Protocol Title:

A Phase II, Single Arm, Open-Label, Multi-Center, Safety and Tolerability Trial with *nab*-Paclitaxel (Abraxane®) Plus Carboplatin Followed by *nab*-Paclitaxel Monotherapy as First-Line Treatment For Subjects With Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC) and an Eastern Cooperative Oncology Group Performance Status of 2 (Abound.PS 2).

NCT Number: NCT02289456

Statistical Analysis Plan Date: 11 April 2017

DISCLOSURE

REDACTED STATISTICAL ANALYSIS PLAN

ABI-007-NSCL-004

A PHASE II, SINGLE ARM, OPEN-LABEL, MULTI-CENTER, SAFETY AND TOLERABILITY TRIAL WITH *nab*-PACLITAXEL (ABRAXANE®) PLUS CARBOPLATIN FOLLOWED BY *nab*-PACLITAXEL MONOTHERAPY AS FIRSTLINE TREATMENT FOR SUBJECTS WITH LOCALLY ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC) AND AN EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS OF 2 (ABOUND.PS 2)

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STATISTICAL ANALYSIS PLAN

A PHASE II, SINGLE ARM, OPEN-LABEL, MULTI-CENTER, SAFETY AND TOLERABILITY TRIAL WITH *nab*-PACLITAXEL (ABRAXANE®) PLUS CARBOPLATIN FOLLOWED BY *nab*-PACLITAXEL MONOTHERAPY AS FIRST-LINE TREATMENT FOR SUBJECTS WITH LOCALLY ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC) AND AN EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS OF 2

(ABOUND.PS 2)

STUDY DRUG:	*nab*-Paclitaxel (Abraxane®)
PROTOCOL NUMBER:	ABI-007-NSCL-004
DATE FINAL:	11 APR 2017

Prepared by:

On behalf of Celgene Corporation
86 Morris Avenue
Summit, NJ 07901

SIGNATURE PAGE

STATISTICAL ANALYSIS PLAN (SAP) AND SAP AMENDMENT APPROVAL SIGNATURE PAGE	
SAP TITLE	ABI-007-NSCL-004 Statistical Analysis Plan
SAP VERSION, DATE	Final 11 APR 2017
SAP AUTHOR	
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INVESTIGATIONAL PRODUCT	*nab*-PACLITAXEL (Abraxane®)
PROTOCOL NUMBER	ABI-007-NSCL-004
PROTOCOL VERSION, DATE	Amendment #1, 12 Jan 2015
SIGNATURE STATEMENT	By my signature, I indicate I have reviewed this SAP and find its contents to be acceptable.

Statistical Therapeutic Area Head

Signature _____

Printed Name _____ Date _____

Lead Clinical Research Physician / Clinical Research Physician

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Lead Product Safety Physician

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Lead Clinical Research Physician / Clinical Research Physician

Signature _____

Printed Name _____ Date _____

Lead Product Safety Physician

Signature _____

Printed Name _____ Date _____

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1. LIST OF ABBREVIATIONS

Table 1: Abbreviations and Specialist Terms

ADT	Analysis date
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase (SGPT)
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the curve
BMI	Body mass index
BSA	Body surface area
CCI	Charlson Co-Morbidity Index
CI	Confidence interval
CR	Complete response
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DMC	Data Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	Epidermal growth factor receptor
EOS	End of study
EQ-5D-5L	EuroQoL Group 5-Dimension 5-Level
FEV1	Forced expiratory volume in 1 second
FNC	Fine needle cytology
FVC	Forced vital capacity
Hgb	Hemoglobin
HR	Hazard ratio

ICF	Informed consent form
IRT	Interactive Response Technology
IV	Intravenous
IVRS	Interactive voice response system
KPS	Karnofsky performance status
KRAS	Kirsten rat sarcoma viral oncogene homolog
LCSS	Lung Cancer Symptom Scale
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NA	Not applicable
NE	Not evaluable
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PEF	Peak expiratory flow
PFS	Progression-free survival
PP	Per protocol
PR	Partial response
PS	Performance status
PT	Preferred term
RECIST	Response evaluation criteria in solid tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SI	International System of Units (Le Système International d'unités)

SMQ	Standardized MedDRA query
SOC	System organ class
TEAE	Treatment-emergent adverse event
TTR	Time-to-response
UE	Unevaluable
US	United States
VAS	Visual analog scale
WBC	White blood cell
WHO	World Health Organization
WHO-DDE	World Health Organization Drug Dictionary Enhanced

2. INTRODUCTION

This statistical analysis plan (SAP) describes the analyses and data presentations for Celgene's protocol ABI-007-NSCL-004 "A PHASE II, SINGLE ARM, OPEN-LABEL, MULTI-CENTER, SAFETY AND TOLERABILITY TRIAL WITH *nab*-PACLITAXEL (ABRAXANE®) PLUS CARBOPLATIN FOLLOWED BY *nab*-PACLITAXEL MONOTHERAPY AS FIRST-LINE TREATMENT FOR SUBJECTS WITH LOCALLY ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC) AND AN EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS OF 2 (ABOUND.PS 2)" which was issued on 11Aug 2014 and amended on 12 Jan 2015. It contains definitions of analysis populations, derived variables and statistical methods for the analysis of efficacy and safety.

These analyses include one interim review and one final analysis. Throughout this SAP, the study treatment will be referred to as induction therapy, consisting of *nab*-paclitaxel plus carboplatin (21-day cycle for 4 cycles), and monotherapy, *nab*-paclitaxel only (continuous 21-day cycles until disease progression or unacceptable toxicity). The purpose of the SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches to the analysis of study data prior to database lock and any data analysis for the first interim/final analysis. This SAP will be finalized and signed prior to the clinical database lock. All statistical analyses detailed in this SAP will be conducted using SAS® Version 9.2 or higher.

An interim review of the percentage of subjects discontinued due to treatment-emergent adverse events (TEAEs) will be conducted when 20 subjects have either completed 4 cycles of induction therapy, or have discontinued due to reasons other than lost to follow-up prior to completing 4 cycles of induction therapy to safeguard the safety of the subjects enrolled in the study.

In August 2016, Celgene management informed sites and regulatory authorities of its decision to end enrollment prior to enrolling the planned number of subjects, due to slower than expected enrollment. The clinical cutoff date for the final safety and efficacy analysis will be 24 February 2017.

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective is as follows:

- To assess the safety and tolerability of the *nab*-paclitaxel and carboplatin combination dosing regimen for first-line treatment of locally advanced or metastatic NSCLC in subjects with an Eastern Cooperative Oncology Group Performance Status 2 (ECOG PS 2).

3.2. Secondary Objectives

The secondary objectives are as follows:

- To evaluate the efficacy (progression-free survival [PFS], disease control rate [DCR], OS, and overall response rate [ORR]) of the *nab*-paclitaxel and carboplatin combination dosing regimen, followed by *nab*-paclitaxel monotherapy for first-line treatment of locally advanced or metastatic NSCLC in subjects with an ECOG PS 2.
- To assess the safety and tolerability of the *nab*-paclitaxel and carboplatin combination dosing regimen, followed by *nab*-paclitaxel monotherapy for first-line treatment of locally advanced or metastatic NSCLC in subjects with an ECOG PS 2.

3.3. Exploratory Objectives

The exploratory objectives are as follows:

- To assess healthcare resource utilization
- To assess co-morbidity status using the Charlson Co-Morbidity Index (CCI)
- To assess quality of life
- To explore the correlation between the physician- and subject-evaluated ECOG PS
- To explore the correlation between the physician- and subject-evaluated Karnofsky performance status (KPS) at baseline
- To assess the safety and efficacy of continuous treatment with *nab*-paclitaxel as monotherapy after 4 cycles of *nab*-paclitaxel in combination with carboplatin

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

Forty subjects (originally planned to be approximately 50 subjects) with stage IIIB or IV NSCLC and ECOG PS 2 will be enrolled in the study to receive *nab*-paclitaxel plus carboplatin for 4 cycles, followed by monotherapy with *nab*-paclitaxel in the absence of disease progression.

The study will consist of a 28-day screening period, induction with 4 cycles of *nab*-paclitaxel and carboplatin followed by *nab*-paclitaxel monotherapy, and follow-up.

The screening period for eligibility determination begins upon subject written informed consent.

Induction Part

In the induction part subjects will receive 4 cycles of *nab*-paclitaxel plus carboplatin, provided all eligibility criteria are met within a 28-day screening period prior to Cycle 1 Day 1.

Induction treatment will consist of:

- *nab*-Paclitaxel 100 mg/m^2 intravenous (IV) infusion on Days 1 and 8 of each 21-day cycle
- Carboplatin area under the curve (AUC) = 5 mg*min/mL IV on Day 1 of each 21-day cycle after completion of *nab*-paclitaxel infusion.

Monotherapy Part

Subjects may continue in the study and receive monotherapy with *nab*-paclitaxel in the absence of disease progression, after the completion of 4 cycles of the induction therapy.
They will receive:

- *nab*-Paclitaxel 100 mg/m2 IV infusion on Days 1 and 8 of each 21-day cycle.

Follow-up Period

All subjects who discontinue treatment for any reason other than lost to follow-up or death, will enter the follow-up period. All subjects will continue to have computed tomography (CT) scans in accordance with their institution's standard of care and the findings will be reported on the appropriate electronic Case Report Form (eCRF) pages. In addition, all post-treatment anti-cancer therapy will be reported on the appropriate eCRF pages. Minimally, all subjects will be followed for OS every 90 days by phone contact or chart review for documentation of last contact for up to 1 year after the last subject is enrolled.

The Screening Period will start from signing the Informed Consent Form (ICF) until Day 1 of Treatment. The Treatment Period will start on the date of the first dose of study drug and will end on the treatment end date. The Follow-up Period will start the day after the treatment end date.

No additional anti-cancer agents are allowed during study treatment. All supportive care (including but not limited to antibiotics, analgesics, anti-emetics, thoracentesis, pleurodesis, blood transfusions, nutritional support, and/or focal external-beam radiation for control of pain,

cough, dyspnea, or hemoptysis, excluding anti-neoplastic agents) is permitted as per the investigator's discretion and will be recorded on the appropriate eCRF pages.

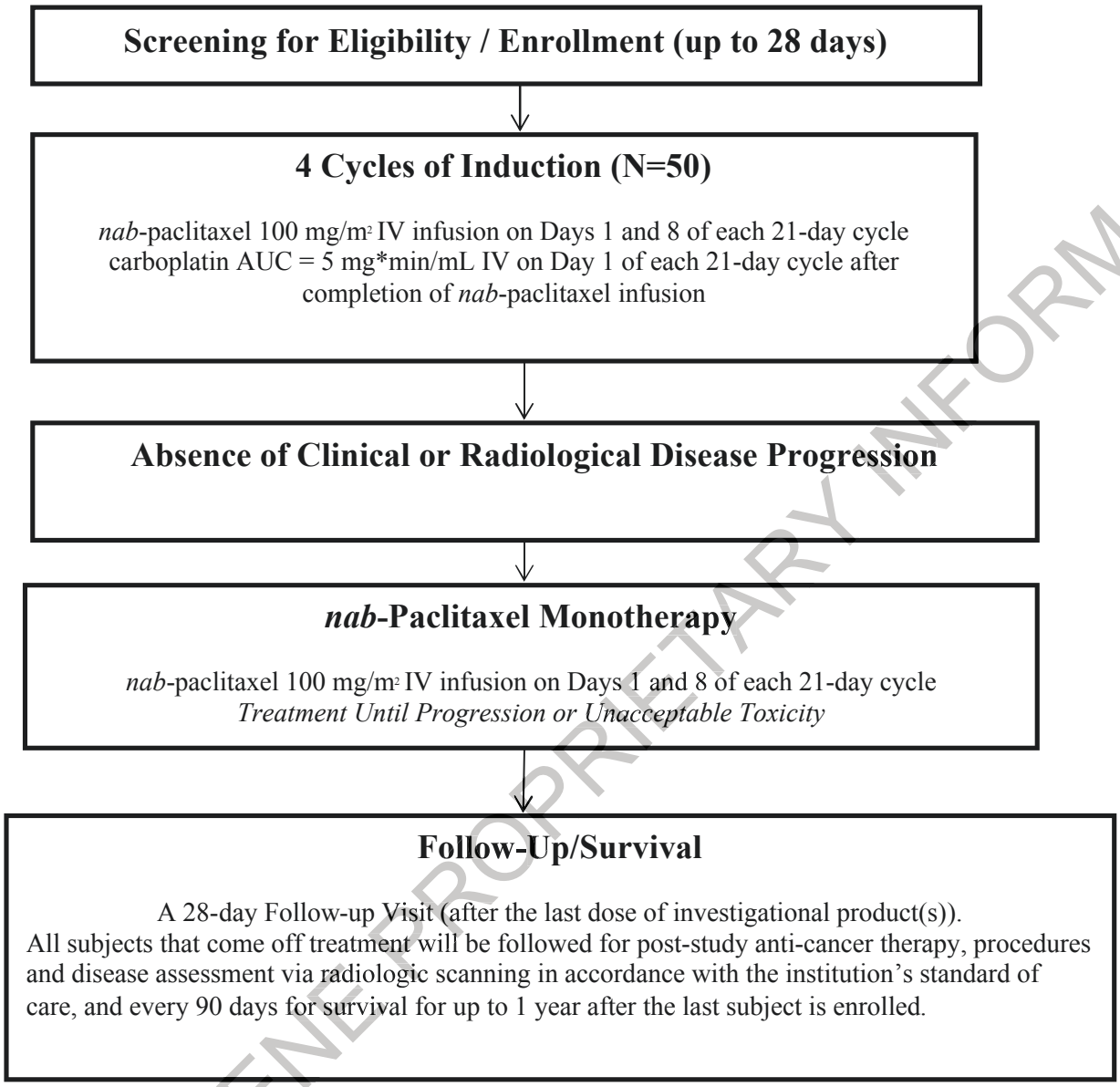
Local laboratory test data for absolute neutrophil count (ANC), white blood cell (WBC) count, platelet count, hemoglobin (Hgb), serum creatinine, calculated creatinine clearance, 24 hour urine collection (where applicable), aspartate transaminase (AST/serum glutamic oxaloacetic transaminase [SGOT]), alanine transaminase (ALT/serum glutamic pyruvic transaminase [SGPT]), albumin, total bilirubin 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 adverse event (AE), or serious adverse event (SAE) and the specific associated laboratory parameter should be recorded in the laboratory assessments eCRF. Local safety laboratory data will also be the primary guide for eligibility and subject management.

Tumor evaluations will be assessed locally and response (Complete Response (CR) or Partial Response (PR) will be determined according to Response Evaluation Criteria in Solid Tumor (RECIST) guidelines, Version 1.1 (Eisenhauer, et al., 2009). Tumor assessments will be conducted at Screening and after every 2 cycles (-3/+7 days) until treatment discontinuation, withdrawal of consent, lost to follow-up, or death. During follow-up, subjects will continue to have computed tomography (CT) scans in accordance with their institution's standard of care and the findings will be reported on the appropriate eCRF pages.

All subjects who discontinue from treatment for reasons other than withdrawal of consent, lost to follow-up or death, will enter the follow-up period. It will consist of a study visit 28 days after the last dose of investigational product. Thereafter subjects will be followed for post-study anti-cancer therapy, procedures, and disease assessment via radiologic scanning in accordance with the institution's standard of care, and every 90 days for survival for up to 1 year after the last subject is enrolled. All data will be reported on the appropriate eCRF page.

The study schematic is given in Figure 1.

Figure 1: Study Schematic for ABI-007-NSCL-004



4.2. Study Endpoints

4.2.1. Primary Endpoint

The primary study endpoint is the percentage of subjects who discontinue study treatment during the induction part due to TEAEs.

4.2.2. Secondary Endpoints

4.2.2.1. Safety

- The type, frequency, and severity of AEs and SAEs graded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0)
- Discontinuation rate
- The dose intensity
- The incidence of dose reduction

4.2.2.2. Efficacy

Efficacy endpoints include the following:

- Progression free survival
- Disease control rate
- Overall survival
- Overall response rate

Other secondary efficacy endpoints include:

- Time to response
- Duration of response

4.2.3. Exploratory Endpoints

The exploratory endpoints listed below will be evaluated across induction and monotherapy parts, unless indicated otherwise.

- Healthcare resource utilization throughout the study using a questionnaire
- Changes from baseline in physician-reported ECOG PS
- Changes from baseline in the EuroQol-5D (EQ-5D-5L) and Lung Cancer Symptom Score (LCSS)
- Summary of the CCI at baseline
- Correlation between subject-reported ECOG PS and physician-reported ECOG PS during the treatment period

- Correlation between subject-reported KPS and physician-reported KPS at baseline
- Changes from baseline in spirometry and pulse oximetry parameters
- Treatment response during the monotherapy part compared with response at the start of monotherapy.

4.3. Stratification, Randomization and Blinding

This is a single arm, open-label study. No randomization or blinding is done.

4.4. Sample Size Determination

The primary objective of this study is to assess the safety and tolerability of *nab*-paclitaxel in combination with carboplatin for 4 cycles for the first-line treatment of locally advanced or metastatic NSCLC in subjects with an ECOG PS 2. All evaluations of the safety and efficacy endpoints will be based on the point estimates and the associated 2-sided 95% confidence intervals (CI) rather than formal inferential statistical tests.

The primary study endpoint (also the primary safety endpoint) is the percentage of subjects who discontinue during the induction part due to TEAEs. With a sample size of 50, the maximum width of the 95% CI for any proportion is 28.9%. Of note, assuming the underlying percentage of subjects who will discontinue from study treatment due to TEAEs is 30%, a sample size of 50 provides 80% power, with a one-sided significance level of 10%, to detect an increase of 15 percentage points from 30%.

Table 5 Section 10.3 of the protocol demonstrates the precision of the estimate that can be attained given a sample size of 50 for a range of hypothetical rates of study treatment discontinuation due to TEAEs during the induction part of the study. For example, for a hypothetical discontinuation rate of 30%, the width of the associated two-sided 95% CI is 26.7%, and the estimated 95% CI is (17.9% - 44.6%).

The data cutoff for the analysis of both the safety and efficacy endpoints for the clinical study report will be 24 February 2017.

5. GENERAL STATISTICAL CONSIDERATIONS

5.1. Reporting Conventions

The following reporting conventions apply generally to tables, listings, and figures:

- Data from all study centers will be combined for analysis;
- P-values will be rounded to 4 decimal places. P-values that round to 0.0000 will be presented as '<0.0001' and p-values that round to 1.0000 will be presented as '>0.9999';
- Confidence intervals will be presented as 2-sided 95% CIs unless specified differently for a given analysis;
- Summary statistics will consist of the number and percentage of subjects (or cycles, if appropriate) in each category for discrete variables, and the sample size, mean, standard deviation, median, the 25th (Q1) and 75th (Q3) percentiles, minimum, and maximum for continuous variables;
- All mean, median, and percentile values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value. Minimum and maximum will be formatted to the same decimal place as the measured value;
- All percentages will be rounded to one decimal place. Tables that show only number and percentage of responses will be presented in the form XX (XX.X), where the percentage is in the parentheses. Tables that show number and percentage of responses in addition to summary statistics will be presented in the form XX (XX.X%), where the percentage is in the parentheses;
- All listings will be sorted for presentation in order of study site, subject, and date of procedure or event. Data for all treated subjects will be included in subject data listings;
- All analysis and summary tables will have the analysis population sample size (i.e., number of subjects);
- Baseline value will be defined as the last non-missing value obtained before or on the day the first dose of study drug is administered; if multiple values are present for the same date, the average of these values will be used as the baseline. For subjects who were not treated, the baseline will be the last non-missing assessment value taken on or before the IRT enrollment visit date;
- Partial dates will be imputed based on the rules specified in Appendix 16.2;
- All laboratory data will be reported using standard international (SI) units;
- Summaries of the most severe toxicity grade in clinical laboratory in each treatment cycle and most severe grade post-baseline overall and shifts from baseline to most severe toxicity grade post-baseline by-visit and overall will include all scheduled and unscheduled assessments;

- For safety analyses, data obtained through the last dose date + 28 days will be used.

5.2. Analysis Populations

5.2.1. Treated Population

The treated population will consist of all subjects who received at least one dose of investigational product. Unless otherwise specified, the treated population will be the analysis population for all safety analyses. Only subjects with clear documentation that no study drug was administered will be excluded from the treated population.

5.2.2. Per-Protocol Population

The per-protocol (PP) population is defined as all eligible subjects enrolled who receive at least one dose of the investigational product; have a baseline and at least one evaluable post baseline radiological assessment; and do not have any relevant protocol violations or deviations. The PP population will be used in a replication of the efficacy analyses.

6. SUBJECT DISPOSITION

The number of subjects screened but not treated, the number and percentage of subjects included in the treated population will be summarized. The percentages will be based on the number of subjects screened. A summary of analysis populations will be presented for treated population and per-protocol population.

Subject study disposition will be presented separately for subjects who signed informed consent but were not treated, and for all treated subjects. Additionally, treatment disposition will be summarized overall and by study part (i.e. induction part and monotherapy part) for all treated subjects.

The primary reasons for study discontinuation will be summarized with the following categories:

- Screen failure
- Death
- Adverse event
- Withdrawal by subject
- Lost to follow up
- Protocol violation
- Study terminated by sponsor
- Other

The primary reasons for treatment discontinuation in the treated population will be summarized by study part (induction, monotherapy and overall) with the following categories:

- Death
- Adverse event
- Progressive disease
- Symptomatic deterioration
- Withdrawal by subject
- Lost to follow-up
- Study terminated by sponsor
- Protocol violation
- Other

Deaths reported during treatment (defined as deaths from the first administration of the study drug through 28 days post last dose of study drug); deaths that occur during the Follow-up Period; and all deaths will be summarized by frequency of occurrence and corresponding percentage by cause of death. Cause of death will be categorized by the categories on the death eCRF and by coded cause of death.

A summary of subjects treated by site will be provided. Listings will be provided for discontinued subjects with reason for treatment discontinuation and reason for study discontinuation, and for screen failure subjects who did not meet eligibility criteria.

7. PROTOCOL DEVIATIONS/VIOLATIONS

The protocol deviations/violations will be identified and assessed by the clinical monitor of the sponsor or designee following company standard operational procedure.

Protocol deviations/violations will be summarized using frequency tabulations. Additionally, a by-subject listing of subjects with protocol violations or deviations in the treated population will be provided.

Protocol deviations and violations will be reviewed before database lock. Not all deviations or violations will constitute the exclusion of subject from the per-protocol population; events that could trigger exclusion from the per protocol population include major inclusion/exclusion criteria violations, failure to take IP as assigned, and prohibited concomitant medications and procedures.

8. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

The demographics and baseline characteristics will be summarized for all treated subjects. Individual subject listings will be provided to support the summary tables. Provided the numbers of subjects are sufficient, the demographics and baseline characteristics will also be summarized within the following subgroups:

- Age (< 65 years, 65 – 74 years, and ≥ 75 years)
- Sex (Male, Female)
- Histology (Squamous, non-Squamous)

8.1. Demographics

Age (years), height (cm), weight (kg), body mass index (BMI; kg/m^2), body surface area (BSA) (m^2) at baseline will be summarized descriptively. Sex, Age category, race, and ethnicity will be summarized by frequency counts.

Age will be calculated as follows: Age = Integer part of [(Date of informed consent– Date of Birth + 1) / 365.25].

BMI will be calculated as follows: BMI = weight in kg / $(\text{height in m})^2$.

For the purposes of data listings and tables, BSA will be calculated as follows:
$\text{BSA} = 0.007184 \times (\text{weight in kg})^{0.425} \times (\text{height in cm})^{0.725}$.

8.2. Baseline Characteristics

Baseline characteristics indicated below will be summarized descriptively:

- Subject- and physician-reported ECOG performance status at baseline and physician-reported ECOG performance status at screening visit
- Charlson Co-morbidity Index score at baseline
- Subject- and physician-reported KPS at baseline
- Histology (squamous cell carcinoma vs. non-squamous cell carcinoma) at baseline
- Baseline tumor, node and metastasis (TNM) stage
- Weight change, expressed as percent change from weight approximately 6 months prior to date of informed consent
- Reversibility of PS 2 status

8.3. Medical History and Cancer Diagnosis

8.3.1. Medical History

A summary of medical and surgical history will be presented by system and organ class (SOC) and preferred term (PT), coded according to the Medical Dictionary for Regulatory Activities

(MedDRA). A similar summary will be generated for the currently active abnormalities only, by SOC and PT.

8.3.2. Lung Cancer History

The following items will be summarized for cancer diagnosis:

- Stage at enrollment
- The time from specimen collection date to first dose date in months, defined as (first dose date – specimen collection date)/ 30.4375
- Method of specimen collection (biopsy, surgical specimen, FNC, other)
- Histology (squamous, adenocarcinoma, large cell, other)
- Squamous cell histology type (papillary, clear cell, basaloid, and other)
- Adenocarcinoma cell type (acinar, papillary, broncholoalveolar carcinoma, solid adenocarcinoma with mucin, adenocarcinoma with mixed subtypes, and other)
- Mutational gene status for patients with adenocarcinoma cell histology confirmed (KRAS, EGFR, FGFR 1/2/3/4, ALK, other)
- Number of prior systemic anti-cancer therapies for non-small cell lung cancer
- Time from latest systemic anti-cancer therapy to first dose date in months
- Number of prior radiation therapies
- Time from latest radiation therapy to first dose date in months
- Number of prior cancer surgeries for non-small cell lung cancer
- Time from latest prior cancer surgery to first dose date in months
- Time from latest cancer therapy (last to occur of systemic anti-cancer therapy, radiation, or cancer surgery) to first dose date in months.

Subject listings will be provided for all of the above, as well as date of specimen collection.

8.4. Prior and Concomitant Therapy

Prior therapies are defined as the therapies that were started before the start of the study treatment.

8.4.1. Prior Systemic Anti-cancer Therapies

Prior systemic therapies (e.g. chemotherapy) will be coded to therapeutic drug class and generic drug names using the World Health Organization (WHO) Drug Dictionary Enhanced version WHO-DDE 01 Mar 2015 or later. The number and percentage of subjects who had prior systemic anti-cancer therapies will be presented by drug class and generic drug name and overall.

Prior systemic anti-cancer therapies will be listed.

8.4.2. Prior Radiation Therapy

The number and percentage of subjects who had any prior radiation therapy will be presented. For subjects with prior radiation therapy, the number and percentage of subjects with each treatment site of radiation therapy will be summarized with frequency counts and percentages. The dose, duration of radiation therapy in days, and the number of fractions (where known), will be summarized descriptively. Intent (adjuvant, curative, palliative, unknown), and setting (stand-alone, concurrent with other anti-cancer therapy, sequential to other anti-cancer therapy) will be summarized. Prior radiation therapies will be listed.

8.4.3. Prior Cancer Surgeries

Prior non-small cell lung cancer surgeries will be coded by MedDRA system organ class and preferred term. A summary showing the number and percentage of subjects who had prior anti-cancer surgery will be presented by system organ class and preferred term, and overall. Additionally, the time from the last prior cancer surgery to the first dose of study drug will be summarized.

Prior surgeries will be listed.

8.4.4. Concomitant Procedures/Surgeries

Concomitant procedures/surgeries are considered any procedures/surgeries that occurred on or after the date of the first dose of study drug. The number of subjects having concomitant surgeries or procedures performed will be summarized.

Concomitant surgeries and procedures will be listed.

8.5. Prior and Concomitant Medications

Medications reported on the Prior and Concomitant medications eCRF pages will be coded to therapeutic drug classes and generic drug names using the WHO drug dictionary version WHO-DDE 01 Mar 2015. Medications initiated prior to the start of study treatment and continued after the start of study treatment will be counted as both prior and concomitant medications.

Prior and concomitant medications will be listed.

8.5.1. Prior Medications

Prior medications are defined as all medications that were started before the date of first dose of study drug. A summary showing the number and percentage of subjects who took prior medications will be presented by WHO drug dictionary therapeutic drug class and generic drug name. This summary will be presented for the treated population.

8.5.2. Concomitant Medications

Concomitant medications are 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. Summaries showing the number and percentage of subjects who took concomitant medications will be presented by WHO therapeutic drug class and generic drug name for the treated population.

9. STUDY TREATMENTS AND EXTENT OF EXPOSURE

All study treatment and extent of exposure summaries will be provided based on the treated population. Descriptive statistics will be provided for treatment duration, number of cycles, cumulative dose, dose intensity, and percentage of protocol dose by study part (induction, monotherapy, and entire study), as applicable. The study treatments and extent of exposure summaries for *nab*-paclitaxel and carboplatin are presented separately for the induction part.

9.1. Treatment and Cycle Start and End Dates

Day 1 of treatment for a subject is the same as Day 1 of treatment for the induction part and is defined as the first day of any study drug administered to the subject in the induction part (i.e., Cycle 1 Day 1). The first day of a cycle in the induction part is the first date of carboplatin administration for that cycle. Day 1 of monotherapy treatment for a subject is the first day of study drug administered to the subject in cycle 5. The first day of a cycle in the monotherapy part is the first administration of *nab*-paclitaxel for that cycle. The last day of a cycle (other than the last cycle) is defined as the day before the first day of the next cycle.

The treatment end date and the end date of the last cycle will be defined as follows:

- For subjects who discontinued treatment, the treatment end date is the discontinuation date from the treatment disposition form on eCRF.
- For subjects who are still on treatment at the time of study closure or clinical cutoff, the treatment end date is defined as the date corresponding to the integer part of the day number of the maximum of the *nab*-paclitaxel dosing period and the carboplatin dosing period. Dosing periods are defined in Section 9.2.

The induction part end date is defined as:

- For subjects who do not participate in the monotherapy part and discontinue prior to the clinical cutoff date, the induction part end date is equal to the treatment end date as defined above.
- For subjects who are still on treatment in the induction part at the time of study closure or clinical cutoff, the induction part end date is equal to the treatment end date as defined above.
- For subjects who participate in the monotherapy part, the induction part end date is the day before the first dose in cycle 5.

The treatment end date in the monotherapy part is defined only for subjects who start monotherapy and is equal to the treatment end date.

9.2. Dosing Period for Each Study Drug

Dosing periods will be defined for each study drug and will be used as the denominators for the calculation of dose intensity for each drug. Dosing period will also be used in the definition of treatment end date for subjects who are still on treatment at the time of study closure or clinical cutoff.

Conceptually, the dosing period for an IP is the time period starting at the first dose of the IP and ending a protocol- and subject-specific number of days after the last dose, depending on the dosing schedule for the IP. Ending the dosing period on the date of last dose would lead to an overestimation of the dose intensity. To avoid such overestimation, additional days of dosing period beyond the date of the last dose allow for the calculated dose intensity to reflect the degree to which the subject's dosing schedule aligned with the protocol-specified dose intensity. A subject's dosing period never extends beyond the date of death, but it can extend beyond the treatment discontinuation date in some circumstances.

For *nab*-paclitaxel, since the two protocol-specified doses are administered at uneven intervals, the end of the dosing period depends on whether the last dose administered was a Day 1 or a Day 8 dose. If the last dose of *nab*-paclitaxel was a Day 1 dose, then the subject had half of the protocol-specified *nab*-paclitaxel doses for the last cycle, so they are allotted half of the cycle's length (10.5 days) in their *nab*-paclitaxel dosing period. If the subject had all of the doses for the last cycle, as is always the case for carboplatin, and for the *nab*-paclitaxel when the last dose was a Day 8 dose, then the end of the dosing period is the last planned day of the cycle. If they have discontinued treatment, then the *nab*-paclitaxel dosing period can be extended to the treatment discontinuation date if that date is beyond the last cycle's halfway point. If death occurs after the treatment discontinuation date but before the cycle's halfway point, then the date of death is the end of the dosing period. The specific calculations of the dosing period for each IP are given in Table 2.

Table 2: Calculation of Dosing Period for Each Study Drug Based on Cycle Day Number of Last Dose of the Study Drug

Overall Dosing Period		
Investigational Product	Last Dose of IP is Day 1	Last Dose of IP is Day 8
nab-Paclitaxel	Min{study day of death, Max[study day treatment discontinuation, study day of last dose of *nab*-paclitaxel + 9.5]}	Min{study day of death, Max[study day of treatment discontinuation, study day of last dose* of *nab*-paclitaxel + 13]}
Carboplatin	Min{study day of death, Max[study day of treatment discontinuation, study day of last dose* of carboplatin + 20]}	NA
Induction Dosing Period		
nab-Paclitaxel	For subjects who do not participate in the monotherapy part and discontinue prior to the clinical cutoff date, equal to overall dosing period. For subjects who are still on treatment in the induction part at the time of clinical cutoff, equal to overall dosing period. For subjects who participate in the monotherapy part, study day number of the treatment end date for the induction part as defined in Section 9.1.	
Carboplatin	Equal to overall dosing period	
Monotherapy Dosing Period		
nab-Paclitaxel	For subjects who participate in the monotherapy part, overall *nab*-paclitaxel dosing period – study day of induction part end date as defined in Section 9.1.	
* date of last dose is the date of the latest dated record on the exposure eCRF (i.e., the last record for which there is a non-missing visit date or dose date, or both)		

9.3. Treatment Duration

Treatment duration (months) is defined as (treatment end date – Day 1 of treatment + 1)/30.4375, where treatment end date is defined as in Section 9.1.

In addition, the following are the treatment duration definitions for the two parts of the study:

- Induction treatment duration (months):

(induction part end date – Day 1 of treatment + 1)/30.4375

- Monotherapy Treatment Duration (months, defined for monotherapy subjects only):

(treatment end date – Day 1 of monotherapy treatment + 1)/30.4375

Descriptive statistics will be provided for treatment duration, total number of cycles administered, and total number of doses of each study drug (where applicable) administered for the entire study and for the Induction and Monotherapy parts separately.

9.4. Cumulative Dose

Cumulative dose for the entire study is defined as the sum of all assigned doses for all visits at which the actual dose administered > 0 mg. Cumulative dose will be computed separately for *nab*-paclitaxel and carboplatin.

Induction part cumulative dose is defined as the sum of all assigned doses for all visits during the induction part at which the actual dose administered > 0mg. The induction doses will be identified by cycle numbers on the corresponding eCRF dose forms. Cumulative dose will be computed separately for *nab*-paclitaxel and carboplatin.

Monotherapy part cumulative dose is defined as the sum of all assigned doses for all visits during the monotherapy part at which the actual dose administered > 0mg. Cumulative dose will be computed for *nab*-paclitaxel only in the monotherapy part.

Descriptive statistics for cumulative dose will be presented for each study drug by study part as applicable (induction, monotherapy, and entire study) for the treated population.

9.5. Dose Intensity

Dose intensity during the treatment is defined as the cumulative dose divided by the dosing period in weeks. Dose intensity will be calculated separately for *nab*-paclitaxel and carboplatin.

Dose intensities will be calculated as follows:

- Dose intensity for carboplatin (mg*min/mL/wk) = [cumulative dose for carboplatin in mg*min/mL] / [carboplatin dosing period in weeks];
- Dose intensity for *nab*-paclitaxel (mg/m2/wk) = [cumulative dose for *nab*-paclitaxel in mg/m2] / [*nab*-paclitaxel dosing period in weeks].
- Induction part dose intensity for *nab*-paclitaxel (mg/m2/wk) = [induction part cumulative dose for *nab*-paclitaxel in mg/m2] / [*nab*-paclitaxel induction part dosing period in weeks].

- Monotherapy part dose intensity for *nab*-paclitaxel (mg/m2/wk) = [monotherapy part cumulative dose for *nab*-paclitaxel in mg/m2] / [*nab*-paclitaxel monotherapy part dosing period in weeks].

Descriptive statistics for dose intensity will be presented for each study drug by study part as applicable (induction, monotherapy, and entire study) for the treated population.

9.6. Percentage of Protocol Dose

Percentage of protocol dose is the dose intensity divided by the protocol weekly dose, expressed as a percentage.

Percentage of protocol dose = (dose intensity / protocol weekly dose) * 100%

The protocol weekly doses are as follows:

- *nab*-Paclitaxel: 100 mg/m2 × 2 doses/cycle ÷ 3 weeks/cycle = 66.67 mg/m2/week
- Carboplatin: 5 mg*min/mL × 1 dose/cycle ÷ 3 weeks/cycle = 1.67 mg*min/mL/week

The percentage of protocol dose for carboplatin and *nab*-paclitaxel will be summarized using descriptive statistics. Percentage of protocol dose will also be categorized and frequency counts will be provided. For *nab*-paclitaxel, the summary will be presented for the induction and monotherapy parts as well as for the entire study using the treated population.

9.7. Exposure, Dose Reduction/Delay and Doses Not Administered

A dose reduction occurs when the dose assigned at a visit is lower than the dose assigned at the previous visit. At Cycle 1 Day 1, any dose lower than 100 mg/m^2 for *nab*-paclitaxel and 5 mg*min/mL AUC for carboplatin is a dose reduction.

Any dose that is administered ≥ 3 days after scheduled date will be considered a dose delay.

Scheduled Day 1 of a cycle (other than Cycle 1 Day 1) is defined as

- the date of Day 1 dose from previous cycle + 21

Scheduled Day 8 of a cycle = date of Day 1 dose + 7

Dose not administered is defined as any visit at which the question "Was dose administered?" on the exposure form is answered "No". The incidences of *nab*-paclitaxel and carboplatin missed doses will be tabulated by frequency.

Treatment exposure, dose reductions, dose delays and missed doses will be summarized for the entire study and for the induction and monotherapy parts as applicable, as follows:

- Number of doses administered by cycle;
- Number and percentage of doses administered at each dose level by cycle;
- Number and percentage of subjects with at least 1 dose reduction, number of dose reductions, and reasons (per protocol, adverse event, or other) for reduction, by study part, cycle and overall;

- Number and percentage of subjects with at least one dose delay, number of dose delays, by study part, cycle and overall;
- Number and percentage of subjects with at least one dose not administered; number of doses not administered, by study part, cycle and overall; reason for dose not administered.

10. SAFETY ANALYSIS

The purpose of this section is to define the safety analyses for the study. All summaries of safety data will be conducted using the treated population. Safety analyses will be presented for the entire study; summaries of adverse events will also be presented by study part in which they started or worsened as applicable.

10.1. Primary Endpoint

The primary endpoint for this study (also the primary safety endpoint) is the percentage of subjects who discontinue study treatment during the induction part due to TEAEs. A subject meets the primary endpoint if:

- Adverse Event is the reason for treatment discontinuation as recorded in the eCRF;

and

- The subject had no doses administered beyond cycle 4.

The number and percentage of subjects who discontinue study treatment during the induction part due to TEAEs will be presented in a summary table along with a two-sided 95% CI.

10.2. Treatment-emergent Adverse Events

TEAEs are defined as any AE or SAE occurring or worsening on or after the day of the first dose of the investigational product through 28 days after the last dose of investigational product. In addition, any serious AE with an onset date more than 28 days after the last dose of investigational product that is assessed by the investigator as related to investigational product will be considered a TEAE.

For subjects who enter monotherapy part, TEAEs with onset *on or before* Cycle 5 Day 1 will be considered TEAEs during the induction part. For subjects who discontinue before entering the monotherapy part, all TEAEs will be considered TEAEs during the induction part. For subjects who enter the monotherapy part, TEAEs with onset *after* Cycle 5 Day 1 will be considered TEAEs during the monotherapy part.

Adverse events will be coded according to the MedDRA, Version 19.0 or higher. Appendix 17.5 gives the dates of application of new versions of MedDRA. The severity of AEs will be graded based on NCI CTCAE, Version 4.0;

The incidence of TEAEs will be summarized by MedDRA system organ class (SOC) and preferred term (PT). For all other AEs not described in the CTCAE criteria, the severity will be assessed by the investigator as mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening (grade 4) or death (grade 5).

The following rules will be implemented for cycle calculations:

- TEAEs which start on Cycle 1 Day 1 belong to only Cycle 1.
- After Cycle 1, TEAEs will be categorized by the “throw-back rule”, that is, AEs that start on Day 1 of a cycle will be allocated to only the previous cycle.

- All TEAEs which start after Day 1 of last cycle will be included only in the last cycle.

A treatment-related TEAE is defined as an adverse event which was suspected to be related to either study drug. Where feasible, summaries of treatment-related TEAEs will be presented by the individual study drug to which the AE was related. If a subject experiences multiple occurrences of the same AE with different relationship to study drug, the subject will be counted once, as treatment-related. AEs with a missing relationship will be presented in the summary table as treatment-related.

If a subject experiences the same AE more than once with different toxicity grade, then the event with the highest grade will be tabulated in "by grade" tables. If a subject experiences multiple AEs under the same PT (and/or SOC), then the subject will be counted only once for that PT (and/or SOC).

Tables summarizing the incidence of TEAEs will be generated for each of the following:

- Overall summary of TEAEs;
- TEAEs presented by MedDRA system organ class, preferred term, and maximum CTCAE grade
- Treatment-related TEAEs by CTCAE grade category (grade 1-2 vs. grade 3-4 vs. grade 5; overall and by cycle);
- Serious TEAEs by maximum CTCAE grade ;
- Treatment-related serious TEAE by maximum CTCAE grade;
- TEAEs with action of study drug withdrawn;
- Treatment-related TEAEs with action of study drug withdrawn;
- TEAEs with action of study drug dose reduced or interrupted;
- Treatment-related TEAEs with action of study drug dose reduced or interrupted;
- TEAEs with fatal outcome;
- Treatment-related TEAEs with fatal outcome;
- All deaths;
- Most frequent TEAEs (≥ 5% of subjects; by PT only, without SOC)
- TEAEs for the following baseline subgroups (provided the number of subjects are sufficient):
    - Age (<65 years, 65 – 74 years, ≥75 years);
    - Sex (male versus female);

The following individual listings will be provided:

- Listing of TEAEs by subject;
- Listing of non-TEAEs by subject;
- Listing of TEAEs of special interest by subject.

10.3. Adverse Events of Special Interest

Specific adverse events of special interest are listed in Appendix 17.4.

The following summaries will be provided for TEAEs included in the selected AEs of special interest:

- All TEAEs by maximum CTCAE grade;
- TEAEs with action of action of study drug withdrawn;
- TEAEs with action of study drug dose reduced or interrupted;
- TEAEs by age group for risks specific to patients older than 75 (<65 years, 65 – 74 years, ≥75 years).

10.4. Peripheral Neuropathy

Peripheral neuropathy events will be reported as AEs and will be included in analyses described in Section 10.2.

10.5. Clinical Laboratory Evaluations

All clinical laboratory data (e.g., hematology and clinical chemistry) will be listed.

11. EFFICACY ANALYSIS

The primary objective of this study is safety. The treated population will be the primary analysis population for all efficacy endpoints. Supportive analysis of the efficacy endpoints PFS, OS, and ORR using the PP population will be conducted to assess the effect of major protocol deviations on efficacy.

The percent change from nadir during the Treatment Period in sum of lengths of longest diameters of target lesions is required to assess target lesions for tumor progression. This is calculated as follows:

Percent change from nadir at a given visit= (total length – nadir in total length) / (nadir in total length) x 100%, where nadir is calculated using all measurements prior to the visit in question, including baseline.

11.1.1. Progression-free Survival

Progression-free survival (PFS) is defined as the time in months from Day 1 of Treatment to the date of disease progression based on investigator assessment according to RECIST 1.1 criteria (documented by radiological assessment) or death (any cause) on or prior to the clinical cutoff date, whichever occurs earlier. Subjects with a single missing radiologic assessment prior to a visit with documented disease progression (or death) will be analyzed as a PFS event at the time of the radiologic assessment that shows progression or the death date (whichever is earlier). Subjects with two or more missing radiologic assessments prior to a visit with documented disease progression (or death) will be censored at the time of the last radiologic assessment where the subject was documented to be progression-free prior to the first of the two missing visits. Missing radiologic assessments will be identified by comparing the dates of non-missing and evaluable overall response records to the 42-day protocol-specified assessment schedule and the 3-day window (see appendix section 17.6). Subjects who do not have disease progression and have not died, regardless of whether they discontinued treatment, will be censored at the date of last tumor assessment, on or prior to the clinical cutoff date, when the subject was progression-free. This is further illustrated in Table 6.

Progression-free survival will be summarized using Kaplan-Meier methods with median PFS time and PFS rates at 2-month intervals from the day of the first dose of IP (including two-sided 95% CI). The Kaplan- Meier curve for PFS will be presented graphically.

An additional analysis of PFS will be performed using the European Medicines Agency methodology for analysis of a PFS endpoint. Similar to the approach described above, PFS will be defined as the time from day 1 of treatment to the date of disease progression or subject death (any cause), whichever occurs first. Subjects who do not have disease progression or have not died will be censored at the last known time that the subject is progression free (i.e. the last tumor assessment). However, occasional missing observations or initiation of subsequent anticancer therapy will not result in censoring for this analysis.

11.1.2. Disease Control Rate

Disease control rate is defined as the percent of subjects who have SD, CR or PR during the course of the study, according to RECIST 1.1 guidelines, as evaluated by the Investigator. Disease control rate will be summarized by number and percent of all treated subjects and presented with the associated Clopper-Pearson 95% confidence interval.

11.1.3. Overall Survival

Overall survival is defined as the time in months between the day 1 of treatment and death from any cause. Thus, it is calculated as follows:

OS = (date of death or censoring – Day 1 of treatment + 1) /30.4375

Subjects who are still alive or lost to follow-up as of the clinical cutoff date will have their overall survival censored at the date of last contact. For subjects not lost to follow-up, the last contact date is the study disposition date. For subjects who are lost to follow-up the date of last contact is the last known alive date.

Overall survival will be summarized similarly to PFS described in Section 11.1.1. In addition, to assess the impact of starting subsequent anticancer therapy on subject survival, a sensitivity analysis will be conducted. Subjects who start a subsequent anti-cancer therapy will be censored at the initiation date of the subsequent chemotherapy; a method similar to the primary analysis will be applied to estimate the median OS and the survival distribution.

11.1.4. Tumor Response and Overall Response Rate

Tumor response will be summarized by timing of lesion assessment and overall. Tumor assessments that occur after the initiation of subsequent anti-cancer therapy are excluded from the analysis. The number and percentage of subjects with a visit response or best overall response of PD, SD, PR, CR, and unevaluable (UE) will be presented. This analysis will be presented for each protocol-specified CT scan. If there is more than one CT scan within a relative day range, the best response will be counted. Relative study day windows are presented in Appendix 17.3.

The overall response rate (ORR) is the percent of subjects who achieve a best overall response of PR or CR compared with baseline, where baseline is the last CT-scan obtained prior to or on Day 1 of study treatment and the best response is the best tumor response occurring between Day 1 of treatment and the start of subsequent anti-cancer therapy, death, or study discontinuation. . The ORR along with 95% Clopper-Pearson confidence interval will be presented.

11.1.5. Time to Response

Time to response (TTR) is defined as the time from Day 1 of Study Treatment to the first occurrence of response (CR or PR). Only subjects with a CR or PR as a best overall response will be included in this analysis. TTR will be analyzed using descriptive statistics.

11.1.6. Duration of Response

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

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

Duration of response will be analyzed using the Kaplan-Meier method. The median time of response (including 2-sided 95% CI) will be summarized.

11.1.7. Subgroup Analyses

If subject numbers in the subgroups are sufficient, PFS, OS, and ORR will be analyzed within the following subgroups (with subgroup data based on the clinical database rather than IRT). These analyses will parallel the analyses for the endpoint performed on the whole population:

- Age (< 65 years and ≥ 65 years, < 70 years and ≥ 70 years, < 75 years and ≥ 75 years);
- Sex (Male, Female);
- Histology (Squamous, Non-squamous)

12. EXPLORATORY ANALYSIS

12.1.1. Healthcare Care Utilization

Frequency tabulations for location of care (number of office visits, hospital outpatient visits, hospital inpatient visits, emergency room visits, home healthcare visits, hospice, unknown, and other utilizations) and provider (general physician, specialist, nurse practitioner/physician assistant, paramedical care, unknown, and other) will be presented.

12.1.2. Quality of Life

The Lung Cancer Symptom Scale (LCSS) and EQ-5D-5L questionnaires will be used to measure quality of life (QoL) for subjects in the trial. The LCSS is a 9 question assessment the subject completes using a visual analogue scale (VAS) to denote intensity of a symptom. The EQ-5D-5L comprises 5 questions on mobility, self-care, usual activities, pain/discomfort, anxiety/depression and a VAS for overall QoL. In addition, there is an overall utility score that is derived from the 5 questions. These questionnaires will be completed at Day 1 of every cycle, and at End of Treatment. Baseline scores are defined as scores captured on Day 1 of treatment (first dose date). In the case of multiple assessments on Day 1 of treatment, the later assessment will be used. Missing baseline scores will not be imputed.

12.1.2.1. Lung Cancer Symptom Scale

The Lung Cancer Symptom Scale (LCSS) is designed to measure quality of life specifically affected by lung cancer and its symptoms. It evaluates burden due to six major symptoms:

- Appetite
- Fatigue
- Coughing
- Shortness of breath
- Blood in sputum
- Pain

In addition, it measures how bad a subject's symptoms are, how much it has affected normal activities, and quality of life.

The LCSS consists of two scales: one to be filled out by the subject and one by the health care provider. For this study, only the portion filled out by the subject will be used. The subject will respond to each of the 9 items using marks on a 100 mm visual analog scale (VAS). For analysis and presentation purposes, the scores will be presented such that 0 mm corresponds to the worst possible health state and 100 mm corresponds to the best possible health state. This reversal of scores will be accomplished by subtracting the raw score from 100 mm. The reversed scores will be used for all subsequent calculations, e.g., the summary scores.

The average of the VAS score of all 9 items will be calculated for each subject and will be referred to as the LCSS total score. The symptom burden index is the average of the 6 symptom-specific items (the first 6 items). The average of the coughing, shortness of breath and blood in sputum items will be referred to as the Respiratory Symptom Scale. The average of the appetite

and fatigue items (the first 2 items) will be referred to as the overall constitutional score. The sum of the symptoms item (item 7), the normal activities item (item 8), and the global quality of life item (item 9) will be referred to as the 3-item scale.

Summary statistics of the individual LCSS items and summary scale scores, and the change from baseline will be summarized for the Treated population at every time point at which the instrument is given. In addition, the change from baseline to the best LCSS score during treatment will be presented. For each individual LCSS item, the best score on treatment is the highest reversed score at cycle 2 day 1 through the treatment discontinuation visit. For the summary scores, the best score on treatment is the highest value of the summary score at cycle 2 day 1 through the treatment discontinuation visit. Finally, the change from baseline to the last LCSS score, defined as the difference between the last reported LCSS score at the treatment discontinuation visit or the last reported LCSS score before clinical cutoff for subjects who have not had a treatment discontinuation visit will be presented.

12.1.2.2. EuroQoL Group 5-Dimension 5-Level

The EQ-5D-5L has been designed as an international, standardized, generic instrument for describing and valuing health-related quality of life. It contains only the domains common to generic health status measures, contains the minimum number of questions for each domain, was designed for ease of self-administration, and produces a single index for analysis.

Five dimensions are covered by the EQ-5D-5L:

- Mobility
- Self-care
- Usual Activities
- Pain/Discomfort
- Anxiety/Depression

The 5 dimensions are scored on a 5-point Likert scale. In addition, there is a question covering perceived change in health status over the previous 12 months measured on a 20 cm vertical visual analog scale "thermometer" to summarize one's overall health status at administration on a 100 point scale.

Responses from the 5 dimensions are coded so that a '1' indicates no problem on that dimension, and '5' indicates the most serious problem. A profile is comprised of 5 digits consisting of 1s, 2s, 3s, 4s, and 5s. For instance, a profile of 11111 indicates no problem with any of the 5 dimensions, while a profile of 55555 indicates the most difficulty on all 5. Health state scores are based on the VAS with zero corresponding to the worst imaginable health state and 100 corresponding to the best imaginable health state. Missing or uninterpretable values (e.g. lines that cross the VAS twice) that are not recoverable by queries will be coded as '999.'

A utility score will be calculated using the US Crosswalk Index Value set obtained from the EuroQol website. The range of possible values for the utility score based on the US Crosswalk Index Value Set is -0.109 to 1.000.

Shifts from baseline to each time point at which the instrument is given, as well as from baseline to the best post-baseline value and the last on-treatment value, will be presented for each dimension for the Treated population.

The utility score change from baseline in the utility score will be summarized for every time point at which the instrument is given for the Treated Population. In addition, the change from baseline to the best utility score reported during treatment, including the end of treatment visit, will be presented. Finally, the change from baseline to the last on-treatment utility score, defined as the utility score at the end of treatment visit or the last reported overall score before clinical cutoff for subjects who have not had an end of treatment visit will be presented.

Summaries of the VAS results and the change from baseline will be presented for every time point at which the instrument is given. In addition, the change from baseline In addition, the change from baseline to the best VAS reported during treatment, including the end of treatment visit, will be presented. Finally, the change from baseline to the last on-treatment VAS, defined as the utility score at the end of treatment visit or the last reported overall score before clinical cutoff for subjects who have not had an end of treatment visit will be presented.

12.1.3. Charlson Comorbidity Index Score

The Charlson comorbidity index (Charlson et al., 1987) predicts the ten-year mortality for a patient who may have a range of comorbid conditions, such as heart disease, AIDS, or cancer . Each condition is assigned a score of 1, 2, 3, or 6, depending on the risk of dying associated with each one. Scores are summed to provide a total score to predict mortality.

Clinical conditions and associated scores are as follows:

- 1 each: Myocardial infarction, heart failure, peripheral vascular disease, Alzheimer's, dementia from any etiology or serious cognitive impairment, cerebrovascular accident or transient ischemic heart disease, asthma, chronic lung disease, chronic bronchitis, emphysema, rheumatic or connective tissue disease, gastric or peptic ulcers, mild chronic liver disease, diabetes without end-organ damage.
- 2 each: Hemiplegia, moderate or severe renal disease, diabetes with end organ damage, any hematologic cancer (i.e., lymphoma, leukemia or myeloma).
- 3 each: Moderate or severe liver disease.
- 6 each: Metastatic solid tumor (all patients will have a weight of 6 assigned for their advanced NSCLC), AIDS (patients with a known HIV infection will be excluded from this study).

A summary of Charlson comorbidity index values will be presented in the demographic baseline characteristics table.

12.1.4. Physician- and Subject-Reported ECOG Performance Status

The Eastern Cooperative Oncology Group (ECOG) score (Oken, 1982) runs from 0 to 5, with 0 denoting perfect health and 5 death. These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The ECOG performance scores are as follows:

- 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, e.g., light house work, office work.
- 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
- 3: Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
- 4: Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
- 5: Dead.

Physician-reported ECOG PS will be assessed and reported on the appropriate eCRF at screening, Day 1 of each cycle and at treatment discontinuation. Subject-reported ECOG PS will be completed at Day 1 of each cycle, and at treatment discontinuation. The agreement between the two sets of ECOG PS scores will be explored by cross-tabulation of the two endpoints. Percent agreement will be provided as a measure of agreement between subject and physician. A shift table representing the shift from the baseline to the worst post-baseline ECOG PS scores will be provided for subject-reported and physician-reported ECOG PS scores. Finally, the number and percent of subjects who improved and worsened in ECOG PS compared to baseline by visit and over the course of the study will be summarized.

12.1.5. Physician- and Subject-Reported Karnofsky Performance Status

The Karnofsky Performance Status (KPS) Index allows patients to be classified as to their functional impairment. It is a standard way of measuring the ability of cancer patients to perform ordinary tasks. KPS scores range from 0 to 100. A higher score means the patient is more able to carry out daily activities. KPS scores may be used to determine a patient's prognosis and to measure changes in a patient's ability to function.

The physician- and subject-reported KPS will be completed on Day 1 of Cycle 1 only.

KPS as reported by the physician and the subject at baseline will be summarized with descriptive statistics. In addition, KPS scores will be categorized into the following: ≤40, 50, 60 ~70, 80 ~90 and 100, and frequency counts by these categories will be provided. The boundaries of these categories may be adjusted if necessary depending on the distribution of the data. The correlation between the two sets (physician vs. self-reported) of KPS scores will be explored by cross-tabulation with the above categories. Cohen's kappa coefficient will be provided as a measure of inter-rater agreement of agreement between subject and physician.

12.1.6. Spirometry and Pulse Oximetry

Summary statistics of actual values, as well as change and percent change from baseline in lung function as measured by the spirometry items below will be summarized for the treated population by visit.

- Forced expiratory volume in 1 second (FEV1)
- Forced vital capacity (FVC)
- Peak expiratory flow (PEF)

Summary statistics of actual values, change from baseline, and percent change from baseline in oxygen saturation of blood as measured by pulse oximetry will be summarized for the treated population by visit. For subjects who use bronchodilators, both pre- and post-bronchodilator values will be presented in listings; post-bronchodilator values will be included in the statistical summaries.

12.1.7. Tumor Response During the Monotherapy Part

A separate summary for tumor response during the monotherapy part will be presented: the number and percentage of subjects who attain a greater degree of treatment response (SD to PR or CR, PR to CR) during the monotherapy part compared with the response at the start of monotherapy will be summarized.

13. FOLLOW UP TREATMENTS

First subsequent systemic anti-cancer regimens will be summarized.

To assess how quickly the second line therapy will be initiated for the subjects who discontinued the study treatment for reasons other than lost to follow-up or death and enter follow-up, the time to first subsequent systemic anti-cancer therapy during follow up period will be analyzed. Time to first subsequent systemic anti-cancer therapy is defined as the time interval from the date of treatment discontinuation to the date that subsequent therapy is initiated. The start date of the first subsequent anti-cancer regimen is the earliest start date of any anti-cancer therapy taken in the follow-up/survival period. Subjects who don't have a subsequent therapy and have not died as of the cutoff date for the statistical analysis will be censored at the last follow up date. Subjects who died before initiating a subsequent therapy will be censored at the date of death.

The time to second line therapy will be analyzed using the Kaplan-Meier method. The median time (including 2-sided 95% CI) will be summarized.

In addition, first subsequent anti-cancer treatment regimens will be summarized by the number and percentage of subjects receiving each regimen category and regimen; the number of cycles overall, and the number of cycles for each regimen category and regimen administered. The best response overall and for each regimen category and regimen administered will be summarized. Treatment duration, defined as (date of last dose of any treatment in a regimen - date of first dose of any treatment in the same regimen) + 1 will be summarized as well. Additional subsequent anti-cancer treatment regimens will be listed

Anti-cancer surgeries during follow-up will be summarized by system organ class and preferred term Follow-up surgeries will be listed.

Radiation therapy during follow-up will be summarized by category (prior, concomitant, follow up); type (External beam, radio-immuno therapy, brachytherapy, other); location (if external beam); dose; fraction; intent (adjuvant, curative, palliative, unknown); and setting (stand-alone radiation therapy, concurrent with other anti-cancer therapy, sequential to other anti-cancer therapy). Follow-up radiation therapy will be listed.

14. INTERIM ANALYSIS

An interim review of the primary safety endpoint will be conducted when approximately a total of 20 treated subjects have either completed 4 cycles of study treatment or discontinued due to reasons other than lost to follow-up prior to completing 4 cycles of induction therapy to safeguard the safety of the subjects enrolled in the study. Data will be reviewed by the Scientific Steering Committee.

15. CHANGES TO THE STATISTICAL ANALYSES SECTION OF THE PROTOCOL

The protocol stated that approximately 50 subjects would be enrolled. After the interim review, it was decided by the Steering Committee as well as Celgene Leadership to close enrollment early. A total of 40 subjects were treated in this study.

Differing from the definition in Protocol Section 10.2.2, the per-protocol (PP) population in this SAP is defined as all eligible subjects enrolled who receive at least one dose of the investigational product; have a baseline and at least one evaluable post baseline radiological assessment; and do not have any relevant protocol violations or deviations.

In Protocol Section 10.4, it was stated that "the baseline characteristics of all enrolled 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." In this SAP, the demographics and baseline characteristics will be summarized for all treated subjects. Individual subject listings will be provided to support the summary tables.

The protocol stated that PFS, DCR, ORR, and OS over the entire study are the key efficacy endpoints of the study. The following secondary efficacy endpoints will be added to the efficacy analysis section of the SAP to further characterize the ORR endpoint: time to response and duration of response. Additionally, PFS, OS, and ORR will be analyzed on the whole population and on subgroups (i.e. age, sex, race and histology type). The PFS censoring rules given in protocol section 10.7.1.1 are elaborated with clarification of derivation rules in section 11.1.1 of this document.

Finally, while the collection of spirometry and pulse oximetry data were specified in the protocol, this SAP adds changes from baseline in spirometry and pulse oximetry parameters as exploratory endpoints.

16. REFERENCES

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Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol, 1982 5:649-655.

17. APPENDICES

17.1. Handling of Dates

Dates will be stored as numeric variables in the SAS analysis files and reported in DDMMMYYYY format (ie, the Date9. datetime format in SAS). Dates in the clinical database are classified into the categories of procedure dates, log dates, milestone dates, outcome dates, and special dates.

- **Procedure Dates** are the dates on which given protocol-specified procedure are performed. They include the dates of laboratory testing, physical examinations, tumor scans, etc. They should be present whenever data for a protocol-specified procedure are present and should only be missing when a procedure are marked as NOT DONE in the database. Procedure dates will not be imputed.
- **Log Dates** are dates recorded in eCRF data logs. Specifically, they are the start and end dates for adverse events and concomitant medications/procedures. They should not be missing unless an event or medication is marked as *ongoing* in the database. Otherwise, incomplete log dates will be imputed according to the rules in Appendix 16.2 (e.g., for duration or cycle assignment, etc). However, in listings, log dates will be shown as recorded without imputation.
- **Milestone Dates** are dates of protocol milestones such as study drug start date, study drug termination date, study closure date, etc. They should not be missing if the milestone occurs for a subject. They will not be imputed.
- **Outcome Dates** are dates corresponding to study endpoints such as survival, progression, etc. In most cases they are derived either from a milestone (e.g., the survival date is derived from the death date), or a procedure date (e.g., the progression date is derived from the date of the tumor scan that was used to determine progression). They may be subject to endpoint-specific censoring rules if the outcome did not occur, but are not otherwise subject to imputation.
- **Special Dates** cannot be classified in any of the above categories and they include the date of birth. They may be subject to variable-specific censoring and imputation rules.
- **Last Contact Dates** for the survival analysis are the maximum date collected in the database, if the imputed date used for response date or AE date, the last contact dates should be the latest date of those imputed date and maximum date in the database.

Dates recorded in comment fields will not be imputed or reported in any specific format.

Calculation Using Dates

Calculations using dates (*e.g.*, subject's age or relative day after the first dose of study drug) will adhere to the following conventions:

- Study days after the start day of study drug will be calculated as the difference between the date of interest and the first date of dosing of study drug plus 1 day. The generalized calculation algorithm for relative day is the following:

- If TARGET DATE >= DSTART then STUDY DAY = (TARGET DATE – DSTART) + 1;
- Else use STUDY DAY = TARGET DATE – DSTART.

Note that Study Day 1 is the first day of treatment of study drug. Negative study days are reflective of observations obtained during the baseline/screening period. Note: Partial dates for the first study drug are not imputed in general. All effort should be made to avoid incomplete study drug start dates.

- Age (expressed in days) is calculated: AGE = INFORMED CONSENT DATE – DATE of BIRTH + 1. In practice, age will be transformed to years by dividing the difference by 365.25 days, then truncating.
  - Partial birth date: impute missing day as 15th of the month; impute missing month as July; set missing age for missing year
- Intervals that are presented in weeks will be transformed from days to weeks by using (without truncation) the following conversion formula:

  WEEKS = DAYS /7
- Intervals that are presented in months will be transformed from days to months by using (without truncation) the following conversion formula:

  MONTHS = DAYS /30.4375

17.2. Date Imputation Guideline

17.2.1. Impute Missing Dates for Adverse Events/ Prior or Concomitant Medications

Incomplete Start Date:

- If the stop date is not missing, and the imputed start date is after the stop date, the start date will be imputed by the stop date.

Missing day and month

- If the year is the **same** as the year of the first dosing date, then the day and month of the first dosing date will be assigned to the missing fields.
- If the year is **prior to** the year of first dosing date, then December 31 will be assigned to the missing fields.
- If the year is **after** the year of first dosing, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year are the **same** as the year and month of first dosing date, then the first doing date will be assigned to the missing day.
- If either the year of the partial date is **before** the year of the first dosing date or the years of the partial date and the first dosing date are the same but the month of partial date is

before the month of the first dosing date, then the last day of the month will be assigned to the missing day.

- If either the year of the partial date is **after** the year of the first dosing date or the years of the partial date and the first dose date are the same but the month of partial date is **after** the month of the first dosing date, then the first day of the month will be assigned to the missing day.

Missing day, month, and year

- No imputation is needed, the corresponding AE will be included as TEAE if end date of AE is after the first dose date or the end date is also missing.

Incomplete End Date:

Missing day and month

- December 31 will be assigned to the missing fields.

Missing day only

- The last day of the month will be assigned to the missing day.

17.3. Relative Day Ranges for CT-Scans

Table 3: Relative Day Ranges for CT Scans

Study Week	Relative Days in Study	Study Week	Relative Days in Study
6	2 - 63	78	526 - 567
12	64 - 105	84	568 - 609
18	106 - 147	90	610 - 651
24	148 - 189	96	652 - 693
30	190 - 231	102	694 - 735
36	232 - 273	108	736 - 777
42	274 - 315	114	778 - 819
48	316 - 357	120	820 - 861
54	358 - 399	126	862 - 903
60	400 - 441	132	904 – 945
66	442 - 483	138	946 - 987
72	484 - 525		

17.4. Adverse Events of Special Interest

Table 4 provides the spreadsheets of adverse events of special interest that were used for data summaries up to the dates provided.

Table 4: Treatment-emergent Adverse Events of Special Interest File and Dates

For reports through:	File	MedDRA version
04May2015 – 01May2016	ABRAXANE ABI-007-NSCL-004_V1	18.0
02May2016 - present	ABRAXANE ABI-007-NSCL-004_V	19.0

17.5. MedDRA Versions and Dates

Table 5 gives the MedDRA versions used in this study and the dates of implementation.

Table 5: MedDRA Versions and Dates

For reports dated:	MedDRA version
04May2015 – 01May2016	18.0
02May2016 – present	19.0

17.6. PFS Censoring Rules

Table 6 gives the specific rules for determining PFS analysis dates and identifying events and censored observations. The 91 day criterion assumes that tumor assessments should be performed every 42 days plus up to 3 days. Therefore, after 45 days have passed, one tumor assessment has been missed. After 90 days have passed (starting from 91 days) two tumor assessments have been missed.

Table 6: PFS Censoring Rules

Situation	Analysis Date	Censored or Event
Disease progression, and time interval between progression date and previous tumor assessment date with progression-free response is less than or equal to **91** days	Date of disease progression recorded on overall response form where overall response is PD	Event
Disease progression at first post-baseline tumor assessment and the time interval between progression date and first dose date is less than or equal to 91 days	Date of disease progression recorded on overall response form where overall response is PD	Event

Disease progression, and time interval between the progression date and the previous tumor assessment date with progression-free response is greater than **91** days.	The last progression-free assessment date	Censored
Disease progression at first post-baseline tumor assessment and time interval between the progression date and first dose date is greater than **91** days.	First dose date	Censored
Death without any post-baseline radiological assessment, and time interval between death date and first dose date is less than or equal to **91** days	Death date	Event
Death before documented progression, and time interval between death date and previous tumor assessment date with progression-free response is less than or equal to **91** days	Death date	Event
Death without any post-baseline radiological assessment, and time interval between death date and first dose date is greater than **91** days	First dose date	Censored
Death before documented progression, and time interval between death date and previous tumor assessment date with progression-free response is greater than **91** days	The last progression-free assessment date	Censored
No death or disease progression and no new anti-cancer therapy (i.e., systemic anti-cancer therapy, anti-cancer surgery, curative radiotherapy).	Latest of • the last progression-free assessment date • first dose date	Censored
Subsequent anti-cancer treatment (i.e., systemic anti-cancer therapy, anti-cancer surgery, curative radiotherapy) started prior to progression	Latest of • the last progression-free assessment date prior to start of anti-cancer treatment • first dose date	Censored
Note: Progression-free response refers to a response that was neither progressive disease (PD) nor un-evaluable (UE).		