DISCLOSURE

REDACTED ORIGINAL PROTOCOL

ABI-007-NSCL-003

A PHASE III, RANDOMIZED, OPEN-LABEL, CROSSOVER, MULTI-CENTER, SAFETY AND EFFICACY STUDY TO EVALUATE NAB-PACLITAXEL (ABRAXANE®) AS MAINTENANCE TREATMENT AFTER INDUCTION WITH NAB-PACLITAXEL PLUS CARBOPLATIN IN SUBJECTS WITH SQUAMOUS CELL NON-SMALL CELL LUNG CANCER (NSCLC)

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A PHASE III, RANDOMIZED, OPEN-LABEL, CROSS-OVER, MULTI-CENTER, SAFETY AND EFFICACY STUDY TO EVALUATE NAB-PACLITAXEL (ABRAXANE®) AS MAINTENANCE TREATMENT AFTER INDUCTION WITH NAB-PACLITAXEL PLUS CARBOPLATIN IN SUBJECTS WITH SQUAMOUS CELL NON-SMALL CELL LUNG CANCER (NSCLC)

INVESTIGATIONAL PRODUCT (IP):	**nab-Paclitaxel (Abraxane®)**
PROTOCOL NUMBER:	**ABI-007-NSCL-003**
DATE FINAL:	**27 Sep 2013**
IND NUMBER:	**114882**
SPONSOR NAME / ADDRESS:	Celgene Corporation 86 Morris Avenue Summit, NJ 07901

MEDICAL MONITOR / EMERGENCY CONTACT INFORMATION

Contact Information:	
Name:	
Title:	
Address:	Celgene Corporation 86 Summit Avenue Summit, NJ 07901
Phone:	
E-mail:	

Contact Information:	
Name:	
Title:	
Address:	Celgene Corporation 86 Summit Avenue Summit, NJ 07901
Phone:	
E-mail:	

Note: The back-up 24 hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

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PROTOCOL SUMMARY

Study Title

A Phase III, randomized, open-label, cross-over, multi-center, safety and efficacy study to evaluate nab-paclitaxel (Abraxane) as maintenance treatment after induction with nab-paclitaxel plus carboplatin in subjects with squamous cell non-small cell lung cancer (NSCLC).

Indication

Maintenance treatment of squamous cell NSCLC.

Objectives

Primary

- To evaluate progression free survival (PFS) with nab-paclitaxel as maintenance treatment after response or stable disease (SD) with nab-paclitaxel plus carboplatin in subjects with squamous cell NSCLC.

Secondary

- To evaluate the safety and tolerability of nab-paclitaxel as maintenance treatment after response or SD with nab-paclitaxel plus carboplatin in subjects with squamous cell NSCLC.
- To further assess the efficacy with nab-paclitaxel as maintenance treatment after response or SD with nab-paclitaxel plus carboplatin in subjects with squamous cell NSCLC, as measured by secondary efficacy endpoints.

Exploratory

- To determine baseline tumor characteristics which predict response and resistance to nab-paclitaxel/carboplatin during the Induction part of the study.
- To determine what changes in peripheral tumor characteristics during treatment are associated with acquisition of resistance in the subjects who had initial clinical benefit.
- To evaluate the safety and efficacy of nab-paclitaxel as Cross-over treatment after progression during the Maintenance part of the study in subjects with squamous cell NSCLC.
- To assess healthcare resource utilization during the Maintenance part of the study.
- To assess the Lung Cancer Symptom Scale (LCSS) and EuroQol Group 5-Dimension Self-Report Questionnaire score (EQ5D).

Study Design

This is a Phase III, randomized, open-label, cross-over, multi-center study of nab-paclitaxel or best supportive care (BSC) as maintenance treatment after response or SD with nab-paclitaxel plus carboplatin as induction in subjects with squamous cell NSCLC. Approximately 540 subjects with stage IIIB or IV squamous cell NSCLC will be enrolled in the Induction part of the

study to receive nab-paclitaxel plus carboplatin for 4 cycles. If after the 4 cycles, the subject has a complete response (CR), partial response (PR), or SD, they will be randomized (2:1) in the Maintenance part of the study to receive nab-paclitaxel plus BSC or BSC alone. BSC is defined as the best palliative care per investigator (including but not limited to: antibiotics, analgesics, antiemetics, thoracentesis, pleurodesis, blood transfusions, nutritional support, and/or focal external-beam radiation for control of pain, cough, dyspnea, or hemoptysis), excluding antineoplastic agents. Approximately 260 subjects will be evaluable for the primary endpoint of PFS in maintenance. Once a subject in the BSC arm during the Maintenance part of the study experiences radiologic progression of disease, they will be eligible to cross-over to receive nab-paclitaxel.

Induction Part

The main purpose of the Induction part is to identify those subjects who are eligible for randomization in the Maintenance part of the study. Approximately 540 subjects eligible for standard treatment with nab-paclitaxel plus carboplatin for 4 cycles will be enrolled, provided if all inclusion/exclusion criteria are met within a 28-day screening period prior to Cycle 1 Day 1.

Induction treatment will commence on Day 1:

- nab-Paclitaxel 100 mg/m^2 intravenous (IV) infusion over 30 minutes on Days 1, 8, and 15 of each 21-day cycle
- Carboplatin AUC = 6 mg*min/mL IV on Day 1 of each 21-day cycle after completion of nab-paclitaxel infusion

Once 4 cycles have been completed for Induction, if the subject has a radiologically assessed CR, PR, or SD, and has met all eligibility criteria, they will continue on to the Maintenance part of the study. If the subject has radiological or clinical PD, they will be discontinued from the study and will not be followed.

Maintenance Part

Once 4 cycles have been completed for Induction, if the subject has a radiologically assessed CR, PR, or SD without clinical progression, and has met all eligibility criteria, they will be randomized 2:1 to receive:

- nab-Paclitaxel 100 mg/m^2 IV infusion over 30 minutes on Days 1 and 8 of each 21-day cycle plus BSC until disease progression or unacceptable toxicity (see Section 8.3 for guidelines on starting dose for the Maintenance part of the study if the subject had dose reduced during the Induction part of the study)

OR

- BSC until disease progression

Maintenance therapy should start at the time of randomization. If this is not possible, a maximum of 7 days will be allowed from the date of randomization to the start date of Maintenance therapy. Subjects must start Maintenance therapy no earlier than 21 days and no later than 35 days from Day 1 of the fourth cycle of Induction therapy.

Cross-over

A subject in the BSC alone arm during the Maintenance part of the study who experiences radiological progression of disease, will be eligible to cross-over to receive nab-paclitaxel 100 mg/m^2 IV infusion over 30 minutes on Days 1 and 8 of each 21-day cycle until unacceptable toxicity or discontinuation for any other reason, if the benefit : risk is considered appropriate by the treating investigator (see Section 8.3 for guidelines on starting dose for the Cross-over part of the study if the subject had dose reduced during the Induction part of the study, and Sections 7.2 and 7.3 for eligibility criteria).

Follow-up Period

All subjects who discontinue from the Maintenance or Cross-over parts of the study for any reason other than withdrawal of consent, lost to follow-up, or death, will enter the Follow-up period that will have a visit 28 days after progression or discontinuation. Those subjects entering the follow up period without documented progression will continue to have CT scan in accordance with standard of care until documented progression of disease. Additionally, subjects will be followed for overall survival (OS) by phone approximately every 90 days for up to 1.5 years after final analysis of approximately 182 PFS events or approximately 218 deaths have been observed for the final OS analysis, whichever is earlier.

Study Population

Subjects with squamous cell NSCLC stage IIIB or IV with no prior chemotherapy for metastatic disease and ≥ 18 years old will be eligible for this study. The Induction part of the study will enroll approximately 540 subjects. Based on results from the nab-Paclitaxel Phase 3 NSCLC development study (Protocol CA031) it is estimated that approximately 260 subjects with CR, PR, or SD from the Induction part of the study will be randomized to the Maintenance part of the study. Enrollment into the Induction part of the study will be monitored and adjusted to ensure that approximately 260 subjects are randomized into the Maintenance part of the study.

Length of Study

The Induction part of the study will last approximately 36 months to enroll sufficient subjects for the Maintenance part of the study. The total length of this Phase III study with Induction, Maintenance, Cross-over, and Follow-up is estimated to last approximately 5 years.

Study Treatments

Induction

The nab-paclitaxel and carboplatin treatments are designated as non-investigational products during induction and will not be supplied by Celgene. Investigative sites will use standard of care (commercially available) product via prescription.

Maintenance and Cross-over

Subjects will be randomized to receive open-label nab-paclitaxel plus BSC or BSC during the Maintenance part of the study. Subjects will receive open-label nab-paclitaxel during the Cross-over part of the study. The nab-paclitaxel used in the Maintenance and Cross-over parts of the study is designated as investigational product (IP) and will be packaged and supplied by Celgene Corporation.

The preparation for IV administration procedures for IP should be followed as per package insert.

Statistical Methods

Approximately 540 subjects will be enrolled in the open-label Induction part of the study. All subjects will receive nab-paclitaxel 100 mg/m^2 administered weekly followed by carboplatin AUC = 6 mg*min/mL on Day 1 of each cycle, repeated every 21 days, for 4 cycles.

At the end of Cycle 4, subjects who achieve a radiologically assessed complete response (CR), partial response (PR), or stable disease (SD) without clinical progression based on the Investigator's evaluation using the Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 guidelines will be further evaluated for their eligibility to participate in the Maintenance part of the study. Approximately 260 subjects are expected to be randomized in the Maintenance part of the study.

The actual number of subjects that will be enrolled in the Induction part will be monitored and adjusted to ensure that the target number of subjects for the Maintenance part is attained. Similarly, the percentage of subjects manifesting a PFS event in the Maintenance part will be tracked on an ongoing basis. If the observed percentage of subjects with a PFS event is trending lower than the assumed 70%, the number of subjects enrolled in the Induction and Maintenance parts will be increased to ensure that at least 182 PFS events will be observed within the anticipated duration of the study.

Induction Part

Efficacy Analyses

All efficacy endpoints will be analyzed based on the intent-to-treat (ITT) population, which includes all subjects who are enrolled regardless of whether the subjects receive any nab-paclitaxel or have any efficacy assessments collected.

The main purpose of the Induction part is to identify those subjects who are eligible for randomization in the Maintenance part of the study. Subjects will have CT scans performed every 42 days (-3/+7 days). Subjects who attain a radiologically assessed CR, PR, or SD without clinical progression according to the investigator's assessment of the scan performed at the end of Cycle 4, based on RECIST 1.1 guidelines, and satisfy eligibility criteria will be eligible to be randomized in the Maintenance part.

The secondary objective of the Induction part is to estimate the Overall Response Rate (ORR, percent of subjects who have a CR or PR according to RECIST 1.1 guidelines as determined by the investigator and confirmed by repeat assessments performed no less than 28 days after the criteria for response were first met). Descriptive statistics (point estimate and the associated two-sided 95% confidence interval) will be calculated for this endpoint.

Safety Analyses

The safety population, includes all subjects enrolled who received at least 1 dose of study treatment, will be the analysis population for all safety analyses. Adverse events will be summarized by worst severity grade. Adverse events (AEs), as well as treatment-emergent AEs, will be summarized by system organ class, and preferred term. Adverse event severity/grade will

be summarized by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

Laboratory test results will not be collected in the eCRFs unless they are determined to be clinically significant laboratory abnormalities. Abnormal and clinically significant laboratory assessments at Screening will be recorded as medical history, and after Screening, as AE or serious adverse event (SAE). If a clinically significant laboratory abnormality is captured as medical history, AE, or SAE, the specific laboratory parameter(s) should be recorded on the laboratory assessments CRF.

Maintenance Part

Approximately 260 subjects will be randomized in the Maintenance part of the study. These subjects will be randomized in a 2:1 ratio to the nab-paclitaxel plus BSC and BSC alone groups, respectively. The nab-paclitaxel group will receive nab-paclitaxel 100 mg/m^2 on Day 1 and 8 of each 21-day cycle plus BSC (the actual starting dose may be adjusted as specified in Section 8.3), while the BSC group will receive the standard BSC regimen. All subjects will receive the assigned regimen until disease progression or unacceptable toxicity. Subjects in the BSC alone group who have radiologic progression will be eligible to crossover and receive the nab-paclitaxel regimen until unacceptable toxicity or discontinuation for any other reason, if the benefit:risk is considered appropriate by the treating investigator.

Randomization will be stratified by the following 3 baseline and prognostic stratification factors: Eastern Cooperative Oncology Group (ECOG) performance status at the end of the Induction part (0 vs. 1), tumor response to induction chemotherapy (CR/PR vs. SD), and disease stage before administration of induction therapy (IIIB vs. IV). It is postulated that subjects will benefit from maintenance therapy with nab-paclitaxel, therefore a randomization ratio of 2:1 will reduce subject exposure to treatment with BSC alone while providing sufficient data for testing the treatment difference with respect to the primary endpoint, progression free survival.

The Maintenance part of the study is designed to detect a hazard ratio (HR) of 0.60 for PFS improvement with the nab-paclitaxel plus BSC regimen over the BSC alone regimen with 90% power and an overall type-I error rate of 5% (two-sided). The final analysis will be conducted after approximately 182 PFS events (ie, events of disease progression or deaths from any cause) have occurred. Assuming an exponential distribution with a median time to PFS of 2 months for the BSC alone group and proportional hazards, a hazard ratio of 0.60 constitutes a 1.33 months improvement for the nab-paclitaxel plus BSC group over that of the BSC alone group.

A non-binding interim analysis for futility with PFS will be planned at approximately 91 events. The stopping rules and the final marginal significance level are determined based on O'Brien-Fleming type boundaries (O'Brien, 1979). The study may be stopped early for futility if the conditional power is < 10%.

There will be 2 analyses for the OS endpoint. The interim analysis (non-binding) of OS will be conducted based on the number of deaths observed at the time of the final PFS analysis. However, all subjects will continue to be followed for OS up to 1.5 years after final analysis of approximately 182 PFS events or approximately 218 deaths have been observed for the final OS analysis, whichever is earlier. The marginal significance levels for OS are determined based on O'Brien-Fleming type boundaries and will be adjusted based on the actual number of deaths observed at each stage.

A Step-down procedure from PFS to OS will be used to control the family-wise two-sided Type-I error rate to 5%.

Efficacy Analyses

The Maintenance part of the study starts on the date the subject is randomized to either of the treatment arms. All efficacy analyses in the Maintenance part will be based on the ITT population, which includes all randomized subjects regardless of whether they receive any IP or have any efficacy assessments collected.

The primary efficacy endpoint is PFS based on investigator's assessment of the subject's radiologic response using RECIST 1.1 guidelines. Baseline tumor measurements will be determined by the computed tomography (CT)-scan performed less than 28 days before the first dose of nab-paclitaxel in the Induction part of the study. Progression-free survival will be counted from the date of randomization to the start of disease progression or subject death from any cause, whichever occurs first. Subjects who do not have disease progression or have not died as of the data cutoff date for the statistical analysis will be censored at the time of the last radiologic assessment prior to the data cutoff date. Rules for censoring for missing visits and start of anticancer treatment are provided in Section 10.

The null (H_o) and alternative (H_a) hypotheses for the primary efficacy endpoint are:

H_o: HR $_{nab\text{-paclitaxel plus best supportive care / best supportive care}} = 1$

H_a: HR $_{nab\text{-paclitaxel plus best supportive care / best supportive care}} \neq 1$

Progression-free survival will be summarized using the Kaplan-Meier method and by median PFS time (including two-sided 95% CI) for each treatment regimen along with the hazard ratio (including two-sided 95% CI). The Kaplan-Meier curve for PFS will be presented graphically for each treatment regimen and differences in the curves will be tested using a stratified log-rank test with the 3 baseline and prognostic factors described above.

Secondary efficacy endpoints include OS and ORR (percent of subjects who attain a CR or PR according to RECIST 1.1 guidelines as determined by the investigator and confirmed by repeat assessments performed no less than 28 days after the criteria for response are first met). Overall survival will be analyzed by the same method described for PFS, while ORR will be analyzed by chi-square test.

Safety Analyses

The safety population includes all randomized subjects in the BSC alone arm and those who receive at least one dose of nab-paclitaxel in the nab-paclitaxel plus BSC arm in the Maintenance part of the study. Adverse events will be summarized by worst severity grade. AEs, as well as treatment-emergent AEs, will be summarized by system organ class, and preferred term. Adverse event severity/grade will be summarized by NCI CTCAE v4.0.

Laboratory test results will not be collected in the eCRFs unless they are determined to be clinically significant laboratory abnormalities. Abnormal and clinically significant laboratory assessments at Screening will be recorded as medical history, and after Screening, as AE or serious adverse event (SAE). If a clinically significant laboratory abnormality is captured as medical history, AE, or SAE, the specific laboratory parameter(s) should be recorded on the laboratory assessments CRF.

Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be established with the responsibilities for safeguarding the interests of study participants and monitoring the overall conduct of the study. Final recommendations of the DMC will reflect the judgment of the DMC members and will be considered advisory in nature to the Sponsor. The decision to implement the recommendations of the DMC will be made by the Sponsor, following consultation with the trial Coordinating Principal Investigator and Steering Committee. A DMC charter will be established.

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1. INTRODUCTION

1.1. Non-small Cell Lung Cancer (NSCLC)

Lung cancer is the leading cause of cancer-related deaths (men and women) worldwide, with 1.2 million new cases diagnosed each year. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for 80% of all new cases. There are an estimated 1.1 million lives lost per year (approximately 500,000 in the United States [US] and European Union [EU] alone) due to NSCLC. Smoking is the causative factor for up to 85% of cases (http://www.lungcancercoalition.org/en/pages/about/awareness).

The majority of patients are not diagnosed until the tumor has progressed beyond the primary site. Despite recent advances in identifying optimal chemotherapy regimens, patients with advanced NSCLC continue to have a poor prognosis (especially those without identifiable biomarkers), with only 10% to 15% of those treated still alive after 2 years of diagnosis.

Platinum-containing chemotherapy regimens remain the standard first-line treatment in the majority of patients, in the US and Japan. In the EU, a third-generation chemotherapeutic agent (docetaxel, gemcitabine, paclitaxel, or vinorelbine), most commonly gemcitabine or vinorelbine, plus a platinum drug is used for advanced NSCLC (NICE, 2011). For first-line therapy in patients with Stage IV NSCLC and good performance status, the American Society of Clinical Oncology (ASCO) clinical practice guideline recommends treatment with a platinum-based two-drug combination of cytotoxic drugs (Azzoli, 2009). A trend that is becoming more prevalent is personalized NSCLC treatment based on tumor histology (squamous vs non-squamous), on molecular characteristics of the tumor, and on the patient's clinical status using agents targeting specific receptors and kinases and pathways (ie, epidermal growth factor receptor [EGFR], echinoderm microtubule-associated protein-like 4 [EML4] and anaplastic lymphoma kinase [ALK] fusion protein).

In advanced NSCLC, the prevalently used combination of solvent-based paclitaxel/carboplatin results in modest response rate, survival, and toxicity. Paclitaxel is currently available in the proprietary product Taxol® (paclitaxel) Injection, manufactured by Bristol-Myers Squibb (New York, NY) and by several other generic drug manufacturers. Taxol consists of paclitaxel dissolved in a proprietary solvent, Cremophor® EL (BASF, Ludwigshafen, Germany), and ethanol. While this solvent system addresses the poor water solubility of paclitaxel, the Taxol formulation has a number of other limitations. For example, Taxol administration requires routine premedication with corticosteroids, diphenhydramine, and H2 antagonists to reduce the incidence of hypersensitivity reactions and histamine release caused by a response to the formulation vehicle (Gelderblom, 2001; Lorenz, 1997; Weiss, 1990). Also, Taxol must be administered over a period of either 3 hours or 24 hours, and requires the use of specialized infusion sets and in-line filters that do not contain di[2-ethylhexyl] phthalate (DEHP).

1.2. nab-Paclitaxel

nab-Paclitaxel has been developed to reduce the toxicities associated with Taxol and the Cremophor EL/ethanol vehicle while maintaining or improving the chemotherapeutic effect of the drug. The Cremophor EL-free medium enables nab-paclitaxel to be given in a shorter

duration without the need for premedication to prevent solvent-related hypersensitivity reactions. In addition, standard tubing and IV bags may be used for the IV administration of nab-paclitaxel.

nab-Paclitaxel for Injectable Suspension is approved for the treatment of metastatic breast cancer, pancreatic cancer and NSCLC. For NSCLC in the US, nab-Paclitaxel is approved for the treatment of patients with locally advanced or metastatic NSCLC, as first-line treatment in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy. The recommended dose of nab-paclitaxel for the NSCLC indication is 100 mg/m^2 administered as an intravenous infusion over 30 minutes on Days 1, 8, and 15 of each 21-day cycle.

The Food and Drug Administration (FDA) approval of nab-paclitaxel was based on the evaluation of Phase I and II data (Rizvi, 2008; Socinski, 2010; Belani, 2008), as well as the pivotal Phase III study: A multicenter, randomized, open-label study was conducted in 1052 chemonaive patients with Stage IIIB/IV non-small cell lung cancer to compare nab-paclitaxel in combination with carboplatin to paclitaxel injection in combination with carboplatin as first-line treatment in patients with advanced non-small cell lung cancer. nab-paclitaxel was administered as an intravenous infusion over 30 minutes at a dose of 100 mg/m^2 on Days 1, 8, and 15 of each 21-day cycle. Paclitaxel injection was administered as an intravenous infusion over 3 hours at a dose of 200 mg/m^2, following premedication. In both treatment arms carboplatin at a dose of AUC = 6 mg*min/mL was administered intravenously on Day 1 of each 21-day cycle after completion of nab-paclitaxel/paclitaxel infusion. Treatment was administered until disease progression or development of an unacceptable toxicity. The primary efficacy outcome measure was overall response rate as determined by a central independent review committee using RECIST guidelines (Version 1.0). In the intent-to-treat (all-randomized) population, the median age was 60 years, 75% were men, 81% were white, 49% had adenocarcinoma, 43% had squamous cell lung cancer, 76% were ECOG PS 1, and 73% were current or former smokers. Patients received a median of 6 cycles of treatment in both study arms. Patients in nab-paclitaxel/carboplatin arm had a statistically significantly higher overall response rate compared to patients in the paclitaxel injection/carboplatin arm [(33% versus 25%), see Table 1]. There was no statistically significant difference in the secondary endpoint OS between the two study arms.

Table 1: Blinded Radiology Assessment of Overall Response Rate (ITT Population)

Variable Category/Statistic	ABI-007/ carboplatin (N=521)	Taxol/ carboplatin (N=531)	Response Rate Ratio (p_A/p_T)	P-value
Patients with Confirmed Complete or Partial Overall Response				
n (%)	170 (33%)	132 (25%)	1.313	0.005*
Confidence Interval (CI) [a]	28.6, 36.7	21.2, 28.5	1.082, 1.593	
Complete Response	0	1 (< 1%)		
Partial Response	170 (33%)	131 (25%)		

Source Data on File

[a] 95% CI of response rate and 95.1% CI of response rate ratio.
Note: P-value is based on a chi-square test.
* Indicates p-value < 0.049

Per protocol, patients were stratified by NSCLC histology (squamous cell carcinoma vs adenocarcinoma vs other histology). Subgroup analyses were performed to assess the influence of squamous vs non-squamous histology on the primary efficacy endpoint of overall response rate (the percentage of patients who achieved an objective confirmed CR or PR based on the blinded radiological review using RECIST response guidelines, Version 1.0). The proportion of patients with squamous cell carcinoma who responded was significantly higher for the ABI-007/carboplatin regimen relative to the Taxol/carboplatin regimen (41% vs 24%: p_A/p_T: 1.680; $p < 0.001$). The proportion of patients with non-squamous cell carcinoma with a confirmed complete or partial overall response was comparable between the ABI-007 and Taxol/carboplatin arms (26% vs 25%: p_A/p_T: 1.034; $p = 0.808$).

Table 2: Blinded Radiology Assessment of Response Rate for Patients with Squamous or Non-squamous Histologies (ITT Subgroups)

Prognostic Factor Category/Statistic/N	ABI-007/ carboplatin	Taxol/ carboplatin	Response Rate Ratio (p_A/p_T)	P-value
Patients with Confirmed Complete or Partial Overall Response				
Squamous cell carcinoma	94/229 (41%)	54/221 (24%)	1.680	< 0.001*
95% Confidence Interval			1.271, 2.221	
Non-squamous cell carcinoma	76/292 (26%)	78/310 (25%)	1.034	0.808
95% Confidence Interval			0.788, 1.358	

Abbreviations: ITT = intent-to-treat
Note: P value is based on a chi-square test.
* Indicates p-value < 0.05.

Adverse reactions were assessed in 514 nab-paclitaxel/carboplatin-treated patients and 524 paclitaxel injection/carboplatin-treated patients. Patients in both treatment arms received a median of 6 cycles of treatment. The following common (≥ 10% incidence) adverse reactions were observed at a similar incidence in nab-paclitaxel plus carboplatin-treated and paclitaxel injection plus carboplatin-treated patients: alopecia 56%, nausea 27%, fatigue 25%, decreased appetite 17%, asthenia 16%, constipation 16%, diarrhea 15%, vomiting 12%, dyspnea 12%, and rash 10% (incidence rates are for the nab-paclitaxel plus carboplatin treatment group). Laboratory-detected abnormalities which occurred with a difference ≥ 5% for nab-paclitaxel plus carboplatin vs paclitaxel injection plus carboplatin (Grades1-4 [and G3-4]) are: anemia (98% vs 91% [28% vs 7%]), neutropenia (85% vs 83% [47% vs 58%]) and thrombocytopenia (68% vs 55% [18% vs 9%]).

1.3. Rationale for Development of nab-Paclitaxel as Maintenance Treatment in Squamous Cell NSCLC

Although significant advances have been made in the treatment options and outcomes of patients with non-squamous NSCLC, progress for patients with squamous cell NSCLC has been disappointing. Furthermore, the data of maintenance therapy that resulted in the FDA approval of pemetrexed (Alimta) and erlotinib (Tarceva), seems to confer benefit (and choice) primarily for non-squamous NSCLC patients.

Both Alimta studies as well as the Tarceva study demonstrated an overall survival benefit with maintenance vs. placebo (Paz-Arez, 2012; Tarceva package insert). However, both of the Alimta maintenance studies showed benefit in non-squamous patients only. Whereas Tarceva showed significant benefit in the non-squamous cell NSCLC patients, only modest improvement was observed in squamous cell NSCLC patients (Neal, 2010).

To date there have been no randomized studies showing benefit of maintenance therapy in squamous NSCLC patients. Therefore, there is still an unmet medical need for maintenance treatment in squamous cell NSCLC.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to evaluate PFS with nab-paclitaxel as maintenance treatment after response or SD with nab-paclitaxel plus carboplatin in subjects with squamous cell NSCLC.

2.2. Secondary Objectives

The secondary objectives of the study are:

- To evaluate the safety and tolerability of nab-paclitaxel as maintenance treatment after response or SD with nab-paclitaxel plus carboplatin in subjects with squamous cell NSCLC.
- To further assess the efficacy with nab-paclitaxel as maintenance treatment after response or SD with nab-paclitaxel plus carboplatin in subjects with squamous cell NSCLC, as measured by secondary efficacy endpoints.

2.3. Exploratory Objectives

The exploratory objectives of the study are:

- To determine baseline tumor characteristics which predict response and resistance to nab-paclitaxel/carboplatin during the Induction part of the study.
- To determine what changes in peripheral tumor characteristics during treatment are associated with acquisition of resistance in the subjects who had initial clinical benefit.
- To evaluate the safety and efficacy of nab-paclitaxel as cross-over (re-induction) treatment after progression during the Maintenance part of the study in subjects with squamous cell NSCLC.
- To assess healthcare resource utilization during the Maintenance part of the study.
- To assess the LCSS and EQ5D.

3. STUDY ENDPOINTS

3.1. Primary Endpoint

Progression free survival from randomization into the Maintenance part of the study.

3.2. Secondary Endpoints

3.2.1. Safety

Safety parameters including AEs and SAEs.

3.2.2. Efficacy

- Overall survival from randomization into the Maintenance part of the study.
- Overall response rate during the Induction and Maintenance parts of the study.

3.3. Exploratory Endpoints

- Overall response rate and disease control rate of subjects in the Cross-over part of the study.
- The correlation between pretreatment tumor characteristics and response and resistance to the study treatment determined using next-generation sequencing methods, immunohistochemistry, or other analysis methods.
- The association between the changes in tumor characteristics and the acquisition of resistance to therapy from plasma samples taken at treatment failure during Maintenance.
- The relationships between variants in subject pharmacogenomics, such as polymorphisms in enzymes involved in drug metabolism, and treatment efficacy and toxicity.
- Healthcare resource utilization during the Maintenance part of the study using a questionnaire including hospitalizations, emergency room visits, doctor or nurse visits, procedures, and/or additional medication.
- Change in the LCSS and EQ5D.

4. OVERALL STUDY DESIGN

4.1. Study Design

This is a Phase III, randomized, open-label, cross-over, multi-center study of nab-paclitaxel plus BSC or BSC alone as maintenance treatment after response or SD with nab-paclitaxel plus carboplatin as induction in subjects with squamous cell NSCLC. Approximately 540 subjects with Stage IIIB/IV squamous cell NSCLC eligible to receive standard treatment of nab-paclitaxel plus carboplatin for 4 cycles will be enrolled in the Induction part of the study. If after the 4 cycles, the subject has a radiologically assessed CR, PR, or SD without clinical progression, they will be randomized (2:1) in the Maintenance part of the study to receive nab-paclitaxel plus BSC or BSC alone. BSC is defined as the best palliative care per investigator (including but not limited to: antibiotics, analgesics, antiemetics, thoracentesis, pleurodesis, blood transfusions, nutritional support, and/or focal external-beam radiation for control of pain, cough, dyspnea, or hemoptysis) excluding antineoplastic agents. Approximately 260 subjects will be evaluable for the primary endpoint of PFS in maintenance. Once a subject in the BSC arm during the Maintenance part of the study experiences radiologic progression of disease, they will be eligible to cross-over to receive nab-paclitaxel.

4.1.1. Induction Part

The main purpose of the Induction part is to identify those subjects who are eligible for randomization in the Maintenance part of the study. Approximately 540 subjects eligible for standard treatment with nab-paclitaxel plus carboplatin for 4 cycles will be enrolled, provided if all inclusion/exclusion criteria are complied within a 28-day screening period prior to Cycle 1 Day 1.

Induction treatment will commence on Cycle 1 Day 1:

- nab-Paclitaxel 100 mg/m^2 IV infusion over 30 minutes on Days 1, 8, and 15 of each 21-day cycle
- Carboplatin AUC = 6 mg*min/mL IV on Day 1 of each 21-day cycle after completion of nab-paclitaxel infusion

Once 4 cycles have been completed for Induction, if the subject has a radiologically assessed CR, PR, or SD, and has met all eligibility criteria, they will continue on to the Maintenance part of the study. If the subject has radiological or clinical PD, they will be discontinued from the study and will not be followed.

4.1.2. Maintenance Part

Once 4 cycles have been completed for Induction, if the subject has a radiologically assessed CR, PR, or SD without clinical progression, they will be screened for eligibility over a 7-day period. Subjects (approximately 260) who satisfy all inclusion/exclusion criteria, will be randomized 2:1 to receive either:

- nab-Paclitaxel 100 mg/m^2 IV infusion over 30 minutes on Days 1 and 8 of each 21-day cycle plus BSC until disease progression (see Section 8.3 for guidelines on

starting dose for the Maintenance part of the study if the subject had dose reduced during the Induction part of the study)

OR

- BSC until disease progression

Maintenance therapy should start at the time of randomization. If this is not possible, a maximum of 7 days will be allowed from the date of randomization to the start date of Maintenance therapy. Subjects must start Maintenance therapy no earlier than 21 days and no later than 35 days from Day 1 of the fourth cycle of Induction therapy.

Randomization will be stratified by disease stage (IIIB vs IV), response in induction (CR/PR vs SD), and performance status (0 vs 1).

4.1.3. Cross-over

A subject in the BSC arm during the Maintenance part of the study who experiences radiological progression of disease, will be eligible to cross-over to receive nab-paclitaxel 100 mg/m^2 IV infusion over 30 minutes on Days 1 and 8 of each 21-day cycle until unacceptable toxicity or discontinuation for any other reason, if the benefit : risk is considered appropriate by the treating investigator (see Section 8.3 for guidelines on starting dose for the Cross-over part of the study if the subject had dose reduced during the Induction part of the study, and Sections 7.2 and 7.3 for eligibility).

4.1.4. Follow-up Period

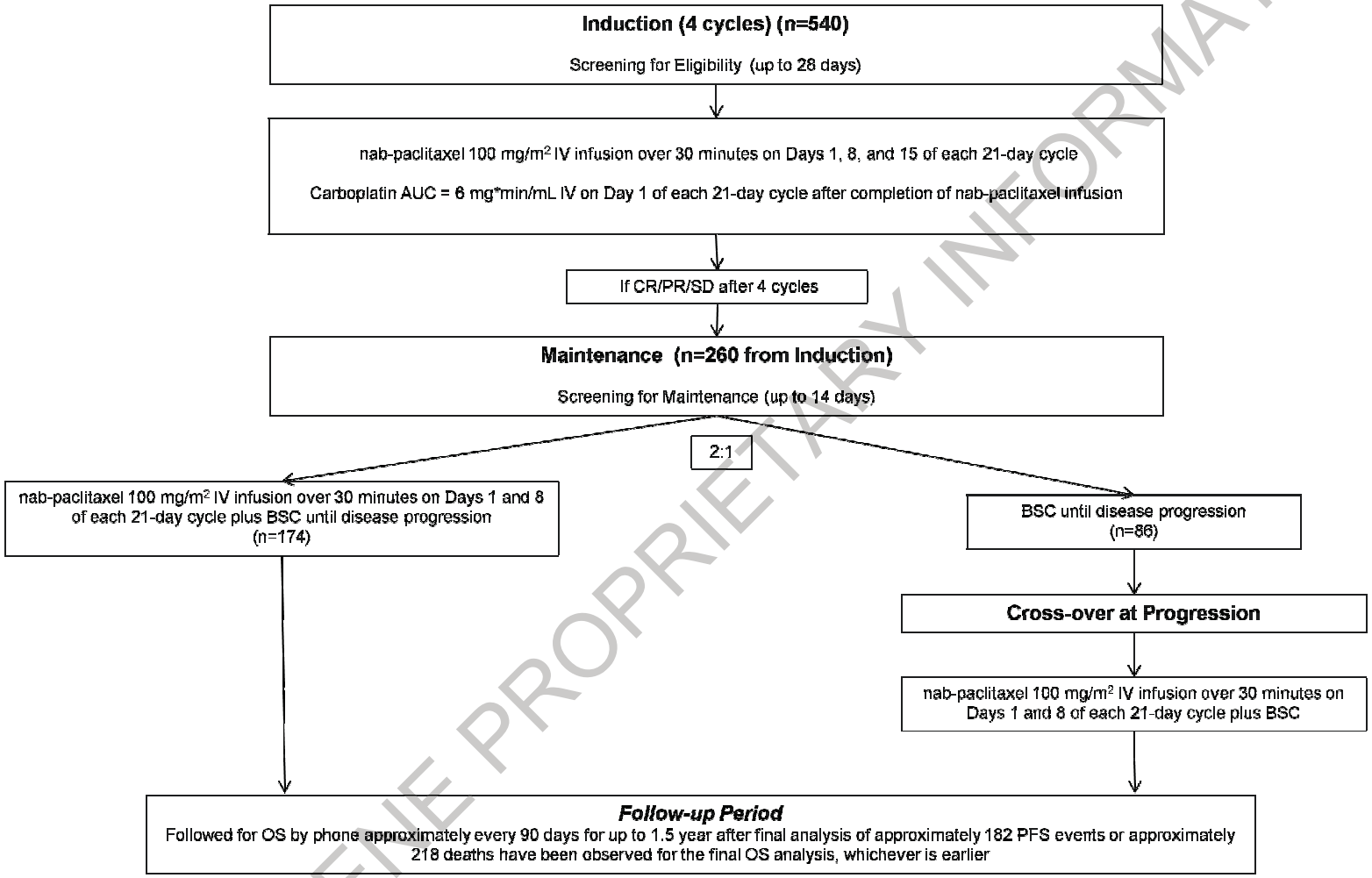
All subjects who discontinue from the Maintenance or Cross-over parts of the study for any reason other than withdrawal of consent, lost to follow-up, or death, will enter the Follow-up period that will have a visit 28 days after progression or discontinuation. Those subjects entering the follow up period without documented progression will continue to have CT scans in accordance with standard of care until documented progression of disease. Additionally, subjects will be followed for OS by phone approximately every 90 days for up to 1.5 year after final analysis of approximately 182 PFS events or approximately 218 deaths have been observed for the final OS analysis, whichever is earlier.

4.2. Study Design Rationale

The results of promising activity with nab-paclitaxel in NSCLC, especially in squamous cell NSCLC, underscore the hypothesis for this Phase III study as a superiority trial to compare nab-paclitaxel/BSC vs BSC as maintenance therapy in subjects with squamous cell NSCLC (randomizing subjects with CR/PR/SD after Induction treatment with nab-paclitaxel/ carboplatin). The nab-paclitaxel regimen used for Induction will be in accordance with the FDA approved label, 100 mg/m^2 administered once per week on Days 1, 8 and 15 of each 21-day cycle with no break combined with carboplatin AUC = 6 mg*min/mL administered on Day 1 every 21 days. Four cycles of doublet-chemotherapy is chosen as the cut-off, based on observed risk:benefit results that additional cycles of doublet chemotherapy did not confer significant advantages (Socinski, 2002); furthermore, 4 cycles of doublet-chemotherapy represents general trends of practice (Stinchcombe, 2009).

The nab-paclitaxel regimen used for Maintenance will be 100 mg/m^2 administered on Days 1 and 8 of each 21-day cycle until progression (the actual starting dose may be adjusted as specified in Section 8.3). The nab-paclitaxel dosing regimen was reduced to Days 1 and 8 of each 21-day cycle in the Maintenance part of the study to decrease potential toxicity and possibly optimize tolerability of treatment and drug exposure in subjects. Sufficient subjects will be enrolled to provide adequate power to compare PFS. The safety and tolerability of nab-paclitaxel will be assessed.

Figure 1: Overall Study Design



4.3. Study Duration

The Induction part of the study will last approximately 36 months to randomize sufficient subjects for the Maintenance part of the study. The total length of this Phase III study with Induction, Maintenance, Cross-over, and Follow-up is estimated to last approximately 5 years.

4.4. End of Trial

The End of Trial is defined as either the date of the last visit of the last subject to complete the study, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as pre-specified in the protocol and/or the Statistical Analysis Plan (SAP), whichever is the later date.

5. TABLE OF EVENTS

Table 3: Table of Events – Induction

Assessment	Screening/ Baseline (up to 28 days)	CYCLE 1 and 3 (21-day)			CYCLE 2 and 4 (21-day)			Every 42 days (-3/+7 days)	Early Treat-ment Discon-tinuation / End of 4 Cycles	Unsched-uled
		Day 1 (C3: ±2 days)	Day 8 (±2 days)	Day 15 (±2 days)	Day 1 (±2 days)	Day 8 (±2 days)	Day 15 (±2 days)			
Informed Consent	X	-	-	-	-	-	-	-	-	-
Medical History	X	-	-	-	-	-	-	-	-	-
Prior Medication and Procedures	X	-	-	-	-	-	-	-	-	-
Serum β-hCG[b]	X	X	-	-	X	-	-	-	X	-
Complete Chest CT Scan (including adrenal gland) with contrast and any other studies required for tumor imaging[c]	X	-	-	-	-	-		X	X	X[a]
Weight	X	X	X	X	X	X	X	-	X	X[a]
Archived Tumor Tissue Sample for Biomarker (biopsy, surgical specimen, or other diagnostic tumor sample)	-	X (C1D1 only)	-	-	-	-	-	-	-	-
Plasma for Biomarker Analyses	-	X (C1D1 only)	-	-	-	-	-	-	X	-
Blood for Pharmacogenomic Analyses	-	X (C1D1 only)	-	-	-	-	-	-	-	-
Body Surface Area (BSA) Calculation and Height[d]	X	-	-	-	-	-	-	-	-	X[a]
ECOG status	X	X	-	-	X	-	-	-	X	X[a]
Concomitant Medication/Procedures	X	X	X	X	X	X	X	X	X	X[a]
Peripheral Neuropathy Assessment[e]	X	X	X	X	X	X	X	-	X	X[a]

Table 3: Table of Events – Induction (Continued)

Assessment	Screening/ Baseline (up to 28 days)	CYCLE 1 and 3 (21-day)			CYCLE 2 and 4 (21-day)			Every 42 days (-3/+7 days)	Early Treat-ment Discon-tinuation / End of 4 Cycles	Unsched-uled
		Day 1 (C3: ±2 days)	Day 8 (±2 days)	Day 15 (±2 days)	Day 1 (±2 days)	Day 8 (±2 days)	Day 15 (±2 days)			
Hematology and Serum Chemistry [f]	X	X	X	X	X	X	X	-	X[a]	X
Adverse Event Evaluation	X	X	X	X	X	X	X	X	X	X[a]
nab-paclitaxel Administration	-	X	X	X	X	X	X	-	-	-
Carboplatin Administration	-	X	-	-	X	-	-	-	-	-
LCSS and EQ5D	-	X	-	-	X	-	-	-	X	-
Electrocardiogram (ECG)	Will be done as per standard of care during the study and as clinically indicated, however results will not be routinely collected in the eCRFs, However if abnormal and clinically significant results, will be collected as AE or SAE and if scans show documented progression of disease will be collected on eCRF.									
CT Scan of Head or Brain Magnetic Resonance Imaging (MRI)										
Bone Scan (X-rays if needed)										
Physical Examination										
Vital Signs										

C3: Cycle 3, eCRF: electronic Case Report Form, C1D1: Cycle 1 Day 1, AE: Adverse Event, SAE: Serious Adverse Event, ECOG: Eastern Cooperative Oncology Group, CT: Computed Tomography, b-HCG: beta human chorionic gonadotropin, RECIST: Response Evaluation Criteria in Solid Tumors, LCSS: Lung Cancer Symptom Scale, EQ5D: EuroQol 5D

[a] If clinically indicated.

[b] A pregnancy test is required for women of child-bearing potential only. For women of child-bearing potential a Serum β-hCG pregnancy test must be performed to assess eligibility at Screening/Baseline and within 72 hours of the first administration of study drug before beginning each new cycle. Note: the screening serum pregnancy test can be used as the test prior to Day 1 study therapy if it is performed within the 72-hour timeframe.

[c] All subjects must have a radiographically documented measurable tumor(s) by RECIST criteria: Complete chest CT scan (including adrenal gland) with and without contrast are performed at Screening, every 42 days (-3/+7 days) while on-treatment (schedule based on calendar, not start of cycle), early termination, and if clinically indicated while on-treatment. The methods of assessment chosen at baseline to follow tumors are to remain consistent throughout study duration. Scans will be archived as per institution standards.

[d] BSA calculated at baseline and recalculated if body weight changes by more than 10% from baseline.

[e] The occurrence of peripheral neuropathy should be reported by the investigator per protocol as an AE or SAE.

[f] Laboratory assessments will be done prior to each nab-paclitaxel treatment by local laboratories as per standard of care during the study and as clinically indicated. The results from laboratory assessments will be captured as per Section 6.18.

Table 4: Table of Events – Maintenance and Cross-over

Assessment	Screening/ Baseline (up to 14 days)	EVERY CYCLE (21-day)		Every 42 days (-3/+7 days)	Early Treatment Discon-tinuation / Disease Progression	28-day Follow-up visit	Survival (every 90 days) up to as specified in Section 6.20	Unsched-uled
		Day 1 (±2 days, except 1st cycle)	Day 8 (±2 days)					
Serum β-hCG[b]	X	X	-	-	X	-	-	-
Complete Chest CT Scan (including adrenal gland) with contrast and any other studies required for tumor imaging [c]	X[g]	-	-	X	X	-	-	X[a]
Weight	X	X	X	-	X	X	-	X[a]
Plasma for Biomarker Analyses		-	-	-	X	-	-	-
Body Surface Area (BSA) Calculation and Height[d]	X	-	-	-	-	-	-	X[a]
ECOG status	X[f]	X	-	-	X	-	-	X[a]
Concomitant Medication/Procedures	X	X	X	X	X	X	X	X[a]
Peripheral Neuropathy Assessment[e]	X	X	X	-	X	X	-	X[a]
Hematology and Serum Chemistry [h]	X	X	X	-	X	X	-	X[a]
Adverse Event Evaluation	X	X	X	X	X	X	-	X[a]
nab-paclitaxel Administration	-	X	X	-	-		-	-
Survival phone call	-	-	-	-	-	-	X	-
Healthcare Resource Utilization Questionnaire	-	X	-	-	X	-	-	-
LCSS and EQ5D	-	X	-	-	X	-	-	-

Table 4: Table of Events – Maintenance and Cross-over (Continued)

Assessment	Screening/ Baseline (up to 14 days)	EVERY CYCLE (21-day)		Every 42 days (-3/+7 days)	Early Treatment Discon-tinuation / Disease Progression	28-day Follow-up visit	Survival (every 90 days) up to as specified in Section 6.20	Unsched-uled
		Day 1 (±2 days, except 1st cycle)	Day 8 (±2 days)					
Electrocardiogram (ECG)	Will be done as per standard of care during the study and as clinically indicated, however results will not be routinely collected in the eCRFs, However if abnormal and clinically significant results, will be collected as AE or SAE and if scans show documented progression of disease will be collected on eCRF.							
CT Scan of Head or Brain Magnetic Resonance Imaging (MRI)								
Bone Scan (X-rays if needed)								
Physical Examination								
Vital Signs								

C1: Cycle 1, eCRF: electronic Case Report Form, AE: Adverse Event, SAE: Serious Adverse Event, ECOG: Eastern Cooperative Oncology Group, CT: Computed Tomography, b-HCG: beta human chorionic gonadotropin, LCSS: Lung Cancer Symptom Scale, EQ5D: EuroQol 5D

[a] If clinically indicated.

[b] A pregnancy test is required for women of child-bearing potential only. For women of child-bearing potential a Serum β-hCG pregnancy test must be performed to assess subject eligibility at Screening/Baseline and within 72 hours of the first administration of study drug before beginning each new cycle. Note; the screening serum pregnancy test can be used as the test prior to Day 1 study therapy if it is performed within the 72-hour timeframe.

[c] Complete chest CT scan (including adrenal gland) with and without contrast is performed at baseline, every 42 days (-3/+7 days) while on-treatment (schedule based on calendar, not start of cycle), early termination, and if clinically indicated while on-treatment. The methods of assessment chosen at baseline to follow tumors are to remain consistent throughout study duration. Scans will be archived as per institution standards. Those subjects entering the follow up period without documented progression will continue to have CT scans in accordance with standard of care until documented progression of disease.

[d] BSA calculated at baseline and recalculated if body weight changes by more than 10% from baseline.

[e] The occurrence of peripheral neuropathy should be reported by the investigator per protocol as an AE or SAE.

[f] The ECOG performance status must be 0 or 1 for subjects to start maintenance treatment.

[g] Induction End of Cycle 4 information may serve as baseline for Maintenance.

[h] Laboratory assessments will be done prior to each nab-paclitaxel treatment by local laboratories as per standard of care during the study and as clinically indicated. The results from laboratory assessments will be captured as per Section 6.18.

6. PROCEDURES

Subjects will be provided with a written informed consent form (ICF), given the opportunity to ask any questions concerning the study, and will sign an ICF prior to participating in any study procedures. After giving written informed consent, subjects will undergo a screening period to be assessed for eligibility. All subjects who sign an ICF must be screened into the Interactive Voice Response System (IVRS) immediately upon signature on the document. Subjects who do not meet the inclusion/exclusion criteria will be considered screening failures and will not be eligible for the study. Subjects that have satisfied all eligibility criteria after the screening period will be eligible to be enrolled. Subjects who screen fail may re-screen up to 3 times and an ICF will need to be signed at each re-screen, as well as all screening procedures repeated (some procedures may not need to be done if previously done within 28 days prior to screening again).

6.1. Medical History

A complete medical history including, but not limited to, evaluation for past (up to 5 years) or present cardiovascular, respiratory, gastrointestinal, renal, hepatic, neurological, endocrine, lymphatic, hematological, immunologic, dermatological, psychiatric, genitourinary, obstetrical, surgical history or any other diseases or disorders will be performed at Screening.

6.2. Prior Medications/Procedures

All prior medications/procedures within 28 days of time of signature on the ICF should be recorded. All NSCLC-related prior medications/procedures should be recorded regardless of time.

6.3. Pregnancy Testing

Serum pregnancy test with sensitivity of at least 25 mIU/mL is to be obtained in females of childbearing potential (FCBP) at Screening for Induction, Maintenance and Cross-over. A serum pregnancy test must be done within 72 hours prior to Cycle 1 Day 1 of starting study therapy, repeated before beginning each new cycle, and at discontinuation or end of treatment. The subject may not receive treatment until the investigator has verified that the result of the pregnancy test is negative. See inclusion criteria for pregnancy testing requirements. Any pregnancies that occur in women who have received study drug must be immediately reported to Celgene Drug Safety (See Section 11.4).

6.4. Complete Chest Computed Tomography (CT) Scan (including adrenal gland) With and Without Contrast

Complete Chest CT Scan (including adrenal gland) with and without contrast and any other studies required for tumor imaging will be done at Screening, every 42 days (-3/+7 days) (schedule for scans will be based on calendar, not start of cycle), and at Early Treatment Discontinuation/End of Cycle 4 during the Induction part of the study. During the Maintenance and Cross-over parts of the study scans will be done every 42 days (-3/+7 days) (schedule for scans will be based on calendar, not start of cycle) and at Early Treatment Discontinuation/Disease Progression. Additional CTs may be done at any time during the study

if clinically indicated. CT scans are preferred, however MRI would be acceptable. The same scanning modality for lesion assessment should be used throughout the study. All scans and reports should be archived as per institution standards.

6.5. Weight

Weight will be collected at every visit during the Induction, Maintenance, and Cross-over parts of the study. Additional weights may be collected at any time during the study as needed.

6.6. Body Surface Area (BSA) Calculation and Height

BSA and height will be collected and calculated at Screening during Induction, Maintenance, and Cross-over parts of the study. BSA may be recalculated if body weight changes by more than 10% from baseline.

6.7. ECOG Performance Score

ECOG performance score will be collected at Screening, Day 1 of every cycle and at Early Treatment Discontinuation/End of Cycle 4 during the Induction part of the study. During the Maintenance and Cross-over parts of the study, ECOG performance score will be collected at Screening, Day 1 of every cycle, and at Early Treatment Discontinuation/Disease Progression. Additional ECOG may be collected at any time during the study as needed.

6.8. Concomitant Medications/Procedures

All subjects will have concomitant medications and procedures recorded from the time of signature on the ICF until progression during the Induction part of the study or the 28-day follow-up visit during the Maintenance part of the study or after Cross-over. Only NSCLC associated concomitant medications/procedures will be recorded, including BSC. During survival follow-up, anti-cancer treatment information will be collected, if available.

6.9. Peripheral Neuropathy Assessment

Peripheral neuropathy assessment will be done from the time of signature on the ICF until progression during the Induction part of the study or the 28-day follow-up visit during the Maintenance part of the study or after Cross-over. Additional peripheral neuropathy assessments may be done at any time during the study as needed.

6.10. Adverse Event Reporting

All subjects will have AEs recorded from time of signature on the ICF until progression during the Induction part of the study or the 28 days after the last dose of study drug during the Maintenance part of the study or after Cross-over, including any unscheduled visits. See Section 11 for details.

6.11. Lung Cancer Symptom Scale Questionnaire and EQ5D

The Lung Cancer Symptom Scale (LCSS) and (EQ-5D) questionnaires will be used to measure quality of life (QoL) for subjects in the trial. The LCSS is a 9 question analysis the subject completes using a visual analogue scale (VAS) to denote intensity of a symptom. The EQ-5D

comprises 5 questions on mobility, self-care, usual activities, pain/discomfort, anxiety/depression and a VAS for overall QoL. These questionnaires will be completed at Day 1 of every cycle, and at Early Treatment Discontinuation/End of Cycle 4 during the Induction part of the study. During the Maintenance and Cross-over parts of the study, at Day 1 of every cycle, and at progression of disease. The quality of life data generated from these questionnaires will be analyzed per the description in the SAP.

6.12. Healthcare Resource Utilization Questionnaire

A healthcare resource utilization questionnaire will be used to capture the additional use of healthcare resources, including hospitalizations, emergency room visits, doctor or nurse visits, procedures, and/or additional medication during the study period. The assessment will be completed at Day 1 of every cycle, and at progression of disease during the Maintenance and Cross-over parts of the study.

6.13. Electrocardiogram

Electrocardiograms (ECGs) will be done as per standard of care during the study and as clinically indicated, however results will not be collected in the eCRFs (if results are abnormal and clinically significant at Screening, they will be recorded as medical history, and if results are abnormal and clinically significant after Screening, they will be recorded as AE or SAE).

6.14. CT Scan of Head or Brain Magnetic Resonance Imaging (MRI)

CT scan of head or brain MRI will be done as per standard of care during the study and as clinically indicated, however results will not be collected in the eCRFs. If scans show progression of disease, this information will be collected on eCRF.

6.15. Bone Scans and X-rays

Bone scans and x-rays will be done as per standard of care during the study and as clinically indicated, however results will not be collected in the eCRFs. If scans show progression of disease, this information will be collected on eCRF.

6.16. Physical Examinations

Physical examinations will be done as per standard of care during the study and as clinically indicated, however results will not be collected in the eCRFs (if results are abnormal and clinically significant at Screening, they will be recorded as medical history, and if results are abnormal and clinically significant after Screening, they will be recorded as AE or SAE).

6.17. Vital Signs

Vital signs will be done as per standard of care during the study and as clinically indicated, however results will not be collected in the eCRFs (if results are abnormal and clinically significant at Screening, they will be recorded as medical history, and if results are abnormal and clinically significant after Screening, they will be recorded as AE or SAE).

6.18. Laboratory Assessments

Laboratory assessments will be done prior to each nab-paclitaxel treatments by local laboratories as per standard of care during the study and as clinically indicated, however results will not be collected in the eCRFs unless they are determined to be clinically significant laboratory abnormalities. It is the responsibility of the Investigator to assess the clinical significance of all abnormal values as defined by the reference ranges from the local laboratory. Abnormal and clinically significant laboratory assessments at Screening will be recorded as medical history, and after Screening, as AE or SAE (clinically significant laboratory abnormalities at Screening may result in a subject being ineligible for the study and should not be captured as an AE). If a clinically significant laboratory abnormality is captured as medical history, AE, or SAE, the specific laboratory parameter(s) should be recorded on the laboratory assessments CRF. Any abnormal values that persist should be followed at the discretion of the Investigator. The Investigator should file all copies of the reports, including faxes with the subject's medical chart.

6.19. Tumor Tissue Sample Collection and Peripheral Blood Collection (Exploratory Assessments)

If archival tumor biopsy blocks or (preferably) surgical specimens from subjects with prior resections are available, 10 or more slides of at least 4 um thickness will be collected at Cycle 1 Day 1 of Induction. Additionally a core of an area representing viable tumor epithelium be collected from the block. If the amount of tumor tissue available is not sufficient, fewer slides may be collected.

If a fine needle aspirate (FNA) specimen is available, slides of at least 4 um thickness will be collected with the goal of obtaining at least 100,000 cells (preferably more) of material. If sufficient material cannot be collected, fewer slides/cells may be collected.

If only other types of diagnostic samples such as endoscopies, lavage, or sputum are available, this material should be optionally collected when possible, and collection is strongly encouraged when tissue such as endoscopy samples with multiple needle passes exists in quantities comparable to a core biopsy. In this instance, 10 slides and a core sample of tumor tissue should be collected as per biopsy and surgical samples above.

Plasma for biomarker analyses will be collected on Day 1 of Cycle 1 during Induction and at progression during the Maintenance and Cross-over parts of the study. When progression occurs during Induction and before Cycle 4, a plasma sample will be collected at the time of study withdrawal.

Peripheral blood will be collected for pharmacogenomic analyses on Cycle 1 Day 1 of Induction. This sample will be collected in a CPT tube and shipped on dry ice to the central lab for processing to Peripheral Blood Mononuclear Cells (PBMC) and stored as a frozen pellet.

Types of techniques planned to be used for tumor and blood analyses include:

- Gene expression by RNA sequencing
- Immunohistochemistry
- DNA sequencing

Details regarding the collection, storage, and shipment of the samples are given in the Laboratory Manual.

6.20. Survival

After discontinuation from the Maintenance or Cross-over part of the study, the subjects will be followed for survival by phone approximately every 90 days for up to 1.5 year after final analysis of approximately 182 PFS events, or approximately 218 deaths have been observed for the final OS analysis, whichever is earlier. The subjects will also be asked questions of other medications they may be taking for their NSCLC.

7. STUDY POPULATION

7.1. Number of Subjects and Sites

Subjects with squamous cell NSCLC stage IIIB or IV with no prior chemotherapy for metastatic disease who are ≥ 18 years old will be eligible for this study. The Induction part of the study will enroll approximately 540 subjects. Based on results from the nab-Paclitaxel Phase 3 NSCLC development study (Protocol CA031) it is estimated that approximately 260 subjects with CR, PR, or SD from the Induction part of the study will be randomized to the Maintenance part of the study. Enrollment into the Induction part of the study will be monitored and adjusted to ensure that approximately 260 subjects are randomized into the Maintenance part of the study. The study will be conducted at approximately 120 sites in the United States.

7.2. Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the Induction, Maintenance, and Cross-over parts of the study (except if specified at study entry only):

General and Demographics

1. Age ≥ 18 years of age at the time of signing the ICF.
2. Understand and voluntarily provide written consent to the ICF prior to conducting any study related assessments/procedures.
3. Able to adhere to the study visit schedule and other protocol requirements

Disease Specific

4. Histologically or cytologically confirmed Stage IIIB or IV squamous cell NSCLC at study entry.
5. No prior history of other malignancies, except basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ of the cervix.
6. Radiographically documented measurable disease at study entry (as defined in Appendix A; lesions in previously irradiated areas [or areas with local therapy] should not be selected as target lesions, unless there has been demonstrated progression in the lesion).
7. No prior chemotherapy for the treatment of metastatic disease at study entry. Adjuvant chemotherapy is permitted providing cytotoxic chemotherapy was completed 12 months prior to starting the study and without disease recurrence.
8. Absolute neutrophil count (ANC) ≥ 1500 cells/mm^3.
9. Platelets ≥ 100,000 cells/mm^3.
10. Hemoglobin (Hgb) ≥ 9 g/dL.
11. Aspartate transaminase (AST/serum glutamic oxaloacetic transaminase [SGOT]), alanine transaminase (ALT/serum glutamic pyruvic transaminase [SGPT]) ≤ 2.5 × upper limit of normal range (ULN) or ≤ 5.0 × ULN if liver metastases.

12. Total bilirubin ≤ 1.5 × ULN except in cases of Gilbert's disease and liver metastases.
13. Creatinine ≤ 1.5 mg/dL.
14. Expected survival of > 12 weeks for the Induction part of the study.
15. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
16. For Maintenance part of the study, subjects must have received at least one dose of nab-paclitaxel in each of the 4 cycles during Induction

Pregnancy

17. Females of childbearing potential [defined as a sexually mature woman who (1) have not undergone hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or (2) have not been naturally postmenopausal for at least 24 consecutive months (ie, has had menses at any time during the preceding 24 consecutive months)] must:

    a. Have a negative pregnancy test as verified by the study doctor prior to starting study therapy. She must agree to ongoing pregnancy testing during the course of the study, and after end of study therapy. This applies even if the subject practices true abstinence* from heterosexual contact.
    b. Either commit to true abstinence* from heterosexual contact (which must be reviewed on a monthly basis) or agree to use, and be able to comply with, effective contraception without interruption, 28 days prior to starting study drug, during the study therapy (including dose interruptions), and for 3 months after discontinuation of study therapy.

    Male subjects must:

    c. practice true abstinence* or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 3 months following study drug discontinuation, even if he has undergone a successful vasectomy.

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

18. Females must abstain from breastfeeding during study participation and 3 months after IP discontinuation.

7.3. Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment into the Induction, Maintenance, or Cross-over parts of the study (except if specified at study entry only):

1. Evidence of active brain metastases, including leptomeningeal involvement (prior evidence of brain metastasis are permitted only if treated and stable and off therapy for ≥ 42 days prior to signing ICF).
2. Only evidence of disease is non-measurable at study entry.
3. Preexisting peripheral neuropathy of Grade 2, 3, or 4 (per CTCAE v4.0).

4. Venous thromboembolism within 6 months prior to signing ICF.
5. Current congestive heart failure (New York Heart Association class II-IV).
6. Myocardial infarction (MI) within 6 months prior to signing ICF.
7. Treatment with any investigational product within 28 days prior to signing ICF.
8. History of allergy or hypersensitivity to nab-paclitaxel or carboplatin.
9. Currently enrolled in any other clinical protocol or investigational trial that involved administration of experimental therapy and/or therapeutic devices.
10. Any other clinically significant medical condition and/or organ dysfunction that will interfere with the administration of the therapy according to this protocol.
11. Any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study.
12. Any condition that confounds the ability to interpret data from the study.
13. Pregnant and nursing females.

8. DESCRIPTION OF STUDY TREATMENTS

8.1. Description of Investigational Product(s)

Induction

Subjects will receive open-label nab-paclitaxel and carboplatin during the Induction part of the study as non-investigational products and will not be supplied by Celgene. Investigative sites will use standard of care (commercially available) product via prescription.

Maintenance and Cross-over

Subjects will be randomized to receive nab-paclitaxel plus BSC or BSC alone during the Maintenance part of the study. Once a subject in the BSC alone arm during the Maintenance part of the study experiences radiologic progression of disease, they will be eligible to cross-over to receive nab-paclitaxel. The nab-paclitaxel used in the Maintenance and Cross-over parts of the study is designated as IP and will be packaged and supplied by Celgene Corporation.

The preparation for IV administration procedures should be followed as per package insert.

8.1.1. nab-Paclitaxel

nab-Paclitaxel will be supplied by the Sponsor, Celgene Corporation, for the Maintenance and Cross-over parts of the study in single-use vials in single count cartons. Each single-use 50 mL vial will contain paclitaxel (100 mg) and approximately 900 mg human albumin as a stabilizer.

Unreconstituted nab-paclitaxel should be stored in accordance with the product label. Reconstituted nab-paclitaxel should be used immediately. If not used immediately, the vial of reconstituted nab-paclitaxel must be placed in its carton and be placed in a refrigerator at 2° to 8°C (36° to 46°F) for a maximum of 8 hours, the time of reconstitution should be recorded to ensure compliance with the 8 hour requirement. Both forms should be stored in an area free of environmental extremes and must be accessible only to study personnel.

Temperature records for nab-paclitaxel must be made available to Celgene or other Sponsor-nominated monitoring teams for verification of proper study drug storage.

8.1.2. Carboplatin

Carboplatin is a platinum coordination compound that is used as a cancer chemotherapeutic agent. The chemical name for carboplatin is platinum diammine [1,1-cyclobutanedicarboxylato (2-)0,0']-,(SP-4-2). Carboplatin is a crystalline powder with the molecular formula of $C_6H_{l2}N_20_4Pt$ and a molecular weight of 371.25. It is soluble in water at a rate of approximately 14 mg/mL, and the pH of a 1% solution is 5 to 7. It is virtually insoluble in ethanol, acetone, and dimethylacetamide.

For additional information about carboplatin storage, preparation, and administration please refer to the package insert.

8.2. Treatment Administration and Schedule

Induction

The main purpose of the Induction part is to identify those subjects who are eligible for randomization in the Maintenance part of the study. Approximately 540 subjects will be treated with nab-paclitaxel plus carboplatin for 4 cycles.

Induction treatment will commence on Day 1, in accordance with standard of care of 1st line treatment of metastatic NSCLC:

- nab-Paclitaxel 100 mg/m^2 IV infusion over 30 minutes on Days 1, 8, and 15 of each 21-day cycle
- Carboplatin AUC = 6 mg*min/mL IV on Day 1 of each 21-day cycle after completion of nab-Paclitaxel infusion

Maintenance Part

Once 4 cycles have been completed for Induction, if the subject has a radiologically assessed CR, PR, or SD without clinical progression, they will be randomized 2:1 (approximately 260 subjects) to receive:

- nab-Paclitaxel 100 mg/m^2 IV infusion over 30 minutes on Days 1 and 8 of each 21-day cycle plus BSC until disease progression (the actual starting dose may be adjusted as specified in Section 8.3)

OR

- BSC until disease progression

Maintenance therapy should start at the time of randomization. If this is not possible, a maximum of 7 days will be allowed from the date of randomization to the start date of Maintenance therapy. Subjects must start Maintenance therapy no earlier than 21 days and no later than 35 days from Day 1 of the fourth cycle of Induction therapy.

Cross-over Part

A subject in the BSC arm during the Maintenance part of the study experiences radiologic progression of disease, they will be eligible to cross-over to receive nab-paclitaxel 100 mg/m^2 IV infusion over 30 minutes on Days 1 and 8 of each 21-day cycle until unacceptable toxicity or discontinuation for any other reason, if the benefit : risk is considered appropriate by the treating investigator (see Section 8.3 for guidelines on starting dose for the Cross-over part of the study if the subject had dose reduced during the Induction part of the study, and Sections 7.2 and 7.3 for eligibility).

Subjects may receive BSC as needed per Investigator discretion and should be recorded.

All IP will be administered by the clinical site and administration will be documented in the study source record.

8.3. Dose Modifications

Subjects will be evaluated for AEs at each visit with the NCI CTCAE v4.0 used as a guide for the grading of severity. The dose of nab-paclitaxel and carboplatin for each subject will be modified following toxicity as described in Table 5.

Subjects who experience any of the adverse drug reactions in Table 5 will be dose reduced as per Table 5 during the Induction, Maintenance, or Cross-over parts of the study. If a subject is dose reduced in the Induction part of the study, please refer to Table 5 for guidelines on dose and schedule for the Maintenance and Cross-over parts of the study.

- Do not administer nab-paclitaxel on Day 1 of a cycle until ANC is at least 1500 cells/mm^3 and platelet count is at least 100,000 cells/mm^3.
- In subjects who develop severe neutropenia or thrombocytopenia, on Day 1 of any cycle, withhold treatment until the ANC recovers to at least 1500 cells/mm^3 and the platelet count recovers to at least 100,000 cells/mm^3. On Days 8 and 15 the ANC should recover to at least 500 cells/mm^3 and platelet count of at least 50,000 cells/mm^3. When dosing is resumed, the subject should be dosed at the next lower dose level of nab-paclitaxel and carboplatin as outlined in Table 5.
- Withhold nab-paclitaxel for Grade 3 or 4 peripheral neuropathy. Resume nab-paclitaxel and carboplatin at reduced doses (Table 5) when peripheral neuropathy improves to Grade 1 or completely resolves.

Table 5: Permanent Dose Reductions for Hematologic and Neurologic Adverse Events and Dosing for Maintenance and Cross-over Parts of the Study

Dose Modification During Induction, Maintenance and Cross-over				Starting Dose Maintenance	Starting Dose Cross-over
Adverse Drug Reaction	**Occurrence**	**Weekly nab-paclitaxel Dose (mg/m^2)**	**Every 21-Days Carboplatin Dose (AUC mg•min/mL)**	**nab-paclitaxel Dose (mg/m^2) Days 1 and 8 of each 21-day Cycle**	**nab-paclitaxel Dose (mg/m^2) Days 1 and 8 of each 21-day Cycle**
Neutropenic Fever (ANC < 500/mm^3 with fever >38°C) OR Delay of next cycle by > 7 days for ANC < 1500/mm^3 OR ANC < 500/mm^3 for > 7 days	First	75	4.5	If subject at 100, 75 or 50 at end of Induction and ANC > 1500/mm^3, will start at 100, 100 or 75 respectively during Maintenance and Cross-over	
	Second	50	3		
	Third	Discontinue Treatment			
Platelet count < 50,000/mm^3	First	75	4.5	If subject at 100 or 75 at end of Induction and platelet > 100,000/mm^3, will start at 100 during Maintenance and Cross-over	
	Second	Discontinue Treatment			
Sensory Neuropathy Grade 3 or 4	First	75	4.5	If subject at 100, 75 or 50 at end of Induction and Grade 1 or no peripheral neuropathy, will start at 100, 100 or 75 respectively during Maintenance and Cross-over	
	Second	50	3		
	Third	Discontinue Treatment			

ANC: Absolute Neutrophil Count

8.4. Method of Treatment Assignment

The Induction, Maintenance and Cross-over parts of the study are open-label. In the Maintenance part of the study, subjects will be randomized 2:1 to nab-paclitaxel plus BSC or BSC alone. Enrollment/randomization will occur via IVRS for all parts of the study.

8.5. Packaging and Labeling

The label(s) for IP (nab-paclitaxel) will include Sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

8.6. Investigational Product Accountability and Disposal

Celgene (or designee) will review with the Investigator and relevant site personnel the process for IP return, disposal, and/or destruction including responsibilities for the site vs. Celgene (or designee).

Celgene will instruct the Investigator on the return, disposal and/or destruction of IP and/or medical device materials if applicable. Only completely unused IP vials should be retained by the site until a representative from Celgene or other Celgene-designated personnel have completed an inventory. Partially used an completely used vials should be destroyed according to local guidelines, and disposition should be recorded on the Investigational Drug Accountability Record Form.

The investigator, or designee, shall record the dispensing of IP to subjects in an IP accountability record. The IP record will be made available to Celgene, or other authorized Celgene-designated monitoring personnel for the purpose of accounting for the IP supply. Inspections of the IP supply for inventory purposes and assurance of proper storage will be conducted as necessary. Any significant discrepancy will be recorded and reported to Celgene or their designee and a plan for resolution will be documented.

Investigational product will not be loaned or dispensed by the investigator to another investigator or site. Under certain circumstances, and with sponsor permission, cooperative groups may manage IP between locations within their network as clinical trial agreement and local guidelines permit.

8.7. Investigational Product Compliance

All IP will be administered only by study site personnel and accurate recording of all IP administration will be made in the appropriate section of the subject's eCRF and source documents.

8.8. Overdose

Overdose, as defined for this protocol, refers to nab-paclitaxel or carboplatin dosing only.

On a per dose basis, an overdose is defined as 10% over the protocol-specified dose of nab-paclitaxel or carboplatin to a given subject, regardless of any associated adverse events or sequelae.

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

On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form. See Section 11.1 for the reporting of adverse events associated with overdose.

9. CONCOMITANT MEDICATIONS AND PROCEDURES

9.1. Permitted Concomitant Medications and Procedures

All supportive care is permitted.

9.2. Prohibited Concomitant Medications and Procedures

Other antineoplastic agents or IP other than what is specified in the protocol is prohibited.

9.3. Required Concomitant Medications and Procedures

Not applicable.

10. STATISTICAL ANALYSES

Statistical analyses for the primary and key secondary endpoints of the Induction and Maintenance parts of the study are described below by study part. Although some definitions for the efficacy and safety endpoints, and the analysis populations are the same for both parts of the study, they are repeated in the respective section to ensure that each part is self-contained. Furthermore, while key analyses for the primary and key secondary endpoints are described in this section, additional analyses of these endpoints as well as exploratory endpoints will be described in details in the SAP.

10.1. Induction Part

10.1.1. Overview

This is the open-label, single-arm, Induction part of the study. Subjects receiving nab-paclitaxel 100 mg/m^2 administered weekly followed by carboplatin at AUC = 6 mg*min/mL on Day 1 of each cycle, repeated every 21 days, for 4 cycles will be enrolled. Subjects will have CT scans performed every 42 days (-3/+7 days). At the end of the 4 cycles, subjects who achieve a radiologically assessed CR, PR, or SD without clinical progression based on the Investigator's evaluation using RECIST 1.1 guidelines, and meet inclusion/exclusion criteria will be randomized in the Maintenance part of the study.

An independent DMC will be established to monitor the study conduct. Details will be provided in the DMC charter.

10.1.2. Study Population Definitions

10.1.2.1. Intent-to-Treat Population

The primary efficacy analysis will be performed on the ITT population, which includes all enrolled subjects regardless of whether the subject receives any dose of nab-paclitaxel or has any efficacy assessments collected.

10.1.2.2. Safety Population

The safety population will be the analysis population for all safety/ tolerability analyses. The safety population includes all subjects enrolled who received at least 1 dose of study treatment. Only subjects with clear documentation that no study treatment was administered will be excluded from the safety population.

10.1.3. Sample Size and Power Considerations

Approximately 540 subjects will be enrolled in the Induction part of the study. This sample size is expected to provide approximately 260 subjects eligible for randomization in the Maintenance part.

In the nab-Paclitaxel Phase 3 NSCLC development study (Protocol CA031), 42% (13/31) and 63% (125/198) of the squamous subjects from the North American and ex-North American sites, respectively, were progression free after 4 cycles of treatment and remained in the study in Cycle

5 and beyond. To be conservative, it is assumed that approximately 50% (270/540) of the subjects in the Induction part of this study will meet the radiologic and clinical progression free criteria at the end of Cycle 4. Furthermore, it is expected that approximately 4% of these 270 subjects will not meet the other inclusion/exclusion criteria for the Maintenance part, yielding a total of approximately 260 subjects entering the Maintenance part of the study.

The actual number of subjects that will be enrolled in the Induction part will be monitored on an ongoing basis and adjusted to ensure that the target number of subjects for the Maintenance part is attained. Enrollment of the Induction part, therefore, could be discontinued early or extended beyond the planned number of 540 subjects.

The ORR is the secondary endpoint in the Induction part. The point estimate and the associated two-sided 95% confidence interval will be calculated for this endpoint. No multiplicity adjustment will be made for this endpoint as no formal inferential testing will be performed.

The percentage of subjects with an AE of Grade 3 or higher peripheral neuropathy will be captured along with the associated two-sided 95% confidence interval without inferential testing.

Table 6 below demonstrates the precision of the estimate for a proportion that can be attained given a sample size of 540. For example, for a hypothetical ORR rate of 40% at the end of Cycle 4, the half-width of the associated two-sided 95% confidence interval will be 4.1%, and the estimated 95% confidence interval will be (35.9%, 44.1%).

Table 6: Precision of the Estimate for a Proportion Given a Sample Size of 540

Endpoint	Hypothetical Event Rate	Half Width[a] of 95% Confidence Interval	two-sided 95% Confidence Interval[a]
Overall Response Rate	35%	4.0%	(31.0% to 39.0%)
	40%	4.1%	(35.9% to 44.1%)
	45%	4.2%	(40.8% to 49.2%)
Peripheral Neuropathy ≥ Grade 3	5%	1.8%	(3.2% to 6.8%)
	10%	2.5%	(7.5% to 12.5%)
	15%	3.0%	(12.0% to 18.0%)

[a] Estimated based on normal approximation.

10.1.4. Background and Demographic Characteristics

The baseline characteristics of all subjects enrolled will be summarized. Subject's age, height, weight, and baseline characteristics will be summarized using descriptive statistics, while gender, race and other categorical variables will be provided using frequency tabulations. Medical history data will be summarized using frequency tabulations by system organ class and preferred term.

10.1.5. Subject Disposition

Subject disposition including the number and percent of subjects enrolled, randomized, treated, and the primary reason for discontinuation of therapy will be summarized by study site. Protocol deviations will be summarized using frequency tabulations.

10.1.6. Efficacy Analysis

10.1.6.1. Primary Purpose

The main purpose of the Induction part is to identify those subjects who are eligible for randomization in the Maintenance part of the study. There is no formal statistical analysis planned for this purpose. Subjects who attain a radiologically assessed CR, PR, or SD without clinical progression according to the investigator's assessment of the scan performed at the end of Cycle 4, based on RECIST 1.1 guidelines, and satisfy the inclusion/exclusion criteria will be eligible to be randomized into the Maintenance part of the study.

10.1.6.2. Secondary Endpoints

10.1.6.2.1. Overall Response Rate

The percentage of subjects who achieve an overall complete or partial response (ORR) according to RECIST 1.1 guidelines as determined by the investigator and confirmed by repeat assessments performed no less than 28 days after the criteria for response were first met will be calculated. The associated two-sided 95% CI of the ORR will be presented.

Given that the confirmation CT-scan for the ORR could be taken after the start of the Maintenance part in which subjects will be receiving either nab-paclitaxel plus BSC or BSC alone, the ORR will be reported for all subjects enrolled as 1 group, and also by the Maintenance treatment regimen, if necessary.

It is important to note that the Induction part is analogous to a 4-cycle fixed duration study with all subjects exiting this part prior to or at the end of Cycle 4. Therefore, the analysis results for all secondary efficacy endpoints should be interpreted accordingly.

10.1.7. Safety Analysis

All subjects who take at least 1 dose of nab-paclitaxel will be included in the safety analyses. Adverse events will be summarized by worst severity grade. AEs, as well as treatment-emergent AEs, will be summarized by system organ class, and preferred term. nab-Paclitaxel-related adverse events, adverse events leading to death or to discontinuation from treatment, events classified as CTCAE Grade 3 or Grade 4, and serious adverse events, and events of interest will be summarized separately.

Cross tabulations will be provided to summarize frequencies of abnormalities.

By subject listings will be provided for all relevant safety data. Graphical displays and figures will be provided where useful to assist in the interpretation of results.

10.1.7.1. Adverse Events

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA).

Adverse events will be analyzed in terms of treatment emergent adverse events (TEAEs), defined as any AEs that began or worsened in grade after the start of nab-paclitaxel to the start of the Maintenance part for those who randomize in the Maintenance part, or through end of treatment of nab-paclitaxel for those who do not randomize in the Maintenance part.

Adverse events will be summarized by system organ class, relative and absolute frequency, severity/grade based on the NCI CTCAE version 4.0 and relationship to treatment. Study medication-related AEs, SAEs, and events leading to discontinuation or death will be listed separately.

10.1.7.2. Laboratory Assessments

Laboratory test results will not be collected in the eCRFs unless they are determined to be clinically significant laboratory abnormalities. Abnormal and clinically significant laboratory assessments at Screening will be recorded as medical history, and after Screening, as AE or SAE. If a clinically significant laboratory abnormality is captured as medical history, AE, or SAE, the specific laboratory parameter(s) should be recorded on the laboratory assessments CRF.

10.1.8. Study Treatment Termination

Reasons for stopping study treatment during the Induction part will be summarized in listings by frequency of occurrence and corresponding percentage of occurrence.

10.1.9. Deaths

Deaths reported during treatment (defined as deaths after the start of nab-paclitaxel to the start of the Maintenance part for those who are randomized in the Maintenance part, or through end of treatment of nab-paclitaxel for those who are not randomized in the Maintenance part) will be summarized by frequency of occurrence and corresponding percentage by cause of death per period.

10.2. Maintenance Part

10.2.1. Overview

This is the open-label, randomized, Maintenance part of the study for the evaluation of the benefit of a maintenance treatment after an initial 4 cycles of Induction treatment for subjects with squamous NSCLC.

Approximately 260 radiologic and clinical progression free subjects from the Induction part will be randomized in the Maintenance part. These subjects will be randomized in a 2:1 ratio to the nab-paclitaxel plus BSC and BSC alone groups, respectively. The nab-paclitaxel group will receive nab-paclitaxel 100 mg/m^2 on Day 1 and 8 of each 21-day cycle plus BSC (the actual starting dose may be adjusted as specified in Section 8.3), while the BSC group will receive the standard BSC. All subjects will receive the assigned regimen until disease progression or unacceptable toxicity. Subjects in the BSC alone group who have radiologic progression will be

eligible to crossover and receive the nab-paclitaxel regimen until unacceptable toxicity or discontinuation for any other reason.

A permuted-block randomization method and an Interactive Voice Response System (IVRS) will be utilized to ensure a central randomization. The randomization will be stratified based on following 3 baseline and prognostic factors:

- ECOG performance status at the end of the Induction part (0 vs. 1)
- Tumor response to induction chemotherapy (CR or PR vs. SD), and
- Disease stage before administration of induction therapy (IIIB vs. IV).

It is hypothesized that subjects will benefit from maintenance treatment with nab-paclitaxel. A randomization ratio of 2:1 will, therefore, minimize subject exposure to treatment with BSC only while providing sufficient data for testing the treatment difference with respect to the primary endpoint, PFS, in the Maintenance part of the study.

A DMC will be used to monitor the study conduct. Details will be provided in the DMC charter.

10.2.2. Study Population Definitions

10.2.2.1. Intent-to-Treat Population

The primary efficacy analysis will be performed on the ITT population, which includes all randomized subjects regardless of whether the subject receives any IP or has any efficacy assessments collected.

10.2.2.2. Response Evaluable Population

Response evaluable population includes all randomized subjects who meet eligibility criteria, take at least one dose of IP or on BSC and have at least one baseline and post baseline efficacy assessment. The response evaluable population may be used for additional analyses which will be described in the SAP.

10.2.2.3. Per-protocol (PP) Population

The PP population is defined as all subjects randomized in the Maintenance part who receive at least one dose of the study therapy and do not have any known major protocol deviations and fulfill the study enrollment criteria. The PP population may be used for additional analyses which will be described in the SAP.

10.2.2.4. Safety Population

The safety population includes all randomized subjects in the BSC alone arm and those who receive at least one dose of nab-paclitaxel in the nab-paclitaxel plus BSC arm in the Maintenance part of the study. The safety population will be the population for all safety analyses.

10.2.3. Sample Size and Power Considerations

Progression free survival is the primary endpoint while OS and ORR are the secondary endpoints in this part of the study.

One non-binding interim analysis for PFS with early stopping rule for futility will be conducted when approximately 91 events are observed. The study may be stopped for futility if conditional power is < 10%.

The final analysis of the primary endpoint will be performed when approximately 182 PFS events have been observed. A total of approximately 260 subjects will need to be randomized assuming an approximate 36 months accrual period and an approximate 2 months follow-up and an approximate 9% per year dropout rate.

This study is designed to provide approximately 90% power to detect a HR of 0.60 for PFS improvement with nab-paclitaxel plus BSC over BSC alone with a two-sided 5% significance level. Assuming an exponential distribution with a median time to PFS of 2 months for the BSC alone and proportional hazard, a hazard ratio of 0.60 constitutes an approximate 1.33 months increase in median PFS or a 40% hazard risk reduction by the nab-paclitaxel plus BSC regimen over that of the BSC alone.

There will be 2 analyses for the OS endpoint. The interim analysis (non-binding) of OS will be conducted based on the number of deaths observed at the time of the final PFS analysis. However, all subjects will continue to be followed for OS up to 1.5 years after final analysis of approximately 182 PFS events or approximately 218 deaths have been observed for the final OS analysis, whichever is earlier. The marginal significance levels for OS will be adjusted according to O'Brien-Fleming type boundary based on the actual number of deaths observed at each stage. For example, if 163 and 218 deaths (~75% information) are observed by the time of the interim and final analyses of OS, respectively, the marginal critical values will be $p \leq 0.01106$ and $p \leq 0.04794$, correspondingly.

Assuming an exponential distribution, proportional hazards, and median OS times of 7.2 and 10.30 months for the BSC alone and nab-paclitaxel plus BSC regimens, respectively, this design provides 70% marginal power to detect a hazard ratio of 0.70 between the 2 maintenance regimens with an overall two-sided 5% significance level.

A step-down procedure from PFS to OS will be used to control family-wise Type-I error rate to 5%. That is, OS will be tested only if the nab-paclitaxel plus BSC regimen demonstrates superiority over the BSC alone with PFS.

As an illustration for timeline projection, assuming an exponential distribution for PFS, a 36-month recruitment period for 260 subjects, and a median PFS of approximately 2.0 months for the BSC alone, it will take approximately 23 months from the first subject randomized to observe 91 PFS events for the interim analysis. The final analysis of PFS (with 182 events) is estimated to take place at approximately 15 months after that, which is approximately 2 months after the last subject randomized.

Assuming an exponential distribution for OS and a median OS of 7.2 months for the BSC arm, it will take approximately an additional 1.5 years follow-up after the final analysis of PFS to observe a total of 218 death events in the entire Maintenance part.

10.2.4. Background and Demographic Characteristics

The baseline characteristics of all randomized subjects will be summarized. Subject's age, height, weight, and baseline characteristics will be summarized using descriptive statistics, while gender, race and other categorical variables will be provided using frequency tabulations.

Medical history data will be summarized using frequency tabulations by system organ class and preferred term.

10.2.5. Subject Disposition

Subject disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent for both treatments and follow-up parts. A summary of subjects enrolled by site will be provided. Protocol deviations will be summarized using frequency tabulations.

10.2.6. Efficacy Analysis

While key analyses are described in this section, additional analyses will be specified in the SAP.

10.2.6.1. Primary Endpoint

The primary endpoint, PFS, will be based on investigator's assessment of response using RECIST 1.1 guidelines. Baseline tumor measurements will be determined from the radiology evaluation performed within 28 days of the start of Induction therapy. Time to Progression will be calculated from the date of randomization (start of Maintenance part) to the first date of progressive disease or death from any cause.

Progression-free survival will be summarized using Kaplan-Meier methods. Subjects who do not have disease progression or have not died as of the data cutoff date for the statistical analysis will be censored at the time of the last radiologic assessment prior to the data cutoff date. In the event that a new anticancer treatment occurs prior to documented progression, the subject will be censored at the time of the last radiologic assessment where the subject was documented to be progression-free prior to the new anticancer treatment. Subjects with a single missing radiologic assessment prior to a visit with documented disease progression (or death) will be analyzed as a PFS event at the time of the radiologic assessment that shows progression or death (whichever is earlier). Subjects with two or more missing radiologic assessments prior to a visit with documented disease progression (or death) will be censored at the time of the last radiologic assessment where the subject was documented to be progression-free prior to the first of the two missing visits.

The null (H_o) and alternative (H_a) hypotheses for testing the primary efficacy endpoint are:

H_o: HR $_{nab\text{-paclitaxel plus best supportive care/ best supportive care}} = 1$

H_a: HR $_{nab\text{-paclitaxel plus best supportive care/ best supportive care}} \neq 1$

Progression-free survival will be summarized by median PFS time (including two-sided 95% CI) for each treatment regimen along with the hazard ratio estimated using Cox proportional hazards model (including two-sided 95% CI). The Kaplan-Meier curve for PFS will be presented graphically for each treatment regimen and differences in the curves will be tested using the stratified log-rank test, where the strata include ECOG performance status at the end of the Induction part (0 vs.1), tumor response to induction chemotherapy (CR or PR vs. SD), and disease stage before administration of induction therapy (IIIB vs. IV), if the number of events in each cell is adequate. Other factors may be included if indicated by the actual population enrolled.

To assess the impact on PFS of radiologic assessments not occurring at the regularly scheduled assessment times, the frequency of these unscheduled/off-scheduled assessments will be presented for each treatment regimen. In addition, confirmatory and sensitivity analyses will be performed to further assess the impact of missed radiologic assessments. An additional analysis of PFS, where death or new treatment will be considered as an event, will be conducted to address the impact of second line therapy.

Additional analyses of PFS calculated from the date of the first dose of Induction therapy will be conducted using the same statistical methods described for PFS measured from the date of randomization above.

10.2.6.2. Key Secondary Endpoints

Key secondary efficacy endpoints include OS and ORR (percent of subjects who had a radiologic complete or partial response according to RECIST 1.1 guidelines determined by the investigator and confirmed by repeat assessments performed no less than 28 days after the criteria for response were first met).

10.2.6.2.1. Overall Survival

Overall survival is defined as the time between randomization and death. All deaths, regardless of the cause of death, will be included. All subjects who are lost to follow-up prior to the end of the trial or who are withdrawn from the trial will be censored at the time of last contact. Subjects who are still receiving treatment as of the data cutoff date will be censored at the cut-off date. Overall survival will be analyzed similarly as PFS.

Additional analyses of OS calculated from the date of the first dose of induction therapy will be conducted using the same statistical methods described for OS calculated from the date of randomization above.

10.2.6.2.2. Overall Response Rate

The percentage of randomized subjects having an overall confirmed CR or PR based on the investigator's assessment using RECIST 1.1 guidelines over the entire study (Induction and Maintenance) will be calculated (scans will be performed every 42 days [-3/+7 days] and confirmation scan will be performed no less than 4 weeks after the criteria for response were first met). Baseline tumor measurements will be determined from the radiology evaluation performed within 28 days of the start of Induction therapy.

The two-sided 95% CI of the response rates will be presented. Differences in response rates between treatment regimens will be tested using chi-square test at a two-sided 5% significance level.

10.2.6.3. Other Secondary Efficacy Endpoints

10.2.6.3.1. Disease Control Rate

Disease Control rate (ie, SD for ≥ 6 weeks or confirmed CR or PR) over the entire study will be analyzed in the same manner as overall response rate. Baseline tumor measurements will be determined from the radiology evaluation performed within 28 days of the start of Induction therapy.

10.2.6.4. Exploratory Endpoints

10.2.6.4.1. Overall Response Rate in Maintenance Part

Tumor reductions during maintenance treatment beyond the response to induction therapy will be explored by the percentage of randomized subjects achieving an overall confirmed CR or PR compared with the radiologic assessment before randomization (i.e, using end of cycle 4 CT-scan as the baseline measurement) according to the investigator's evaluation using RECIST 1.1 guidelines.

The two-sided 95% CI of the response rates will be presented. Differences in response rates between treatment regimens may be tested using chi-square test at a two-sided 5% significance level.

10.2.6.4.2. Response Rate Subsequent to Cross-over to nab-Paclitaxel Regimen

The number and percentage of subjects from the BSC group who cross over to the nab-paclitaxel plus BSC regimen after radiologic disease progression, who subsequently achieve CR or PR will be estimated with the associated two-sided 95% confidence interval.

For this endpoint, baseline tumor measurements will be determined from the radiologic evaluation that renders the subject as having progressive disease by the investigator prior to crossing over to receive the nab-paclitaxel plus BSC regimen.

10.2.6.4.3. Health Care Utilization and Quality of Life Questionnaire

The analysis of health care utilization and quality of life questionnaire will be described in detail in the SAP.

10.2.6.4.4. Biomarkers and Pharmacogenomic Data

Statistical analysis of the biomarkers and pharmacogenomic data collected from the plasma and blood samples will be covered under a separate SAP from that mentioned above.

10.2.7. Safety Analysis

All subjects in the BSC arm and all subjects who take at least 1 dose of nab-paclitaxel in the nab-paclitaxel plus BSC in the Maintenance part will be included in the safety analyses. Adverse events will be summarized by worst severity grade. AEs, as well as treatment-emergent AEs, will be summarized by system organ class, and preferred term. IP-related adverse events, adverse events leading to death or to discontinuation from treatment, events classified as CTCAE Grade 3 or Grade 4 (or moderate/severe if other rating scale is used), and serious adverse events, and events of interest will be summarized separately.

Cross tabulations will be provided to summarize frequencies of abnormalities.

By-subject listings will be provided for all relevant safety data. Graphical displays and figures will be provided where useful to assist in the interpretation of results.

10.2.7.1. Adverse Events

Adverse events will be analyzed in terms of TEAEs, defined as any AE occurring or worsening on or after the first treatment of the study regimen of the Maintenance part through 28 days after the last dose of study regimen administration. In addition, any AE with an onset date more than 28 days after the last dose of IP that is assessed by the investigator as related to study drug will be considered a TEAE. They will be summarized by system organ class, relative and absolute frequency, severity grade based on the NCI CTCAE version 4.0 and relationship to treatment. Study medication-related AEs, SAEs, and events leading to discontinuation or death will be listed separately.

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA, Version 16.0). The severity/intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0); http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40.

Since laboratory test data will not be collected routinely in the eCRFs, this will not be analyzed.

10.2.7.2. Laboratory Assessments

Laboratory tests will be performed weekly prior to nab-paclitaxel administration, as per standard of care during the study and as clinically indicated. Laboratory test results will not be collected in the eCRFs unless they are determined to be clinically significant laboratory abnormalities. Abnormal and clinically significant laboratory assessments at Screening will be recorded as medical history, and after Screening, as AE or SAE. If a clinically significant laboratory abnormality is captured as medical history, AE, or SAE, the specific laboratory parameter(s) should be recorded on the laboratory assessments CRF.

10.2.8. Study Therapy Termination

Reasons for stopping study therapy will be summarized in listings by frequency of occurrence and corresponding percentage of occurrence per study part (Induction and Maintenance) and combined.

10.2.9. Deaths

Deaths reported during treatment (defined as deaths from the first administration of the study Maintenance regimen through 28 days after the last dose of the study Maintenance regimen) and deaths that occur during the follow-up period will be summarized by frequency of occurrence and corresponding percentage by cause of death per period (during treatment or follow-up). Deaths occurring during the entire study (Induction and Maintenance parts) will also be summarized similarly.

10.2.10. Interim Analysis

There will be one non-binding interim analysis for futility for the primary endpoint, PFS, when approximately 91 events (50% information) have been observed. Futility may be declared and the study discontinued if the conditional power at the interim analysis is < 10%. The final analysis of PFS will be performed when approximately 182 PFS events have been observed.

There will be two analyses for the secondary OS endpoint. The interim analysis of OS (for efficacy) will be conducted based on the number of deaths observed up to the time of the final PFS analysis. The final OS analysis will be performed after approximately 218 deaths have been observed, if applicable.

A Step-down procedure from PFS to OS will be used to control the family-wise two-sided Type-I error rate to 5%.

The marginal significance level for OS will be adjusted according to O'Brien-Fleming type of boundary. The nominal two-sided p-values for declaring superiority will be calculated using the statistical software . The analysis and boundaries will be adjusted based on the actual number of deaths observed.

10.3. Data Monitoring Committee

An independent DMC will be established with the responsibilities for safeguarding the interests of study participants and monitoring the overall conduct of the study. Final recommendations of the DMC will reflect the judgment of the DMC members and will be considered advisory in nature to the Sponsor. The decision to implement the recommendations of the DMC will be made by the Sponsor, following consultation with the coordinating PI and Steering Committee. A DMC charter will be established.

10.4. Scientific Steering Committee

The conduct of this trial will be overseen by a Steering Committee. The Steering Committee will serve in an advisory capacity to the Sponsor.

Note: the Steering Committee is separate from the Data Monitoring Committee described in Section 10.3.

11. ADVERSE EVENTS

11.1. Monitoring, Recording and Reporting of Adverse Events

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 11.3), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the CRF rather than the individual signs or symptoms of the diagnosis or syndrome.

For the purposes of this study, progressive disease (PD) of squamous cell NSCLC will not require reporting as an adverse event.

An overdose, accidental or intentional, whether or not it is associated with an AE, or abuse, withdrawal, sensitivity or toxicity to an IP should be reported as an AE. If an overdose is associated with an AE, the overdose and adverse event should be reported as separate terms. See Section 8.8 for the definition of overdose.

In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for nab-paclitaxel, or carboplatin overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or other appropriate tests and procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent to 28 days after the last dose of IP or the End of Study Visit, whichever is longer, and those SAEs made known to the investigator at any time thereafter that are suspected of being related to IP. AEs and serious adverse events (SAEs) will be recorded on the AE page of the CRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

11.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

11.2.1. Seriousness

A serious adverse event (SAE) is any AE occurring at any dose that:

- Results in death;

- Is life-threatening (ie, in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events **not considered** to be SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (ie, planned prior to starting of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the eCRF and the SAE Report Form must be completed.

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to IP, action taken regarding IP, and outcome.

11.2.2. Severity / Intensity

For both AEs and SAEs, the Investigator must assess the severity/intensity of the event.

The severity/intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0) http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40.

Adverse events that are not defined in the NCI CTCAE should be evaluated for severity/intensity according to the following scale:

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
- Grade 4 = Life threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death – the event results in death

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious" which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

11.2.3. Causality

The Investigator must determine the relationship between the administration of IP and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected:	The temporal relationship of the adverse event to IP administration makes **a causal relationship unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	The temporal relationship of the adverse event to IP administration makes **a causal relationship possible**, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

If an event is assessed as suspected of being related to a comparator, ancillary or additional IP that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

11.2.4. Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

11.2.5. Action Taken

The Investigator will report the action taken with IP as a result of an AE or SAE, as applicable (eg, discontinuation or reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

11.2.6. Outcome

The investigator will report the outcome of the event for both AEs and SAEs. All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered, recovered with sequelae, not recovered (death due to another cause) or death (due to the SAE).

11.3. Abnormal Laboratory Values

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

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

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

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

11.4. Pregnancy

All pregnancies or suspected pregnancies occurring in either a female subject or partner of a male subject are immediately reportable events.

11.4.1. Females of Childbearing Potential:

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on IP, or within 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 should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

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 (eg, 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 by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety 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.

11.4.2. Male Subjects

If a female partner of a male subject becomes pregnant while the subject is receiving IP or within 3 months of the last dose of IP, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call her healthcare provider immediately. The IP may need to be discontinued in the male subject, but may be resumed later at the discretion of the Investigator and medical monitor.

11.5. Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the eCRF. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

The Investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject signs informed consent to at least 28 days after the last dose of IP or End of Study Visit, whichever is later) and those made known to the Investigator at anytime thereafter that are suspected of being related to IP. SAEs occurring prior to treatment will be captured.

The SAE report should provide a detailed description of the SAE and include summaries of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Celgene Drug Safety as soon as these become available. Any follow-up data will be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Celgene Drug Safety.

Where required by local legislation, the Investigator is responsible for informing the IRB/EC of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC.

11.5.1. Safety Queries

Queries pertaining to SAEs will be communicated from Celgene Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than five (5) business days. Urgent queries (eg, missing causality assessment) may be handled by phone.

11.6. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to nab-paclitaxel based on the Abraxane and Investigator Brochure. For the purpose of regulatory reporting in the EEA, Celgene Drug Safety will determine the expectedness of events suspected of being related to the other IP, carboplatin, based on the EU Summary of Product Characteristics (SmPC).

For countries within the European Economic Area (EEA), Celgene or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, suspected unexpected serious adverse reactions (SUSARs) in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on IP for human use (ENTR/CT3) and also in accordance with country-specific requirements.

Celgene or its authorized representative shall notify the Investigator of the following information:

- Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (ie, SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all pertinent safety information on file including correspondence with Celgene and the IRB/EC. (See Section 15.3 for record retention information).

Celgene Drug Safety Contact Information:

For Celgene Drug Safety contact information, please refer to the Serious Adverse Event Report Form/Completion Guidelines or to the Pregnancy Report Form/Completion Guidelines.

12. DISCONTINUATIONS

12.1. Study Treatment Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the IP:

- Adverse Event(s)
- Disease progression
- Withdrawal of consent
- Death
- Lost to follow-up
- Protocol violation

All subjects discontinued from nab-paclitaxel for any reason will have a treatment discontinuation visit at the time of nab-paclitaxel discontinuation and should undergo early termination procedures.

All subjects discontinued from nab-paclitaxel will be followed for a period of 28 days after PFS or early discontinuation, or until the date of the last study visit (whichever is longer) for the collection of AEs.

Additionally subjects who withdraw from or complete treatment should not be withdrawn from the study (unless specifically requested) and should be followed up for progressive disease, survival and any new therapy given.

The reason for treatment discontinuation should be recorded in the eCRF and in the source documents.

12.2. Study Discontinuation

The following **are** considered sufficient reasons for discontinuing a subject from the study:

- Withdrawal of consent (decision form the subject not to provide follow-up information)
- Death
- Lost to follow-up

The following **may be** considered a sufficient reason for discontinuing a subject from the study:

- Protocol violation

The reason for study discontinuation should be recorded in the eCRF and in the source documents. The Investigator must notify the Medical Monitor immediately when a subject has been discontinued/withdrawn due to an AE (any unacceptable toxicity). All subjects who are withdrawn from the study should complete all protocol-required evaluations scheduled for early termination at the time of withdrawal.

Since follow-up of subjects who discontinue prematurely is of particular importance, every attempt should be made to collect all survival information and NSCLC treatment/therapy, unless the subject has specifically withdrawn consent from further follow-up. The investigator must make every effort to obtain minimal information regarding the subject's survival status before determining the subject lost to follow-up.

12.3. Subject Replacement

Subjects who discontinue will not be replaced.

13. EMERGENCY PROCEDURES

13.1. Emergency Contact

In emergency situations, the Investigator should contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that the Clinical Research Physician/Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page).This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on call Celgene/Contract Research Organization (CRO) Medical Monitor, who will then contact you promptly.

Note: The back-up 24-hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

14. REGULATORY CONSIDERATIONS

14.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Celgene, its authorized representative, and Investigator abide by Good Clinical Practice (GCP), as described in International Conference on Harmonization (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

14.2. Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. Celgene staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions. The Investigator should maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all subjects who sign an ICF and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of CRFs and queries.

14.3. Subject Information and Informed Consent

The Investigator must obtain informed consent of a legal representative prior to any study related procedures.

Documentation that informed consent occurred prior to the subject's entry into the study and of the informed consent process should be recorded in the subject's source documents including the date. The original ICF signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the subject. In addition, if a protocol is amended and it impacts the content of the informed consent, the ICF must be revised. Subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the ICF. The revised ICF signed and dated by the subject and by the person consenting the subject must be maintained in the Investigator's study files and a copy given to the subject.

14.4. Confidentiality

Celgene affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Celgene requires the Investigator to permit Celgene's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed ICF, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

14.5. Protocol Amendments

Any amendment to this protocol must be approved by the Celgene Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the Investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

14.6. Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, ICF, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

IP can only be supplied to an Investigator by Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by Celgene or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the ICF should also be revised.

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the Investigator (or Coordinating Investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by Celgene and the IRB/EC prior to use.

14.7. Ongoing Information for Institutional Review Board / Ethics Committee

If required by legislation or the IRB/EC, the Investigator must submit to the IRB/EC:

- Information on serious or unexpected adverse events as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

14.8. Closure of the Study

Celgene reserves the right to terminate this study at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, regulatory authorities, etc).

In addition, the Investigator or Celgene has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

15. DATA HANDLING AND RECORDKEEPING

15.1. Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the IP are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of CRFs or CD-ROM.

15.2. Data Management

Data will be entered into the clinical database per Celgene Standard Operating Procedures (SOPs). This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

15.3. Record Retention

Essential documents must be retained by the Investigator for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. The investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed ICFs for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, Celgene, and their authorized representative(s);
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- Record of any body fluids or tissue samples retained;

- All other source documents (subject records, hospital records, laboratory records, etc.);
- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify Celgene if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from Celgene prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask Celgene for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. Investigator/Institution should take measures to prevent accidental or premature destruction of these documents.

16. QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by Celgene or its authorized representative for compliance with applicable government regulations with respect to current GCP and standard operating procedures.

16.1. Study Monitoring and Source Data Verification

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the Investigator and the staff at a study initiation visit and/or at an investigator meeting. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, CRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator. Monitoring will include on-site visits with the Investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, IP storage area, CRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative in accordance with the Study Monitoring Plan.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the CRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the CRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

16.2. Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Celgene. Representatives of this unit will conduct audits of clinical research activities in accordance with Celgene SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The Investigator is required to permit direct access to the facilities where the study took place, source documents, CRFs and applicable supporting records of subject participation for audits and inspections by IRB/IECs, regulatory authorities (eg, FDA, European Medicines Agency [EMA], Health Canada) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

17. PUBLICATIONS

The results of this study may be published in a medical publication, journal, or may be used for teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations. Selection and order of authorship will be based on several considerations, including, but not limited to study participation, contribution to the protocol development, and analysis and input into the manuscript, related abstracts, and presentations in the study.

18. REFERENCES

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19. APPENDICES

Appendix A: Response Evaluation Criteria in Solid Tumors (RECIST 1.1)

Eligibility

- Only subjects with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.
  - Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.
  - Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥ 20 mm using conventional techniques or ≥ 10 mm with spiral CT scan.
  - Non-measurable lesions - all other lesions, including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan), ie, bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques.
- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 28 days before the beginning of the treatment.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.
- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

- When the primary endpoint of the study is objective response evaluation, ultrasound should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response when all lesions have disappeared.
- Cytology and histology can be used to differentiate between PR and CR in rare cases (eg, after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline Documentation of "Target" and "Nontarget" Lesions

- All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.
- All other lesions (or sites of disease) should be identified as nontarget 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.

Response Criteria

Table 7: Evaluation of Target Lesions

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

Table 8: Evaluation of Non-target Lesions

Response	Criteria
Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-Target lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

- Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 28 days after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.
- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol.

Duration of Overall Response

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of Stable Disease

- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.
- The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

Appendix B: ECOG Performance Status Score

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Oken, 1982

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