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A Phase II study of weekly Abraxane for patients with advanced NSCLC with EGFR mutations or with durable response to an EGFR tyrosine kinase inhibitor following front line therapy with EGFR tyrosine kinase inhibitors.

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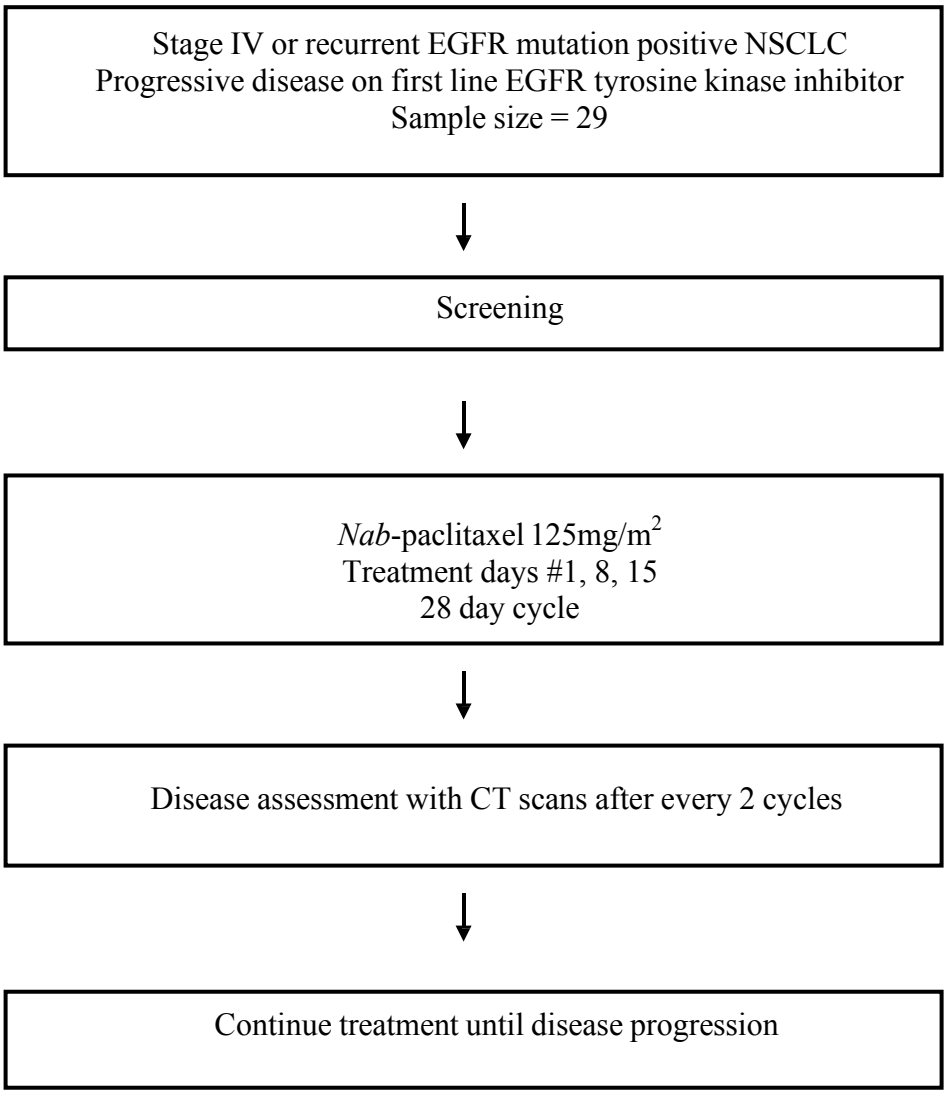
List of Abbreviations

AE	adverse event
AUC	area under curve
BSA	body surface area
CR	complete response
CRF	case report form
CT	computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events, version 4.0
EGFR	epidermal growth factor receptor
IRB	Institutional Review Board
mg	milligram
mL	milliliter
MTD	maximum tolerated dose
Nab-paclitaxel	nanoparticle albumin-bound paclitaxel
NSCLC	non-small-cell lung cancer
PR	partial response
RR	response rate
SAE	serious adverse event
SOP	standard operating procedure
SPARC	secreted protein acidic and rich in cysteine
TKI	tyrosine kinase inhibitor
ULN	upper limit of normal

Study Schema

Study synopsis:
This is a phase II trial of weekly *nab*-paclitaxel 125mg/m^2 in patients with advanced EGFR mutation positive NSCLC after front line therapy with an EGFR tyrosine kinase inhibitor.



1. OBJECTIVES

1.1 Primary

To evaluate the overall response rate of weekly *nab*-paclitaxel in patients with advanced non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutations following front-line therapy with EGFR tyrosine kinase inhibitors (TKI).

1.2 Secondary

To evaluate the safety profile of weekly *nab*-paclitaxel in patients with advanced NSCLC with EGFR mutations following front-line therapy with an EGFR TKI.

To evaluate the time-to-progression and overall survival.

2. BACKGROUND AND RATIONALE

2.1 Concept Summary

Patients with EGFR mutation positive NSCLC represent approximately 10-15% of advanced NSCLC and show remarkable sensitivity to EGFR tyrosine kinase inhibitors such as erlotinib and gefitinib. However, most patients experience disease progression after approximately one year and will require second-line therapy. There is evidence indicating that these patients may be particularly sensitive to taxane-based therapies. This study will evaluate the clinical efficacy of single agent *nab*-paclitaxel in a cohort of patients with EGFR mutation positive NSCLC who have experienced disease progression during front-line therapy with an EGFR TKI.

2.2 NSCLC with EGFR mutations

NSCLC with EGFR mutations is a well described molecular subgroup of lung cancer which is remarkably sensitive to EGFR TKIs. The initial experience with these drugs identified favorable outcomes in patients with adenocarcinoma histology, Asian ethnicity, female sex and never smokers. Later investigations demonstrated that these populations are enriched for EGFR mutated NSCLC, and that the presence of an activating EGFR mutation was highly predictive of response to EGFR TKIs [Pao, Rosell]. The most common mutations are exon 19 deletion and a leucine-to-arginine substitution at position 858 in exon 21 (L858R) and these comprise approximately 90% of the mutations [Rosell]. However, despite the sensitivity of these tumors to EGFR TKIs, most patients experience disease progression after a median of 10 to 14 months of therapy [Oxnard]. For these patients, no standard therapy exists and research is ongoing to identify effective therapeutic options for second line therapy.

2.3 Systemic chemotherapy in patients with EGFR mutation positive NSCLC

Chemotherapy has clearly been shown to be inferior to EGFR TKIs in EGFR mutation positive NSCLC in first line metastatic patients in both response rate and progression free survival; however, it also has been observed that these tumors do exhibit significant response to chemotherapy. In the Iressa Pan-Asia study (IPASS), a phase III trial of gefitinib versus carboplatin/paclitaxel in advanced NSCLC in a population composed of never- or light former smokers, gefitinib was superior to chemotherapy, but patients treated with chemotherapy did exhibit a significant response rate (RR) of 32% and when stratified by mutational status, a RR of 47% was observed among EGFR mutant tumors [Mok]. Other phase III trials of EGFR mutant NSCLC have shown RR ranging from 10.5% to 36% in the chemotherapy arm [Maemondo, Rosell, Zhou]. These studies indicate that while EGFR TKIs are clearly superior in the first line setting, chemotherapy will likely be beneficial in patients who relapse after TKI treatment.

2.3.1 Taxane-based chemotherapy in patients with EGFR mutation positive NSCLC

While EGFR mutation positive NSCLC does exhibit response to cytotoxic chemotherapy, there is no specific regimen that has been shown to be superior in this patient population. However, there is evidence indicating that these patients may be particularly sensitive to taxane-based therapies. In a retrospective analysis of patients with advanced NSCLC who initially experienced disease control with EGFR TKIs and subsequently received second line chemotherapy for disease progression, taxane-based chemotherapy was associated with higher response rate (48% vs. 21%), progression free survival (7 vs. 1.8 months) and overall survival (12.6 months vs. 5.1 months) compared to non-taxane based regimens [Kuo].

2.4 ABRAXANE® in advanced NSCLC

ABRAXANE® is a solvent-free, albumin-bound form of paclitaxel which is currently indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. It also has shown clinical efficacy as first-line therapy for NSCLC, both as mono- and combination therapy and its use in the treatment of other malignancies is under investigation.

2.4.1 Monotherapy

The efficacy of weekly *nab*-paclitaxel monotherapy was shown in a phase II study which assessed first-line *nab*-paclitaxel 125mg/m2 weekly given on days 1, 8 and 15 of a 28-day cycle in 40 patients with advanced NSCLC. After a median of 4 cycles, the study resulted in an overall response rate of 30%, time to progression of 5 months and overall survival of 11 months. This study excluded patients who had received previous chemotherapy for advanced disease; however, it did allow patients who were previously treated with EGFR TKIs who comprised 13% of the participants [Rizvi].

Another study investigated the efficacy of *nab*-paclitaxel 260mg/m2 given every 3 weeks as first-line therapy to 43 patients with advanced NSCLC. After a median of 6 cycles, the response rate was 16%, the median time to progression was 6 months and overall survival was 11 months [Green]. The most frequently reported Grade 3 and 4 adverse events in these trials were

neutropenia, peripheral neuropathy and fatigue. No severe hypersensitivity reactions were observed in these trials without corticosteroid premedication. Above studies demonstrate that *nab*-paclitaxel as monotherapy is a promising strategy in advanced NSCLC.

2.4.2 Combination therapy

Weekly *nab*-paclitaxel has also been investigated in combination with carboplatin in both phase II and III settings. In a phase II study, 56 patients with advanced NSCLC received weekly *nab*-paclitaxel 100mg/m2 on days 1, 8 and 15 of a 28-day cycle in combination with carboplatin area under the curve (AUC) 6 on day 1 of each cycle. Among the 50 evaluable patients, an overall response rate of 50% and a median time to progression of 28 weeks was reported [Allerton].

In a subsequent phase III study, weekly *nab*-paclitaxel 100mg/m2 in combination with carboplatin AUC 6 was compared with solvent-based paclitaxel 200mg/m2 and carboplatin every 3 weeks in 1,052 patients with advanced NSCLC. After a median of 6 cycles, there was significantly improved overall response rate in *nab*-paclitaxel arm with a response rate of 33% by independent review compared to 25% in the solvent-based paclitaxel arm. Interestingly, the response rate was particularly higher with *nab*-paclitaxel in the squamous cell histology (41% vs. 24%). In the final analysis of the study, there was no difference in median progression free survival (6.3 months vs. 5.8 months) or overall survival (12.1 months vs. 11.2 months) between the two arms [Socinski]. Grade 3 and 4 anemia and thrombocytopenia were more frequent in the *nab*-paclitaxel arm while neutropenia and peripheral neuropathy were more frequent in the solvent based paclitaxel arm. The above study shows that *nab*-paclitaxel is as effective, if not superior, to solvent based paclitaxel and is a promising chemotherapeutic agent that warrants further investigation in the patient population with EGFR mutation positive NSCLC.

2.5 SPARC, a potential predictive marker of *nab*-paclitaxel therapy

SPARC (a secreted protein, acidic and rich in cysteine, also known as osteonectin) is an extracellular matrix glycoprotein which has shown to be overexpressed in many different tumors including breast, head and neck, and lung cancers, and its overexpression has been associated with poor prognosis. This protein can be produced by the tumor or the neighboring stroma. SPARC can bind albumin with high affinity and studies have shown that SPARC may play a role in concentrating albumin in the areas near a tumor [Gradishar]. Given these observations, several studies have investigated the role of SPARC as a predictive tumor marker of *nab*-paclitaxel response with the hypothesis that tumor-secreted SPARC could facilitate the accumulation of albumin in the tumor and therefore increase the effectiveness of *nab*-paclitaxel. For instance, a retrospective analysis of *nab*-paclitaxel monotherapy in head and neck cancers showed that the response to *nab*-paclitaxel was higher in patients whose tumors were SPARC-positive by immunohistochemistry compared to SPARC-negative tumors with response rates of 83% vs. 25%, respectively [Desai 2009]. In another study of metastatic pancreatic adenocarcinoma, previously untreated patients were treated with *nab*-paclitaxel followed by gemcitabine and their tumors were evaluated for SPARC status by immunohistochemistry. In this study, the high-SPARC group resulted in higher overall survival when compared to the low-SPARC group with median survival of 17.8 vs. 8.1 months, respectively. Interestingly, stromal SPARC was significantly correlated with overall survival but not tumoral SPARC [Von Hoff].

In lung cancer, the role of SPARC was assessed in a preclinical study of human NSCLC cell lines and patient-derived NSCLC tumor xenografts. This study showed that *nab*-paclitaxel resulted in anti-tumor efficacy, however, this was not associated with SPARC expression by mRNA and gene methylation [Shao]. Above studies demonstrate that SPARC protein expression by immunohistochemistry is a potential predictive biomarker of *nab*-paclitaxel therapy and warrants further investigation.

3. DRUG INFORMATION, ABRAXANE® (*NAB*-PACLITAXEL)

3.1 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.

3.2 Mechanism of action

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 intralumminal 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 [Desai 2004]. A protein specifically secreted by the tumor (SPARC) binds albumin, allowing release of the hydrophobic drug to the tumor cell membrane [Desai 2004]. 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.

3.3 Preclinical studies with ABRAXANE

Preclinical studies comparing *nab*-paclitaxel to Taxol® (paclitaxel Cremophor® EL solvent-based, BMS) demonstrated lower toxicities, with an MTD approximately 50% higher for *nab*-paclitaxel 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, *nab*-paclitaxel 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 *nab*-paclitaxel versus solvent based paclitaxel, indicating more effective intratumoral accumulation of *nab*-paclitaxel [Desai 2006].

3.4 Toxicology

Myelosuppression, nausea and vomiting, diarrhea, mucositis, infections, hypotension, abnormal ECG changes, cough, dyspnea, edema, peripheral 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 1: Frequency[a] of Important Treatment Emergent Adverse Events in the Randomized Study on an Q3W Schedule

	Percent of Patients	
	ABRAXANE[b] 260/30min (n=229)	**Paclitaxel Injection[c,d] 175/3h (n=225)**
Bone Marrow		
Neutropenia < 2.0 x 10^9/L < 0.5 x 10^9/L	80 9	82 22
Thrombocytopenia < 100 x 10^9/L < 50 x 10^9/L	2 <1	3 <1
Anemia < 11 g/dL < 8 g/dL	33 1	25 <1
Infections	24	20
Febrile Neutropenia	2	1
Bleeding	2	2
Hypersensitivity Reaction[e]		
All	4	12
Severe[f]	0	2
Cardiovascular		
Vital Sign Changes[g]		
Bradycardia	<1	<1
Hypotension	5	5
Severe Cardiovascular Events[f]	3	4
Abnormal ECG		
All patients	60	52
Patients with Normal	35	30

Baseline		
Respiratory		
Cough	7	6
Dyspnea	12	9
Peripheral 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 (Patients with Normal Baseline)		
Bilirubin Elevations	7	7
Alkaline Phosphatase Elevations	36	31
AST (SGOT) Elevations	39	32
Injection Site Reaction	<1	1

[a] Based on worst grade
[b] ABRAXANE dose in mg/m^2/duration in minutes
[c] paclitaxel injection dose in mg/m^2/duration in hours

[d] paclitaxel injection pts received premedication

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

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

[g] During study drug dosing.

3.5 Study drug administration

ABRAXANE will be supplied by Celgene. ABRAXANE is a solvent-free, protein-bound particle form of paclitaxel injection with a mean particle size of approximately 130 nanometers. ABRAXANE is supplied as a white-to-yellow, sterile, lyophilized cake containing 100 mg of paclitaxel and approximately 900mg (800 mg theoretical) of human albumin solution as a stabilizer in a 50-mL vial. Each vial of the lyophilized product is reconstituted with 20 mL of 0.9% Sodium Chloride Injection (USP) to create a suspension. Each mL of reconstituted suspension contains 5 mg of paclitaxel.

Vials of ABRAXANE provided for clinical trials are labeled according to country-specific regulatory requirements for labeling of investigational products. ABRAXANE contains paclitaxel, a taxane with the Anatomical Therapeutic Chemical (ATC) code L01C D01.

Preparation for intravenous administration
At any given dose of paclitaxel in mg/m2, the total mg of paclitaxel to be administered should be calculated by the physician, using the height/weight conversion chart or other standard method for calculation of the patient's body surface area (BSA).

Reconstitution
ABRAXANE is supplied as a sterile, lyophilized powder for reconstitution before use. To avoid errors, read preparation instructions prior to reconstitution.

1. Aseptically, reconstitute each vial by injecting 20 mL of 0.9% sodium chloride injection.

2. Slowly inject the 20 mL of 0.9% sodium chloride injection over a minimum of 1 minute, using the sterile syringe to direct the solution flow onto the INSIDE WALL OF THE VIAL.

3. DO NOT INJECT the 0.9% sodium chloride injection directly onto the lyophilized cake as this will result in foaming.

4. Once the injection is complete, allow the vial to sit for a minimum of 5 minutes to ensure proper wetting of the lyophilized cake/powder.

5. 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.

6. If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides.

Administration

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration whenever the solution and container permit. The reconstituted sample should be milky and homogenous, without visible particulates. If particulates are visible or settling occurs, the vial should be gently inverted to ensure complete resuspension before use. Discard the reconstituted suspension if precipitates are observed. Discard any unused portion.

Each vial of the reconstituted formulation will contain 5 mg of paclitaxel per mL. The exact total dosing volume of 5 mg/mL suspension required for the patient is calculated using this formula:

Dosing volume (mL) = Total dose (mg) / 5 (mg/mL)

The appropriate amount of reconstituted ABRAXANE is injected into an empty, sterile, PVC- or non−PVC-type IV bag. The use of an in-line filter is not recommended.

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration. Limiting the infusion of ABRAXANE to 30 minutes (or as directed according to the protocol) reduces the likelihood of infusion-related reactions. No premedication to prevent solvent-related HSRs is required with ABRAXANE.

ABRAXANE should be administered under the supervision of a physician experienced in the use of chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

Because of the possibility of myelosuppression with ABRAXANE and the exclusion of patients with a baseline neutrophil count < 1,500 cells/mm3 or a platelet count < 100,000 cells/mm3 from the Phase III trial, ABRAXANE should not be administered to such patients. Blood cell counts should be monitored weekly during ABRAXANE therapy. For patients being treated on protocols using weekly dosing schedules, investigators should consult the requirements in the study-specific protocol concerning dose modifications and withholding treatment.

In addition, patients who experience severe neutropenia (neutrophil count <500 cells/mm3 for ≥ 1 week) or severe peripheral neuropathy during ABRAXANE therapy should have their dosage reduced for subsequent courses of ABRAXANE. For recurrence of severe episodes of either AE, the dosage should be further reduced. For grade 3 peripheral neuropathy, treatment should be withheld until resolution to grade 1 and then reduced for all subsequent courses of ABRAXANE therapy. In addition, investigators should consult the requirements in the study-specific protocol for dose reductions and withholding treatment.

An albumin form of paclitaxel may substantially affect a drug's functional properties relative to those of drug in solution. Do not substitute for or with other paclitaxel formulations.

3.6 Storage and handling of study drug

ABRAXANE is a cytotoxic anticancer drug and, as with other potentially toxic paclitaxel compounds, caution should be exercised in handling ABRAXANE. The use of gloves is recommended.

Procedures for proper handling and disposal of anticancer drugs should be followed. Several guidelines on this subject are available *[Clinical Oncological Society of Australia, Jones, American Medical Association, American Society of Hospital Pharmacists, Occupational Safety and Health Administration, Jeffrey]*. There is no general agreement that all of the procedures recommended in these guidelines are necessary or appropriate. However, according to the Active Pharmaceutical Ingredient manufacturer's safety data for paclitaxel, the product should not be released into the environment despite the fact that it is a natural, biodegradable product. It is recommended that the material be recovered, if possible, and incinerated under controlled conditions in compliance with the local and national regulations currently in force.

No reports of accidental exposure to ABRAXANE have been received; however, tingling, burning, and redness have been reported after topical exposure to Cremophor-based paclitaxel. If ABRAXANE (lyophilized cake or reconstituted suspension) comes in contact with the skin, the skin should be washed immediately and thoroughly with soap and water. Dyspnea, chest pain, burning eyes, sore throat, and nausea have been reported after inhalation of solvent-based paclitaxel. If ABRAXANE comes in contact with mucous membranes, the membranes should be flushed thoroughly with water.

Unopened vials of ABRAXANE are stable until the date indicated on the package when stored in the original cartons at USP Controlled Room Temperature (25ºC [77ºF], excursions permitted between 15°-30°C [59°-86°F]), or as specified on the vial label and as per the country requirements.

Stability of reconstituted suspension in the vial
From a microbiological point of view, the reconstituted suspension in the vial should be filled into an infusion bag immediately. If not filled immediately, storage times and conditions are the responsibility of the user and should not normally be longer than 8 hours at 2−8°C (36−46°F). If not used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from bright light.

Stability of the reconstituted suspension in the infusion bag
From a microbiological point of view, the reconstituted suspension in the infusion bag should be used immediately. If not used immediately, in-use storage times and conditions prior to administration are the responsibility of the user and should not normally be longer than 8 hours at ambient temperature (approximately 25°C [77°F]) and lighting conditions.

3.7 Study 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 Corporationat 908-673-2779.

3.8 Study drug return and destruction

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

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

4. PATIENT SELECTION

4.1 Inclusion criteria

Patients are eligible to be included in the study only if they meet *all* of the following criteria:

- Age $\geq$ 18 years

- Pathologically confirmed non-small cell lung cancer with documented EGFR mutation in tumor DNA or complete / partial response to first line EGFR tyrosine kinase inhibitors with > or = to 6 months duration of response in patients who do not have a confirmed EGFR mutation
- At least one site of measurable disease as determined by the Investigator, using RECIST 1.1 criteria
- Progressive disease with radiographic evidence of disease progression per investigator assessment during therapy with an EGFR tyrosine kinase inhibitor in the metastatic setting. Patients may continue EGFR inhibitor therapy throughout the screening period until the day prior to nab-paclitaxel treatment initiation
- ECOG performance status 0, 1 or 2 at the time of informed consent (Appendix 1)
- Adequate renal, hepatic, hematologic function:
    - Platelet count ≥100,000/uL
    - Absolute neutrophil count ≥1,500/uL
    - Hemoglobin ≥9g/dL
    - AST and ALT ≤2.5 times upper limit of normal
    - Alkaline phosphatase ≤2.5 times upper limit of normal, unless bone metastasis is present in the absence of liver metastasis
    - Bilirubin ≤1.5mg/dL
    - Creatinine ≤1.5mg/dL
- Women of child-bearing potential (WOCP) and sexually active men must agree to use adequate contraception (hormonal or barrier method of birth control or abstinence) prior to study entry, during treatment and for three months after completing treatment
- Negative serum or urine β-hCG pregnancy test at screening for patients of childbearing potential
- Life expectancy of > 12 weeks.
- Signed and dated informed consent document indicating that the patient has been informed of all the pertinent aspects of the trial prior to enrollment.

4.2 Exclusion criteria

- Prior conventional cytotoxic chemotherapy for metastatic or recurrent disease. Prior adjuvant, neoadjuvant or chemoradiotherapy for NSCLC is permitted, provided at least 6 months elapsed prior to documented metastatic recurrence.
- A single dose of a platinum doublet discontinued due to intolerability without evidence of disease progression is permitted.

- Patient is < 5 years free of another primary malignancy, except: a) if the other malignancy is basal cell carcinoma or cervical carcinoma in situ or b) if the other primary malignancy is not considered clinically significant and is requiring no active intervention

- Progressive or symptomatic CNS metastases. Patients with known brain metastasis must have stable disease following treatment with surgery, radiation or both. In addition, they must be off corticosteroids.
- Radiotherapy within 7 days of study treatment
- Peripheral neuropathy grade 2 or greater
- Grade III/IV congestive heart failure, as defined by NYHA criteria or myocardial infarction within 6 months.

- Any serious or uncontrolled concomitant disorder that, in the opinion of the investigator, would compromise the patient's ability to complete the study.

- Patient has known chronic liver disease, e.g. diagnosis of chronic active hepatitis or cirrhosis.

- Major surgery within 21 days of study treatment. Minor surgery within 2 weeks of study treatment. Placement of vascular access device and biopsies allowed and is not considered major or minor surgery.

- Patient with any significant history of non-compliance to medical regimens or with inability to grant reliable informed consent

- Pregnant or breast feeding females

5. STUDY TREATMENT PLAN

Patients enrolled on study will be treated with weekly *nab*-paclitaxel until disease progression or intolerance of treatment. *Nab*-paclitaxel will be administered in the infusion center of the treating physician.

5.1 Administration of schedule of *nab*-paclitaxel

A treatment cycle is defined as one 28-day period and includes three weekly doses of intravenous *nab*-paclitaxel, administered on days 1, 8 and 15. Each *nab*-paclitaxel dose will be calculated based upon patient's body surface area (BSA), with maximum body surface area capped at 2.0m^2. Each *nab*-paclitaxel dose is 125mg/m^2, and will be infused over 30 minutes, or per standard pharmacy protocol. Total dose of *nab*-paclitaxel will be calculated by BSA determination on the first day of each cycle, using actual weight. A delay of cycle as a result of holidays, weekends, bad weather, or other unavoidable circumstances will be permitted and not counted as a protocol violation.

5.2 *Nab*-paclitaxel premedications

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 [Ten Tije], 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 for subsequent doses 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.

5.3 Dose modifications

Administration of Study Drug to Patients with Abnormal Hematologic Function

ABRAXANE dosing should not be administered at the start of each cycle until the absolute neutrophil count (ANC) returns to ≥1.0 x 10^9 cells/L and the platelet count returns to >100 x 10^9 cells/L. For patients receiving weekly ABRAXANE, for each subsequent dose of ABRAXANE within a cycle (Days 8 and 15), patients must have an ANC ≥ 1.0 x 10^9 cells/L and platelets > 75 x 10^9 cells/L.

- If the ANC and platelets are not adequate for treatment on Day 8 and/or 15, the dose will be omitted and the total cycle length remains the same.
- If the ANC and platelets are not adequate for treatment on Day 15 the dose will be omitted and a new treatment cycle will commence the following week, as long as the ANC count has returned to ≥1.0 x 10^9 cells/L and the platelet count has returned to >100 x 10^9 cells/L.

Administration of Study Drug to Patients with Abnormal Hepatic Function

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

Dose Modification Table

Use this table as a guideline to determine any necessary dose modifications. The modification is dependent on the starting dose for the study.

Table 2: Dose Modification

Dose Level	ABRAXANE (mg/m^2)
0	125
-1	100
-2	80

Dose Reductions and guidelines for optional use of Growth Factors for Hematologic Toxicity

The table below provides a guideline for implementing dose reductions and optional use of growth factor treatment for hematologic toxicity:

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

Adverse Event	Occurrence	Action to be Taken
ANC < 500 cells/mm^3 (nadir count) with neutropenic fever > 38° OR Delay of next cycle due to persistent neutropenia (ANC < 1000 cells/mm^3) OR For patients 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). OR Neutropenia < 500 cells/mm^3 for > 1 week	Any Occurrence	At the first occurrence of a hematological toxicity (as outlined in the Adverse Event column), dose reduction to the next lower level will be required for subsequent cycles once ANC is ≥ 1000 cells/mm^3. In the event that a hematological toxicity re-occurs, dose reduction to the next lower level will be required for subsequent cycles once ANC is ≥ 1000 cells/mm^3. Alternatively, the same dose may be maintained and G-CSF is given as outlined below in the event of reoccurrence. 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 ≥ 1000 cells/mm^3. 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	Dose reduction to next lower level
	Recurrence	Dose reduction to next lower level

*See NCI Toxicity Criteria Scale for definition of Grade 3 and Grade 4 events.

G-CSF Administration

For weekly study drug 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

Peripheral Neuropathy

ABRAXANE should be withheld in patients who experience ≥ Grade 3 peripheral neuropathy. Treatment may be resumed at the next lower dose level (see Table 2) in subsequent cycles after the peripheral neuropathy improves to ≤ Grade 1. The time to resolution to Grade ≤ 1 should be the adverse event duration used for adverse event reporting. In those patients who experience Grade 4 peripheral neuropathy, study drug should be withheld, and treatment resumed at a reduction of 2 dose levels (Dose Level -2; see Table 2) in subsequent cycles after the peripheral neuropathy improves to ≤ Grade 1.

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

A dose hold and / or dose reduction is permissible for any grade 2 drug-related adverse events at the treating investigator's discretion, until satisfactory resolution of the AE. If drug related 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).

5.4 Concomitant therapy

Supportive care, including but not limited to anti-emetic medications, may be administered at the discretion of the site investigator. Concurrent treatment with bisphosphonates or other bone sparing agents are allowed. G-CSF may be administered at the discretion of the investigator, consistent with institutional guidelines.

Patients may have interruption in their treatment schedule for palliative radiotherapy and/or brain radiotherapy for progressive brain metastasis during the course of treatment. Patients may

resume study treatment after one week of completion of radiotherapy at the discretion of the investigator if their systemic disease remains stable or continues to respond to study treatment.

No other concurrent investigational drugs or other anticancer drugs will be allowed. Also, concurrent treatment with any of the following may not be administered: Ritonavir, Saquinavir, Indinavir and Nelfinavir.

5.5 Discontinuation of study treatment

Patients will be discontinued from study treatment under the following circumstances:

- The patient may withdraw from the study, at any time and for any reason, without prejudice to future care from the investigator or the institution.
- The investigator decides the patient should be withdrawn from the study. If a serious adverse event, or clinically significant laboratory value, form the basis for this decision, then the investigator will discontinue the study treatment and take appropriate measures.
- Disease progression, as defined by RECIST 1.1 criteria
    - Patients will be able to continue on study if they have progressive brain metastasis as discussed in section 5.4.
- Death
- The study treatment is associated with excess toxicity, such that a third dose reduction would be indicated. (See Tables 2 and 3)
- The study treatment is associated with excess toxicity, such that treatment has been delayed longer than 21 days.
- Peripheral neuropathy ≥ Grade 3 ≥ 21 days
- Significant non-compliance to protocol, as judged by the investigator

5.6 Treatment compliance

Records of study medication used, dosage administered, and intervals between visits will be kept during the study. Drug accountability will be noted at the completion of the trial.

6. CLINICAL AND LABORATORY ASSESSMENT

Patient must be followed at the study center according to the visit schedule, with assessments as outlined in the Study Calendar (Appendix 2). Special attention should be given to the patients with bulky tumors or tumors involving or close to vital organs. These patients should be monitored very closely during the first months of treatment, as judged appropriate by the treating physician.

6.1 Screening assessment

Written, informed consent must be obtained before any study-specific medical procedures are performed. The following screening assessments and laboratory evaluation must be performed within 30 days prior to starting study treatment:

Screening assessments

Assessment	Includes
Inclusion/exclusion criteria	Patient eligibility is to be assessed
Demographics Medical History / Current Medical Conditions	Date of birth, sex and race. Medical history, disease history, and current medical conditions
Tumor Sample	Obtain tissue from prior biopsy in patients that sign consent for optional correlative tissue study.
Previous NSCLC treatment	Previous surgery, radiotherapy and systemic therapy.
Physical Examination / Vital Signs/ Performance Status/ Body weight	Total body examination, including height, weight, pulse rate, blood pressure and performance status according to ECOG criteria (see Appendix 1).
Tumor measurements	CT scan as appropriate (classification of measurable and non-measurable disease according to RECIST 1.1 criteria).[1]
Hematology	Complete blood count with platelets and absolute neutrophil count
Serum chemistry	BUN, creatinine, sodium, potassium, bicarbonate, chloride, calcium, glucose, total protein, albumin, total bilirubin, alkaline phosphatase, AST (SGOT) and ALT (SGPT)
EKG	Electrocardiogram[2]
Pregnancy test	Negative serum or urine β-hCG pregnancy test at screening for patients of childbearing potential[2]

[1] Tumor measurement may occur no more than 30 days prior to study start.
[2] Pregnancy test and EKG must be obtained within 7 days of study start.

6.2 Assessments, treatment period

During study treatment, patients will undergo the following physical and laboratory assessments. Patients will undergo CT scans of known sites of disease after every 2 cycles of therapy (see Study Calendar, Appendix 2).

Days of *nab*-paclitaxel infusion (Days 1, 8 and 15)

- Notation of concurrent illnesses and changes in baseline medications
- Assessment of adverse events and toxicity rating using NCI CTCAE version 4.0
- Physical examination on Day 1 only
- Vital signs including weight, blood pressure and pulse.
- ECOG performance status on Day 1 only
- Complete blood count, with absolute neutrophil count and platelet count

- Serum chemistries including BUN, creatinine, sodium, potassium, bicarbonate, chloride, calcium, glucose, total protein, albumin, total bilirubin, alkaline phosphatase, AST (SGOT) and ALT (SGPT) on Day 1 only.
- CT scan of chest and other known sites of disease after every two cycles of therapy (end of cycle 2, 4, etc.)

End of Treatment Visit

- Notation of concurrent illnesses and changes in baseline medications
- Assessment of adverse events and toxicity rating using NCI CTCAE version 4.0
- Physical examination
- Vital signs including weight, blood pressure, and pulse.
- ECOG performance status
- Complete blood count, with absolute neutrophil count and platelet count
- Serum chemistries including BUN, creatinine, sodium, potassium, bicarbonate, chloride, calcium, glucose, total protein, albumin, total bilirubin, alkaline phosphatase, AST (SGOT) and ALT(SGPT)
- CT scan of chest and other known sites of disease if not done within past four to six weeks.

6.3 Assessments, post-treatment period

Four week visit: The patient will undergo evaluation for toxicity four weeks (+/- 7 days) after the last dose of *nab*-paclitaxel. This evaluation will occur, regardless of reason for stopping *nab*-paclitaxel treatment (i.e. completion of study treatment, disease progression, withdrawal from study). Patients will undergo the following tests and procedures:

- Notation of concurrent illnesses and changes in baseline medications
- Assessment of adverse events and toxicity rating using NCI CTCAE version 4.0
- Physical examination, including weight, blood pressure and pulse
- ECOG performance status
- Complete blood count, with absolute neutrophil count and platelet count
- Serum chemistries including BUN, creatinine, sodium, potassium, bicarbonate, chloride, calcium, glucose, albumin, total bilirubin, alkaline phosphatase, AST (SGOT) and ALT (SGPT) .
- If a treatment-related adverse effect has not stabilized or resolved to ≤ Grade 1 or baseline, the patient will be seen monthly until such resolution has been documented or another anti-neoplastic therapy has begun.

Monthly assessment, post-treatment period: Patients who have stopped study treatment without documentation of disease progression, will be seen monthly by the study physician. Patients will undergo the following evaluation monthly until disease progression is documented, at which time they may be followed by telephone.

- Radiographic efficacy assessment every eight weeks

Telephone follow up: If disease progression is documented, follow-up may thereafter occur by telephone. A study investigator, nurse or coordinator will contact each patient every three months (+/- 2 weeks), until death or the study is stopped by the investigator. The following will be documented:

- Global health status (alive or deceased)

7. EFFICACY ASSESSMENTS

Please see Study Calendar (Appendix 2) for timing of radiographic efficacy assessments.

7.1 Screening evaluation

Within 30 days prior to the first dose of *nab*-paclitaxel, baseline tumor measurement(s) will be performed for each patient. Conventional computed tomography (CT) scan of the chest and upper abdomen should be performed. In addition to imaging of the chest and upper abdomen, other known sites of measurable disease should be quantified by CT.

7.2 Efficacy evaluations, treatment period

An objective assessment of all measurable and unmeasurable disease will be performed according to the Study Calendar (See Appendix 2). Tumor response or progression will be defined by RECIST 1.1 criteria, as detailed below. Objective responses will include both partial and complete responses (PR and CR).

All tumor assessments should be performed within 14 days of the scheduled assessment date. Radiological studies must account for all lesions that were present at baseline. All known disease (measurable and non-measurable, as defined below, section 7.4) must be accounted for when assessing objective tumor status.

The first tumor assessment will occur after two 4-week cycles of study treatment, and every two cycles thereafter. After first documentation of disease progression, no further radiographic assessment is required.

At any time, radiological evaluation may be ordered based on clinical symptoms or signs, prompting concern for disease progression.

7.3 Efficacy evaluations, post-treatment period

Patients who stop study treatment due to toxicity or other circumstances specified in Section 5.6 but continue to exhibit response or stable disease at the end of study treatment will be scheduled for further radiographic efficacy assessments. Tumor assessment by CT will be conducted every 2 months (+/- 2 weeks) until documentation of disease progression.

7.4 Definitions

Measurable disease: the presence of at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm with spiral CT scan for non-lymph nodes or ≥ 1.5 cm in short-axis diameter for lymph nodes

Non-measurable disease: all other lesions, including small lesions (longest diameter <10 mm with spiral CT scan or pathological lymph nodes with ≥10 to <15mm short axis).

7.5 Baseline documentation of tumor burden

Target lesions: All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, should be identified as target lesions. These should be recorded and measured at baseline. Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter for all target lesions will be calculated and reported as the baseline sum longest diameter (SLD). The baseline SLD will be used as the reference by which to characterize the objective tumor response.

Non-target lesions: All other lesions (or sites of disease) should be identified as non-target lesions, and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

7.6 Response criteria

Radiological response will be defined according to the modified RECIST criteria, as follows:

Evaluation of target lesions:

- **Complete response (CR):** disappearance of all target lesions
- **Partial response (PR):** at least a 30% decrease in the sum of the longest diameter of the target lesions, taking as reference the baseline SLD
- **Progressive disease (PD):** at least a 20% increase in the SLD of target lesions, taking as reference the smallest SLD recorded since the treatment started, or the appearance of one or more new lesions
- **Stable disease (SD):** neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for progressive disease, taking as reference the smallest SLD since the treatment started.

Evaluation of non-target lesions:

- **Complete Response (CR):** disappearance of all non-target lesions
- **Incomplete Response/Stable Disease (SD):** persistence of one or more non-target lesion(s)
- **Progressive Disease:** appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

8. SAFETY ASSESSMENT AND ADVERSE REPORTING

Investigators are responsible for monitoring the safety of patients who have entered this study, and for alerting both the Fred Hutchinson/University of Washington Cancer Consortium IRB and Celgene Drug Safety to any event that seems unusual.

Safety assessments will occur on the day of each *nab*-paclitaxel infusion. Safety measurements include history, evaluation for side effects and other adverse events, physical examination, review of concomitant medications and laboratory tests. Toxicities will be graded according to NCI CTCAE version 4.0. Adverse events will be recorded after the first dose of study therapy has been given. Only the following adverse events will be recorded in the case report forms (CRF):

- All grade 3 and higher adverse events
- Any other adverse event that requires a dose reduction or a dose delay

8.1 Adverse events

An adverse event (AE) is any undesirable medical condition (sign, symptom or diagnosis) or worsening of a preexisting medical condition, which occurs after initiating study treatment, whether or not considered causally related to the investigational product. Abnormal laboratory values or test results constitute AEs only if deemed clinically significant by the investigator, e.g. they induce clinical signs or symptoms, or require therapy.

AEs are collected from first dose of study drug until 30 days after the last dose of study drug. An event that, in the judgment of the investigator, is unequivocally due to progression of disease should not be reported as an adverse event.

The following attributes must be recorded by the study personnel for each adverse event:

- Description
- Severity
- Causality
- Action taken

8.2 Serious adverse events

A serious adverse event is defined by regulatory agencies as one that suggests a significant hazard or side effect, regardless of the investigator's opinion regarding relationship to the investigational treatment. This includes any undesirable sign, symptom or medical condition which:

- Is fatal or immediately life-threatening
- Requires or prolongs inpatient hospitalization
- Results in severe or permanent disability or incapacity
- Constitutes a congenital anomaly or a birth defect
- Is medically significant, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

Events not considered to be serious adverse events are hospitalizations for the:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition

- Treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen
- Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions given above and not resulting in hospital admission

An event that, as judged by the investigator, is unequivocally due to progression of disease should not be reported as a serious adverse event.

8.3 Reporting a serious adverse event

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has initiated study therapy and until 30 days after the last dose of drug must be reported. Any SAEs experienced after this 30-day period should only be reported to Celgene Drug Safety if the investigator suspects a causal relationship to the study drug. SAEs that occur at a Network site will be reported to the Network office within 24 hours of learning of its occurrence. The Network Office will then forward the SAE reports to both the Coordinating Center Principal Investigator (or designee) and Celgene Drug Safety within 24 hours of learning of its occurrence.

SAEs will be reported to the Fred Hutchinson/University of Washington Cancer Consortium IRB in accordance with applicable AE reporting policies.

Celgene Drug Safety Contact Information:

Celgene Corporation
Drug Safety
86 Morris Avenue
Summit, N.J. 07901

Toll Free: (800)-640-7854
Phone: (908) 673-9667
Fax: (908) 673-9115

E-mail: drugsafety@celgene.com

9. SPONSOR AND INVESTIGATOR REQUIREMENTS

Sponsors are responsible for selecting qualified investigators, providing them with the information they need to conduct an investigation properly, ensuring proper monitoring of the investigation(s), ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols ensuring that all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug.

9.1 Study initiations

Before the start of this study and the shipment of investigational agent to the main site and any sub-site, the following documents must be on file at the coordinating center (University of Washington).

1. U.S. Food and Drug Administration (FDA) Form 1572, signed by the Principal Investigator
   - The names of any sub-investigators must appear on this form.
2. Current curricula vitae and license of the Principal Investigator
3. A financial disclosure statement from the Principal Investigator
4. Delegation of Authority
5. Written documentation of IRB approval of protocol and ICF (identified by title and date of approval) for each site

10. STATISTICAL CONSIDERATIONS

10.1 Study endpoints

10.1.1 Primary endpoint: Overall response rate

The primary endpoint will be overall response rate. Responses include both complete and partial responses, as defined by RECIST 1.1 criteria.

10.1.2 Secondary endpoints: Time to progression, overall survival, toxicity

Time to tumor progression is defined as time elapsed from date of informed consent, until the first documentation of progressive disease. Overall survival is defined as time elapsed from date of informed consent, until death. Both time to progression and overall survival will be reported as median values. Toxicity rates will be described as percentage of patients experiencing Grade 3 or higher toxicity. Toxicity rates will be presented in two ways: 1) overall percentage of patients experiencing Grade 3 or higher toxicity; 2) overall percentage of patients experiencing toxicity within a clinically significant category – including neutropenia, neutropenic fever and neuropathy.

10.2 Study design

This study is a single-arm, phase 2 study of weekly *nab*-paclitaxel in patients with advanced EGFR mutation positive NSCLC after front line therapy with an EGFR TKI.

10.3 Sample size determination and data analysis

This is a single-arm, phase 2 study and a total of 29 patients will be enrolled in this trial. We will utilize Fleming's single stage design where there is a level of response, P_0, below which the treatment would not be considered for further study, and a higher level, P_1, above which the treatment warrant further investigation [Girling]. Phase II published response rates to single-

agent *nab*-paclitaxel range from 16-30%, with weekly therapy resulting in a 30% response rate [Rizvi]. Therefore, a response rate <10% (P_0) will be considered null and we would not be interested in pursuing this therapy further. If the response rate were 30% (P_1) or better, this therapy would be considered worth further study. With this design, we have 90% power to detect a true response rate of 30%. If the true response rate is 10%, then we have a 5% chance of falsely rejecting the null rate of 10% ($\alpha = 0.05$, $\beta = 0.10$, $P_0 = 10\%$, $P_1 = 30\%$). We will calculate the response rate as the proportion and 95% confidence interval of patients who achieved a complete response or partial response. We will also report time to progression and overall survival as median values with their respective 95% confidence intervals. We will estimate time to event distributions using the Kaplan-Meier method.

10.4 Exploratory analysis

An exploratory analysis will examine the response rates stratified by the following histologic subtypes if available: adenocarcinoma, squamous cell carcinoma, large cell carcinoma, NSCLC others. However, it is expected that the adenocarcinoma subtype will comprise the majority of lung cancers in this study. Given the lack of sufficient statistical power to assess response rates by the stratified subtypes, no formal statistical analysis will be performed. Also, a correlative tissue analysis of SPARC expression will be assessed on available tissue specimens if reliable detection methodology is available at the end of study recruitment (Appendix 3).

Appendix 1: ECOG Performance Status

Score:	Description of functional status:
0	Fully active, able to carry on all pre-disease performance without restrictions
1	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	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care, and confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Deceased

Appendix 2: Study Calendar

Procedure	Screening within 30 days	Screening within 7 days	Every 28 days: Day 1 +/- 3 days	Day 8 +/- 2 days	Day 15 +/- 2 days	End of Treatment (EOT)	30 day post tmt +/- 7 days
Informed Consent	X						
Physical Exam	X		X			X	X
Vital Signs	X		X	X	X	X	X
ECOG Status	X		X			X	X
Medical History	X						
Pregnancy Test		X					
CBC [1]	X		X	X	X	X	X
Serum Chemistries [2]	X		X			X	X
EKG		X					
CT scans [3,4]	X		(X)			X	
ABRAXANE			X	X	X		
AE Assessment			X	X	X	X	X

[1] CBC with platelets and absolute neutrophil count. (Can be done within 2 days of Day1)

[2] Includes sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, total bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, phosphorus. (Can be done within 2 days of Day1)

[3] CT scan of known sites of involvement after every 2 cycles of therapy.

[4] If not done within 4-6 weeks of the EOT visit

Appendix 3. Correlative tissue analysis

Paraffin blocks/slides will be collected from patients who sign the optional correlative tissue study informed consent form. Expression of SPARC and other potential predictive markers will be performed on all samples received if reliable detection methodology is available at the end of study recruitment. We will conduct an exploratory analysis, correlating SPARC expression with response rate and survival in patients treated with *nab*- paclitaxel. Analysis of all tissue samples for SPARC will be blinded with respect to the treatment assignment and to the patient response to treatment. The number and percentage of responding patients (i.e., patients that achieve an objective confirmed complete or partial overall response) and non-responding patients will be tested for association with SPARC expression (i.e., SPARC positive vs. SPARC negative) for each treatment group.

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