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REDACTED PROTOCOL AMENDMENT 2

ABI-007-NSCL-005

SAFETY AND EFFICACY OF nab-PACLITAXEL (ABRAXANE®) IN COMBINATION WITH CARBOPLATIN AS FIRST LINE TREATMENT IN ELDERLY SUBJECTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC): A PHASE IV, RANDOMIZED, OPEN-LABEL, MULTICENTER STUDY (ABOUND.70+)

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SAFETY AND EFFICACY OF *nab*-PACLITAXEL (ABRAXANE®) IN COMBINATION WITH CARBOPLATIN AS FIRST LINE TREATMENT IN ELDERLY SUBJECTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC): A PHASE IV, RANDOMIZED, OPEN-LABEL, MULTICENTER STUDY (ABOUND.70+)

STUDY DRUG	***nab*-Paclitaxel (Abraxane®)**
PROTOCOL NUMBER:	**ABI-007-NSCL-005**
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PROTOCOL SUMMARY

Study Title

Safety and efficacy of *nab*-paclitaxel (Abraxane) in combination with carboplatin as first line treatment in elderly subjects with advanced non-small cell lung cancer (NSCLC): A Phase IV, randomized, open-label, multicenter study (Abound.70+).

Indication

First-line treatment of advanced NSCLC in elderly subjects.

Objectives

Primary

- To assess the safety and tolerability of continuous weekly versus weekly times three with one-week break *nab*-paclitaxel (Abraxane) in combination with carboplatin as first-line treatment for advanced NSCLC in elderly subjects (≥ 70 years old).

Secondary

- To evaluate the efficacy of *nab*-paclitaxel in combination with carboplatin in elderly subjects with advanced NSCLC.

Exploratory

- To assess healthcare resource utilization for the two *nab*-paclitaxel treatment arms.
- To assess the Lung Cancer Symptom Scale (LCSS) and EuroQol Group 5-Dimension Self-Report Questionnaire score (EQ-5D) for the two *nab*-paclitaxel treatment arms.
- [redacted]
- [redacted]

Study Design

This is a Phase IV, randomized, open-label, multicenter study of continuous weekly versus weekly times three with one-week break *nab*-paclitaxel in combination with carboplatin as first-line treatment in elderly subjects (≥ 70 years old) with advanced NSCLC who are not candidates for curative surgery or radiation therapy. Approximately 284 subjects with locally advanced or metastatic NSCLC will be randomized in this study to receive *nab*-paclitaxel in combination with carboplatin and will be randomized 1:1 into one of the two treatment arms prior to starting first dose of study drug. Randomization will be centralized and stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1, see Appendix A) and histology (squamous cell carcinoma versus non-squamous cell carcinoma).

The study will consist of a 28-day Screening Period, a Treatment Period, and a Follow-up Period.

The Screening Period for eligibility determination begins upon subject written informed consent. All screening assessments must be completed within 28 days prior to first dose of study drug.

The Treatment Period begins with the first dose of study drug as described in Section 8. Subjects will receive one of the following treatments based on the randomization assignment:

Arm A (21-day treatment cycle):

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

Arm B (21-day treatment followed by one-week break cycle, *28-day duration*):

- *nab*-Paclitaxel 100 mg/m^2 intravenous (IV) infusion over 30 minutes on Days 1, 8, and 15 of each 21-day treatment followed by one-week break cycle (i.e. every 28 days),
- Carboplatin AUC = 6 mg*min/mL IV on Day 1 of each 21-day treatment followed by one-week break cycle (i.e. every 28 days), after completion of *nab*-paclitaxel infusion.

No additional anticancer agents are allowed during study treatment. All supportive care (including but not limited to growth factors, antiemetics, analgesics, zolendronic acid, denosumab) is permitted as per the investigator's discretion and should be administered according to local institutional practice. Subjects will continue treatment until disease progression, development of an unacceptable toxicity, death, lost to follow-up, or withdrawal of consent, in accordance with local standard of care.

Tumor evaluations will be assessed by the investigative sites and response will be determined according to Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, Version 1.1 (v1.1) (Eisenhauer, 2009).

Local laboratory test data for absolute neutrophil count (ANC), platelet count, hemoglobin and serum creatinine will be collected in the electronic case report forms (eCRFs). All other laboratory test data, except those mentioned above, will not be collected routinely in the eCRF. All abnormal and clinically significant laboratory test results will be reported as adverse events (AEs) or serious adverse events (SAEs), and the specific associated laboratory parameter(s) should be recorded on the laboratory assessments eCRF. Local safety laboratory data will also be the primary guide for eligibility and subject management. In addition, test results for tumor mutational status of genes including but not limited to EGFR, ALK, and KRAS will be collected and recorded on eCRF if these tests have been performed locally for routine diagnosis.

All subjects who discontinue from treatment for any reason other than withdrawal of consent or lost to follow-up will enter the Follow-up Period. It will consist of a visit 28 days after treatment discontinuation. Thereafter, subjects will be followed for survival approximately every 90 days (or when they are seen for routine care) by phone call or chart review for documentation of last contact for up to 6 months after the last subject is randomized or 192 progression-free survival (PFS) events have been observed, whichever comes later.

Those subjects entering the Follow-up Period without documented progression will continue to have computed tomography (CT) scans in accordance with standard of care (at least every 90 days) until documented progression of disease, withdrawal of consent, lost to follow-up, death or study closure.

Study Population

Male and female subjects ≥ 70 years of age, with locally advanced or metastatic NSCLC who have not received chemotherapy for their advanced disease and are not candidates for curative surgery or radiation therapy, will be eligible for this study.

Length of Study

The enrollment of 284 subjects on this study will take approximately 24 months. The total length of this Phase IV study with follow-up is estimated to be approximately 3 years.

Study Treatments

Investigative sites will use standard of care (commercially available) product via prescription for *nab*-paclitaxel and carboplatin.

The preparation for IV administration procedures for *nab*-paclitaxel and carboplatin should be followed in accordance with the approved Prescribing Information for each drug.

Statistical Methods

Approximately 284 subjects will be randomized in a 1:1 ratio to one of two treatment arms (approximately 142 per arm). Arm A will receive *nab*-paclitaxel 100 mg/m^2 administered on Days 1, 8 and 15 in combination with carboplatin AUC = 6 mg*min/mL on Day 1 of each 21-day treatment cycle, and Arm B will receive the same treatment in the same schedule as that of Arm A during the first 21 days, followed by a one-week break prior to the start of the next cycle (28-day duration).

Randomization will be stratified by ECOG performance status (0 versus 1) and histology (squamous cell carcinoma versus non-squamous cell carcinoma).

The primary objective of this study is to assess the safety and tolerability of the two treatment arms for first-line treatment of locally advanced or metastatic NSCLC in elderly subjects (≥ 70 years old). The primary study endpoint, correspondingly, is the percentage of subjects with either peripheral neuropathy of Grade ≥ 2 or myelosuppression AEs Grade ≥ 3 based on the local laboratory values for ANC, platelet count, and hemoglobin, assessed using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (v4.0). The peripheral neuropathy events will be identified from the clinical AE dataset using the Standardised MedDRA Queries (SMQs). For the purpose of this protocol, this endpoint will be referred to as the percentage of subjects with Grade ≥ 2 peripheral neuropathy or Grade ≥ 3 myelosuppression laboratory adverse events.

The study is designed to detect a difference of 16 percentage points between the 2 treatment arms with respect to the primary safety endpoint with 80% power and a Type-I error rate of 5% (two-sided), assuming 139 of the 142 randomized subjects per arm will receive at least one dose of study drug and the percentage of the treated subjects with the AEs specified above is 73% for Arm A.

A non-binding interim analysis for futility with the primary safety endpoint will be conducted when approximately a total of 139 treated subjects have either completed 6 months of study treatment or discontinued from the study due to progression, adverse events, deaths, lost to follow up, or other reasons. The study may be stopped early for futility if the treatment difference is between ± 0.4%, given the interim analysis is performed at 50% information fraction.

Overview of Safety Assessment

The treated population, which includes all randomized subjects who received at least one dose of study drug, will be the analysis population for all safety analyses.

The primary study endpoint (a composite safety endpoint) will be the percentage of subjects with Grade ≥ 2 peripheral neuropathy or Grade ≥ 3 myelosuppression laboratory adverse events.

The null (H_o) and alternative (H_a) hypotheses for this endpoint are as follows, where $\boldsymbol{P}$ is the rate of the AEs described for the primary safety endpoint:

H_o: $\boldsymbol{P}_{Arm\ B} = \boldsymbol{P}_{Arm\ A}$

H_a: $\boldsymbol{P}_{Arm\ B} \neq \boldsymbol{P}_{Arm\ A}$

The AE rate of the primary study endpoint will be summarized within each treatment arm by descriptive statistics. The treatment difference in the AE rate will be analyzed using a Mantel-Haenszel Chi-square test with ECOG performance status (0 versus 1) and histology (squamous cell carcinoma versus non-squamous cell carcinoma) as the stratification factors. The ratio of the AE rates will be summarized along with the two-sided 95% confidence interval (CI).

Adverse events will be analyzed in terms of treatment-emergent adverse events (TEAEs), defined as any AE or SAE that begins or worsens in grade on or after the start of the study drug through 28 days after the last dose of the study drug. Additionally, any SAE that occurs beyond this period of observation and is assessed by the investigator as related to the study drug, will be reported and analyzed.

Treatment-emergent adverse events will be summarized by treatment arm by system organ class and preferred term. Grade 3 or higher TEAEs, SAEs, TEAEs leading to dose modification (reduction, delay not given, and interruption), TEAEs leading to treatment discontinuation, and TEAEs with an outcome of death will be summarized by treatment arm. Adverse events of special interest of the *nab*-paclitaxel and carboplatin combination identified in previous studies in a similar population will be summarized in the same manner.

In order to investigate the maximal degree of myelosuppression, ANC, platelet count, and hemoglobin will be summarized by the most severe grade in each treatment cycle and by the most severe grade during the study using NCI CTCAE v4.0.

Overview of Efficacy Assessment

All efficacy analyses will be based on the intent-to-treat (ITT) population, which includes all randomized subjects regardless of whether they receive any study drugs or have any efficacy assessments performed.

Progression-free Survival (PFS) based on investigator's assessment of the subject's radiologic response using RECIST v1.1 guidelines, Overall Response Rate (ORR), and Overall Survival (OS) are the key efficacy endpoints. Since the primary research interest of this study is to evaluate the relative safety and toxicities of the two treatment arms, the sample size was calculated based on the primary safety endpoint, the percentage of subjects with Grade ≥ 2 peripheral neuropathy or Grade ≥ 3 myelosuppression laboratory adverse events. Consequently, a statistically non-significant treatment difference in PFS, ORR or OS could simply be a function of the sample size and/or the lack of statistical power. Therefore, the assessments of treatment differences in PFS and OS will be based on the hazard ratios and in ORR, the ratio of response rates, and the corresponding 95% confidence intervals. P-values for between-group comparisons will be provided to indicate the strength of association only. No multiplicity adjustment with the Type-I error rate will be made.

Progression-free survival is defined as the time from the randomization date to the start of disease progression or subject death from any cause, whichever occurs first. Subjects who do not have disease progression or have not died as of the data cutoff date for the statistical analysis will be censored at the time of the last radiologic assessment prior to the data cutoff date. Rules for censoring for missing visits and start of anticancer treatment are provided in Section 10.

Progression-free survival will be summarized using the Kaplan-Meier method and by median PFS time (including two-sided 95% confidence interval [CI]) for each treatment arm along with the hazard ratio (including two-sided 95% CI) between treatment arms. The Kaplan-Meier curve for PFS will be presented graphically for each treatment arm. To illustrate the strength of association, the p-value for treatment difference in the curves will be reported from a stratified log-rank test with ECOG performance status (0 versus 1) and histology (squamous versus non-squamous cell carcinoma) as the stratification factors.

Of note, if recruitment is complete in 24 months, assuming that approximately 67% of the 284 subjects randomized will experience a PFS event (approximately 192 PFS events total) within 28 months from first subject randomized, there is 73% power to detect a hazard ratio (HR) of 0.69 for PFS improvement with Arm B over Arm A and an overall Type-I error rate of 5% (two-sided). Assuming an exponential distribution with a median time to PFS of 5.8 months for Arm A and proportional hazards, a hazard ratio of 0.69 constitutes a 2.6 months improvement for Arm B.

Overall response rate (percent of subjects who had a radiologic complete or partial response according to the investigator's assessment of response based on RECIST v1.1 guidelines) and OS also will be assessed by descriptive statistics with the associated 95% CIs. P-values from a Chi-square test and a stratified log-rank test will be provided to indicate the strength of association for the treatment differences in ORR and OS, respectively.

The analyses of the safety and efficacy endpoints for the clinical study report will be performed after ~192 PFS events have been observed.

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1. INTRODUCTION

1.1. Non-small Cell Lung Cancer

Lung cancer is the leading cause of cancer-related deaths among 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 step-wise advances in patient selection, targeted agents and optimizing chemotherapy regimens, patients with advanced NSCLC continue to have an unmet medical need (Schiller, 2013).

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 versus 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). Furthermore, the solvent alters drug pharmacokinetics (PK), leading to highly increased systemic drug exposure, decreased drug clearance, nonlinear PK, and lack of dose-dependent antitumor activity (Sparreboom, 1999; ten Tije, 2003; van Tellingen, 1999). 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).

Compared with solvent-based paclitaxel, *nab*-paclitaxel exhibits 10-fold higher mean Cmax of free paclitaxel, delivers 33% higher drug concentration to tumors in preclinical xenograft

models, and demonstrates enhanced transport across endothelial cell monolayers (Desai, 2006; Gardner, 2008). 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 intravenous (IV) bags may be used for the IV administration of *nab*-paclitaxel. *nab*-Paclitaxel for Injectable Suspension is approved for the treatment of metastatic breast cancer (globally) and for the treatment of adenocarcinoma of the pancreas (US). For NSCLC, *nab*-paclitaxel is approved in the US in combination with carboplatin for first-line treatment of patients with locally advanced or metastatic NSCLC who are not candidates for curative surgery or radiation therapy. The recommended dose of *nab*-paclitaxel for the NSCLC indication is 100 mg/m^2 administered as an intravenous infusion over 30 minutes on Days 1, 8, and 15 of each 21-day cycle.

1.2. *nab*-Paclitaxel in NSCLC

The Food and Drug Administration (FDA) approval of *nab*-paclitaxel was based on the evaluation of Phase I and II data (Belani, 2008; Rizvi, 2008; Socinski, 2010), as well as the pivotal Phase III study (CA031). The pivotal Phase III study was a multicenter, randomized, open-label study conducted in 1052 chemo naive subjects 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, development of an unacceptable toxicity or patient withdrawal. The primary efficacy outcome measure was ORR 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 carcinoma/adenocarcinoma, 43% had squamous cell lung cancer, 76% were ECOG PS 1, 15% were ≥70 years of age and 73% were current or former smokers. Patients received a median of 6 cycles of treatment in both study arms. Patients in the *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].

Non-inferiority analysis of overall survival (OS) demonstrated that *nab*-paclitaxel/carboplatin (nab-p/C) treatment is not inferior to solvent-based paclitaxel/carboplatin (sb-P/C) treatment. Overall survival in the *nab*-paclitaxel arm was 12.1 months versus 11.2 months in the control arm (p = 0.271; HR = 0.922). Toxicities, particularly neuropathy and neutropenia were less pronounced using *nab*-paclitaxel in the dose and schedule employed.

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

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

[a] P_A/P_T equals response rate of *nab*-paclitaxel/response rate of sb paclitaxel.
[b] 95% CI of response rate and 95.1% CI of response rate ratio.
* Indicates p-value < 0.049.Note: P-value is based on a chi-square test.
Source: Data on File.

Adverse events were assessed in 514 *nab*-paclitaxel/carboplatin-treated patients and 524 paclitaxel injection/carboplatin-treated patients. The following common (≥ 10% incidence) adverse events were observed at a similar incidence in *nab*-paclitaxel and paclitaxel arms: 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).

1.3. Rationale for Further Study of *nab*-Paclitaxel as First-line Treatment in Elderly Subjects with Advanced NSCLC

The tolerability of doublet chemotherapy in elderly patients with advanced NSCLC is an important therapeutic consideration, whereby the landmark IFCT 0501 reported that first-line sb-paclitaxel given weekly three weeks out of four coupled with carboplatin every 4 weeks (i.e. 21days of treatment followed by one-week break) improved efficacy over single-agent chemotherapy (either gemcitabine or vinorelbine) in patients 70 years or older with advanced NSCLC. The results demonstrated that doublet chemotherapy was feasible in this elderly population with an acceptable toxicity profile, when sb-paclitaxel/carboplatin was given as 21 days of treatment followed by one-week rest. The combination also resulted in a significant improvement in OS (median, 10.3 versus 6.2 months; HR = 0.639, 95% CI:0.52-0.79, p < 0.0001), with 1-year survival rates of 45.1% versus 26.9% for doublet therapy and monotherapy. This prospective trial set a standard, against which doublet-regimens must be measured in the elderly population with advanced NSCLC.

In the CA031 study of *nab*-paclitaxel (Abraxane) in combination with carboplatin, patients were stratified by age (< 70 years old versus ≥ 70 years old). Fifteen percent of ITT patients were elderly (≥70 years: *nab*-paclitaxel, n = 74: sb-paclitaxel, n = 82). Baseline characteristics were generally well balanced between treatment arms in elderly population, and subgroup analyses were performed to assess the influence of age on the primary efficacy endpoint of overall response rate as well as PFS and OS (Socinski, 2013).

Of note, the post-hoc analysis of the CA031 trial showed marked improvement in survival in the *nab*-paclitaxel/carboplatin arm. Amongst 156 elderly (≥ 70 years of age) subjects randomized on the study, OS was 19.9 months versus 10.4 months (HR: 0.583, p = 0.009) in favor of the *nab*-p/C arm compared to sb-p/C. The proportion of patients who had complete or partial response were consistently higher in all age stratum groups for the *nab*-paclitaxel/carboplatin regimen relative to the sb-paclitaxel/carboplatin regimen (in patients ≥ 70 years of age 34% versus 24% respectively, ratio of rates 1.385, p = 0.196,).

Although it was a statistically significant treatment effect in favor of *nab*-paclitaxel in the elderly subgroup from CA031 trial, 46% of patients in the *nab*-paclitaxel/carboplatin arm experienced dose reductions or dose delays. Approximately 92% of dose modifications and reductions were due to AEs. The most common clinical AEs in this subgroup were hematologic Grade ≥ 3 neutropenia (45%), anemia (22%) and thrombocytopenia (19%). Approximately 18% of the elderly population in the CA031 trial had Grade ≥ 2 peripheral neuropathy. Despite that, approximately 10% more elderly patients in the *nab*-paclitaxel arm were able to receive second-line therapy compared to sb-paclitaxel (61% versus 50%, respectively), possibly because they may have been in better shape due to a better tolerated first-line regimen with *nab*-paclitaxel or better disease and symptom control as demonstrated as improvement in ORR.

The results from the elderly subset in CA031 trial showed the combination of *nab*-paclitaxel and carboplatin to be particularly promising. We hypothesize that the tolerability can be improved further by introducing a one week break at the end of each treatment cycle (similar to the schedule advocated by Quoix, 2011) among elderly patients. Reducing the rate of the most common AEs (Grade ≥ 3 myelosuppression toxicities and Grade ≥ 2 peripheral neuropathy) by 16% will be clinically meaningful as it can potentially improve tolerability, quality of life and allow patients to receive treatment for a longer period of time, without necessarily compromising efficacy.

2. STUDY OBJECTIVES

2.1. Primary Objectives

- To assess the safety and tolerability of continuous weekly versus weekly times three with one-week break *nab*-paclitaxel (Abraxane) in combination with carboplatin as first-line treatment for advanced NSCLC in elderly subjects (≥ 70 years old).

2.2. Secondary Objective

- To evaluate the efficacy of *nab*-paclitaxel in combination with carboplatin in elderly subjects with advanced NSCLC.

2.3. Exploratory Objectives

- To assess healthcare resource utilization for the two *nab*-paclitaxel treatment arms.
- To assess the Lung Cancer Symptom Scale (LCSS) and EuroQol Group 5-Dimension Self-Report Questionnaire score (EQ-5D) for the two nab-paclitaxel treatment arms.
- [redacted]
- [redacted]

3. STUDY ENDPOINTS

3.1. Primary Endpoint

- The primary study endpoint is the percentage of subjects with either peripheral neuropathy of Grade ≥ 2 or myelosuppression AEs of Grade ≥ 3 based on the local laboratory values for ANC, platelet count, and hemoglobin. All AEs will be graded using NCI CTCAE v4.0.

3.2. Secondary Endpoints

The secondary endpoints are:

3.2.1. Safety

- The type, frequency, and severity of AEs and SAEs.
- Discontinuation rate.
- Dose intensity administered.
- The incidence of dose reduction and dose delay.

3.2.2. Efficacy

- Progression-free Survival (PFS).
- Overall response rate (ORR) using RECIST v1.1 guidelines.
- Overall Survival (OS).

3.3. Exploratory Endpoints

- Healthcare resource utilization during the study using a questionnaire.
- Changes in the LCSS and EQ-5D.
- [redacted]
- [redacted]
- Additional exploratory endpoints may be defined in the statistical analysis plan (SAP), if applicable.

4. OVERALL STUDY DESIGN

4.1. Study Design

This is a Phase IV, randomized, open-label, multicenter study of continuous weekly versus weekly times three with one-week break *nab*-paclitaxel in combination with carboplatin as first-line treatment in elderly subjects (≥ 70 years old) with advanced NSCLC who are not candidates for curative surgery or radiation therapy.

Subjects will be randomized 1:1 to receive one of the following treatments:

Arm A (21-day treatment cycle):

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

Arm B (21-day treatment followed by one-week break cycle, *28-day duration*):

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

The study will consist of a 28-day Screening Period, a Treatment Period, and a Follow-up Period.

The Screening Period will start from signing the Informed Consent Form (ICF) until first dose of study drug.

The Treatment Period will start from first dose of study drug until End-of-Treatment Visit (which is defined as visit with last dose of study drug).

Follow-up Period will start after End-of-Treatment visit.

No additional anticancer agents are allowed during study treatment. All supportive care (including but not limited to growth factors, antiemetics, analgesics, zolendronic acid, denosumab) is permitted as per the investigator's discretion and should be administered according to local institutional practice. Subjects will continue treatment until disease progression, development of an unacceptable toxicity, death, lost to follow-up, or withdrawal of consent, in accordance with local standard of care.

Tumor evaluations will be assessed locally and response (Complete Response [CR] or Partial Response [PR]) will be determined according to RECIST guidelines, Version 1.1. In both treatment arms, tumor assessments will be conducted at screening and every 42 days (-3/+7 days) (starting from Day 1 Cycle 1) until disease progression, withdrawal of consent, lost to follow-up, death, or if clinically indicated while on treatment.

Local laboratory test data for ANC, platelet count, hemoglobin and serum creatinine will be collected in the eCRFs. All other routine laboratory test data except those mentioned above will

not be collected in the eCRF unless they are determined to be clinically significant laboratory abnormalities. A clinically significant laboratory abnormality will be reported as an AE, or SAE, and the specific associated laboratory parameter(s) should be recorded in the laboratory assessments eCRF. Local safety laboratory data will also be the primary guide for eligibility and subject management. In addition, test results for tumor mutational status of genes including but not limited to EGFR, ALK, and KRAS will be collected and recorded on eCRF if these tests have been performed locally for routine diagnosis.

4.1.1. Follow-up Period

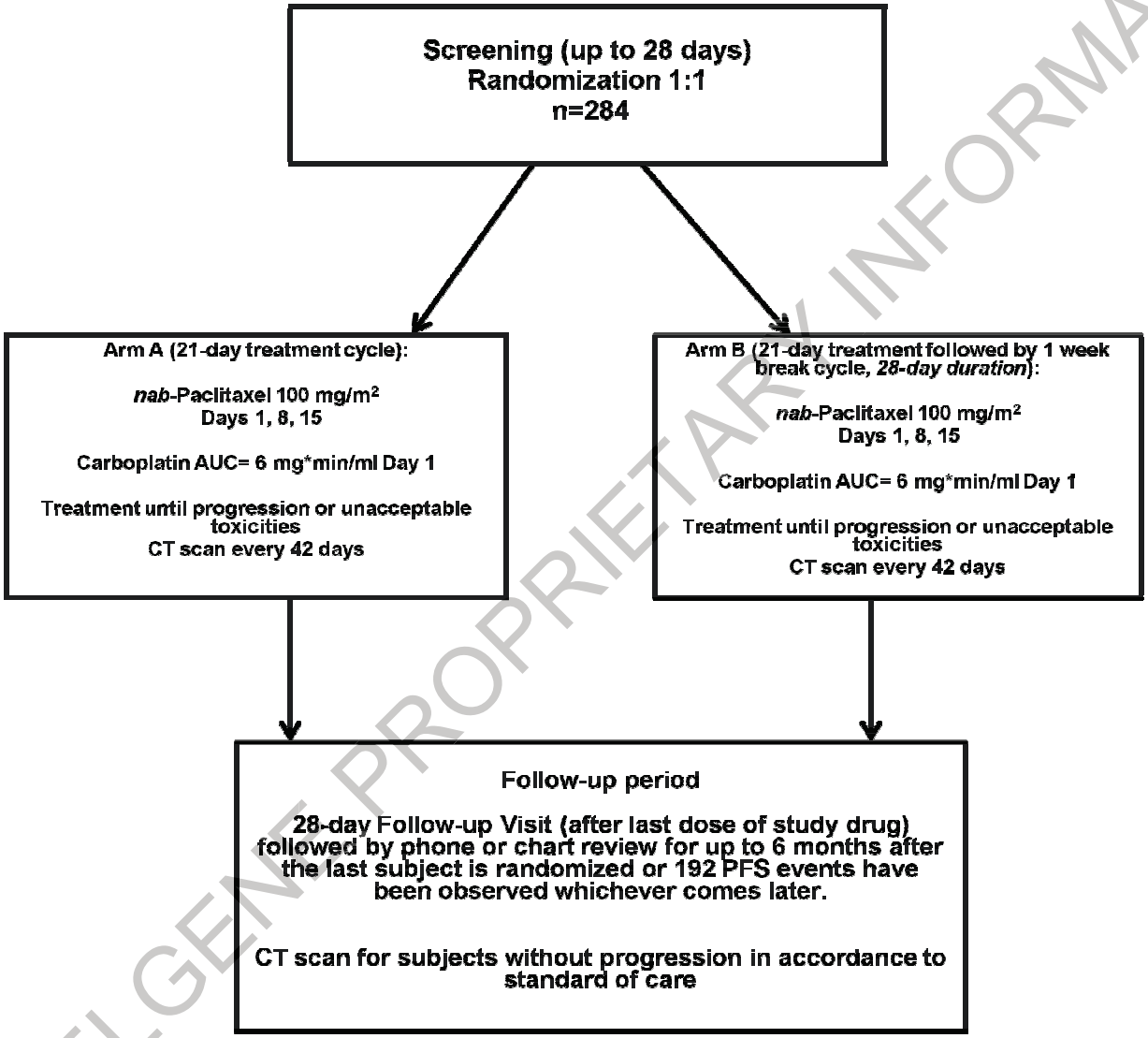
All subjects who discontinue from treatment for reasons other than withdrawal of consent or lost to follow-up will enter the Follow-up Period. It will consist of a visit 28 days after treatment discontinuation following by follow-up for survival approximately every 90 days (+/- 14 days or when they are seen for routine care) by phone call or chart review for documentation of last contact for up to 6 months after the last subject is randomized or 192 PFS events have been observed, whichever comes later.

Those subjects entering the Follow-up Period without documented progression will continue to have CT scans in accordance with standard of care (at least every 90 days) until documented progression of disease, withdrawal of consent, lost to follow-up, death, or study closure.

4.2. Study Design Rationale

The *nab*-paclitaxel schedule used in Arm A is in accordance with pivotal trial CA031, ie,100 mg/m^2 administered once per week on Days 1, 8 and 15 combined with carboplatin AUC = 6 mg*min/mL administered on Day 1 every 21 days, as approved by the FDA. The *nab*-paclitaxel/carboplatin schedule used in Arm B is the same schedule as the current approved *nab*-paclitaxel label with introduction of a one-week break following 21 days of treatment. This study will determine whether the one-week break can further improve tolerability without compromising efficacy (similar to the schedule advocated by Quoix, 2011) among elderly patients. Reducing the rate of the most common AEs (Grade ≥ 3 myelosuppression toxicities and Grade ≥ 2 peripheral neuropathy) by 16% will be clinically meaningful as it can potentially improve tolerability, quality of life and allow subjects to receive treatment for a longer period of time.

Figure 1: Overall Study Design



4.3. Study Duration

Recruitment is expected to take approximately 24 months, and the analysis of PFS will be performed when approximately 192 PFS events have occurred, estimated as approximately 28 months from first subject randomized. The total length of this Phase IV study with follow-up is estimated to last approximately 3 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 SAP, whichever is the later date.

5. TABLE OF EVENTS

Table 3: Table of Events

Assessment	Screening / Baseline	Treatment Period[a] Every cycle starting with Cycle 1				End-of-Treatment Visit (last dose of study drug)	Follow-Up Period	
	Day -28 to Day -1	Day 1 (±2 days)	Day 8 (±2 days)	Day 15 (±2 days)	Every 42 days (-3/+7 days) (counting from Day 1 Cycle 1)		28-day Follow-up Visit (after last dose of study drug)	Survival Follow-Up[b] Every 90 days (+/- 14 days) (after 28-day follow-up visit)
Informed Consent	X	-	-	-	-	-	-	-
Medical History, Prior Medication and Procedures	X	-	-	-	-	-	-	-
CT Scan of Complete Chest (including base of neck and adrenal glands) and any other studies required for Tumor Imaging[c]	X	-	-	-	X[c]	X[c]	-	X[c]
Weight and Height[d]	X	X	X	X	-	-	-	-
Body Surface Area (BSA) Calculation[d]	X	-	-	-	-	-	-	-
ECOG status	X	X	-	-	-	X	X	-
Concomitant Medication/Procedures	-	X	X	X	-	X	X	X
Peripheral Neuropathy Assessment[e]	X	X	X	X	-	X	X	-
Healthcare Resource Utilization Questionnaire	-	X	-	-	-	X	X	-
Hematology[f] (ANC, platelet count, Hgb)	X	X	X	X	-	X	X	-
Serum Chemistry[f] (serum creatinine)	X	X	-	-	-	X	X	-

Table 3: Table of Events (Continued)

Assessment	Screening / Baseline	Treatment Period[a] Every cycle starting with Cycle 1				End-of-Treatment (last dose of study drug)	Follow-Up Period	
	Day -28 to Day -1	Day 1 (±2 days)	Day 8 (±2 days)	Day 15 (±2 days)	Every 42 days (-3/+7 days) (starting Day 1 Cycle 1)		28-day Follow-up Visit (after last dose of study drug)	Survival Follow-Up[b] Every 90 days (+/- 14 days) (after 28-day follow-up visit)
Blood for Pharmacogenomic Analyses	-	X (C1D1 only)	-	-	-	-	-	-
Adverse Event Evaluation	After signing ICF and until 28 days after the last dose of study drug							
nab-paclitaxel Administration/accountability[g]	-	X	X	X	-	-	-	-
Carboplatin Administration/accountability[g]	-	X	-	-	-	-	-	-
LCSS and EQ-5D	-	X	-	-	-	X	X	-
Survival phone call (or chart review for documentation of last contact or when they are seen for routine care	-	-	-	-	-	-	-	X[b]
Electrocardiogram (ECG)	Will be done as per standard of care at screening, during the Treatment Period and as clinically indicated; however, results will not be routinely collected in the eCRFs. Results will be collected in the eCRFs as AE or SAE only if results are abnormal and clinically significant.							
CT Scan of the Head or Brain Magnetic Resonance Imaging (MRI)								
Bone Scan (X-rays if needed)								
Physical Examination								
Vital Signs								

AE = Adverse Event; ANC = absolute neutrophil count; C1D1 = Cycle 1, Day 1; CT = Computed Tomography; ECOG = Eastern Cooperative Oncology Group; eCRF = electronicCase Report Form; EQ-5D = EuroQol 5D; ICF = informed consent form; LCSS = Lung Cancer Symptom Scale; SAE = Serious Adverse Event; RECIST=Response Evaluation Criteria in Solid Tumors; PFS=Progression Free Survival.

[a] Treatment Period: Arm A: *nab*-paclitaxel Days 1, 8, and 15 and carboplatin Day 1. Arm B: *nab*-paclitaxel Days 1, 8, and 15 and carboplatin Day 1 followed by one-week break.
[b] Every 90 (+/-14) days (from 28-day Follow-up Visit) or when they are seen for routine care for up to 6 months after the last subject is randomized or 192 PFS events have been observed, whichever comes later.
[c] All subjects must have a radiographically documented measurable tumor(s) by RECIST Version 1.1 criteria: CT scan of complete chest (including base of neck and adrenal glands) are performed at screening, every 42 days (-3/+7 days) thereafter (counting from Day 1 Cycle 1) until disease progression, withdrawal of consent, lost to follow-up, death 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 (at least every 90 days) until documented progression of disease, withdrawal of consent, lost to follow-up, death or study closure.

[d] BSA will be calculated at screening and recalculated if body weight changes by more than 10% since baseline, or since the previous visit when BSA was recalculated. Height will only be obtained at Screening Visit. Weight will be obtained at screening and every visit during the Treatment Period before administration of study drug, but will only be collected on the eCRF for the Screening Visit.

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

[f] Laboratory assessments will be done prior to each *nab*-paclitaxel treatment as per standard of care during the study and as clinically indicated. ANC, platelet count, hemoglobin (Hgb) level and serum creatinine results will be collected in the eCRFs (all other routine laboratory test data except those mentioned above will not be collected in the eCRF unless it is clinically significant, which will then be reported as AEs or SAEs, and the specific associated laboratory parameter(s) should be recorded on the laboratory assessments eCRF).

[g] *nab*-Paclitaxel administration followed by carboplatin administration.

6. PROCEDURES

Subjects will be provided with a written ICF, given the opportunity to ask any questions concerning the study and will sign an ICF prior to participating in any study procedures. Serum 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. After giving written informed consent, subjects will undergo a Screening Period to be assessed for eligibility. All subjects who sign an ICF must be entered into the Interactive Randomization Technology (IRT) system immediately upon signature on the document. Subjects who do not meet the eligibility criteria will be considered screening failures and will not be eligible for the study. Subjects who screen fail may re-screen up to 2 times at any time and an ICF will need to be re-signed, 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). Subjects that have met all eligibility criteria after the Screening Period will be eligible to be randomized.

6.1. Medical History

Only clinically significant or ongoing medical conditions will be recorded at screening on the eCRF.

6.2. Prior and Concomitant Medications/Procedures

Prior medications are defined as all medications that were started before the date of the first dose of study drug. Only prior medications/procedures (of clinically significant or ongoing medical conditions) within 28 days of the time of signature on the ICF should be recorded. All NSCLC-related prior medications/procedures (including radiation therapy) should be recorded regardless of time.

Concomitant medications are considered any medications that were taken on or after the date of the first dose of study drug and on or before 28 days after the last dose of study drug. All subjects will have concomitant medications and procedures (including radiation therapy) recorded from the time of signature on the ICF until the 28-day Follow-up Visit, for conditions that are clinically significant or ongoing. During the Follow-up Period only NSCLC-associated concomitant medications/procedures (including radiation therapy) will be recorded, ie, subsequent-line(s) of anti-cancer therapy.

6.3. Computed Tomography (CT) Scan of Complete Chest (including base of neck and adrenal glands)

A CT scan of complete chest (including base of neck and adrenal glands) and any other studies required for tumor imaging will be done at screening, every 42 days (-3/+7 days) (starting from Day 1 Cycle 1) until treatment discontinuation or withdrawal of consent. Those subjects entering the Follow-up Period without documented progression will continue to have CT scans in accordance with standard of care (at least every 90 days) until documented progression of disease, withdrawal of consent, lost to follow-up, death or study closure. Additional CT scans

may be done at any time during the study if clinically indicated. All CT scans and reports should be archived at the site according to site regulations and copies provided to Sponsor if requested.

6.4. Weight

Weight will be obtained at screening and at every visit during the Treatment Period before administration of study drug, but will only be collected on the eCRF for the Screening Visit. Additional weights may be collected per local standards at any time during the study as needed.

6.5. Body Surface Area (BSA) Calculation and Height

Height will be collected at screening only, and BSA will be calculated at screening of the study. BSA will be recalculated if body weight changes by more than 10% during the study.

6.6. ECOG Performance Score

Eastern Cooperative Oncology Group performance score will be collected at screening, Day 1 of every treatment cycle, at the End-of-Treatment visit and at the 28-day Follow-up Visit. Additional ECOG assessments may be performed at any time during the study as clinically indicated.

6.7. Peripheral Neuropathy Assessment

Peripheral neuropathy (sensory or motor) assessment will be done at screening, Day 1, 8, 15 of every treatment cycle, at the End-of-Treatment visit and at the 28-day Follow-up Visit. Changes in neuropathy grade from baseline will be reported as an AE as per Section 11. Additional peripheral neuropathy assessments may be done at any time during the study as clinically indicated.

6.8. Adverse Event Reporting

Adverse events will be 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.

6.9. Lung Cancer Symptom Scale Questionnaire and EQ-5D

The LCSS and EQ-5D questionnaires will be used to measure quality of life (QoL) for subjects in the study. The LCSS is comprised of 9 questions to be completed by the subject 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 Treatment Period, at the End-of-Treatment Visit and at the 28-day Follow-up Visit.

6.10. 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 treatment cycle, at the End-of-Treatment visit and at 28-day Follow-up Visit.

6.11. Electrocardiogram

Electrocardiograms (ECGs) will be done per standard of care at screening, during the Treatment Period and as clinically indicated. Results will be collected in the eCRFs as AE or SAE only if results are abnormal, changed, and clinically significant.

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

A CT scan of the head, or preferably brain MRI, will be done as per standard of care at screening, during the Treatment Period, and as clinically indicated. Results will be collected in the eCRFs as an AE or SAE only if the results are abnormal and clinically significant.

6.13. Bone Scans and X-rays

Bone scans and x-rays will be done as per standard of care at screening, during the Treatment Period, and as clinically indicated. Results will be collected in the eCRFs as AE or SAE only if results are abnormal and clinically significant.

6.14. Physical Examinations

Physical examinations will be done as per standard of care at screening, during the Treatment Period, and as clinically indicated. Results will be collected in the eCRFs as AE or SAE only if results are abnormal and clinically significant.

6.15. Vital Signs

Vital signs will be done as per standard of care at screening, during the Treatment Period, and as clinically indicated. Results will be collected in the eCRFs as AE or SAE only if results are abnormal and clinically significant.

6.16. Laboratory Assessments

Laboratory assessments will be done as indicated in Table 3 by local laboratories as per standard of care during the study and as clinically indicated. Local laboratory test data for ANC, platelet count and hemoglobin must be collected at screening, each visit before administration of study drug, at the End-of-Treatment visit and at the 28-day Follow-up Visit in the eCRF. Serum creatinine must be collected at screening, Day 1 of each cycle, at the End-of-Treatment visit and at the 28-day Follow-up Visit in the eCRF. Normal ranges for these selected parameters will be collected on the eCRF. All other laboratory test data, except those mentioned above, will not be collected routinely in the eCRF. Local safety laboratory data will also be the primary guide for eligibility and subject management. 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. All clinically significant laboratory abnormalities (Section 11.3) are to be recorded as AEs on the AE eCRF, and the specific laboratory parameter(s) as well as the corresponding normal ranges should be recorded on the laboratory assessments eCRF. Clinically significant laboratory abnormalities at screening may result in subject ineligibility for the study and should not be captured as AE. 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.

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

Provision of tumor tissue is mandatory for study enrollment, except when no tumor tissue is extant and this requirement would necessitate a new procedure such as a biopsy to collect it.

In addition, test results for tumor mutational status of genes including but not limited to EGFR, ALK, and KRAS will be collected and recorded on eCRF if these tests have been performed locally for routine diagnosis.

6.18. Survival

After the End-of-Treatment Visit, the subjects will have a 28-day Follow-up Visit followed by a call or chart review for documentation of last contact approximately every 90 days (or when they are seen for routine care) for up to 6 months after the last subject is randomized or 192 PFS events have been observed, whichever comes later. The subjects will also be asked questions about other medications they may be taking for their NSCLC or their medical records will be reviewed to determine a last contact date for routine purposes. Those subjects entering the Follow-up Period without documented progression will continue to have CT scans in accordance with standard of care (at least every 90 days) until documented progression of disease, withdrawal of consent, lost to follow-up, death or study closure.

7. STUDY POPULATION

7.1. Number of Subjects and Sites

Elderly (≥ 70 years of age) male and female subjects with locally advanced or metastatic NSCLC with no prior chemotherapy for metastatic disease will be eligible for this study. The study will enroll approximately 284 subjects. The study will be conducted at approximately 65 sites in the United States.

7.2. Inclusion Criteria

Subjects must satisfy the following criteria to be randomized in the study:

1. Age ≥ 70 years at the time of signing the ICF.
2. Understand and voluntarily provide written informed consent prior to the conduct of any study related assessments/procedures.
3. Able to adhere to the study visit schedule and other protocol requirements.
4. Histologically or cytologically confirmed locally advanced or metastatic NSCLC who are not candidates for curative surgery or radiation therapy.
5. No other current active malignancy requiring anticancer therapy.
6. Radiographically documented measurable disease per RECIST v1.1.
7. No prior chemotherapy for the treatment of metastatic disease. Adjuvant chemotherapy is permitted providing that cytotoxic chemotherapy was completed 12 months prior to signing the ICF and without disease recurrence. Patients with previously known EGFR mutation or ALK gene translocation must have failed or had intolerance to one treatment with EGFR tyrosine kinase inhibitor or ALK inhibitor therapy, respectively.
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 mg/dL (unless there is a known history of Gilberts Syndrome).
13. Creatinine clearance (CrCl) > 40 mL/min calculated using Cockcroft-Gault equation (if renal impairment is suspected 24 hour urine collection for measurement is required).
14. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
15. Females who (1) have undergone hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or (2) have been naturally postmenopausal for at least 24 consecutive months (ie, has not had menses at any time during the preceding 24 consecutive months).

Male subjects must:

a. Practice true abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions, and for 6 months following study drug discontinuation, 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:

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 signing ICF). MRI of the brain (or CT scan w/contrast) is preferred for diagnosis.
2. History of leptomeningeal disease.
3. Only evidence of disease is non-measurable.
4. Preexisting peripheral neuropathy of Grade 2, 3, or 4 (per CTCAE v4.0).
5. 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.
6. Venous thromboembolism within 1 month prior to signing ICF.
7. Current congestive heart failure (New York Heart Association Class II-IV).
8. 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.
9. Subject has a known infection with hepatitis B or C, or history of human immunodeficiency virus (HIV) infection, or subject receiving immunosuppressive or myelosuppressive medications that would in the opinion of the investigator, increase the risk of serious neutropenic complications.
10. Subject has an active, uncontrolled bacterial, viral, or fungal infection(s) requiring systemic therapy, defined as ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics, antiviral therapy, and/or other treatment.
11. History of interstitial lung disease, sarcoidosis, silicosis, idiopathic pulmonary fibrosis, or pulmonary hypersensitivity pneumonitis.
12. Treatment with any investigational product within 28 days prior to signing the ICF.
13. History of allergy or hypersensitivity to *nab*-paclitaxel or carboplatin.
14. Currently enrolled in any other clinical protocol or investigational trial that involves administration of experimental therapy and/or therapeutic devices.

15. Any other clinically significant medical condition, psychiatric illness, and/or organ dysfunction that will interfere with the administration of the therapy according to this protocol or which, in the views of investigator, preclude combination chemotherapy.
16. Subject has any other malignancy within 5 years prior to randomization. Exceptions include the following: 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 treatment of which should have been completed 6 months prior to signing ICF.
17. Any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study.
18. Any medical condition that confounds the ability to interpret data from the study.
19. Females 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).

8. DESCRIPTION OF STUDY TREATMENTS

8.1. Description of Study Drug(s)

Treatment

Subjects will receive open-label *nab*-paclitaxel and carboplatin during the Treatment Period of the study. Investigative sites will use standard of care (commercially available) product via prescription for *nab*-paclitaxel and carboplatin.

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

8.1.1. *nab*-Paclitaxel

Each single-use 50 mL vial contains paclitaxel (100 mg) and approximately 900 mg human albumin as a stabilizer.

Unreconstituted *nab*-paclitaxel should be stored in accordance with the product label. Reconstituted *nab*-paclitaxel should be used immediately. Both forms should be stored in an area free of environmental extremes and should be accessible only to study personnel. Reconstitution and administration should follow local prescribing information and local practice. Temperature records for *nab*-paclitaxel must be made available to Celgene or other Sponsor- nominated monitoring teams for verification of proper study drug storage.

8.1.2. Carboplatin

Carboplatin is a platinum coordination compound that is used as a cancer chemotherapeutic agent. The chemical name for carboplatin is platinum diammine [1,1-cyclobutane-dicarboxylato (2-)-0,0']-,(SP-4-2). Carboplatin is a crystalline powder with the molecular formula of $C_6H_{12}N_20_4Pt$ and a molecular weight of 371.25. It is soluble in water at a rate of approximately 14 mg/mL, and the pH of a 1% solution is 5 to 7. It is virtually insoluble in ethanol, acetone, and dimethylacetamide.

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

8.2. Treatment Administration and Schedule

Approximately 284 subjects will be treated with *nab*-paclitaxel plus carboplatin until disease progression, development of an unacceptable toxicity, death, lost to follow-up, or withdrawal of consent.

Treatment will commence on Day 1, in accordance with standard of care of first-line treatment of NSCLC:

Arm A:

- *nab*-Paclitaxel 100 mg/m^2 IV infusion over 30 minutes on Days 1, 8, and 15 of each 21-day treatment cycle,

- Carboplatin AUC = 6 mg*min/mL IV on Day 1 of each 21-day treatment cycle, after completion of *nab*-paclitaxel infusion

  OR

Arm B:

- *nab*-Paclitaxel 100 mg/m^2 IV infusion over 30 minutes on Days 1, 8, and 15 of each 21-day treatment with one-week break cycle (i.e. every 28 days),
- Carboplatin AUC = 6 mg*min/mL IV on Day 1 of each 21-day treatment with one-week break cycle (i.e. every 28 days), after completion of *nab*-paclitaxel infusion.

8.3. Dose Modifications

Subjects who experience any of the adverse drug reactions in Table 4 will be dose reduced as per Table 4 during treatment.

- 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 withhold treatment until counts recover to an absolute neutrophil count of at least 1500 cells/mm^3 and platelet count of at least 100,000 cells/mm^3 on Day 1 or to an absolute neutrophil count of at least 500 cells/mm^3 and platelet count of at least 50,000 cells/mm^3 on Days 8 or 15 of the cycle. Upon resumption of dosing, permanently reduce *nab*-paclitaxel and carboplatin doses as outlined in Table 4.
- Withhold *nab*-paclitaxel for Grade 3 or 4 peripheral neuropathy. Resume *nab*-paclitaxel and carboplatin at reduced doses (Table 4) when peripheral neuropathy improves to Grade 1 or completely resolves.

Re-escalation is not permitted at any time.

Table 4: Permanent Dose Reductions for Hematologic and Neurologic Toxicities and Dosing on the Study

Dose Modification During Treatment for A and B arms			
Adverse Drug Reaction	**Occurrence**	***nab*-Paclitaxel Dose (mg/m^2)**	**Carboplatin Dose (AUC mg*min/mL)**
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
	Second	50	3.0
	Third	Discontinue Treatment*	
Platelet count < $50{,}000/mm^3$	First	75	4.5
	Second	Discontinue Treatment*	
Sensory Neuropathy Grade 3 or 4	First	75	4.5
	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
	Second	50	3.0
	Third	Discontinue Treatment*	
Grade 4 cutaneous toxicity, diarrhea or mucositis	First	Discontinue Treatment*	

ANC = Absolute Neutrophil Count; AUC = area under the curve.
* If an adverse event that requires dose reduction recurs after the dose has been reduced twice, the subject should generally have treatment discontinued unless, at the discretion of the investigator, there is evidence of continuing benefit to the subject that outweighs the risk of recurrent toxicity. Re-Escalation is not permitted at anytime.

8.4. Method of Treatment Assignment

The Treatment Period of the study is open-label. Enrollment/randomization will occur via IRT system for all periods of the study.

8.5. Packaging and Labeling

Investigative sites will use standard of care (commercially available) product via prescription for nab-paclitaxel and carboplatin.

8.6. Study Drug Accountability and Disposal

Investigative sites will use standard of care (commercially available) product via prescription for nab-paclitaxel and carboplatin. Accurate recordings of all study drug administration should be made.

Procedures for proper handling and disposal of anticancer drug must comply with the relevant health, safety, and environment regulations.

8.7. Study Drug Compliance

Study drug will be administered only by study site personnel and accurate recording of all study drug 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 given to a subject, regardless of any associated adverse events or sequelae.

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

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

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

9. CONCOMITANT MEDICATIONS AND PROCEDURES

9.1. Permitted Concomitant Medications and Procedures

Over the course of this study, additional medications may be required to manage aspects of the disease state of the subjects, including side effects from study treatments or disease recurrence. All supportive care (including but not limited to antiemetic medications, white blood cell (WBC) growth factors, erythrocyte stimulating agents, zolendronic acid, and denosumab) is permitted and may be administered at the discretion of the investigator, according to local guidelines.

9.2. Prohibited Concomitant Medications and Procedures

Other antineoplastic agents or Investigational Product than what is specified in the protocol are prohibited.

9.3. Required Concomitant Medications and Procedures

Not applicable.

10. STATISTICAL ANALYSES

Statistical analyses for the primary and key secondary endpoints of the study are described below. Additional analyses of these endpoints as well as exploratory endpoints or subgroup analyses will be described in detail in the SAP. The SAP supersedes the analyses described in the protocol should there be differences between the two.

10.1. Overview

Approximately 284 subjects will be randomized in a 1:1 ratio to two treatment arms (142 subjects per group). Arm A will receive *nab*-paclitaxel 100 mg/m^2 administered on Days 1, 8 and 15 followed by carboplatin AUC = 6 mg*min/mL on Day 1 of each 21-day treatment cycle. Arm B will receive the same treatment in the same schedule as that of Arm A during the first 21 days of treatment, but followed by a one-week break prior to the start of next cycle (28-day duration). All subjects will receive the assigned study treatment until disease progression, unacceptable toxicity, death, lost to follow-up, or withdrawal of consent, in accordance of local standard of care. A permuted-block randomization method will be employed, and the randomization will be carried out centrally using an IRT system. The randomization will be stratified based on the following 2 baseline or prognostic factors:

- ECOG performance status (0 versus 1)
- Histology (squamous cell carcinoma versus non-squamous cell carcinoma)

10.2. Study Population Definitions

10.2.1. 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 study drug or has any efficacy assessments performed.

10.2.2. Per-protocol (PP) Population

The PP population is defined as all eligible subjects randomized who receive at least one dose of the study drug and have been treated in the arm they were assigned to. Additional analyses utilizing the PP population will be described in the SAP.

10.2.3. Treated Population

The treated population will consist of all randomized subjects who receive at least one dose of study drug. The treatment groups for the safety analyses will be based on the treatment as received if different from the assigned treatment by randomization.

10.3. Sample Size and Power Considerations

The primary objective of this study is to assess the safety and tolerability of *nab*-paclitaxel in combination with carboplatin administered in 21-day treatment cycles continuously or with a

one-week break in between cycles for the treatment of locally advanced or metastatic NSCLC in elderly subjects (≥ 70 years old).

The primary study endpoint (also the primary safety endpoint) is the percentage of subjects with either peripheral neuropathy of Grade ≥ 2 or myelosuppression AEs of Grade ≥ 3 based on the local laboratory values for ANC, platelet count, and hemoglobin. For the purpose of this protocol, this endpoint will be referred to as the percentage of subjects with Grade ≥ 2 peripheral neuropathy or Grade ≥ 3 myelosuppression laboratory adverse events.

In Protocol CA031, the Phase 3 NSCLC study of the *nab*-paclitaxel development program, approximately 2% of the elderly subjects randomized discontinued from the study prior to receiving any study drug. In addition, approximately 73% of the treated elderly subjects had AEs that fell in the category of AEs described above for the primary safety endpoint of the current study.

The study is designed to detect a difference of 16 percentage points between the 2 treatment arms with respect to the primary safety endpoint with 80% power and a Type-I error of 5% (two-sided), assuming the percentage of subjects with the AEs specified above is 73% for Arm A. Therefore, the current study is planned to randomize approximately 284 subjects to the 2 treatment arms in a 1:1 ratio, with the expectation that approximately 278 subjects (139 per group) will receive at least one dose of study drug (as observed in CA031) and be included in the treated population for the analysis of the primary safety endpoint.

A non-binding interim analysis for futility with the primary safety endpoint will be conducted when approximately a total of 139 treated subjects have either completed 6 months of study treatment or discontinued from the study due to progression, adverse events, deaths, lost to follow up, or other reasons. The stopping rule and the final marginal significance level are determined based on the Gamma family spending function with parameter = -7 (Hwang, 1990) to control the Type-II error rate at 20%. The study may be stopped early for futility if the treatment difference is between ± 0.4% (Z-score ± 0.054) given the interim analysis is performed at 50% information fraction.

Progression free survival, OS, and ORR are the key efficacy endpoints of the study. Since the primary research interest of this study is to evaluate the relative safety and toxicities of the 2 treatment arms, the sample size was calculated based on the primary safety endpoint, the percentage of subjects with Grade ≥ 2 peripheral neuropathy or Grade ≥ 3 myelosuppression laboratory AEs, hence, the study is underpowered for the key efficacy endpoint, PFS, OS and ORR. Consequently, a non-significant treatment difference in PFS, OS or ORR could simply be a function of the sample size and/or the lack of statistical power. Therefore, the assessments of all efficacy endpoints will be based on the point estimates and the associated 95% confidence intervals for the within-group parameters of interest and the between-group differences. P-values for between-group comparisons will be provided to indicate the strength of association only. No multiplicity adjustment with the Type-I error rate will be made.

Of note, based on the data from CA031 it is expected that approximately 67% of the 284 randomized subjects will have a PFS event during the study (i.e. approximately 192 PFS events total). With 192 PFS events, there is 73% power to detect a hazard ratio (HR) of 0.69 for PFS improvement with Arm B over Arm A and an overall Type-I error of 5% (two-sided). Assuming

an exponential distribution with a median time to PFS of 5.8 months for Arm A and proportional hazards, a hazard ratio of 0.69 constitutes a 2.6 months improvement for Arm B.

As an illustration for timeline projection, assuming an exponential distribution for PFS, a 24-month recruitment period for 284 subjects, and a median PFS of approximately 5.8 months for Arm A, it will take approximately 28 months from the first subject randomized to observe 192 PFS events.

The analysis of both the safety and efficacy endpoints for the clinical study report will be performed when approximately 192 PFS events have been observed. No adjustment for the multiple treatment comparisons among the primary and secondary study endpoints will be made. Subjects will be followed for OS for at least 6 months after the last subject is randomized or 192 PFS events have been observed, whichever comes later.

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

10.5. Subject Disposition

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

10.6. Safety Analysis

The treated population, which includes all randomized subjects who received at least one dose of study drug, will be the analysis population for all safety analyses.

The safety/tolerability of the two treatment arms will be monitored through continuous reporting and evaluated by the primary safety endpoint, adverse events and serious adverse events, abnormalities in ANC, platelet count and hemoglobin, and incidence of subjects experiencing dose modifications, dose interruptions, and/or premature discontinuation of study drug.

10.6.1. Primary Safety Endpoint

The primary endpoint for this study is a composite safety endpoint, namely, the percentage of subjects who develop either peripheral neuropathy of Grade ≥ 2 or myelosuppression AEs of Grade ≥ 3 based on the local laboratory values for ANC, platelet count and hemoglobin. The peripheral neuropathy events will be identified from the clinical AE dataset using the Standardised MedDRA Queries (SMQs).

The null (H_o) and alternative (H_a) hypotheses for this endpoint are as follows, where ***P*** is the rate of the AEs described for the primary safety endpoint:

H_o: $\boldsymbol{P}_{Arm\ B} = \boldsymbol{P}_{Arm\ A}$

H_a: $\boldsymbol{P}_{Arm\ B} \neq \boldsymbol{P}_{Arm\ A}$

The rate of the AEs described for the primary endpoint will be summarized within each treatment schedule by descriptive statistics. The treatment difference in the AE rate will be analyzed using a Mantel-Haenszel Chi-square test with ECOG performance status (0 versus 1) and histology (squamous cell carcinoma versus non-squamous cell carcinoma) as the stratification factors. The ratio of the AE rates will be summarized along with the two-sided 95% confidence interval (CI).

10.6.2. Adverse Events

Adverse events will be analyzed in terms of TEAEs, defined as any AE or SAE occurring or worsening on or after the first dose of the study drug through 28 days after the last dose of study drug. 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 coded according to the Medical Dictionary for Regulatory Activities (MedDRA). The severity of AEs will be graded based on NCI Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0); http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

Treatment-emergent adverse events, Grade 3 or higher TEAEs, serious AEs, TEAEs leading to dose reduction, dose delay, and dose interruption, TEAEs leading to treatment discontinuation, and TEAEs with an outcome of death will be summarized per treatment arms by MedDRA system organ class and preferred terms.

Adverse events of special interest of the *nab*-paclitaxel plus carboplatin combination identified in previous studies in a similar population will be summarized in the same manner.

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.

10.6.3. Laboratory Assessments

Hematology Parameters: In order to investigate the maximal degree of myelosuppression, the NCI CTCAE v 4.0 grades for ANC, platelet count, and hemoglobin concentration will be summarized by the most severe grade in each treatment cycle and by the most severe grade anytime during the study for each treatment arm.

All other laboratory parameters reported on the eCRFs will be summarized by descriptive statistics by visit and treatment if the number of subjects with data is adequate. In addition, NCI CTCAE v 4.0 grades for the reported parameters will be summarized, if applicable.

10.6.4. Study Drug Exposure

The extent of exposure to the study drugs will be assessed based on the descriptive statistics on the number of cycles and study drug doses administered, cumulative dose, average dose intensity, and percentage of protocol dose administered. The incidences of *nab*-paclitaxel and/or carboplatin dose reductions, dose interruptions, and dose delays will be summarized by treatment arm.

10.7. Efficacy Analysis

10.7.1. Key Efficacy Endpoints

10.7.1.1. Progression-free Survival

Progression-free survival is defined as the time from the date of randomization to the date of disease progression or death (any cause) on or prior to the data cutoff date for analyses, whichever occurred first, based on the investigator's assessment of the data from CT scans using RECIST 1.1 guidelines. Baseline tumor measurements will be determined from the radiologic evaluation performed within 28 days before the start of study therapy.

Subjects who do not have disease progression, or are alive as of the data cutoff date for the statistical analysis will be censored at the date of the last radiologic assessment prior to the data cutoff date. Similarly, subjects who discontinue from the study prior to disease progression or death will be censored at the date 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 date 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 date 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 date of the last radiologic assessment where the subject was documented to be progression-free prior to the first of the two missing visits. Subjects who drop out early or die without any post-baseline radiologic tumor assessment will be censored on the date of randomization.

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

H_o: $HR_{\text{Arm B / Arm A}} = 1$

H_a: $HR_{\text{Arm B / Arm A}} \neq 1$

Progression-free survival will be summarized using Kaplan-Meier methods with median PFS time (including two-sided 95% CI) for each treatment schedule along with the hazard ratio estimated using Cox proportional hazards model (including two-sided 95% CI). The Kaplan-Meier curve for PFS will be presented graphically for each treatment schedule. P-value from a stratified log-rank test will be reported as an indication for the strength of association for the difference between the two curves, where the strata include ECOG performance status (0 versus 1) and histology (squamous versus non-squamous cell carcinoma), if the number of events in each cell is adequate.

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

10.7.1.2. 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 study or who are withdrawn from the study 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 cutoff date. Overall survival will be analyzed similarly as PFS.

10.7.1.3. Overall Response Rate

Overall response rate is defined as the percent of subjects who had a radiologic complete or partial response according to RECIST Version 1.1 guidelines determined by the investigator and confirmed by repeat radiologic assessment performed no less than 28 days after the criteria for response were first met.

Overall response rate for each treatment arm will be presented with the two-sided 95% CI. Relative treatment effect will be summarized by the difference in response rate and the associated two-sided 95% CI. P-value from a Chi-square test will be reported to indicate the strength of association of the relative treatment effect.

10.7.2. Exploratory Endpoints

10.7.2.1. Health Care Utilization and Quality of Life Questionnaire

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

10.8. Study Therapy Termination

Reasons for stopping study therapy will be presented in listings and summarized by frequency of occurrence and corresponding percentage of occurrence.

10.9. Deaths

Deaths reported during treatment (defined as deaths from the first administration of the study drug through 28 days post last dose of the study drug) 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).

10.10. Interim Analysis

A non-binding interim analysis for futility with the primary safety endpoint will be conducted when approximately a total of 139 treated subjects have either completed 6 months of study treatment or discontinued from the study due to progression, adverse events, deaths, lost to follow up, or other reasons. The stopping rule and the final marginal significance level are determined based on the Gamma family spending function with parameter = -7 (Hwang, 1990) to control the Type-II error rate at 20%. The study may be stopped early for futility if the treatment difference is between ± 0.4% (Z-score ± 0.054) given the interim analysis is performed at 50% information fraction.

10.11. Scientific Steering Committee

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

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 eCRF rather than the individual signs or symptoms of the diagnosis or syndrome.

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

An overdose, accidental or intentional, whether or not it is associated with an AE, or abuse, withdrawal, sensitivity or toxicity to a study drug 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 findings from 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 study drug, and those SAEs made known to the investigator at any time thereafter that are suspected of being related to study drug. AEs and serious adverse events (SAEs) will be recorded on the AE page of the eCRF 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 eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of or an elective procedure for 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 study drug, action taken regarding study drug, 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 study drug and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected:	Means a causal relationship of the adverse event to study drug administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	Means there is a **reasonable possibility** that the administration of study drug caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the study drug and the adverse event.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary or additional study drug 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 study drug as a result of an AE or SAE, as applicable (eg, discontinuation or reduction of study drug, 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 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 study drug 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 eCRF. 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. Female Subjects

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 study drug, or within 28 days of the subject's last dose of study drug, are considered immediately reportable events. Study drug 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 or another appropriate healthcare professional for further evaluation.

The investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (eg, spontaneous 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 study drug 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 study drug or within 6 months of the last dose of study drug, the male subject taking study drug should notify the investigator, and the pregnant female partner should be advised to call her healthcare provider immediately. If the male subject is receiving study drug, the study drug 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 study drug) that occur during the study (from the time the subject signs informed consent to at least 28 days after the last dose of study drug) and those made known to the investigator at anytime thereafter that are suspected of being related to study drug. SAEs occurring prior to treatment (after signing the ICF) will be captured.

The SAE report should provide a detailed description of the SAE and include a concise summary 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 Independent Review Board/Ethics Committee (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 Investigator Brochure.

In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

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

- Any AE suspected of being related to the use of study drug 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 study drug:

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

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.

All subjects discontinued from study drug for any reason will have a treatment discontinuation visit at the time of discontinuation and should undergo treatment discontinuation procedures.

All subjects discontinued from *nab*-paclitaxel will be followed for a period of 28 days after last dose of study drug for the collection of AEs.

Additionally subjects who withdraw from or discontinue treatment should be followed for progressive disease (if applicable), survival and any new anticancer therapy given.

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

12.2. Study Discontinuation

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

- Withdrawal of consent
- Death
- Lost to follow-up

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

- Adverse events(s)
- 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 that the subject is lost to follow-up.

12.3. Subject Replacement

Subjects who discontinue will not be replaced.

13. EMERGENCY PROCEDURES

13.1. Emergency Contact

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

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

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

14. REGULATORY CONSIDERATIONS

14.1. Good Clinical Practice

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

14.2. Investigator Responsibilities

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

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

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

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

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 distribution of the study drug 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 eCRFs 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 study drug. 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 eCRFs (if paper) and of documentation of corrections for all subjects;
- Study drug 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, eCRFs, 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, eCRFs, 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 eCRFs 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 eCRFs 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, eCRFs 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 of first 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 a study.

18. REFERENCES

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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: Saturday, 06 December 2014, 01:11 PM Eastern Daylight Time
Meaning: Approved, no changes necessary.
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