DISCLOSURE

REDACTED ORIGINAL STATISTICAL ANALYSIS PLAN

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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STATISTICAL ANALYSIS PLAN

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

PROTOCOL NUMBER: ABI-007-NSCL-005

DATE FINAL: 24JUN2016

Prepared by:

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SAP VERSION, DATE	Version 1.0, 24-JUN-2016
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PROTOCOL 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+)
INVESTIGATIONAL PRODUCT	*nab*-PACLITAXEL (Abraxane®)
PROTOCOL NUMBER	ABI-007-NSCL-005
PROTOCOL VERSION, DATE	Amendment 3, 17-MAR-2016
SIGNATURE STATEMENT	By my signature, I indicate I have reviewed this Statistical Analysis Plan (SAP) and find its content to be acceptable.
Statistical Therapeutic Area Head Signature _____ Printed Name _____ Date _____	
Lead Clinical Research Physician / Clinical Research Physician Signature _____ Printed Name _____ Date _____	
Lead Product Safety Physician	

SAP AND SAP AMENDMENT APPROVAL SIGNATURE PAGE

Signature _____

Printed Name _____ Date _____

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Signature _____

Printed Name _____ Date _____

Lead Clinical Research Physician / Clinical Research Physician

Signature _____

Printed Name _____ Date _____

Lead Product Safety Physician

Signature _____

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Lead Product Safety Physician/Trial Safety Physician Signature [redacted] Printed Name [redacted] Date [redacted]	

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Lead Clinical Research Physician / Clinical Research Physician Signature _____ Printed Name _____ Date _____	
Lead Product Safety Physician Signature _____ Printed Name _____ Date _____	

1. LIST OF ABBREVIATIONS

Table 1: Abbreviations and Specialist Terms

ADT	Analysis date
AE	Adverse event
AESI	Adverse event of Special Interest
ALK	Anaplastic lymphoma kinase
ANC	Absolute neutrophil count
AUC	Area under the curve
BMI	Body mass index
BSA	Body surface area
CI	Confidence interval
CR	Complete response
CRF	Case report form
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	Epidermal growth factor receptor
EQ-5D-5L	EuroQoL Group 5-Dimension
FNC	Fine needle cytology
HR	Hazard ratio
IRT	Interactive Randomization Technology
ITT	Intent-to-treat
IV	Intravenous
IVRS	Interactive voice response system
KRAS	Kirsten rat sarcoma
LCSS	Lung Cancer Symptom Scale
MedDRA	Medical Dictionary for Regulatory Activities

NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PN	Peripheral neuropathy
PP	Per protocol
PR	Partial response
PT	Preferred term
RECIST	Response evaluation criteria in solid tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SI	International System of Units (Le Système International d'unités)
SMQ	Standardized MedDRA query
SOC	System organ class
STDEV	Standard deviation
TEAE	Treatment-emergent adverse event
UE	Unevaluable
US	United States
VAS	Visual analog scale
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-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+)" which was issued on 06MAR2014 (amended 09APR2014 and 05DEC2014). It contains definitions of analysis populations, derived variables and statistical methods for the analysis of efficacy and safety.

These analyses include one (1) non-binding interim analysis and one final analysis. Throughout this SAP, the treatment arms will be referred to as Arm A (21-day cycle) and Arm B (28-day cycle). 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 for the first interim/final analysis. All statistical analyses detailed in this SAP will be conducted using SAS® Version 9.2 or higher.

A non-binding interim analysis will be conducted when approximately a total of 120 treated subjects have either completed 4 months of study treatment or discontinued from the study due to disease progression, adverse events, death, lost to follow up, or other reasons.

The clinical cutoff date for the final analysis will be when approximately 192 progression-free survival (PFS) events have been observed. Subjects will be followed for overall survival (OS) for at least 6 months after the last subject is randomized or after 192 PFS events have been observed, whichever comes later.

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective is as follows:

- 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 non-small cell lung cancer (NSCLC) in elderly subjects (≥ 70 years old).

3.2. Secondary Objective

The secondary objective is as follows:

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

3.3. Exploratory Objectives

The exploratory objectives are as follows:

- 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]

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

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, stratified by ECOG performance status and histology, will be randomized 1:1 to one of the following treatment arms:

Arm A (21-day treatment cycle):

- *nab*-Paclitaxel 100 mg/m² 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/m² 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 until Day 1 of treatment (defined in Section 9.1).

The Treatment Period will start on Day 1 of treatment and will end on the treatment end date (defined in Section 9.1).

The Follow-up Period will start the day after the treatment end date.

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.

Local laboratory test data for absolute neutrophil count (ANC), platelet count, hemoglobin, serum creatinine and baseline creatinine clearance will be collected in the electronic case report forms (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(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 FGFR. EGFR, ALK, and KRAS will be collected and recorded on eCRF, if these tests have been performed locally for routine diagnosis.

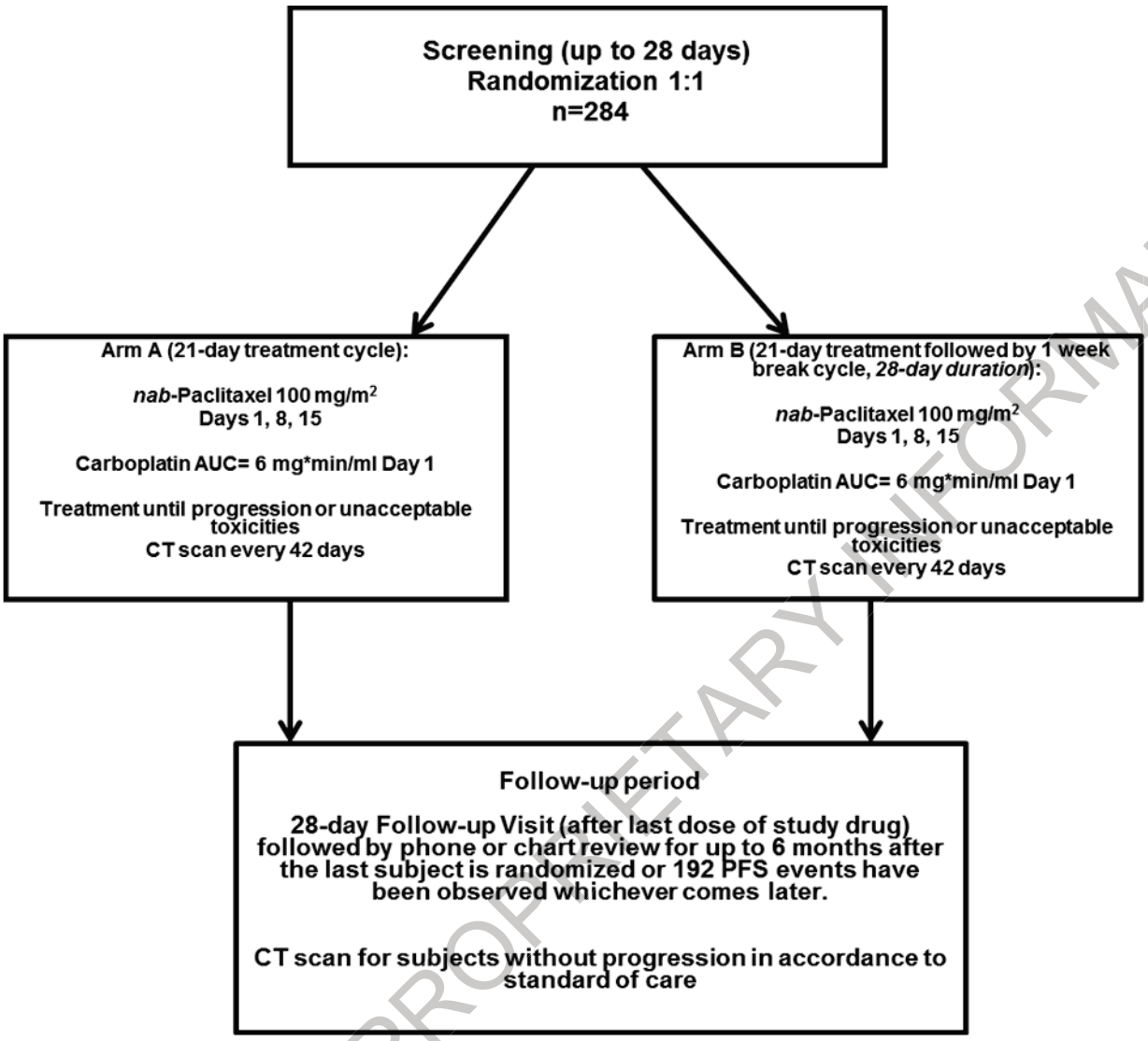
Tumor evaluations will be assessed locally and response (Complete Response (CR) or Partial Response (PR)) will be determined according to Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, Version 1.1 (Eisenhauer, et al., 2009). In both treatment arms, tumor assessments will be conducted at Screening, 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.

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. Thereafter, subjects will be followed 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 after 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.

The study schematic is given in Figure 1.

Figure 1: Study Schematic for ABI-007-NSCL-005



4.2. Study Endpoints

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

4.2.2. Secondary Endpoints

Secondary endpoints are as follows:

4.2.2.1. Safety

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

4.2.2.2. Efficacy

- Progression-free survival (PFS)
- Overall survival (OS)
- Overall response rate (ORR)

4.2.3. Exploratory Endpoint(s)

- Healthcare resource utilization during the study using a questionnaire.
- Changes in the LCSS and EQ-5D.
- [redacted]
- [redacted]

4.3. Stratification, Randomization, and Blinding

Randomization will be carried out centrally using an Interactive Randomization Technology (IRT) system. Treatment assignment follows a 1:1 ratio between two treatment arms. Randomization method is based on permutated-block randomization. Randomization will be stratified by the following factors:

1. Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1)
2. Histology (squamous cell carcinoma versus non-squamous cell carcinoma)

The study is open label due to the differences in scheduling the treatments.

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 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 evaluation of dosing, primary safety endpoint, and efficacy data will be conducted when approximately a total of 120 treated subjects have either completed 4 months of study treatment or discontinued treatment due to progression, adverse events, deaths, lost to follow up, or other reasons. The stopping rule and the final marginal significance level for this endpoint are determined based on the Gamma family spending function with parameter = -7 (Hwang, 1990) to control the Type-II error rate at 20%. Futility criterion for this endpoint is met if the treatment difference (Arm B minus Arm A) is ≥ -0.2%, given the interim analysis of this endpoint is performed at 43% information fraction.

Progression free survival, OS, and ORR are the 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 efficacy endpoints, 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.

5. GENERAL STATISTICAL CONSIDERATIONS

5.1. Reporting Conventions

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

- For each dry-run prior to database lock, the treatment arm on the tables, listings, figures will be displayed in a blinded format using the dummy codes and marked as ARM A and ARM B.
- Data from all study centers will be combined for analysis;
- All stratified efficacy analyses will use the stratification factors for randomization including histology (squamous cell carcinoma versus non-squamous cell carcinoma) and ECOG performance status at randomization (0 versus 1).
- The statistical test of the treatment effect with respect to the primary endpoint will be interpreted based on the stopping boundaries determined at the pre-specified interim analyses and the final analysis.
- All other statistical tests of the treatment effect will be performed at significance level of 0.050 for 2-sided tests. Testing of interactions will be performed at the 0.100 significance level;
- 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 (CIs) 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 randomized treatment arm, study site, subject, and date of procedure or event;

- 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, with the exception of lab data, where the value with the worst CTC grade is the baseline. For subjects who were not treated, the baseline will be the last non-missing value obtained on or prior to the randomization date;
- Partial dates will be imputed based on the rules specified in Appendix 15.2;
- All laboratory data will be reported using international system of units (SI);
- 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. The similar approach will be used for summaries of ECOG performance status and peripheral neuropathy (PN) grades;
- SAS® Version 9.2 (or higher) will be the statistical software package used to produce all data summaries, listings, graphs, and statistical analyses.

5.2. Analysis Populations

The number of subjects included in each of the populations described below will be summarized based on the number of subjects randomized.

5.2.1. Intent-to-Treat Population

The primary efficacy analysis will be performed on the intent-to-treat (ITT) population, which includes all randomized subjects regardless of whether the subject receives any study drug or has any efficacy assessments performed. Unless otherwise specified, the ITT population will be the analysis population for all efficacy analyses.

5.2.2. Treated Population

The treated population includes all subjects who are randomized and receive at least one dose of study drug. If a subject consistently receives study drug other than the subject's randomized treatment assignment, and if the change in dosing schedule was not due to TEAEs, then the subject is assigned to the treatment arm reflecting the treatment that the subject actually received during the study. 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.

5.2.3. Per-Protocol Population

The per-protocol (PP) population is defined as all eligible subjects randomized who receive at least one dose of the study drug; have been treated in the arm they were assigned to; and do not have any major protocol violations. For the per protocol safety analysis, subjects must have at

least one post-baseline hematology panel that includes ANC, platelet, and hemoglobin. For the efficacy per protocol analysis, subjects must have at least one post-baseline radiologic evaluation.

The PP population will be used in a replication of the primary safety analysis and efficacy analyses of PFS, OS, and ORR.

6. SUBJECT DISPOSITION

The total number of subjects screened will be presented, and subjects with screen failure and reasons for screen failure will be summarized by frequency and percentage of total number of subjects screened.

The number and percentage of subjects screened will be summarized by their eligibility or non-eligibility for the study, and the number of subjects randomized under each protocol amendment will be summarized by treatment arm. Subjects enrolled by site will be presented.

The number and percentage of subjects who are randomized and treated, discontinued treatment, and discontinued the study will be presented for the ITT population by treatment arm and for all subjects combined. Reasons for treatment discontinuation will be summarized in the subject disposition table 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

Reasons for study discontinuation will be summarized in the subject disposition table with the following categories:

- Screen failure
- Death
- Adverse event
- 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 per period (during treatment or follow-up). Cause of death will be categorized by both the categories on the death eCRF and by coded cause of death.

The number of subjects who entered the post-treatment follow-up period and the number of subjects who are in survival follow-up at the time of analysis will be presented.

Listings will be provided for discontinued subjects with reason for treatment discontinuation and reason for study discontinuation, for subjects randomized but not treated, 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.

A summary and by-subject listing of subjects with protocol violations in the ITT population will be provided.

Protocol deviations and violations will be reviewed before database lock to determine the per protocol population (defined in Section 5.2.3). It should be noted that 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 inclusion/exclusion criteria violations, failure to take any study drug as assigned, randomization errors, and prohibited concomitant medications and procedures.

8. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

The demographics and baseline characteristics will be summarized for the ITT population by treatment arm and overall. Individual subject listings will be provided to support the summary tables.

8.1. Demographics

Age (years), height (cm), weight (kg), body mass index (BMI), body surface area (BSA) (m^2) at baseline will be summarized descriptively. Sex, age category (70-74 years, 75-79 years, 80-84 years, 85-89 years, ≥90 years), race, and ethnicity will be summarized by frequency counts.

Age will be calculated as follows: age = greatest integer ≤ [(informed consent date – date of birth + 1) / 365.25].

BMI will be calculated as follows: BMI = weight in kg / (height in m)^2.

BSA will be calculated as follows: BSA $m^2 = 0.007184 \times (\text{weight in kg})^{0.425} \times (\text{height in cm})^{0.725}$.

8.2. Baseline Characteristics

The number and percentage of subjects in each of the following categories will be presented:

1. ECOG performance status at randomization (0 versus 1)
2. Histology (squamous cell carcinoma versus non-squamous cell carcinoma)
3. Physician assessment of peripheral neuropathy at baseline
4. Creatinine clearance at baseline (< 45 mL/min versus ≥ 45 mL/min).

8.3. Medical History

A summary of medical and surgical history will be presented by MedDRA version 18.0 or higher system and organ class (SOC) and preferred term (PT). A similar summary will be generated for the currently active abnormalities only, by SOC and PT.

8.4. Lung Cancer History

The following items will be summarized for lung cancer history:

- Stage at enrollment
- The time from specimen collection date to randomization date in months, defined as (first dose date – specimen collection date + 1)/ 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, bronchioloalveolar carcinoma, solid adenocarcinoma with mucin, adenocarcinoma with mixed subtypes, and other)
- Mutational gene status (FGFR, KRAS, EGFR, ALK, other)
- Time from latest systemic anti-cancer therapy to randomization date in months
- Time from latest radiation therapy to randomization date in months
- Time from latest prior cancer surgery to randomization date in months
- Time from latest cancer therapy (last to occur of systemic anti-cancer therapy, radiation, or cancer surgery) to randomization date in months.
-

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

In the event that there is a record of a screening-period radiological assessment confirming lung cancer that is earlier than specimen collection date, the date of the radiological assessment will be used in place of the specimen collection date.

8.5. Prior and Concomitant Therapy for NSCLC

Any therapies administered for NSCLC will be summarized separately.

Therapies administered during the follow up period are described in Section 12.

8.5.1. Prior Systemic Anti-cancer Therapies

Prior systemic therapies (e.g. chemotherapy) will be coded to therapeutic drug classes and generic drug names using the World Health Organization (WHO) Drug Dictionary Enhanced version WHO-DDE Q3 2014 or later. The number of subjects with prior systemic anti-cancer therapies (including EGFR TKI and ALK rearrangement inhibitors) and number of cycles (where known) will be summarized by drug class and therapy. The best response for all prior treatments by subject will be summarized by treatment arm.

Prior systemic anti-cancer therapies will be listed. The duration, whether the number of cycles is known, the number of cycles (if known), and the best response will be presented in the listing.

8.5.2. 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.

8.5.3. Prior Non-small Cell Lung Cancer Surgeries

The number and percentage of subjects who had any prior non-small cell lung cancer surgery will be presented by system organ class and preferred term. Prior surgeries will be listed.

8.5.4. Concomitant Radiation and Procedures/Surgeries

Concomitant procedures are considered any procedures that occurred on or after the date of randomization. The number of subjects having concomitant radiation therapy, concomitant surgeries or procedures performed will be summarized in separate tables.

Concomitant radiation therapy, surgeries and procedures will be listed.

8.6. Prior and Concomitant Medications

Medications reported on the Prior and Concomitant medications CRF pages will be coded to therapeutic drug classes and generic drug names using the WHO drug dictionary version WHO-DDE Q3 2014 or later. 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.

8.6.1. Prior Medications

Prior medications are defined as all medications that were started before the date of randomization. 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 ITT population.

8.6.2. Concomitant Medications

Concomitant medications are any non-study medications that were taken on or after the date of randomization 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 will be presented for the ITT 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 administered by treatment arm.

9.1. Treatment and Cycle Start and End Dates

Planned cycle lengths are 21 days (Arm A) and 28 days (Arm B). Day 1 of treatment is the first day any study drug is administered to a subject.

The first day of a cycle is the first Day 1 carboplatin administration as recorded on the eCRF. The end of a cycle is the day before the first day of the next cycle. The treatment end date and the end date of the last cycle will be calculated as follows:

- For subjects who discontinue prior to the clinical cutoff date, the treatment end date is the date of treatment discontinuation from the treatment disposition form in the eCRF.
- For subjects who are still ongoing at the time of study closure or clinical cutoff, the treatment end date is the maximum of the end dates of the nab-paclitaxel and carboplatin dosing periods (see Section 9.2).

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 duration for subjects who are still on treatment at the time of study closure or clinical cutoff.

Conceptually, the dosing period for a study drug is the time period in weeks starting at the first dose of any study drug and ending a protocol- and subject-specific number of days after the last dose of the specific study drug, depending on the dosing schedule for the treatment arm and the subject's status. Ending the dosing period on the date of last dose would lead to an overestimation of the dose intensity. Similarly, ending the dosing period on the date of treatment discontinuation, if such date closely follows the 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.

The specific calculations of the dosing period for each study drug and arm are given in Table X below:

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

Arm	***nab*-Paclitaxel**			**Carboplatin**
	Last dose record is D1	Last dose record is D8	Last dose record is D15	Last dose record is D1
Arm A (21-day cycle)	min{study day of death date, max[study day of treatment discontinuation date, study day of date of last dose of *nab*-paclitaxel + 6]}			min{study day of death date, max[study day of treatment discontinuation date, study day of date of last dose of carboplatin +20]}
Arm B (28-day cycle)	min {study day of death date, max[study day of treatment discontinuation date, study day of date of last dose of *nab*-paclitaxel + 8.33]}	min {study day of death date, max[study day of treatment discontinuation date, study day of date of last dose of *nab*-paclitaxel + 10.67]}	min {death date, max[treatment discontinuation date, date of last dose of *nab*-paclitaxel + 13]}	min{study day of death date, max[study day of treatment discontinuation date, study day of date of last dose of carboplatin + 27]}

For the dosing period calculations, the date of last dose is the latest record on the exposure eCRF for the respective study drug regardless of the actual dose or whether the dose was administered.

9.3. Treatment Duration

For a given study drug, treatment duration (in weeks) is defined as:

[(Treatment end date as defined in Section 9.1) – (Day 1 of treatment) + 1]/7.

Cycle duration is defined as the time period from Day 1 of each cycle to the day prior to Day 1 of subsequent cycle. For the last cycle, the end date is the treatment end date and will be used in the calculation of duration of the last cycle.

Descriptive statistics will be provided for treatment duration, and cycle duration for both *nab*-paclitaxel and carboplatin. Number of subjects will also be tabulated by total number of cycles received for both *nab*-paclitaxel and carboplatin.

9.4. Cumulative Dose

Cumulative dose is defined as the sum of the values entered on the dose assigned field on the exposure eCRF for visits at which actual dose administered > 0 mg, taken across the study in mg/m² for *nab*-paclitaxel or mg*min/mL for carboplatin. Cumulative dose will be computed separately for *nab*-paclitaxel and carboplatin. Only doses that were actually administered will be included in the cumulative dose. Descriptive statistics will be presented for cumulative dose 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 for that study drug. 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/m^2/wk) = [cumulative dose for *nab*-paclitaxel in mg/m^2]/[*nab*-paclitaxel dosing period in weeks].

Dose intensity will be presented by study drug 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 for Arm A (21 day cycle) are as follows:

- *nab*-Paclitaxel: 100 mg/m^2/wk (100 mg/m^2 on days 1, 8, and 15 of each 3 week cycle)

- Carboplatin: 2 mg*min/mL/wk (6 mg*min/mL on day 1 of each 3 week cycle)

The protocol weekly doses for Arm B (28 day cycle) are as follows:

- *nab*-Paclitaxel: 75 mg/m^2/wk (100 mg/m^2 on days 1, 8, and 15 for each 4 week cycle)
- Carboplatin: 1.5 mg*min/mL/wk (6 mg*min/mL on day 1 of each 4 week cycle)

Percentage of protocol dose for carboplatin and *nab*-paclitaxel will be categorized into <70%, ≥70% to < 80%, and ≥80 to <90% and ≥90%, and frequency counts will be provided for the treated population.

9.7. Exposure, Dose Reduction, Delay, and Skipped Doses

Dose reduction is defined as when the assigned dose at any visit after Cycle 1 Day 1 is at a lower dose level than the assigned dose at the previous dosing visit. In addition, a Cycle 1 Day 1 assigned dose that is lower than 100 mg/m^2 for *nab*-paclitaxel or AUC 6 for carboplatin is considered a dose reduction.

Dose delay is defined as when the scheduled dose is administered greater than or equal to 3 days after the scheduled dosing date.

Treatment exposure, dose reductions and delays, and doses not administered will be summarized as follows:

- Number of cycles and doses administered;
- Number and percentage of subjects with at least 1 dose reduction, number of dose reductions, and reasons (adverse event or other) for reduction, by cycle and overall;
- Number and percentage of subjects with at least one dose delay, number of dose delays, by cycle and overall;
- Number and percentage of subjects with at least 1 dose not administered, number of doses not administered, and reasons (adverse event or other) for dose not administered, by cycle and overall.

The reason for dose reduction will be summarized using the data in the "reason for dose adjustment" field in the exposure CRF for identified dose reductions.

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.

Of note, the primary objectives of this study regard safety endpoints.

10.1. Primary Safety Endpoint

The primary endpoint for this study is a composite safety endpoint, namely, the percentage of subjects who develop treatment-emergent peripheral neuropathy of Grade ≥ 2 or treatment-emergent myelosuppression AEs of Grade ≥ 3 based on the local laboratory values for ANC, platelet count and hemoglobin (with lower values corresponding to higher grades). The peripheral neuropathy events will be identified from the clinical AE dataset using the adverse events MedDRA preferred terms that are identified with adverse events of special interest category equal to "Peripheral Neuropathy" in the embedded spreadsheet in Appendix 16.4.

The myelosuppression AEs of grade ≥ 3 will be identified from the local laboratory values for ANC, platelet count and hemoglobin, which will be graded according to the NCI CTCAE Version 4.0. The specific cutoff values to identify myelosuppression AEs for the primary endpoint are as follows:

- Absolute neutrophils < 1,000 cells/mm^3 (which is equivalent to < 1.0 x 10^9 /L and < 1.0 x 10^3/mm^3);
- Hemoglobin < 8 g/dL (which is equivalent to < 80 g/L);
- Platelets <50,000 cells/mm^3 (which is equivalent to < 50.0 x 10^9 /L and < 50.0 x 10^3/mm^3);

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 estimated within each treatment arm and presented with two-sided 95% confidence intervals. The treatment difference in the AE rate will be analyzed using a Cochran-Mantel-Haenszel Chi-square test (Mantel, 1959) with ECOG performance status at randomization (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 estimated along with the two-sided 95% confidence interval (CI). If stratum cell sizes are too small based on the Mantel-Fleiss criterion (Mantel, 1980) a Pearson Chi-square test will be used instead.

10.2. Adverse Events

Adverse events will be analyzed in terms of treatment-emergent adverse events (TEAEs), which are defined as any AEs that begin or worsen on or after the first dose date through 28 days after the last dose of study drug recorded on the treatment disposition CRF. In addition, any SAE with an onset date more than 28 days after last dose of study drug that is assessed by the investigator as related to study drug will be considered a TEAE. All AEs will be coded using the Medical Dictionary for Regulatory Affairs® (MedDRA) dictionary Version 18.0 or above. Appendix 16.5

gives the dates of application of new versions of MedDRA. The severity will be graded based on NCI CTCAE Version 4.0.

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.

For the summary of treatment-related AEs, a treatment-related TEAE is defined as an adverse event which was considered to be related, reported as "suspected" in eCRF, to either component of combination drugs. Additionally, for related AEs reported as "suspected" in eCRF to each individual drug, *nab*-Paclitaxel or Carboplatin will be summarized for each study drug. If a subject experiences multiple occurrences of the same AE with different relationship to study medication categories, the subject will be counted once, as a relationship category of 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 preferred term (system organ class), then the subject will be counted only once for that preferred term (system organ class).

The incidence of TEAEs will be summarized by MedDRA system organ class (SOC) and preferred term (PT). The intensity of AEs will be graded 1 to 5 according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. For all other AEs not described in the CTCAE criteria, the intensity will be assessed by the investigator as mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening (grade 4) or death (grade 5). Tables summarizing the incidence of TEAEs by treatment arm and overall will be generated for each of the following:

- Overall summary of TEAEs;
- All TEAEs by MedDRA system organ class and preferred term, and worst CTCAE grade;
- Treatment-related TEAEs by grade category (grade 1-2 versus ≥ grade 3-4 versus grade 5) (overall and by cycle);
- Serious TEAEs by worst CTCAE grade;
- Treatment-related serious TEAE by worst 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 death within 28 days of last dose with cause of death;
- Most frequent TEAEs (≥ 5% in either arm; sorted by Preferred Term, without SOC)
- TEAEs for the following baseline subgroups (provided the number of subjects are sufficient):
  - Age (70-74 years, ≥75 years);
  - Sex (male and female);
  - Race

Listings for treatment-emergent and non-treatment-emergent AEs, and treatment-emergent and non-treatment-emergent serious AEs will be provided.

10.3. Peripheral Neuropathy

Peripheral neuropathy (PN) events will be collected on the Assessment of Peripheral Neuropathy eCRF reported as AEs and will be included in analyses described in Section 10.2. A summary of PN grade by treatment arm and cycle will be provided based on the eCRF data. In addition, time from first dose to the first occurrence or worsening of peripheral neuropathy and time from occurrence or worsening to improvement in peripheral neuropathy will be presented by treatment arm as follows:

- Time to first onset of grade 3 or higher peripheral neuropathy;
- Time to improvement of grade 3 or higher peripheral neuropathy by at least 1 grade;
- Time to improvement of grade 3 or higher peripheral neuropathy to grade 1 or better.

Summaries of time to first onset will present summary statistics for those subjects who experienced peripheral neuropathy of the relevant grade. There will be no censoring.

Summaries of time to improvement will include only subjects who experienced peripheral neuropathy of the relevant grades. Subjects who do not experience improvement will be censored at the last time the subject is evaluated for adverse events. Kaplan Meier methods will be used to attain the median and 95% confidence interval.

10.4. Adverse Events of Special Interest

The adverse events of special interest (AESI) listed in Appendix 16.4 will be summarized.

The following summaries will be provided for TEAEs of special interest:

- TEAEs by maximum CTCAE grade;
- Serious TEAEs;
- Treatment-related TEAEs

- TEAEs by age group for risks specific to safety in patients older than 75 years (70-74 years, ≥75 years).

In addition to the above, the following time to event analyses will be performed for each class of AE of special interest (with the exception of hypersensitivity):

- Time to first onset of grade 3 or higher;
- Time to improvement of grade 3 or higher by at least 1 grade;
- Time to improvement of grade 3 or higher to grade 1 or better;

Summaries of time to first onset will present summary statistics for those subjects who experienced AESI of the relevant grade. There will be no censoring.

Summaries of time to improvement will be presented for AESI categories in which at least 20 subjects experienced an event. The summaries will include only subjects who experienced AESI of the relevant grades. Subjects who do not experience improvement will be censored at the last time the subject is evaluated for adverse events. Kaplan Meier methods will be used to attain the median and 95% confidence interval.

10.5. Clinical Laboratory Evaluations

All laboratory data will be listed. Laboratory parameters regularly collected on the eCRFs (ANC, platelets, hemoglobin, and serum creatinine) will be summarized by descriptive statistics by visit and treatment if the number of subjects with data is adequate. Local laboratory values for ANC, platelets, and hemoglobin that meet the CTCAE criteria for grade 3 or higher myelosuppression will be identified as described in section 10.1.

11. EFFICACY ANALYSIS

Note that the primary objective of this study is safety. All efficacy evaluations will be conducted using the ITT population. Supportive analysis of the efficacy endpoints PFS, OS, and ORR using the PP population will be conducted for the final analysis. 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.

Listings will be provided for all endpoints. Data review of tumor response (CR, PR, SD, and PD) will be performed based on programmed data listings according to RECIST 1.1 criteria:

- Overall best response for subject
- Per subject visit:
    - Date of assessment
    - Number of target lesions
    - Total length of target lesions
    - Percent change from nadir of sum of total length, defined as (total length – nadir in total length) / (nadir in total length) x 100%, where nadir is calculated using all measurements before (but not including) the visit in question, including baseline
    - Percent change from baseline of sum of total length to review assessment of response
    - Assessment of target lesions
    - Assessment of nontarget lesions
    - Presence of symptomatic deterioration
    - Overall tumor response assessment
    - Best overall response
- Per lesion at each subject visit:
    - Location
    - Method of assessment
    - Tumor length (target lesions only)

Confirmation of response is required for some efficacy analyses. Confirmation of response will be determined based on the RECIST 1.1 criteria. Confirmed complete or partial response will be declared if the criteria for response are met at two consecutive radiological assessments at least 28 days apart, or if two assessments meeting the criteria for response are separated by a single assessment with overall response of Not Evaluable. The specific sequences of responses and the best confirmed overall response associated with those sequences are presented in Table 7 in Appendix 16.6.

For all efficacy evaluations that make use of tumor assessment data, post-baseline tumor assessments that occur after the initiation of subsequent anti-cancer therapy will be excluded.

11.1. Multiplicity

No formal adjustment will be made for testing multiple endpoints. Adjustments made based on the interim analysis are described in Section 13.

11.2. Analysis of Efficacy Endpoints

11.2.1. Progression-free Survival

Progression-free survival (PFS) will be analyzed using the p-value from the stratified log-rank test of PFS based on the ITT population and will be considered the primary efficacy analysis, with the unstratified analysis considered a supporting analysis.

PFS is defined as the time in months from the date of randomization to the date of disease progression based on investigator assessment according to RECIST 1.1 criteria (documented by radiological assessment, not including symptomatic deterioration) 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. 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 that the subject was progression-free. The calculation of PFS is a two-step process:

- Determination of date of disease progression, which is recorded on the Overall Response eCRF at the first tumor assessment when the overall tumor response is "Progressive Disease"
- Calculation of duration from randomization to disease progression, death, or censoring date as described below in Table 3

Table 3: Censoring Rules for PFS

Situation on or before Clinical Data Cutoff Date for CSR	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 at the first tumor assessment with overall response of 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.	Latest of: • the last progression-free assessment date • randomization date	Censored
Death without any post-baseline radiological assessment, and time interval between death date and randomization 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 randomization date is greater than **91** days	Randomization 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, no treatment discontinuation due to symptomatic deterioration, and no subsequent anti-cancer therapy (i.e., systemic anti-cancer therapy, anti-cancer surgery, curative radiotherapy).	Latest of • the last progression-free assessment date • randomization 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 • randomization date	Censored

Treatment discontinuation due to symptomatic deterioration prior to disease progression or death	Latest of • the last progression-free assessment date before treatment discontinuation date • randomization date	Censored
Note: Progression-free response refers to a response that was neither progressive disease (PD) nor un-evaluable (UE).		

Progression-free survival is calculated as follows:

PFS = (Analysis date defined above – randomization date + 1)/30.4375

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 arm. The associated hazard ratio and two-sided 95% CI will be estimated using a stratified Cox proportional hazards model (Cox, 1972). The stratification factors are ECOG performance status at randomization (0 versus 1) and histology (squamous versus non-squamous cell carcinoma). The Kaplan-Meier curve for PFS will be presented graphically for each treatment arm. PFS rates, including two-sided 95% CIs, will be provided for every 2 months relative to randomization (Greenwood's formula, Klein, 2003). The p-value from a stratified log-rank test (Klein 2003) will be reported as an indication of the strength of association for the difference between the two curves.

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, sensitivity analyses will be performed where subjects with events and censorings that occur at a time other than the regularly scheduled visit assessment will have PFS time based on the date of the next regularly scheduled assessment rather than the actual off-schedule date. Methods similar to the primary analysis will be used to estimate the median PFS along with HRs.

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 the randomization date to the start 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.

An additional analysis of PFS, where the initiation of a subsequent treatment will be considered as an event, will be conducted to address the impact of second-line therapy.

PFS will be analyzed on the ITT and PP populations.

11.2.2. Overall Survival

Overall survival (OS) is defined as the time in months between randomization and death. Thus, it is calculated as follows

OS = (date of death – date of randomization + 1) /30.4375

All deaths prior to the data cutoff date, regardless of the cause of death, will be included. All subjects who are lost to follow-up prior to the end of the study, who are still receiving treatment as of the data cutoff date, or who are withdrawn from the study will be censored at the time of last contact, defined as the date of the latest record in the database for that subject or, if the record indicates the subject is dead, the last known alive date.

Overall survival will be analyzed similarly to PFS on the ITT and PP populations and presented for each treatment arm.

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 new chemotherapy.

11.2.3. Overall Response Rate and Tumor Response

Overall response rate (ORR) is defined as the percent of all ITT subjects who had a radiologic complete response (CR) or partial response (PR) compared to baseline (radiographic evaluation on the day of or within 28 days prior to randomization) according to RECIST Version 1.1 guidelines determined by the investigator; confirmed by repeat radiologic assessment performed no less than 28 days after the criteria for response were first met; and occurring between Day 1 of treatment and the start of subsequent anti-cancer therapy, death, or study discontinuation.

ORR for each treatment arm will be presented with the two-sided 95% CI by timing of CT scans per protocol as Week 6, Week 12, etc., and overall. For CT scans that do not fall on those exact dates, the windows given in Section 16.3 will be used to determine the week. If there is more than one CT scan during the relevant window, the scan with the best response (as determined by the investigator) will be used. The relative treatment effect will be estimated by the response rate ratio (ORR in Arm B/ORR in Arm A) over the entire study and the associated two-sided 95% CI. The p-value from a Cochran-Mantel-Haenszel Chi-square test, stratified by ECOG status and histology, will be reported to indicate the strength of association of the relative treatment effect. If stratum cell sizes are too small based on the Mantel-Fleiss criterion (Mantel, 1980) a Pearson Chi-square test will be used instead.

As a supportive analysis, the percentage of subjects that achieve an overall complete or partial response based on investigator's assessment of response using RECIST 1.1 guideline, regardless of confirmation status, will also be summarized with 2-sided 95% exact confidence interval for each treatment regimen.

The number and percentage of subjects with a tumor response of complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), unevaluable (UE) and the corresponding 95% CI will be presented for each protocol-specified CT scan (Week 6, Week 12, etc.). For CT scans that do not fall on those exact dates, the windows given in Section 15.3 will be used to determine the week. 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 Section 15.3. Subjects who do not have post-baseline tumor assessments will be counted as NE.

11.3. Subgroup Analysis

PFS, OS, and ORR will all be analyzed within the following subgroups (with subgroup data based on the clinical database). Subgroup factors will not be used as stratification factors or regression adjustment covariates for relevant analyses, but otherwise these analyses will parallel the analyses for the endpoint performed on the whole population:

- Age (70 – 74 years, 75 – 79 years, ≥ 80 years)
- ECOG status at randomization (0 versus 1);
- Histology (squamous versus non-squamous);
- Sex (male versus female);
- Creatinine clearance (< 45 mL/min versus ≥45 mL/min)

The p-value from the treatment-by-subgroup interaction term in the Cox model will be presented for all subgroups. A forest plot will be provided displaying the HRs and corresponding 95% CIs for PFS and OS for each subgroup. These HRs and 95% CIs will be obtained from Cox proportional hazards models using only subjects in the relevant subgroup.

11.4. Exploratory analysis

11.4.1. Healthcare utilization

Summary statistics 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 by treatment arm at each time point the utilization questionnaire is given (i.e. Day 1 of every cycle, Early Treatment Discontinuation, and 28 day follow up visit).

11.4.2. Quality of Life Analysis

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 index score that is derived from the 5 questions. These questionnaires will be completed at Day 1 of every cycle, at End of Treatment, and at the 28-day follow-up visit. Baseline scores are defined as scores captured on Day 1 (first dose date). In the case of multiple assessments on Day 1, the later assessment will be used. Missing baseline scores will not be imputed. In the case of multiple assessments at post-baseline assessments, the later assessment will be used.

11.4.2.1. 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.

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

Statistical comparisons will be made between the treatment arms for change from baseline to last administration using analysis of covariance. Histology (squamous cell carcinoma versus non-squamous cell carcinoma) and ECOG status (0 versus 1) at baseline will be the covariates.

11.4.2.2. EQ-5D-5L

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.

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 will be presented for each dimension for the ITT 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 ITT 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 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 and percent change from baseline will be presented for every time point at which the instrument is given. In addition, the change from baseline to the last reported overall score, either 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.

Statistical comparisons will be made between the treatment arms for change from baseline to last administration in utility score and VAS scores using analysis of covariance. Histology (squamous cell carcinoma versus non-squamous cell carcinoma) and ECOG status (0 versus 1) at baseline will be the covariates.

12. FOLLOW UP TREATMENTS

Follow up anti-cancer treatments will be coded to therapeutic drug classes and generic drug names using the World Health Organization (WHO) Drug Dictionary Enhanced version WHO-DDE Q3 2013 or later. Combinations of treatments will be classified into regimens.

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 therapy (systemic anti-cancer therapies during follow up period) will be analyzed, which is defined as the time interval from the date of last dose of study drug to the date that the first subsequent therapy is initiated. 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 die before initiating a new 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 for each treatment arm; the associated hazard ratio with two-sided 95% confidence interval will be estimated using a non-stratified Cox proportional hazard model (Cox, 1972).

Time to second-line therapy will be summarized for all discontinued subjects, and for subjects who discontinued due to disease progression and subjects who discontinued for reasons other than disease progression.

The duration, whether the number of cycles is known, the number of cycles (if known), and the best response for all subsequent anti-cancer treatments will all be presented in a listing. These follow up treatments will be summarized by treatment arm and ATC class and preferred term. In addition, the following summaries by treatment arm will be generated:

13. INTERIM ANALYSIS

13.1. Interim Evaluation of Dosing, Safety and Efficacy

A non-binding interim evaluation of dosing, primary safety endpoint, and efficacy data will be conducted when approximately a total of 120 treated subjects have either completed 4 months of study treatment or discontinued study treatment due to progression, adverse events, deaths, lost to follow up, or other reasons. The interim evaluation will be conducted by an independent statistician and the results will be reviewed by the SSC. The SSC may recommend to stop the study early based on the study dosing data in relation to the primary hypothesis, or meeting of the futility criterion of the primary endpoint (if the treatment difference [Arm B minus Arm A] is ≥ -0.2% given the interim analysis of this endpoint is performed at 43% information fraction), or totality of the dosing, safety, and efficacy data as well as clinical significance.

13.2. Interim Analysis of Quality of Life Questionnaire Data

For administrative purposes (eg, planning of new studies, publication of data) the LCSS and EQ-5D measurements will be summarized for the two treatment groups combined using descriptive statistics when approximately 50, 100, 150, and all subjects, respectively, have completed four cycles of treatment or discontinued treatment.

14. CHANGES TO THE STATISTICAL ANALYSES SECTION OF THE PROTOCOL

The PFS censoring rules given in protocol section 10.7.1 are elaborated with clarification of derivation rules in section 11.2.1 of this document.

The following secondary efficacy endpoint was added to further characterize the ORR endpoint:

- ORR without the requirement of confirmation of response.

15. REFERENCES

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16. APPENDICES

16.1. Handling of Dates

Dates will be stored as numeric variables in the SAS analysis files and reported in DDMMMYYYY format (i.e., 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 CRF 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 (egg, 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 randomization, 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 (egg, the survival date is derived from the death date), or a procedure date (egg, 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 (*egg*, 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.

- 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

16.2. Date Imputation Guideline

16.2.1. 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.

16.2.2. Medical History

Partially missing medical history start dates will be imputed in the derived dataset for medical history. The 16th of the month will be used to impute a partially missing start date that has only the day missing, and July 1st will be used to impute a partially missing start date that has both the month and day missing.

16.3. Relative Day Ranges for CT-Scans

Table 4: Relative Day Ranges for CT Scans

Study Week	Relative Days in Study
6	2 - 63
12	64 - 105
18	106 - 147
24	148 - 189
30	190 - 231
36	232 - 273
42	274 - 315
48	316 - 357
54	358 - 399
60	400 - 441
66	442 - 483
72	484 - 525
78	526 - 567
84	568 - 609

90	610 - 651
96	652 - 693
102	694 - 735
108	736 - 777
114	778 - 819
120	820 - 861
126	862 - 903
132	904 – 945
138	946 - 987

16.4. Treatment-emergent Adverse Events of Special Interest

Table 5 below provides the spreadsheets of adverse events of special interest that were used for data summaries up to the dates provided.

Table 5: Treatment-emergent Adverse Events of Special Interest File and Dates

For reports dated:	File	MedDRA version
June 2015 – 01May2016	 ABRAXANE ABI-007-NSCL-005_V1	18.0
02May2016 – present	 ABRAXANE ABI-007-NSCL-005_V	19.0

16.5. MedDRA Versions and Dates

Table 6 gives the MedDRA versions used in this study and the dates of implementation.

Table 6: MedDRA Versions and Dates

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

16.6. RECIST 1.1 Best Overall Response with Confirmation of Complete and Partial Response

Table 7 gives the interpretation of best overall response with the requirement of confirmation of CR and PR based on the RECIST 1.1 criteria (Eisenhauer) as applicable to this study.

Table 7: RECIST 1.1 Best Overall Response with Confirmation of Complete and Partial Response

Overall response First time point	Overall response Subsequent time point	Best overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD
CR	PD	SD
CR	NE	SD
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD
PR	NE	SD
NE	NE	NE
[a] If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, event disease meeting PR criteria relative to baseline, makes the disease PD at that time point.		