DISCLOSURE

REDACTED PROTOCOL AMENDMENT 3

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, 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®)**
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SPONSOR NAME / ADDRESS:	Celgene Corporation 86 Morris Avenue Summit, NJ 07901

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PROTOCOL SUMMARY

Study Title

A Phase III, randomized, open-label, multi-center, safety and efficacy study to evaluate *nab*®-paclitaxel[1] (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 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, 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 450 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

[1] *nab*® is a registered trademark of Celgene Corporation.

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 216 subjects will be evaluable for the primary endpoint of PFS in maintenance.

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 450 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.

Follow-up Period

All subjects who discontinue from the Maintenance part 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 136 PFS events in which a total of 147 deaths are expected to be observed for the final OS analysis.

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 450 subjects. Based on results from the *nab*-Paclitaxel Phase 3 NSCLC development study (Protocol CA031) it is estimated that approximately 216 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 216 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, and Follow-up is estimated to last approximately 5 years.

Study Treatments

Induction

The *nab*-paclitaxel and carboplatin treatments will not be supplied by Celgene during Induction in those countries where *nab*-paclitaxel plus carboplatin is available for the treatment of NSCLC. Investigative sites will use standard of care (commercially available) product via prescription in these countries.

In those countries where *nab*-paclitaxel plus carboplatin is not available for the treatment of NSCLC, or is available but designated as investigational product (IP) as per local regulations, both agents will be packaged and supplied by Celgene.

Maintenance

Subjects will be randomized to receive open-label *nab*-paclitaxel plus BSC or BSC during the Maintenance part of the study. The *nab*-paclitaxel used in the Maintenance part of the study will be packaged and supplied by Celgene Corporation.

Please see local prescribing information for Abraxane for detailed instructions on the reconstitution, storage conditions, and IV administration of *nab*-paclitaxel.

Statistical Methods

Approximately 450 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 216 subjects are expected to be randomized in the Maintenance part of the study.

Similarly, the percentage of subjects manifesting a PFS event in the Maintenance part will be tracked on an ongoing basis.

Induction Part

Efficacy Analyses

All efficacy endpoints will be analyzed based on the intent-to-treat (ITT) population for the Induction part, which includes all enrolled subjects who received at least one dose of study treatment regardless of whether they 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 at the end of Cycle 2 and 4. 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 v1.1 (Eisenhauer, 2009) 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 v1.1 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 along with appropriate point estimates and 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 216 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.

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). Tumor response to Induction part chemotherapy for stratification is the response assessed at the last CT scan before randomization. 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.

Analysis of Progression Free Survival (PFS)

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 80% power for a two-sided test conducted at a 5% level of significance. This hazard ratio of 0.60 assumes an underlying exponential distribution for both treatment groups with a median time to PFS of 2 months for the BSC alone group and a median time to PFS of 3.33 months for the *nab*-paclitaxel plus BSC group. Hence, the final analysis will be conducted after 136 PFS events (ie, events of disease progression or deaths from any cause) have occurred.

One non-binding interim analysis will be used to assess futility using the PFS endpoint only, and is planned when approximately a total of 91 events have been observed. The study may be stopped early for futility only if the conditional power for PFS is < 10% under the assumed hazard ratio of 0.60, but there is no allowance to stop the study early to declare superior efficacy.

Analysis of Overall Survival (OS)

There will be two analyses for the OS endpoint, one of which involves an interim analysis that corresponds to the final analysis of PFS (approximately 136 PFS total events). However, OS collection may continue until 1.5 years after the final analysis of PFS with an expected number of total deaths of 147. The interim analysis for the OS endpoint will utilize a Lan-DeMets alpha-spending function to account for the exact timing of the interim based upon the actual number of observed events with an O'Brien-Fleming boundary in order to perform an appropriate group-sequential hypothesis testing procedure for a two-sided test conducted at a 5% level of significance.

A step-down procedure from the PFS final analysis to this group sequential testing approach for OS will be used to address multiplicity of testing.

OS analysis, the study may be stopped if the conditional power is below the threshold specified in the SAP.

General Considerations for the Efficacy Analyses of PFS, OS, and ORR

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 for the Maintenance part, which includes all randomized subjects regardless of whether they receive any IP or have any efficacy assessments collected.

For the primary efficacy endpoint, PFS, the progressive disease component of this endpoint will be based on the 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 (PFS) will be defined from the date of randomization to the start date of disease progression or date of subject death due to 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*-paclitaxel plus best supportive care / best supportive care = 1

H_a: HR *nab*-paclitaxel plus best supportive care / best supportive care ≠ 1

Progression-free survival distributions will be summarized using a graphical display of the Kaplan-Meier product limit estimates by treatment group, median PFS time estimates (including two-sided 95% CI) by each treatment group, and with an estimated hazard ratio (including two-sided 95% CI) from an unstratified Cox regression model. The hypothesis test of a hazard ratio of 1 with respect to the PFS distributions, as shown above, will be evaluated using a stratified log-rank test with the 3 baseline and prognostic factors described under the randomization scheme in Section 4.1.2. In addition to the stratified log-rank test, a stratified Cox regression model will be employed to evaluate the strength of the treatment effect using the estimated hazard ratio and corresponding 95% confidence interval.

The 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 a stratified Cochran-Mantel-Haenszel test at a nominal 5% level of significance.

If there exists unacceptable sparseness in some stratum cells (ie, a stratum cell that has less than 5 BSC subject counts in the ITT population of the Maintenance part of the study), then an algorithm for collapsing some full strata will be employed until there are at least 5 BSC subjects in any given revised stratum cell. The initial stratum cells for the BSC treatment group will start out as 8 cells that represent all possible permutations of the 3 strata (baseline 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]). Hence, the 8 cells representing all possible permutations among the strata may be reduced down to either 4 cells (all possible permutations of just 2 relatively large strata), 2 cells (just 1 large stratum); or no strata at all when implementing the algorithm for the BSC group, the smallest treatment group based on the 2:1 randomization. However, it is extremely unlikely that the algorithm will result in no stratum. Once the revised strata have been determined through the algorithm, then it will be used consistently for all stratified analyses.

Safety Analyses

The safety population includes all randomized subjects. 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 under the trade name of ABRAXANE in the first-line setting in combination with carboplatin for patients with non-small cell lung cancer who are not candidates for curative surgery or radiation therapy in several countries (eg, US, Japan, Argentina, Australia, New Zealand, Ecuador, Chile and Guatemala). 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. *nab*-Paclitaxel is also approved for the treatment of patients with metastatic breast cancer and for the first-line treatment of metastatic adenocarcinoma of the pancreas.

The 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 (Grades 1-4 [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 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.
- PFS from Day 1 Cycle 1.
- OS from Day 1 Cycle 1.
- ORR in Maintenance Part beyond response in Induction Part.
- Disease control rate during the Induction Part and over the entire study.
- Time to response during the Induction Part and over the entire study, with and without the requirement of confirmation of response.
- Duration of response over the entire study, with and without the requirement of confirmation of response.

3.3. Exploratory Endpoints

- 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 association between DNA nucleotide polymorphisms in subject's germ line DNA and association with treatment efficacy and or 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, 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 450 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 216 subjects will be evaluable for the primary endpoint of PFS in maintenance.

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 450 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 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 216) 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. Follow-up Period

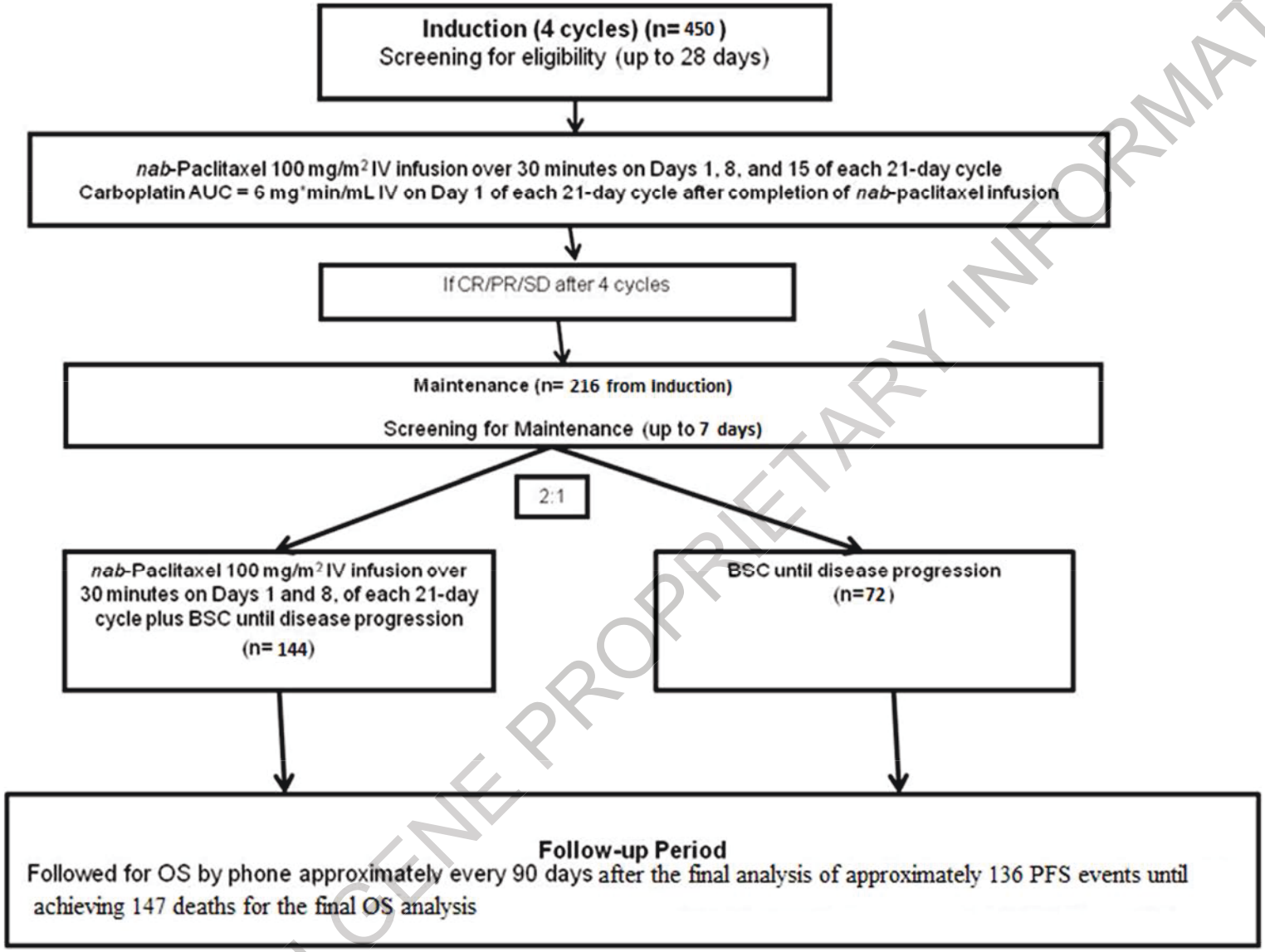
All subjects who discontinue from the Maintenance part of the study for any reason other than withdrawal of consent, lost to follow-up, or death, will enter the Follow-up period that will have a visit 28 days after progression or discontinuation. Those subjects entering the follow up period without documented 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 approximately 1.5 years after final analysis of approximately 136 PFS events in which a total of 147 deaths are expected to be observed for the final OS analysis.

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, 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)			At the end of Cycles 2 and 4 (-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[a]	X	X	-	-	X	-	-	-	X	-
Complete Chest CT Scan (including adrenal gland) and any other studies required for tumor imaging[b]	X	-	-	-	-	-		X	X	X[c]
Weight	X	X	X	X	X	X	X	-	X	X[c]
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[c]
ECOG status	X	X	-	-	X	-	-	-	X	X[c]
Concomitant Medication/Procedures	X	X	X	X	X	X	X	-	X	X[c]
Peripheral Neuropathy Assessment[e]	X	X	X	X	X	X	X	-	X	X[c]

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)			At the end of Cycle 2 and 4 (-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[c]	X
Adverse Event Evaluation	X	X	X	X	X	X	X	-	X	X[c]
nab-paclitaxel Administration	-	X	X	X	X	X	X	-	-	-
Carboplatin Administration	-	X	-	-	X	-	-	-	-	-
LCSS and EQ5D	-	X	-	-	X	-	-	-	X	-
Electrocardiogram (ECG)	X	-	-	-	-	-	-	-	-	X[c]
CT Scan of Head or Brain Magnetic Resonance Imaging (MRI) [g]	X	-	-	-	-	-	-	-	-	X[c]
Bone Scan (X-rays if needed)[g]	X									X[c]
Physical Examination	X	-	-	-	-	-	-	-	X	X[c]
Vital Signs	X	-	-	-	-	-	-	-	X	X[c]

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] 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.

[b] All subjects must have a radiographically documented measurable tumor(s) by RECIST v1.1 criteria. Complete chest CT scan (including adrenal gland) is performed at Screening, at the end of Cycles 2 and 4 during Induction part, 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. A CT scan with (if not contraindicated) and without contrast is preferred throughout the study. A CT scan with contrast only could be performed if not contraindicated per local site standard of practice, if the presence of liver metastasis can be assessed accurately. Scans will be archived as per institution standards.

[c] If clinically indicated.
[d] BSA calculated at baseline and recalculated if body weight changes by more than 10% since baseline or since the previous visit when BSA was recalculated.
[e] The occurrence of peripheral neuropathy should be reported by the investigator as an AE or SAE.
[f] Laboratory assessments will be done prior to each treatment by local laboratories and as clinically indicated. The results from laboratory assessments will be captured as per Section 6.18.
[g] At Screening, if lesions are suspected.

Table 4: Table of Events – Maintenance

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[a] (±2 days)					
Serum β-hCG[b]	X	X	-	-	X	-	-	-
Complete Chest CT Scan (including adrenal gland) and any other studies required for tumor imaging[c]	X[d]	-	-	X	X	-	-	X[e]
Weight	X	X	X	-	X	X	-	X[e]
Plasma for Biomarker Analyses		-	-	-	X	-	-	-
Body Surface Area (BSA) Calculation and Height[f]	X	-	-	-	-	-	-	X[e]
ECOG status	X[g]	X	-	-	X	-	-	X[e]
Concomitant Medication/Procedures	X	X	X	X	X	X	X	X[e]
Peripheral Neuropathy Assessment[h]	X	X	X	-	X	X	-	X[e]
Hematology and Serum Chemistry[i]	X	X	X	-	X	X	-	X[e]
Adverse Event Evaluation	X	X	X	X	X	X	-	X[e]
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 (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] Adherence to Day 1 and 8 visits during Maintenance part is preferred and strongly encouraged. Per local standard of care assessment of Day 8 visit may be done over the phone for subjects randomized to BSC arm if there are no safety concerns.

[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) 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. 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. A CT scan with (if not contraindicated) and without contrast is preferred throughout the study. A CT scan with contrast only could be performed if not contraindicated per local site standard of practice if the presence of liver metastasis can be assessed accurately. Scans will be archived as per institution standards.

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

[e] If clinically indicated.

[f] BSA calculated at baseline and recalculated if body weight changes by more than 10% since baseline or since the previous visit when BSA was recalculated.

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

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

[i] 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).

A CT scan with (if not contraindicated) and without the contrast is preferred throughout the study.

Chemistry assessments or CT scans performed in accordance with the local standard of care within 28 days before the first dose of study drug, even if they took place prior to signing of the ICF, can be used for the screening assessment (in this instance if only the CT scan with contrast is available, a CT scan without the contrast should be performed).

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, smoking 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 and Maintenance. 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) and any other studies required for tumor imaging will be done at Screening, at the end of Cycles 2 and 4, and at Early Treatment Discontinuation during the Induction part of the study. During the Maintenance part 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. A CT scan with (if not contraindicated) and without contrast is preferred throughout the study. A CT scan with contrast only could be performed if not contraindicated per local site standard of practice, if the presence of liver metastasis can be assessed accurately. All scans and reports will be archived as per institution standards.

6.5. Weight

Weight will be collected at every visit during the Induction and Maintenance 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 and Maintenance parts of the study. BSA may be recalculated if body weight changes by more than 10% since baseline or since the previous visit when BSA was recalculated.

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 part 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. 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. 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 28 days after the last dose of study drug, 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 part 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 part of the study.

6.13. Electrocardiogram

An Electrocardiogram (ECG) will be performed at screening and as clinically indicated; however, normal and non-clinically significant results will not be collected in the eCRFs. If results are abnormal and clinically significant at Screening, they will be recorded as medical history. 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 performed at screening if lesions are suspected and as clinically indicated during the study; however, results will not be collected in the eCRFs. If scans show progression of disease, this information will be collected on the eCRF.

6.15. Bone Scans and X-rays

Bone scans and x-rays will be performed at screening if lesions are suspected and as clinically indicated during the study; however, results will not be collected in the eCRFs. If scans show progression of disease, this information will be collected on the eCRF.

6.16. Physical Examinations

Physical examinations will be performed at screening and treatment discontinuation and any other time as clinically indicated/per the institutional practice. However, results will not be routinely collected on the eCRFs. If the findings are abnormal and clinically significant at

screening, they will be recorded as medical history, and if findings are abnormal and clinically significant after screening, they will be recorded as an AE or SAE.

6.17. Vital Signs

Vital signs will be measured at screening, treatment discontinuation, and any other time as clinically indicated / standard of care for the institution. However, results will not be routinely collected on the eCRFs. If the findings are abnormal and clinically significant at screening, they will be recorded as medical history, and if findings are abnormal and clinically significant after screening, they will be recorded as an 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 will 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 part 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.

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 part of the study, the subjects will be followed for survival by phone approximately every 90 days for up to 1.5 years after final analysis of approximately 136 PFS events in which a total of 147 deaths are expected to be observed for the final OS analysis. 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 450 subjects. Based on results from the *nab*-Paclitaxel Phase 3 NSCLC development study (Protocol CA031) it is estimated that approximately 216 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 216 subjects are randomized into the Maintenance part of the study. The study will be conducted at approximately 120 sites in the United States and European Union (EU).

7.2. Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the Induction and Maintenance 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 other current active malignancy requiring anticancer therapy.
6. Radiographically documented measurable disease at study entry (as defined by the RECIST v1.1 criteria).
7. No prior chemotherapy for the treatment of metastatic NSCLC at study entry. Adjuvant, neo-adjuvant chemotherapy or chemoradiotherapy with curative intent for non-metastatic disease is permitted providing it 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. agree to take a pregnancy test prior to starting study medication and throughout the study participation.
    b. commit to complete abstinence from heterosexual contact, or agree to use medical doctor-approved contraception throughout the study without interruption, and while receiving study medication or for a longer period if required by local regulations.

    Male subjects must:

    c. agree to complete abstinence from heterosexual contact or use a condom during sexual contact with a female of child bearing potential while receiving study medication and within 6 months after last dose of study medication, even if he has undergone a successful vasectomy.

7.3. Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment into the Induction and Maintenance 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 ≥ 4 weeks prior to first dose of study drug).
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). For the Maintenance part of the study subjects with peripheral neuropathy of Grade 3 and higher are excluded.
4. Venous thromboembolism (VTE) within 1 month prior to signing ICF. If the subject has a history of VTE earlier than 1 month prior to signing the ICF the event should be resolved, stable and without clinically significant bleeding, such as hematuria, gastrointestinal bleeding or hemoptysis.
5. Current congestive heart failure (New York Heart Association class II-IV).
6. History of the following within 6 months prior to first administration of a study drug: a myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, New York Heart Association (NYHA) Class III-IV heart failure, uncontrolled

hypertension, clinically significant cardiac dysrhythmia or clinically significant ECG abnormality, cerebrovascular accident, transient ischemic attack, or seizure disorder.

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. Subject has any other malignancy within 5 years prior to randomization. Exceptions are malignancies with a negligible risk of metastasis or death (eg, expected 5-year OS > 90%) that were treated with an expected curative outcome such as squamous cell carcinoma of the skin, in-situ carcinoma of the cervix, uteri, non-melanomatous skin cancer, carcinoma in situ of the breast, or incidental histological finding of prostate cancer (TNM stage of T1a or T1b) — all treatments should have been completed 6 months prior to signing ICF.
12. Subject has received radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to starting IP, and/or from whom ≥ 30% of the bone marrow was irradiated. Prior radiation therapy to a target lesion is permitted only if there has been clear progression of the lesion since radiation was completed.
13. Any condition, including the presence of laboratory abnormalities, that places the subject at unacceptable risk if he/she were to participate in the study.
14. Any condition that confounds the ability to interpret data from the study.
15. Pregnant and nursing females.

8. DESCRIPTION OF STUDY TREATMENTS

8.1. Description of Investigational Product(s)

Induction

The *nab*-paclitaxel and carboplatin treatments will not be supplied by Celgene during induction in those countries where *nab*-paclitaxel plus carboplatin is available for the treatment of NSCLC. Investigative sites will use standard of care (commercially available) product via prescription in these countries.

In those countries where *nab*-paclitaxel plus carboplatin is not available for the treatment of NSCLC, or is available but designated as investigational product (IP) as per local regulations both agents will be packaged and supplied by Celgene.

Maintenance

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

The preparation for IV administration procedures for IP should be followed as per Prescribing Information.

8.1.1. *nab*-Paclitaxel

nab-Paclitaxel will be supplied by the Sponsor, Celgene Corporation, for the Maintenance part in all countries and for the Induction part if either not available or designated as IP in a country. *nab*-Paclitaxel will be supplied 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.

Please see local prescribing information for Abraxane for detailed instructions on the reconstitution, storage conditions and IV administration of *nab*-paclitaxel.

Unreconstituted *nab*-paclitaxel should be stored in accordance with the product label. Reconstituted *nab*-paclitaxel should be used immediately. 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 IP 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 $C_6H_{12}N_2O_4Pt$ 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

Following administration of *nab*-paclitaxel, the intravenous line should be flushed with sodium chloride 9 mg/mL (0.9%) solution for injection to ensure administration of the complete dose, according to local practice.

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 450 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 216 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.

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 and Maintenance 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 part 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 Non-Hematologic Toxicities on the Study

Adverse Drug Reaction	Occurrence	*nab*-Paclitaxel Dose (mg/m^2)	Carboplatin Dose (mg*min/mL)	Starting Dose Maintenance: *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
	Second	50	3.0	
	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
	Second	Discontinue Treatment*		
Peripheral 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
	Second	50	3.0	
	Third	Discontinue Treatment*		
Grade 2 or 3 cutaneous toxicity Grade 3 diarrhea Grade 3 mucositis Any other Grade 3 or 4 nonhematologic toxicity	First	75	4.5	If subject at 100, 75 or 50 at end of Induction and < a Grade 2 or none of the noted events, will start at 100, 100 or 75 respectively during Maintenance
	Second	50	3.0	
	Third	Discontinue Treatment*		
Grade 4 cutaneous toxicity, diarrhea or mucositis	First	Discontinue Treatment*		

ANC: Absolute Neutrophil Count.

8.4. Method of Treatment Assignment

The Induction and Maintenance 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 and 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. For *nab*-paclitaxel, an infusion completed in less than 25 minutes may increase C_{max} by approximately 20%; therefore, a *nab*-paclitaxel infusion completed in less than 25 minutes will meet the infusion rate criterion for an overdose.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form. 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 detail in the SAP.

10.1. Induction Part

10.1.1. Overview

This is an 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 at the end of Cycle 2 and Cycle 4. 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 who received at least one dose of study treatment regardless of whether they have 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 up to 450 subjects will be enrolled in the Induction part of the study. This sample size would provide approximately 216 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. It is assumed that approximately 50% (225/450) 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 225 subjects will not meet the other inclusion/exclusion criteria for the Maintenance part, yielding a total of approximately 216 subjects entering the Maintenance part of the study.

The actual number of subjects enrolling into the Induction part, and then being randomized in the Maintenance part of the study will be monitored on an ongoing basis and adjusted accordingly to ensure that the targeted number of required PFS events for the Maintenance part is attained. Enrollment of the Induction part, therefore, could be discontinued early or extended beyond the planned number of 450 subjects.

The sample size in the Induction part of the study does not support any pre-defined hypothesis and hence power is not relevant for this part of the study. Sample sizes for this part of the study are based on the pragmatic requirements for achieving the necessary PFS events in the Maintenance part of the study. (See Section 10.2.3).

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 inferential testing 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 adverse events of special 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 until 28 days after the last dose of study drug for those who do not randomize in the Maintenance part. In addition, any serious AE with an onset date more than 28 days after the last dose of study drug that is assessed by the investigator as related to study drug will be considered a TEAE.

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.

10.1.10. Interim Analysis (Quality of Life Questionnaire and Biomarker Data)

For administrative purposes (eg, planning of new studies, publication of data) the LCSS, EQ-5D measurements and biomarker data collected during the Induction part will be summarized using descriptive statistics when approximately 50, 100, 200 and all subjects, respectively, have either discontinued during or completed the Induction part of the study.

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 216 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.

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).

Tumor response to Induction part chemotherapy for stratification is the response assessed at the last CT scan before randomization.

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 or on BSC arm 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 and 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 only will be conducted when approximately 91 events are observed. The study may be stopped for futility only if conditional power is < 10% under the assumed design hazard ratio of 0.60, but there is no allowance to stop the study early to declare superior efficacy.

The final analysis of the primary endpoint will be performed when approximately 136 PFS events have been observed. A total of approximately 216 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 month dropout rate.

Analysis of Progression Free Survival (PFS)

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. There is an 80% power to detect a hazard ratio of 0.60 using a two-sided test conducted at the 5% level of significance. This hazard ratio of 0.60 assumes an underlying exponential distribution for both treatment groups with a median time to PFS of 2 months for the BSC alone group and a median time to PFS of 3.33 months for the *nab*-paclitaxel plus BSC group. Hence, the final analysis will be conducted after 136 PFS events (ie, events of disease progression or deaths from any cause) have occurred.

The required number of PFS events and power calculation were obtained from

Analysis of Overall Survival (OS)

There will be two analyses for the OS endpoint, one of which involves an interim analysis that corresponds to the final analysis of PFS (approximately 136 PFS total events with a corresponding total of 92 deaths). However, OS collection may continue until 1.5 years after the final analysis of PFS in which a total of 147 total deaths are expected to be observed. The interim analysis for the OS endpoint will utilize a Lan-DeMets alpha-spending function to account for the exact timing of the interim based upon the actual number of observed events with an O'Brien-Fleming boundary in order to perform an appropriate group-sequential hypothesis testing procedure at the 5% level of significance (two-sided).

Assuming an underlying exponential distribution for both treatment groups with median OS times of 7.2 and 10.3 months for the BSC alone and *nab*-paclitaxel plus BSC regimens, respectively, there is 53% power to detect a hazard ratio of 0.70 using this two-sided group sequential testing procedure at an overall 5% level of significance, provided that the study has an opportunity to continue up to 147 observed events.

A step-down procedure from the PFS final analysis to this group sequential testing approach for OS will be used to address multiplicity of testing.

OS analysis, the study may be stopped if the conditional power is below the threshold specified in the SAP.

The required number of OS events and power calculation were obtained from

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 some efficacy analyses are described in this section, additional analyses may 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*-paclitaxel plus best supportive care/ best supportive care $= 1$

H_a: HR *nab*-paclitaxel plus best supportive care/ best supportive care $\neq 1$

Progression-free survival distributions will be summarized using a graphical display of the Kaplan-Meier product limit estimates by treatment group, median PFS time estimates (including two-sided 95% CI) by each treatment group, and with an estimated hazard ratio (including two-sided 95% CI) from an unstratified Cox regression model. The hypothesis test of a hazard ratio of 1 with respect to the PFS distributions, as shown above, will be evaluated using a stratified log-rank test with the 3 baseline and prognostic factors described under the randomization scheme in Section 4.1.2. In addition to the stratified log-rank test, a stratified Cox regression model will be employed to evaluate the strength of the treatment effect using the estimated hazard ratio and corresponding 95% confidence interval.

Pooling of Sparse Strata

If there exists unacceptable sparseness in some stratum cells (ie, a stratum cell that has less than 5 BSC subject counts in the ITT population of the Maintenance part of the study), then an algorithm for collapsing some full strata will be employed until there are at least 5 BSC subjects in any given revised stratum cell. The initial stratum cells for the BSC treatment group will start out as 8 cells that represent all possible permutations of the 3 strata (baseline 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]). Hence, the 8 cells representing all possible permutations among the strata may be reduced down to either 4 cells (all possible permutations of just 2 relatively large strata), 2 cells (just 1 large stratum); or no strata at all when implementing the algorithm for the BSC group, the smallest treatment group based on the 2:1

randomization. However, it is extremely unlikely that the algorithm will result in no stratum. Once the revised strata have been determined through the algorithm, then it will be used consistently for all stratified analyses.

Sensitivity and Supplemental Analyses

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, sensitivity analyses will be performed to further assess the impact of missed radiologic assessments. An additional analysis of PFS, where new treatment will be considered as an event, will be conducted to address the impact of second line therapy.

10.2.6.2. 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 in the same manner as PFS (primary endpoint), including the stratification variables.

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. Relative response rates between treatment regimens will be tested using a stratified Cochran-Mantel-Haenszel chi-square test at a two-sided 5% significance level. The stratification variables for the analysis will be the same as the PFS analysis (primary endpoint).

10.2.6.2.3. 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.

10.2.6.2.4. Progression Free Survival From Day 1 Cycle 1

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.

10.2.6.2.5. Overall Survival from Day 1 Cycle 1

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.

10.2.6.2.6. Overall Response Rate in Maintenance Part Beyond Response in Induction 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 (ie, 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.

10.2.6.2.7. Time to Response During the Induction Part and Over the Entire Study, With and Without the Requirement of Confirmation of Response

Time to response is defined as the time from Day 1 Cycle 1 to the first occurrence of confirmed response (CR or PR). Time to response will be summarized with descriptive statistics. Only subjects with a CR or PR as a best overall confirmed response during induction will be included in this analysis.

The same analysis will be performed for time to response without confirmation of response.

10.2.6.2.8. Duration of Response Over the Entire Study, With and Without the Requirement of Confirmation of Response

For subjects who had a confirmed CR or PR, the duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is radiologically documented (taking as reference for progressive disease the smallest measurements recorded on study).

Subjects who are non-responders (ie, do not achieve at least a PR) will be excluded from this analysis. Subjects who do not have PD after the response will be censored on the date of last tumor assessment. If a subject died before PD, then the subject will be censored on the date of death.

The duration of response will be analyzed using the Kaplan-Meier method. The median time (including 2-sided 95% CI) will be summarized for each treatment arm; the associated hazard ratio with two-sided 95% confidence interval will be estimated using a stratified Cox proportional hazard model. For this analysis, the stratification factors will be the same as those used in the primary efficacy analysis, if stratum sizes are sufficient.

The same analysis will be performed for duration of response without confirmation of response.

10.2.6.3. Exploratory Endpoints

10.2.6.3.1. 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.

10.2.6.3.2. 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

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 adverse events of special 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 date of randomization through 28 days after the last administration of the study regimen. 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). 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

Progression Free Survival (PFS)

One non-binding interim analysis will be used to assess futility using the PFS endpoint only, and is planned when approximately a total of 91 events have been observed. The study may be stopped early for futility only if the conditional power for PFS is < 10% under the assumed design hazard ratio of 0.60, but there is no allowance to stop the study early to declare superior efficacy.

The final analysis of PFS will be performed when approximately 136 PFS events have been observed, provided the study is not terminated early due to futility or other administrative reasons.

An observed hazard ratio at the interim of greater than or equal to 0.94 corresponds to the conditional power boundary of less than or equal to 10%. These boundaries were calculated using

Overall Survival (OS)

The interim analysis for the OS endpoint will utilize a Lan-DeMets alpha-spending function to account for the exact timing of the interim based upon the actual number of observed events with an O'Brien-Fleming boundary in order to perform an appropriate group-sequential hypothesis testing procedure at the 5% level of significance (two-sided).

Assuming an underlying exponential distribution for both treatment groups with median OS times of 7.2 and 10.3 months for the BSC alone and *nab*-paclitaxel plus BSC regimens, respectively, there is 53% power to detect a hazard ratio of 0.70 using this two-sided group sequential testing procedure at an overall 5% level of significance, provided that study has an opportunity to continue up to 147 observed events.

The two-sided nominal value p-value stopping boundary for first interim analysis is 0.009, while the final two-sided nominal p-value stopping boundary is 0.047. These stopping boundaries and

previous power calculation for the OS endpoint were calculated using

OS analysis, the study may be stopped if the conditional power is below the threshold specified in the SAP.

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. However, signs and symptoms (events) related to disease progression may be reported as adverse events. If reported, events of disease progression for squamous cell NSCLC disease under the study (including deaths due to disease progression for indications that are considered to be fatal) will be assessed as **expected** AEs and **will not** be expedited safety reports to regulatory authorities.

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 Treatment 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 28 days 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 6 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 Treatment Visit, whichever is later) and those made known to the Investigator at any time 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.

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.

The decision to discontinue a subject remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, prior to discontinuing a subject, the Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

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 Council for 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 the subject and/or the subject's 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.

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19. APPENDICES

Appendix A: 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.

Celgene Signing Page

This is a representation of an electronic record that was signed electronically in Livelink. This page is the manifestation of the electronic signature(s) used in compliance with the organizations electronic signature policies and procedures.

UserName:
Title:
Date: Friday, 31 March 2017, 10:31 AM Eastern Daylight Time
Meaning: Approved, no changes necessary.
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