical Monitor will also be consulted in the case of exception requests or the evaluation of deviations that may compromise subject safety or disrupt the design of the study. This information will be communicated to the Medical Monitor via email and filed in the Regulatory Binder/Subject Chart appropriately. As applicable, copies of this correspondence will be included in the corresponding IRB/ACC DSMC submission of these events.

The Medical Monitor will also be asked to review study data and comprehensive adverse event data at least bi-annually (every 6 months). This meeting will take place in person, and all study/safety information will be presented appropriately. This meeting will be clearly documented on a Medical Monitor Review Sheet, signed off on by the Medical Monitor. At any point during the course of the study, the Medical Monitor may recommend reporting of adverse events and relevant safety data not previously reported and may recommend suspension or termination of the trial.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists,

pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. The Velos eCRF system will be utilized for this study. All data requested on the CRF must be recorded. All missing data must be explained.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. This monitoring will include a regular assessment of the number and type of serious adverse events. The PI will comply with the CTSRMC approved Monitoring Plan.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

This investigator-initiated protocol is considered high risk as per the Abramson Cancer Center Data and Safety Monitoring Plan (DSMP). As such, high risk protocols are audited approximately six months from the first subject enrolled and approximately every six months thereafter for the duration of the study by the ACC Department of Compliance and Monitoring (DOCM). However, this schedule may be changed at the discretion of the DSMC. High or quick enrolling studies may be audited more frequently as necessary.

The investigator will be notified in advance of the selection of their protocol for review and cases are randomly selected. Three randomly selected subjects or 10% of the total accrual (up to 10 subjects), whichever is higher, are audited. A formal report is written to the PI within about 10 business days of the audit. The committee may alter the frequency of re-monitoring based on the audit findings and degree of deficiencies.

Upon review of inspection findings, the Committee designates the audit outcome as Minor, Moderate, or Major deficiencies. The deficiency assigned by the Committee initiates specific follow-up actions.

11 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB and CTSRMC for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject, and the investigator-designated research professional obtaining the consent.

The Informed Consent Form shall clearly state the following:
1. Study Drug will be provided at no charge to the Study Subjects;
2. Celgene shall have full access to the Study Subject's data;
3. Informed Consent must not state or imply that Celgene is the sponsor nor be responsible for any Study Subject injury.

12 Study Finances

12.1 Funding Source

The study will be supported by funds through Celgene.

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All University of Pennsylvania investigators will follow the University conflict of interest policy.

13 Publication Plan

Publication policy shall be as provided the Research Support Agreement between the University of Pennsylvania and Celgene.

Target meeting ASCO meeting May 23, 2016
Planned final manuscript Journal of Clinical Oncology Jul 01, 2016

14 References

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