

DISCLOSURE

REDACTED STATISTICAL ANALYSIS PLAN

ABI-007-NSCL-006

A PHASE 2, RANDOMIZED, OPEN-LABEL, MULTICENTER STUDY TO ASSESS SAFETY AND EFFICACY OF NAB[®]-PACLITAXEL (ABI-007) WITH EPIGENETIC MODIFYING THERAPY OF CC-486, AND NAB[®]-PACLITAXEL MONOTHERAPY AS SECOND-LINE TREATMENT IN SUBJECTS WITH ADVANCED NONSQUAMOUS NONSMALL CELL LUNG CANCER (NSCLC): ABOUN2L

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STATISTICAL ANALYSIS PLAN

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STUDY DRUG: nab-PACLITAXEL (ABRAXANE[®]), CC-486

PROTOCOL NUMBER: ABI-007-NSCL-006

DATE FINAL: 25Aug2016

Prepared by:

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On behalf of

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INVESTIGATIONAL PRODUCT

nab-PACLITAXEL (ABRAXANE®), CC-486

PROTOCOL NUMBER

ABI-007-NSCL-006

PROTOCOL VERSION, DATE

Final, 29-May-2014; Amended 18-Jul-2014

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Date _____

Lead Clinical Research Physician / Clinical Research Physician

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1. LIST OF ABBREVIATIONS

Table 1: Abbreviations and Specialist Terms

ADT	Analysis date
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase (SGOT)
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CR	Complete response
CRF	Case Report Form
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
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-5L	EuroQol 5-dimensional quality of life instrument
HR	Hazard ratio
IP	Investigational product
IRT	Interactive Response Technology
ITT	Intent-to-treat
IV	Intravenous

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
PR	Partial response
PP	Per-Protocol
PT	Preferred term
QoL	Quality of Life
RECIST	Response evaluation criteria in solid tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SE	Standard error
SOC	System organ class
STDEV	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase (AST)
SGPT	Serum glutamic pyruvic transaminase (ALT)
TEAE	Treatment emergent adverse event
TEAEoSI	TEAEs of special interest
UE	Un-evaluable
US	United States
VAS	Visual analog scale
WBC	White blood cell
WHO	World Health Organization

2. INTRODUCTION

This statistical analysis plan (SAP) describes the analyses and data presentations for Celgene's protocol ABI-007-NSCL-006 "A PHASE 2, RANDOMIZED, OPEN-LABEL, MULTICENTER STUDY TO ASSESS SAFETY AND EFFICACY OF NAB[®]-PACLITAXEL (ABI-007) WITH EPIGENETIC MODIFYING THERAPY OF CC-486, AND NAB[®]-PACLITAXEL MONOTHERAPY AS SECOND-LINE TREATMENT IN SUBJECTS WITH ADVANCED NONSQUAMOUS NON-SMALL CELL LUNG CANCER (NSCLC): ABOUND.2L" which was amended on 18 JULY 2014.

These analyses include all the dry runs described in the Scope of Work, the non-binding interim analysis described in the protocol, and the final analysis for the clinical study report. Throughout this SAP, the monotherapy arm will be referred to as the *nab*-paclitaxel arm, while the combination treatment arm will be referred to as the *nab*-paclitaxel with CC-486 treatment arm. 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 interim analysis. This SAP is developed after the finalization of the protocol and will be finalized and signed prior to the clinical database lock for the interim analysis. All statistical analyses detailed in this SAP will be conducted using SAS[®] Version 9.2 or higher. The clinical cutoff date will be determined based on the occurrence of approximately 60 progression-free survival (PFS) events for the non-binding interim analysis (for futility, analyzing PFS) and approximately 120 PFS events for the final analysis. All subjects who discontinue from treatment will continue to be followed for overall survival (OS) up to 12 months after the last subject is randomized or 120 PFS events have been observed, whichever comes later.

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective of the study is:

- To assess the efficacy of *nab*-paclitaxel administered intravenously (IV) on Days 8 and 15 with CC-486 once daily (QD) on Days 1 to 14 every 21 days, and *nab*-paclitaxel administered IV on Days 1 and 8 every 21 days as second-line treatment for advanced nonsquamous NSCLC, and the relative efficacy of these two treatment regimens.

3.2. Secondary Objectives

The secondary objective of the study is:

- To evaluate the safety and tolerability of *nab*-paclitaxel administered IV on Days 8 and 15 with CC-486 once daily (QD) on Days 1 to 14 every 21 days, and *nab*-paclitaxel administered IV on Days 1 and 8 every 21 days as second-line treatment for advanced nonsquamous NSCLC.

3.3. Exploratory Objectives

The exploratory objectives of the study are:

- To assess healthcare resource utilization for the two treatment arms.
- To assess the quality of life (QoL) for the two treatment arms.
- To determine baseline tumor characteristics which predict response to *nab*-paclitaxel as a single agent and in combination with epigenetic modifying therapy of CC-486.
- To evaluate genomic correlates of response to *nab*-paclitaxel as a single agent and in combination with epigenetic modifying therapy of CC-486.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a Phase 2, randomized, open-label, multicenter study to assess efficacy and safety of *nab*-paclitaxel in combination with epigenetic modifying therapy of CC-486, and *nab*-paclitaxel monotherapy as second-line treatment in subjects with advanced nonsquamous NSCLC who have received one platinum-containing chemotherapy regimen.

Approximately 160 subjects with advanced nonsquamous NSCLC will be randomized 1:1 into one of the two treatment arms: *nab*-paclitaxel/CC-486 combination therapy or *nab*-paclitaxel monotherapy prior to receiving first dose of investigational product (IP). Randomization will be centralized and stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1), gender (males versus females), and current smoker (yes versus no).

The study will consist of up to a 28-day Screening Period, a Treatment Period and a Follow-up Period. The Treatment Period begins with the first dose of IP (CC-486 for the *nab*-paclitaxel with CC-486 arm or *nab*-paclitaxel for the *nab*-paclitaxel arm). Subjects will receive one of the following treatments based on the randomization assignment:

- *nab*-paclitaxel 100 mg/m² IV infusion over 30 minutes on Days 8 and 15 and CC-486 200 mg orally QD on Days 1 to 14 of each 21-day treatment cycle, or
- *nab*-paclitaxel 100 mg/m² IV infusion over 30 minutes on Days 1 and 8 of each 21-day treatment cycle

No additional anticancer agents are allowed during study treatment. All supportive care 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, withdrawal of consent, or termination of the study by the sponsor. Tumor evaluations will be assessed by the investigative sites and response will be determined according to Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, Version 1.1. All subjects who discontinue from treatment for any reason other than withdrawal of consent, lost to follow-up, death, or termination of the study by the sponsor will enter the Follow-up Period. It will consist of a visit 28 days after treatment discontinuation. Thereafter, subjects will be followed for survival by phone call contact approximately every 90 days (+/- 14 days) for 12 months after the last subject is randomized or 120 PFS events have been observed, whichever comes later. During the study, subjects will have computed tomography (CT) scans every 42 days (-3/+7 days) until documented progression of disease, withdrawal of consent, lost to follow-up, death, or termination of the study by the sponsor. Those subjects entering the Follow-up Period without documented progression will continue to have CT scans in accordance with local standard of care (or approximately every 90 days) until documented progression of disease, withdrawal of consent, lost to follow-up, death, or termination of the study by the sponsor. All post-treatment anticancer therapies will be recorded during the Follow-up Period. The study schematic is presented in Section 17.1.

4.2. Study Endpoints

4.2.1. Primary Efficacy Endpoint

The primary endpoint is PFS in months, which is defined as the time from the date of randomization to the date of disease progression or death (from any cause) on or prior to the data cutoff date for analyses, whichever occurs first, based on the investigator's assessment of the data from CT scans using RECIST 1.1 guidelines.

4.2.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints specified in the protocol include the following:

- Disease control rate (DCR)
Disease control rate is defined as the percent of subjects who have a radiologic complete response, partial response, or stable disease according to RECIST 1.1 guidelines, as determined by the investigator.
- Overall survival (OS)
Overall survival is defined as the time between randomization and death. All deaths, regardless of the cause of death, will be included.
- Overall response rate (ORR)
Overall response rate is defined as the percent of subjects who have a radiologic complete or partial response according to RECIST 1.1 guidelines determined by the investigator.

Other secondary efficacy endpoints:

- Time to Response (TTR)
Time to response is defined as the time from the date of randomization to the first occurrence of response (complete response or partial response).
- Duration of Response (DOR)
For subjects who have a complete response (CR) or partial response (PR), duration of response is defined as the time interval from the first occurrence of CR or PR according to RECIST 1.1 criteria to the first documented progressive disease date.

4.2.3. Safety Endpoints

- The type, frequency, and severity of adverse events (AEs) and serious adverse events (SAEs) graded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0)
- Discontinuation rate
- The median dose intensity
- The incidences of dose reductions

4.2.4. Exploratory Endpoints

- Healthcare resource utilization during the study using a questionnaire.
- Changes in the Lung Cancer Symptom Scale (LCSS), European Organisation for Research and Treatment of Cancer (EORTC) QLQ C30, and EuroQoL 5D-5L (EQ-5D-5L).

The following exploratory endpoints will be described in a separate SAP:

- The correlation between pretreatment tumor characteristics and response to the study treatment determined using next-generation sequencing methods, immunohistochemistry, or other analysis methods.

4.3. Stratification, Randomization, and Blinding

Once the subject has met all eligibility criteria during the Screening Period, they will be randomized to one of two treatment arms to enter the Treatment Period. Randomization will be centralized using an Interactive Response Technology (IRT) system and stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1), gender (males versus females), and current smoker (yes versus no). Approximately 160 subjects will be randomized to one of two treatment arms in a 1:1 ratio. A permuted-block randomization method will be employed. The Treatment Period which is open label, begins with the first dose of IP (CC-486 for the *nab*-paclitaxel with CC-486 arm or *nab*-paclitaxel for the *nab*-paclitaxel arm). Subjects will receive one of the following treatments based on the randomization assignment:

- *nab*-paclitaxel 100 mg/m² IV infusion over 30 minutes on Days 8 and 15 and CC-486 200 mg orally QD on Days 1 to 14 of each 21-day treatment cycle, or
- *nab*-paclitaxel 100 mg/m² IV infusion over 30 minutes on Days 1 and 8 of each 21-day treatment cycle

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

4.4. Sample Size Determination

Assuming the median times of PFS are 4.17 and 2.5 months, respectively, for the *nab*-paclitaxel with CC-486 arm and the *nab*-paclitaxel monotherapy arm, and an approximate 24 months accrual period for a total of 160 subjects, it is estimated that a total of 120 PFS events will have been observed approximately 2 months after the last subject is randomized, assuming an exponential distribution for PFS. With 120 PFS events, this study has an 80% power (1-sided, Type-1 error of 2.5%) to detect a hazard ratio (HR) of 0.60 for PFS improvement with the *nab*-paclitaxel with CC-486 arm over the *nab*-paclitaxel monotherapy arm.

One nonbinding interim analysis for PFS with an early stopping rule for futility will be conducted when approximately 60 events are observed. The *nab*-paclitaxel with CC-486 arm of the study may be stopped early for futility if the observed HR is > 1.10 given an approximate 60 PFS events have occurred at the time of the interim analysis. A HR > 1.10 when half of the target events of 120 have occurred signals a low probability for observing a meaningful difference in favor of the *nab*-paclitaxel with CC-486 therapy should the study continue to the end. With the

assumptions stated above, it will take approximately 16 months from the first subject randomized to observe approximately 60 PFS events for the interim analysis.

If futility is declared, enrollment in the monotherapy *nab*-paclitaxel arm will continue up to a total of 80 subjects.

Table 2 below summarizes the precision that can be achieved given different scenarios of hypothetical observed hazard ratios between the two treatment arms for PFS events, assuming a total of 120 events are observed.

Table 2: Progression-Free Survival – Two-Sided 95% Confidence Interval of Hypothetical Observed Hazard Ratio between Treatment Arms

Hypothetical Number of Events Observed	Hypothetical Observed Hazard Ratio of PFS Events	95% Confidence Interval of Hazard Ratio ^a
120	0.60	(0.42, 0.86)
	0.65	(0.45, 0.93)
	0.70	(0.49, 1.00)

^a Assuming a standard error of 0.18 for the log hazard ratio.

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 pooled for analysis.
- All stratified efficacy analyses will use the stratification factors for randomizations, including ECOG performance status (0 versus 1), gender (males versus females), and current smoker (yes versus no).
- 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 (SD), median, first and third quartile (Q1, Q3), minimum, and maximum for continuous variables.
- All mean, median, and percentile/quartiles 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. The number and percentage of responses 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 treatment arm, study site, subject, and date of procedure or event. Data for all subjects will be included in subject data listings, according to the analysis population specified.
- 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. For subjects who were not treated, the baseline will be the last non-missing value obtained on or prior to the randomization date.
- All laboratory data will be reported using international system of units (SI).

5.2. Analysis Populations

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 IP or has any

efficacy assessments performed. Efficacy analyses will be based on this population and randomized treatment groups.

5.2.2. Per-protocol (PP) Population

The PP population is defined as all eligible subjects randomized who receive at least one dose of the IP and have been treated on the arm they were assigned to, and meet the major inclusion/exclusion criteria of the protocol.

The PP population will be used for the analyses of the primary efficacy endpoint PFS and key secondary efficacy endpoint DCR, as part of sensitivity/robustness analysis of efficacy findings.

5.2.3. Treated Population

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

6. SUBJECT DISPOSITION

The total number of subjects screened will be presented. The subjects with screen failure and reasons for screen failure will be summarized by frequency and percentage of total number of subjects screened. A summary of analysis populations will also 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 for all subjects who discontinue study treatment with the following categories:

- Death
- Adverse event
- Pregnancy
- 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 for all subjects who discontinue study with the following categories:

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

Finally, the number and percentage of subjects who enter into the follow up period of the study will be presented. The above disposition tables, along with all subjects enrolled and subjects randomized will also be presented for each site.

Listings will be provided for analysis population, for subjects randomized but not treated, for discontinued subjects with reasons for study or treatment discontinuation, and for screen failure subjects who did not meet eligibility criteria.

CELGENE PROPRIETARY INFORMATION

7. **PROTOCOL DEVIATIONS/VIOLATIONS**

The protocol deviations/violations were identified and assessed by clinical research physician or designee following company standard operational procedure. Protocol deviations and violations will be reviewed before database lock to determine the per protocol population.

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 but are not limited to non-adherence to inclusion/exclusion criteria, failure to take study drug as assigned, randomization errors, prohibited concomitant medications and procedures.

The protocol deviations/violations will be summarized separately by treatment arm for the ITT population. A by-subject listing of subjects with protocol violations in the ITT population will be provided.

8. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

The demographics and baseline characteristics will be summarized for the ITT population. 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) at baseline will be summarized descriptively. Age category (<65 versus ≥65 years, <70 versus ≥70 years, and < 75 versus ≥ 75 years), sex, race, and ethnicity will be summarized by frequency counts.

Age will be calculated as follows: $\text{age} = \text{Integer} \leq [(\text{Date of informed consent} - \text{Date of Birth} + 1) / 365.25]$.

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

BSA will be calculated as follows: $\text{BSA m}^2 = 0.007184 \times (\text{weight in kg})^{0.425} \times (\text{height in cm})^{0.725}$ (Du Bois, 1917).

Provided the numbers of subjects are sufficient, demographics will also be summarized within the following subgroups:

1. Age (< 65 years and ≥ 65 years, < 70 years and ≥ 70 years, < 75 years and ≥ 75 years);
2. ECOG status (0 vs. 1) at baseline;
3. Sex (male and female);
4. Current smoker (yes vs. no).

8.2. Baseline Characteristics

The following baseline characteristics will be presented descriptively:

- ECOG performance status at baseline (0 or 1);
- Smoking history (current vs. past vs. never);

8.3. Medical History and Cancer Diagnosis

8.3.1. Medical History

A summary of medical and surgical history will be presented by system organ class (SOC) and preferred term (PT), coded according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 17.0 or above. A similar summary will be generated for the currently active abnormalities only, by SOC and PT.

8.3.1.1. Smoking/Tobacco Exposure History

A detailed summary of smoking and other tobacco exposure will be reported as follows:

- Smoking status (current vs. past vs. never);
- For past and current smokers: duration, and number of packs/pipes/cigars. For current smokers, the date of informed consent will be used for duration. Frequency of use will also be summarized;
- Exposure to second hand smoke;
- Frequency of tobacco chewing;
- Frequency of tobacco sniffing.

8.3.2. Lung Cancer History

The following items will be summarized for cancer diagnosis:

- Disease stage at enrollment;
- The time from specimen collection date to randomization date in months, defined as (randomization date – specimen collection date + 1)/ 30.4375;
- Method of specimen collection (biopsy, surgical specimen, fine needle cytology (FNC), other);
- Confirmation of nonsquamous cell histology (Adenocarcinoma, Large cell carcinoma, Adenosquamous carcinoma, Carcinoid tumor, other);
- Mutational gene status (KRAS, EGFR, ALK, other or unknown).
- Time from latest systemic anti-cancer therapy to the randomization date in months
- Time from latest radiation therapy to the randomization date in months
- Time from latest prior cancer surgery to the randomization date in months
- Time from latest cancer therapy (last to occur of systemic anti-cancer therapy, radiation, or cancer surgery) to the randomization date in months

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

8.4. Prior Therapy

8.4.1. Prior Systemic Anti-Cancer Therapy

Prior systemic therapies (e.g. chemotherapy) will be coded to therapeutic drug classes and generic drug names using the Anatomical Therapeutic Chemical (ATC) drug classification by the World Health Organization (WHO) Drug Dictionary Enhanced version WHO-DDE Q3 2014 or later. Prior systemic anti-cancer therapy will be summarized by treatment group and ATC levels.

The start/end date and/or the duration, the number of cycles (if known), intent, and the best response will all be presented in a listing.

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 site of

radiation therapy will be presented. Dose and fraction (where known) will be summarized. Intent (adjuvant, curative, palliative, unknown) and setting (stand-alone, concurrent with other anti-cancer therapy, sequential to other anti-cancer therapy) will also be summarized.

8.4.3. Prior Non-small Cell Lung 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 non-small cell lung cancer surgery will be presented by system organ class and preferred term.

Prior surgeries will be listed.

8.5. Prior and Concomitant Medications

Medications reported on the Prior and Concomitant medications case report form (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 randomization and continued afterwards 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 medications that were started before randomization. A summary showing the number and percentage of subjects who took prior medications will be presented by WHO therapeutic drug class and generic drug name for the ITT population.

8.5.2. Concomitant Medications

Concomitant medications are defined as medications that were either initiated before randomization and continued afterwards, or initiated on/after the date of randomization and within 28 days after the last dose date.

A summary 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 ITT population.

The summary of concomitant immunostimulants (growth factors) initiation by cycle may also be presented.

8.5.3. Concomitant Radiation Therapy and Surgeries/Procedures

The number of subjects having concomitant radiation, surgeries, or procedures performed will be summarized.

Concomitant radiation, surgeries, and procedures will be listed.

9. STUDY TREATMENTS AND EXTENT OF EXPOSURE

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 treatment arm. The summary of full doses, dose level by week and number of doses by cycle will also be presented.

9.1. Treatment and Cycle Start and End Dates

Treatment will commence on Day 1, and planned cycle lengths are 21 days. Day 1 of Treatment is defined as the first day of any study drug.

Start date of a cycle is defined as the Day 1 of study drug for that cycle as recorded on the eCRF. The end date of a cycle is defined as the day before Day 1 of the following cycle. Cycle end date of the last cycle is the treatment end date.

9.2. Dosing Period for Each Study Drug

Dosing period for each study drug will be defined and used as the denominator 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.

For each study drug, dosing period = dosing period end date – Day 1 of Treatment +1, where Day 1 of treatment is defined as the first day of any study drug.

For this study, the dosing period for a study drug is the time period starting at the first dose of the any study drug and ending a protocol- and subject-specific number of days after the last dose, depending on the subject dosing schedule for the study drug. 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 date of the dosing period depends on whether the last dose administered day is a Day 1 or a Day 8 dose for monotherapy, or Day 8 or Day 15 for combination therapy. If the subject is administered only one dose during the last cycle, then the subject will be given half of the protocol-specified *nab*-paclitaxel doses for the last cycle, he/she will be allotted half of the cycle's length (the closest integer 11 days is given) in their *nab*-paclitaxel dosing period for the last cycle. If the subject is given both of the 2 protocol-specified doses for the last cycle, then the end date of the dosing period will be the last planned day of the cycle.

For CC-486, since the protocol-specified 14 doses are credited over 21 days of cycle length, proportionally, 1.5 days (i.e., 21 days divided by 14 doses) of dosing period will be credited for each dose. Hence, the dosing period end date will depend on the number of doses of CC-486 recorded on eCRF during the last cycle. That is, the dosing period for the last cycle will be

derived as the number of dose recorded for the last cycle multiply by 1.5 days and rounded to integer.

More specifically, dosing period end date will be derived as follows:

1. If the subject is still on treatment at the time of study closure or clinical cutoff, the following rules will be used to derive the dosing period end date for each drug:

For nab-paclitaxel monotherapy treatment arm:

- If the last dose given for the last cycle is Day 1, the dosing period end date for nab-paclitaxel will be derived as Day 1 date of the last cycle + 10 days (i.e., rounded integer of protocol specified cycle length/number of doses planned for each cycle);
- If the last dose given for the last cycle is Day 8, the dosing period end date for nab-paclitaxel will be derived as min [(Day 8 date + 13), Day 21 date].

For nab-paclitaxel with CC-486 combination therapy arm:

- Dosing period end date for CC-486 will be derived as the date of last cycle Day of {the number of doses recorded in the last cycle \times 1.5 days and rounded to integer}. The number of doses recorded in the last cycle will be calculated as the end date of the last dosing record - the start date of the first dosing record in the last cycle + 1, no matter whether the actual dose is taken or not.
 - Dosing period end date for nab-paclitaxel will be derived as follows:
 - If the last dose given for the last cycle is Day 8, then the dosing period end date for nab-paclitaxel will be derived as max[(Day 1 date + 10), Day 8 date];
 - If the last dose given for the last cycle is Day 15, then the dosing period end date for nab-paclitaxel will be derived as min[(Day 15 date + 6), Day 21 date].
2. If the subject discontinued the treatment, the dosing period end date for each study drug will be derived as min {death date, max[treatment discontinuation date, dosing period end date for that specific drug as derived above]}.

The above derivation rules of dosing period end date can be illustrated in the following Table 3.

Table 3 Derivation of Dosing Period End Date for Each study Drug

For Subjects Who Are Still on Treatment at the Time of Study Closure or Clinical Cutoff				
Treatment Arm	Study Drug	Last Dose Date is Day 1	Last Dose Date is Day 8	Last Dose Date is Day 15
<i>nab</i> -paclitaxel Monotherapy	<i>nab</i> -paclitaxel	Day 1 date + 10 days	min [(Day 8 date + 13), Day 21 date]	-
<i>nab</i> -paclitaxel + CC-486 Combination Therapy	CC-486	Date of last cycle Day of {the number of doses recorded in the last cycle × 1.5 days and rounded to integer}.		-
	<i>nab</i> -paclitaxel	-	max [(Day 1 date + 10), Day 8 date]	min [(Day 15 date + 6), Day 21 date]
For Subjects Who Discontinued Treatment				
For each drug: min{death date, max[treatment discontinuation date, dosing period end date for that specific drug as derived above]}				

9.3. Treatment Duration

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

$$\text{Treatment Duration} = [(\text{Treatment end date}) - (\text{Day 1 of Treatment}) + 1]/7.$$

For subjects who discontinued treatment, the treatment end date will be derived as the discontinuation date from treatment disposition form on eCRF. For the subjects who are still on treatment at the time of study closure or clinical cutoff, the treatment end date will be derived as the maximum of the dosing period end date for CC-486 and the dosing period end date for *nab*-paclitaxel.

Cycle duration is defined as the time period from Day 1 of each cycle to one day prior to Day 1 of subsequent cycle; for the last treatment cycle, the end date is the treatment end date as defined above.

Descriptive statistics will be provided for treatment duration and total number of cycles for both the *nab*-paclitaxel with CC-486 and the *nab*-paclitaxel arms. Descriptive statistics will also be provided for number of doses received for both *nab*-paclitaxel (the *nab*-paclitaxel with CC-486 and the *nab*-paclitaxel arms) and CC-486 separately.

9.4. Cumulative Dose

Cumulative dose will be computed separately for *nab*-paclitaxel and CC-486. Cumulative dose for *nab*-paclitaxel is defined as the sum of the values entered on the dose assigned field on the

exposure eCRF, taken across the treatment period in mg/m^2 . Only the assigned doses when the doses were actually administered (i.e., when the actual doses administered not equal to 0) will be included in the calculation of the cumulative dose.

Cumulative dose for CC-486 is defined as the sum of all actual doses, defined as the values entered on the actual dose administered field on the dosing eCRF, taken across the treatment period in mg. Descriptive statistics will be presented for cumulative dose for the subjects treated.

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 CC-486.

Dose intensities will be calculated as follows:

- Dose intensity for nab-paclitaxel ($\text{mg}/\text{m}^2/\text{wk}$) = [cumulative dose for nab-paclitaxel in mg/m^2]/[dosing period for nab-paclitaxel in weeks].
- Dose intensity for CC-486 (mg/wk) = [cumulative dose for CC-486 in mg]/[dosing period for CC-486 in weeks].

Dose intensity for the treatment period will be presented for each study drug by treatment arm for the treated population.

9.6. Percentage of Protocol Dose

Percentage of protocol dose (also called relative dose intensity) 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 the nab-paclitaxel with CC-486 arm are as follows:

- nab-paclitaxel: $200/3 \text{ mg}/\text{m}^2/\text{wk}$ (100 mg/m^2 each for days 8 and 15 for each 21 day cycle)
- CC-486: $2800/3 \text{ mg}/\text{wk}$ (200 mg each day on days 1 to 14 of each 21 day cycle)

The protocol weekly doses for the nab-paclitaxel arm are as follows:

- nab-paclitaxel: $200/3 \text{ mg}/\text{m}^2/\text{wk}$ (100 mg/m^2 each for days 1 and 8, for each 21 day cycle)

Percentage of protocol dose nab-paclitaxel and CC-486 will be categorized into <70%, $\geq 70\%$ to < 80%, and ≥ 80 to <90% and $\geq 90\%$, and frequency counts will be provided for the treated population.

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

Dose reduction is defined as when the dose assigned after Cycle 1 Day 1 is at a lower dose level than the assigned dose at the previous dosing visit.

Dose delay is defined as when the scheduled dose is administered greater than or equal to 3 days after the scheduled dosing date. Dose delay is only defined for the doses that were administered. If a dose is not administered, dose delay will not be defined for that particular dosing record.

To determine whether the current administered dose is a dose delay or not, if the previous dose is not administered (skipped dose) with missing dose date but non-missing visit date, the non-missing visit date will be used as the reference date to determine if the current dose is delayed. If, however, there is no visit date either for the skipped dose, then the previous last dose record that had at least either a visit date or dose date will be searched and its dose date (or visit date if dose date is missing) will be used as the start reference date to calculate the missing dose date and thereafter to determine if a dose is delayed. Since the protocol allows a ± 2 -day window for each dosing schedule, we will add in 2 extra days when we calculate the missing dosing date for the skipped dose visit when define dose delay. For example, if a dose is not administered and with both visit date and dose date missing, we will assume the scheduled date for this skipped dose as the previous dose date (or visit date if the dose date is missing) + 9 days. Same logic will be used for each skipped dose visit when multiple doses were not administered consecutively and with both dose date and visit date missing. That is, 9-day interval between dosing visits were assumed and used to calculate the missing dose date for each skipped dose visit when we define dose delays. Dose not administered (missed dose) is defined as a case when the dose for a visit is recorded on eCRF as not administered.

Treatment exposure and dose reductions and delays will be summarized as follows (separately for each IP):

- 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 one dose not administered, number of dose not administered, and reasons (adverse events or other) for dose not administered, by cycle and overall. If the reason for dose not administered is not given, it will be categorized as “Data Not Available” in summary tables.

10. EFFICACY ANALYSIS

All efficacy evaluations will be conducted using the ITT population and subjects will be analyzed according to the treatment arm to which they were randomized. Supportive analysis of the primary and key secondary efficacy endpoints using the PP population will be conducted for the final analysis.

The percent change from nadir 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 = $(\text{total length} - \text{nadir in total length}) / (\text{nadir in total length}) \times 100\%$, where nadir is calculated using all measurements prior to the visit in question, including baseline.

Data review of tumor response (CR, PR, SD, and PD) will be performed based on programmed data listings according to the RECIST 1.1 criteria:

- Per subject visit:
 - Date of assessment
 - Total length of target lesions
 - Percent change from nadir of sum of longest diameters of target lesions (derived as above to review assessment of progressive disease)
 - Percent change from baseline of sum of longest diameters of target lesions to review assessment of response
 - Assessment of target lesions
 - Assessment of non-target lesions
 - Appearance of new lesions
 - Presence of symptomatic deterioration
 - Overall tumor response
- Per lesion at each subject visit:
 - Location
 - Method of assessment
 - Tumor length (target lesions only)
- Overall per subject
 - The best overall response

10.1. Multiplicity

Not applicable for this study, as no formal statistical inferential testing will be conducted.

10.2. Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is PFS, which is defined as the time in months from the date of randomization to the date of disease progression according to RECIST 1.1 criteria (documented by CT-scan result, not including symptomatic deterioration) or death (any cause) on or prior to the clinical cutoff date, whichever occurs earlier.

Subjects who do not have disease progression and have not died, regardless of whether they were discontinued from treatment or not, will be censored at the date of last tumor assessment, on or

prior to the clinical cutoff date that the subject was progression-free. If a subject begins a subsequent anti-cancer chemotherapy prior to documented disease progression (or death), the subject will be censored at the date of last assessment when the subject was documented as progression-free prior to the intervention. In the event that curative radiotherapy or surgery at lesion sites occurs, the subject will be censored at the date of last assessment when the subject was documented as progression-free prior to the intervention. Subjects with a single missing radiologic assessment immediately prior to a visit with documented disease progression (or death) will be analyzed as a PFS event at the time of the radiologic assessment that shows progression or death (whichever is earlier). Subjects with two or more consecutive missing radiologic assessments immediately prior to an assessment with documented progression (or death) will be censored at the date of last assessment when the subject was documented as progression-free prior to the first of the two or more missing assessments. Subjects who are discontinued due to symptomatic deterioration without documented progression will be censored at the last assessment where the subject was documented as progression-free before treatment discontinuation. This is further illustrated in Table 4.

Table 4: Censoring Rules for PFS

Situation On or Before Clinical Cutoff Date	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: <ul style="list-style-type: none"> 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, and no subsequent anti-cancer therapy (i.e., systemic anti-cancer therapy, anti-cancer surgery, curative radiotherapy).	Latest of <ul style="list-style-type: none"> 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 <ul style="list-style-type: none"> 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 <ul style="list-style-type: none"> the last progression-free assessment date before treatment discontinuation randomization date 	Censored
Note: Progression-free response refers to a response that was neither progressive disease (PD) nor un-evaluable (UE).		

The survival distribution of PFS will be estimated using the Kaplan-Meier method, the median PFS including two-sided 95% CI for each treatment arm will be provided. Stratification factors include ECOG performance status (0 versus 1), gender (males versus females), and current smoker (yes versus no). The associated HR and two-sided 95% CI will be estimated by using stratified Cox proportional hazard model. Kaplan-Meier curves will be provided by treatment arm.

The number and percent of subjects surviving without progression will be provided for every 2 months relative to randomization. The denominator for percentages at each time point will be the number of subjects at risk at each time point.

The following analyses will be conducted as supporting or sensitivity analyses using the same methods (i.e. HR and two-sided 95% CI from the Cox model with stratification factors):

- PFS where subsequent anti-cancer therapy is considered an event.

- 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) on or prior to the clinical cutoff date, 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.
- In addition, to assess the effect of unscheduled radiologic assessments, the frequency and percentage of unscheduled or off-schedule radiologic assessments will be presented by treatment group. Sensitivity analyses may 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.
- Sensitivity analyses to address the impact of measurability of endpoints and adherence to protocol will be done by performing the PFS analyses mentioned above on the per protocol population.

10.3. Analyses of Secondary Efficacy Endpoints

All secondary efficacy endpoints will be analyzed using the ITT population. For the tumor response evaluations, the lesion data and response assessments that occur on or after the date of a subsequent anti-cancer therapy, subsequent curative-intent radiation therapy, or subsequent curative-intent surgery will be excluded.

10.3.1. Disease Control Rate

Disease Control rate is defined as the percent of subjects who have stable disease (SD) or complete response (CR) or partial response (PR) according to RECIST 1.1 guidelines, as evaluated by the Investigator. Disease control rate along with associated Clopper-Pearson 95% CI will be presented. The relative treatment effect will be summarized by the ratio of the disease control rate and the associated two-sided 95% CI.

10.3.2. Overall Survival

Overall survival (OS) is defined as the time (in months) between randomization and death and will be calculated as follows:

$$OS = (\text{Date of Death} - \text{Date of Randomization} + 1) / 30.4375$$

Subjects who die before or on the date of data cut-off will be considered to have had an OS event. All deaths, regardless of the cause of death, will be included. All subjects who do not have a death record prior to or on the cutoff date will be censored at the 'last date known alive'.

Last date known alive is defined as the last valid date of subject assessment prior to or on the data cutoff date in the clinical database. For subjects who have withdrawn consent during the study, the last date known alive will be the date of consent withdrawal from the study. For all other subjects, the last date known alive will be derived by searching through all valid

assessment dates in all study datasets to identify the last valid subject assessment date available for each subject. If the last valid subject assessment date available is on or prior to the data cutoff date, it is used as the last date known alive. If the last valid subject assessment date available is after the data cutoff date, the data cut-off date is used as the last date known alive.

Overall survival will be analyzed in a similar manner as that for PFS.

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 or surgery will be censored at the initiation date of the subsequent anti-cancer therapy or surgery; a method similar to the primary analysis will be applied to estimate the medians of OS and compare the survival distributions between two treatment arms.

10.3.3. Tumor Response and Overall Response Rate

The number and percentage of those with a best overall tumor response of SD, PR, or CR will be presented, as well as the number and percentage with each of progressive disease (PD), SD, PR, CR, and un-evaluable (UE). This analysis will be presented for each protocol-specified CT as defined in Section 17.4. If there is more than one CT scan within a relative day range, the best response will be counted.

Overall response rate (ORR) –a secondary efficacy endpoint- is the percentage of subjects who achieved best response of PR or CR compared with baseline among all tumor assessments, where baseline is the last CT scan obtained prior to or on Day 1 of Treatment. In this study, per RECIST1.1, since ORR is not a primary endpoint, confirmation of response is not required. The ORR along with 95% Clopper-Pearson CI will be presented. The relative treatment effect will be summarized by the ratio of the response rates and the associated two-sided 95% CI.

10.3.4. Time to Response (TTR)

Time to response is defined as the time from the date of randomization 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.

10.3.5. Duration of Response

For subjects who have a CR or PR, duration of response is defined as the time interval from the first occurrence of Complete or Partial Response (CR or PR) according to RECIST 1.1 criteria to the first documented progressive disease date.

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 without 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 for each treatment arm; the associated hazard ratio with two-sided 95% confidence interval will be estimated using the Cox proportional hazard model (Cox, 1972).

10.4. Subgroup Analyses

Progression-free survival, OS, and DCR will all be analyzed within the following subgroups (with subgroup data based on the clinical database rather than IRT). Subgroup factors will not be used as regression adjustment covariates for relevant analyses, but otherwise these analyses will parallel the analyses for the endpoint performed on the whole population. The following subgroup factors will be used:

1. Age (< 65 years and \geq 65 years, < 70 years and \geq 70 years, < 75 years and \geq 75 years);
2. ECOG status (0 vs. 1) at baseline;
3. Sex (male and female);
4. Current smoker (yes vs. no).

For the time-to-event endpoints PFS and OS, forest plots will be provided displaying the HR and corresponding 95% CIs for each subgroup.

For DCR, forest plots will be provided displaying the rate ratios and corresponding 95% Clopper-Pearson CIs for each subgroup.

10.5. Analyses of Exploratory Endpoints

10.5.1. Healthcare Resource Utilization

Summary statistics for number/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, End-of -Treatment Visit, and 28-day follow up visit).

11. SAFETY ANALYSIS

The purpose of this section is to describe the safety analyses for the study. All summaries of safety data will be conducted using the treated population.

11.1. Adverse Events

Adverse events will be analyzed in terms of treatment-emergent adverse events (TEAEs), defined as any AE or SAE occurring or worsening on or after the day of the first dose of the IP through 28 days after the last dose of IP. In addition, any serious AE with an onset date more than 28 days after the last dose of IP that is assessed by the investigator as related to IP will be considered a TEAE.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA, Version 17.0 or above). The severity of AEs will be graded based on NCI CTCAE, Version 4.0.

The following rules will be implemented for cycle calculations for TEAEs:

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

Adverse events of special interest of the *nab*-paclitaxel with CC-486 and the *nab*-paclitaxel regimens will be summarized by worst NCI CTCAE grade, AEs of special interest categories and MedDRA preferred terms.

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 drug. Additionally, for treatment-related AEs, reported as “suspected” in eCRF to each individual drug, *nab*-paclitaxel or CC-486 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. AE relationship to a study drug should always be collected on eCRF. In the rare cases relationships are missing, the relationships to a study drug will be taken as “related” in all relevant statistical analyses.

The incidence of TEAEs/treatment related TEAEs will be summarized by MedDRA system organ class (SOC) and/or preferred term (PT). 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 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). 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. In addition, AEs with a missing intensity will be presented in the summary table as an intensity category of “Missing.”

Tables summarizing the number of subjects experiencing TEAEs and subject incidence for TEAEs will be generated for each of the following:

- Overall summary of TEAEs;
- TEAEs presented by MedDRA system organ class and preferred term;
- All TEAEs by worst CTCAE grade as well as grade category;
- Treatment-related TEAEs;
- Treatment-related TEAEs by grade category;
- Serious TEAE;
- Treatment-related serious TEAEs;
- TEAEs with action as study drug withdrawn;
- Treatment-related TEAEs with action as study drug withdrawn;
- TEAEs with action as study drug dose reduced or interrupted;
- Treatment-related TEAEs with action as study drug dose reduced or interrupted;
- TEAEs with fatal outcome ;
- Treatment-related TEAEs with fatal outcome ;
- All deaths within 28 days of last dose with cause of death and deaths during follow up period with cause of death (ITT population for both);
- Most frequent TEAEs ($\geq 5\%$ in either treatment arm);
- TEAEs for the following baseline subgroups (provided the number of subjects are sufficient):
 - Age (<65, 65 - ≤ 74 and ≥ 75 years);
 - ECOG status (0 vs. 1) at baseline;
 - Sex (male and female);
 - Current smoker (yes vs. no).

In addition TEAEs will be summarized by cycle.

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





11.3. Peripheral Neuropathy

Peripheral neuropathy events will be reported as AEs and will be included in analyses described in Section 11.1. In addition, time from first dose to the first onset of peripheral neuropathy based on Standardized MedDRA Queries and time to improvement in peripheral neuropathy will be evaluated as follows:

- Time to first onset of grade 3 or higher peripheral neuropathy: The summary of time to first onset will be presented descriptively for those subjects who experienced peripheral neuropathy of grade 3 or higher.
- Time to improvement of grade 3 or higher peripheral neuropathy by at least 1 grade: The summary of time to improvement will include only subjects who experienced peripheral neuropathy of grade 3 or higher. Subjects who do not experience improvement by at least 1 grade 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% CI.
- Time to improvement of grade 3 or higher peripheral neuropathy to grade 1 or better: The summary of time to improvement will include only subjects who experienced peripheral neuropathy of grade 3 or higher. Subjects who do not experience an improvement to grade 1 or better 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% CI.

11.4. Clinical Laboratory Evaluations

Clinical laboratory values from the central laboratory will be **graded** according to NCI CTCAE version 4.0 for applicable tests. Normal ranges will be used to **determine** the categories of High, Low, and Normal for lab tests that have no severity grade, **if available**.

Listings will be provided for the central laboratory data.

11.4.1. Hematology

The worst NCI CTCAE grade for absolute neutrophil counts (ANC), white blood cell (WBC) counts, platelet counts, and hemoglobin at each treatment cycle and overall will be cross-tabulated with the grade at baseline (shift table).

A summary of hematology lab results and changes from baseline by visit and/or overall may be needed. Additionally, the nadir of each myelosuppression parameter may be needed for each treatment cycle and overall. Therefore, these variables will be derived in the analysis datasets.

11.4.2. Clinical Chemistry

The worst NCI CTCAE grade for alkaline phosphatase, ALT (SGPT), AST (SGOT), total bilirubin, creatinine, creatinine clearance, glucose, and fibrinogen at each treatment cycle and overall will be cross-tabulated with the grade at baseline (shift table).

A summary of chemistry lab results and changes from baseline by visit and/or overall may be needed. Additionally, the most severe value of each chemistry parameter may be needed for each treatment cycle and overall. Therefore, these variables will be derived in the analysis datasets.

12. QUALITY OF LIFE ANALYSIS

The Lung Cancer Symptom Scale (LCSS), EORTC QLQ C30 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. The EORTC QLQ-C30 includes five functional scales, three symptom scales, a global health status/QoL scale, and six single items. These questionnaires will be completed at Day 1 of every cycle, and at the End-of-Treatment Visit and at the 28-day Follow-up Visit and analyzed by treatment arm. 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.

12.1. LCSS

The 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 as well as the change from baseline in this average will be calculated for each subject and will be referred to as the LCSS score. The symptom burden score is the average of the 6 major symptom scores. 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 LCSS score and symptom burden score, and the change from baseline, will be summarized for the ITT population at every time point at which the instrument is given, and at End of Treatment. Descriptive statistics will be presented for each individual item at each

time point. 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 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 LCSS score during treatment, defined as the difference between the last reported LCSS score, either the end of treatment visit or the last reported LCSS score before clinical cutoff for subjects who have not had an end of treatment visit, will be presented.

12.2. 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.

The EQ-5D-5L consists of EQ-5D-5L descriptive system and the EQ Visual Analogue scale (EQ VAS). The descriptive system comprises 5 dimensions:

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

Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. Responses from the 5 dimensions are coded so that a '1' indicates no problem on that dimension, and '5' indicates the most serious problem. The responses for the five dimensions can be combined in a five-digit number describing the respondent's health state. For instance, a state of 11111 indicates no problem with any of the 5 dimensions, but a state of 55555 indicates the most difficulty on all 5. Missing and un-interpretable values (e.g. two responses are given for a single dimension) which are not recoverable through queries will be coded as '9'.

The EQ VAS records the respondent's self-rated health on a 20 cm vertical, visual analogue scale with endpoints labeled 'the best health you can imagine' and 'the worst health you can imagine'. The EQ VAS scale is numbered from 0 to 100 with 0 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.

The utility score and 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 utility score during treatment, defined as the difference between the last reported utility score, either 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.

Summary statistics of the EQ VAS (with the exception of the missing values) score, change from baseline, and percent change from baseline will also be presented for every time point at which the instrument is given. In addition, the change from baseline to the last reported overall score, 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.

Shifts from baseline to each time point at which the instrument is given will be presented for each dimension for the ITT population.

12.3. EORTC QLQ C30

The EORTC QLQ-C30 (version 3.0) is composed of both multi-item scales and single-item measures. These include five functional scales (physical, role, emotional, cognitive, social), three symptom scales (fatigue, nausea/vomiting, pain), a global health status / QoL scale, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties). Each of the multi-item scales includes a different set of items - no item occurs in more than one scale. All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. Thus a high score for a functional scale represents a high / healthy level of functioning, a high score for the global health status / QoL represents a high QoL, but a high score for a symptom scale / item represents a high level of symptomatology / problems. Scale scores are calculated by averaging items within scales and transforming average scores linearly. Scoring schemas for each scale are provided on the EORTC website.

Summary statistics for the scale scores and the change from baseline will be presented for global health dimension and each functional and symptom scale or single item at each time point. In addition, the change from baseline to the scale score during treatment, defined as the difference between the last reported scale score, either the end of treatment visit or the last reported scale score before clinical cutoff for subjects who have not had an end of treatment visit will be presented.

13. FOLLOW UP TREATMENTS

First subsequent systemic anti-cancer regimens will be summarized by treatment arm.

To assess how quickly the third 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, time to third line therapy (systemic anti-cancer therapies during follow-up period), defined as the time interval from the last dose date of study drug to the start date of the first subsequent anti-cancer regimen. 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 die before initiating a subsequent therapy will be censored at the date of death.

Time to third 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 the Cox proportional hazard model (Cox, 1972).

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 period will be summarized by treatment group and by system organ class and preferred term. Follow-up surgeries will be listed.

Radiation therapy during follow-up period will be summarized by treatment arm and 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

14.1. General Information

An independent Data Monitoring Committee (DMC) will be convened with experts not otherwise involved in the study as investigators. During the course of the study, the DMC will review the progression-free survival efficacy data once and overall survival data separately in accordance with the guidelines for the pre-planned interim analysis. The committee will also review safety data periodically. Operational details for the DMC and the algorithm and its validation by an expert panel will be detailed in the DMC charter.

The DMC is advisory in nature, and the decision to implement DMC recommendations will be made by the sponsor. Specifically, the futility analysis for PFS is non-binding.

14.2. Statistical Approaches for Control of Alpha

There will be one nonbinding interim analysis for PFS with an early stopping rule for futility that will be conducted when approximately 60 events are observed. The *nab*-paclitaxel with CC-486 arm of the study may be stopped early for futility if the observed HR is > 1.10 given an approximate 60 PFS events have occurred at the time of the interim analysis (Hwang, 1990). A HR > 1.10 when half of the target events of 120 have occurred signals a low probability for observing a meaningful difference in favor of the *nab*-paclitaxel with CC-486 therapy should the study continue to the end. With the assumptions stated above, it will take approximately 16 months from the first subject randomized to observe approximately 60 PFS events for the interim analysis.

If futility is declared, enrollment in the *nab*-paclitaxel monotherapy arm will continue up to a total of 80 subjects.

This study is for estimation only, so no control of alpha is planned.

15. CHANGES TO THE STATISTICAL ANALYSES SECTION OF THE PROTOCOL

The PFS censoring rules given in protocol section 10.6.1 are elaborated with clarification of derivation rules in section 10.2 of this document.

The protocol states that PFS is the primary efficacy endpoint, DCR, OS, and ORR are the secondary efficacy endpoints of the study. The following secondary efficacy endpoints will be added to the efficacy analysis section of the SAP:

- Time to response
- Duration of response

16. REFERENCES

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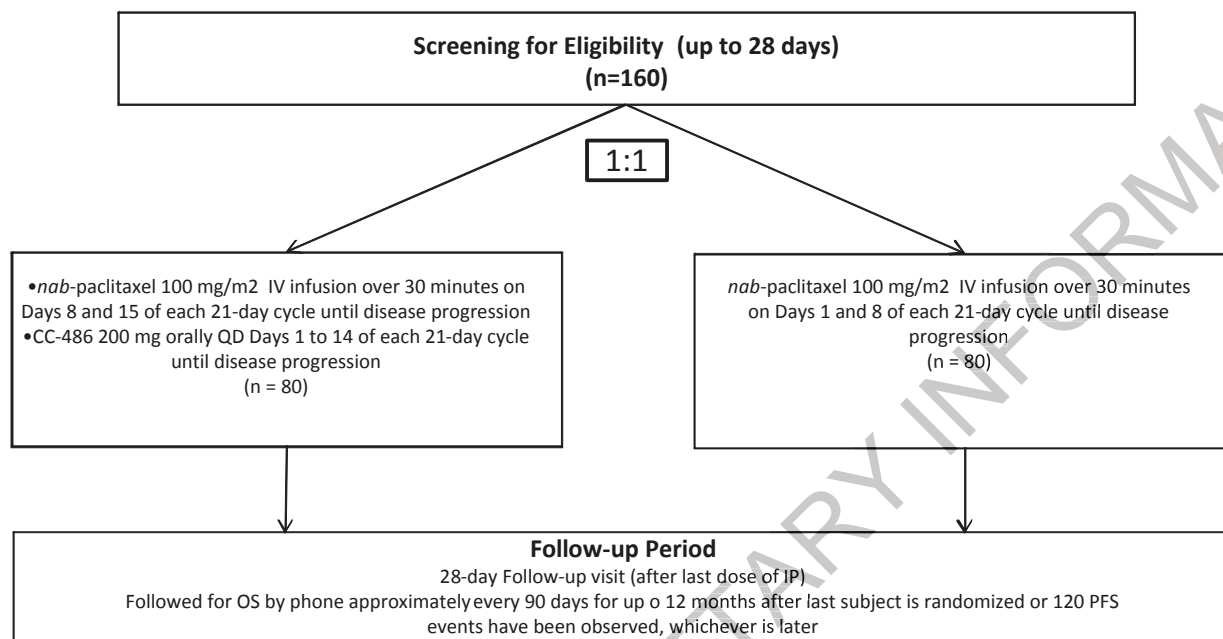
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17. APPENDICES

17.1. Study schematic



17.2. Handling of Dates

Dates will be stored as numeric variables in the SAS analysis files and reported in DDMMYYYY 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 17.3.1 (eg, 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 (eg, the survival date is derived from the death date), or a procedure date (eg, 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.

17.2.1. Calculation Using Dates

Calculations using dates (eg, 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 \geq 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:

$$\text{WEEKS} = \text{DAYS} / 7$$

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

$$\text{MONTHS} = \text{DAYS} / 30.4375$$

17.3. Date Imputation Guideline

17.3.1. 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 dosing 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 Stop Date

- If the imputed stop date is before the start date, then the imputed stop date will be equal to the start date.

Missing day and month

- If the year of the incomplete stop date is the **same** as the year of the last dosing date, then the day and month of the last dosing date will be assigned to the missing fields.
- If the year of study drug start and stop are different, and the year of the incomplete stop date is the **same** as the year of the first dosing date, then December 31 will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date but is the same as the year of the first dosing date, then the first dosing date will be assigned to the missing date.
- If the year of the incomplete stop date is **after** the year of the last dosing date, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year of the incomplete stop date are the **same** as the month and year of the last dosing date, then the day of the last dosing date will be assigned to the missing day.
- If either the year of the partial date is **not equal to** the year of the last dosing date or the years of the partial date and the last dosing date are the same but the month of partial date is **not equal to** the month of the last dosing date, then the last day of the month will be assigned to the missing day.

17.3.2. Adverse Events

Partially missing AE start dates will be imputed in the derived dataset for AEs, but partially missing AE end dates will not be imputed in the same dataset. If the AE end date is complete with no missing year, month, or day, and the partially missing start date imputed by the rules below is after the AE end date, then the start date will be imputed by the AE end date.

17.3.3. Prior/Concomitant Medications/Procedures

Partially missing start/stop dates for prior/concomitant medications and partially missing start dates for prior/concomitant procedures will be imputed in the derived dataset for prior/concomitant medications/procedures. For prior/concomitant medications, if the stop date is complete with no missing year, month, or day, and the partially missing start date imputed by the rule below is after the stop date, then the start date will be imputed by the stop date.

Partially missing prior/concomitant medication/procedure start dates will be imputed by the earliest possible date given the non-missing field(s) of the date.

Partially missing prior/concomitant medication stop dates will be imputed by the latest possible date given the non-missing field(s) of the date.

17.3.4. 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.

17.4. Tumor Response Windows**Table 5. 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

17.6. MedDRA Versions and Dates

Table 7 gives the MedDRA versions used in this study and the dates of implementation

Table 7 MedDRA Versions and Dates

For reports dated:	MedDRA Version
May 2016 - present	19.0
May 2015 – May 2016	18.0
June 2014 – May 2015	17.0