



**Protocol Title: A Phase 2 Multicenter, Randomized, Placebo Controlled, Double-Blind Study To Assess The Safety And Efficacy Of CC-486 (Oral Azacitidine) In Combination With Pembrolizumab (Mk-3475) Versus Pembrolizumab Plus Placebo In Subjects With Previously Treated Locally Advanced Or Metastatic Non-Small Cell Lung Cancer**

**NCT Number: NCT02546986**

**Final Statistical Analysis Plan: 28 June 2017**

# DISCLOSURE

## REDACTED STATISTICAL ANALYSIS PLAN

CC-486-NSCL-001

### **A PHASE 2 MULTICENTER, RANDOMIZED, PLACEBO CONTROLLED, DOUBLE-BLIND STUDY TO ASSESS THE SAFETY AND EFFICACY OF CC-486 (ORAL AZACITIDINE) IN COMBINATION WITH PEMBROLIZUMAB (MK-3475) VERSUS PEMBROLIZUMAB PLUS PLACEBO IN SUBJECTS WITH PREVIOUSLY TREATED LOCALLY ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER**

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## STATISTICAL ANALYSIS PLAN

A PHASE 2 MULTICENTER, RANDOMIZED, PLACEBO CONTROLLED, DOUBLE-BLIND STUDY TO ASSESS THE SAFETY AND EFFICACY OF CC-486 (ORAL AZACITIDINE) IN COMBINATION WITH PEMBROLIZUMAB (MK-3475) VERSUS PEMBROLIZUMAB PLUS PLACEBO IN SUBJECTS WITH PREVIOUSLY TREATED LOCALLY ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER

**STUDY DRUG:** CC-486  
**PROTOCOL NUMBER:** CC-486-NSCL-001  
**DATE FINAL:** 28 June 2017

Prepared by:

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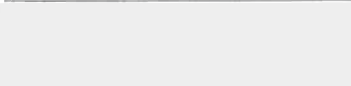
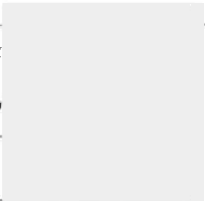
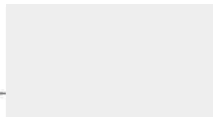
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## 1. LIST OF ABBREVIATIONS

**Table 1: Abbreviations and Specialist Terms**

ALT	Alanine aminotransferase (SGPT)
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the curve
BLQ	Below the limit of quantitation
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CSR	Clinical study report
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
ECI	Events of clinical interest
EE	Efficacy evaluable
EOS	End of study
Hgb	Hemoglobin
HR	Hazard ratio
ir	Immune-related
irDCR	Immune-related Disease control rate
irPFS	Immune-related Progression-free survival

irORR	Immune-related Overall response rate
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
IP	Investigational product
ITT	Intent-to-treat
IV	Intravenous
LDH	Lactic dehydrogenase
MRI	Magnetic resonance imaging
NA	Not applicable
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PK	Pharmacokinetic
PS	Performance Status
PR	Partial response
RECIST	Response Evaluation Criteria in Solid Tumors
RMP	Risk Management Plan
SAP	Statistical Analysis Plan
SD	Stable disease
STDEV	Standard deviation
SE	Standard error
SGOT	Serum glutamic oxaloacetic transaminase (AST)
SGPT	Serum glutamic pyruvic transaminase (ALT)
TIL	Tumor-infiltrating lymphocytes
TTP	Time to progression
ULN	Upper limit of normal
US	United States

## 2. INTRODUCTION

This statistical analysis plan (SAP) describes the analyses and data presentations for Celgene's protocol CC-486-NSCL-001 "A PHASE 2 MULTICENTER, RANDOMIZED, PLACEBO CONTROLLED, DOUBLE-BLIND STUDY TO ASSESS THE SAFETY AND EFFICACY OF CC-486 (ORAL AZACITIDINE) IN COMBINATION WITH PEMBROLIZUMAB (MK-3475) VERSUS PEMBROLIZUMAB PLUS PLACEBO IN SUBJECTS WITH PREVIOUSLY TREATED LOCALLY ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER" which was issued on 15 May 2015 and amended on 14 December 2015. It contains definitions of analysis populations, derived variables and statistical methods for the analysis of efficacy and safety.

These analyses include 3 Data Monitoring Committee (DMC) interim analyses and one final analysis. Throughout this SAP, the treatment arms will be referred to as "CC-486 plus pembrolizumab" and "pembrolizumab plus placebo". 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 final 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 final analysis. All statistical analyses detailed in this SAP will be conducted using SAS® Version 9.2 or higher. The final database lock will occur after 70 progression-free survival events are achieved.

### 3. STUDY OBJECTIVES

#### 3.1. Primary Objective

The primary objective is:

- To estimate the efficacy of CC-486 plus pembrolizumab versus pembrolizumab plus placebo based on progression-free survival (PFS) as measured using RECIST 1.1 criteria

#### 3.2. Secondary Objectives

The secondary objectives of the study are:

- To estimate disease control rate (DCR) of CC-486 plus pembrolizumab versus pembrolizumab plus placebo
- To estimate overall survival (OS) of CC-486 plus pembrolizumab versus pembrolizumab plus placebo
- To estimate overall response rate (ORR) of CC-486 plus pembrolizumab versus pembrolizumab plus placebo
- To evaluate safety and tolerability of CC-486 plus pembrolizumab versus pembrolizumab plus placebo
- To evaluate the impact of pembrolizumab on the pharmacokinetics of CC-486

#### 3.3. Exploratory Objectives

The exploratory objectives of the study are:

- To determine the preliminary efficacy (immune-related [ir] PFS, irDCR, irORR) of CC-486 plus pembrolizumab versus pembrolizumab plus placebo based on irRECIST criteria (see Appendix B of the protocol for details on irRECIST).
- To explore mechanism and biomarkers associated with efficacy of CC-486 plus pembrolizumab versus pembrolizumab plus placebo, [REDACTED]

## 4. INVESTIGATIONAL PLAN

### 4.1. Overall Study Design and Plan

This is a Phase 2, multicenter, international, randomized, placebo controlled double-blind study to assess the safety and efficacy of the combination therapy of CC-486 plus pembrolizumab versus pembrolizumab plus placebo in previously treated subjects with locally advanced or metastatic NSCLC who have received one prior platinum-based chemotherapy regimen.

Approximately 90 subjects meeting the inclusion criteria will be randomized 1:1 to one of the 2 treatment arms:

- Arm A: CC-486 300 mg administered orally daily on days 1-14 plus pembrolizumab 200 mg administered as a 30-minute IV infusion on day 1 of a 21-day cycle, or
- Arm B: Placebo administered orally daily on days 1-14 plus pembrolizumab 200 mg administered as a 30-minute IV infusion on day 1 of a 21-day cycle.

The randomization will be stratified by histology (non-squamous versus squamous).

Subjects may remain on treatment until radiologic disease progression, unacceptable toxicity, and initiation of a new anticancer therapy, withdrawal of consent, subject refusal, physician decision, or death.

The study consists of a 3-week screening period, a treatment period consisting of 21-day cycles, and a follow-up period. The subjects will be seen at Day 1 and Day 14 for the first 2 cycles, and only on Day 1 for subsequent cycles. Tumor evaluation (i.e. efficacy follow-up period) will be assessed by the Investigator according to RECIST 1.1 guidelines at screening and every 6 weeks ( $\pm 5$  days) from randomization for the first 24 weeks, and every 9 weeks thereafter until disease progression, start of a new anticancer treatment or withdrawal consent. Subjects will also be evaluated according to irRECIST guidelines in cases of progressive disease (PD) per RECIST 1.1.

In the follow-up phase, anticancer treatment administered following the last dose of investigational product (IP) and survival will be followed every 8 weeks ( $\pm 5$  days) until death, withdrawal of consent, or lost-to-follow-up, whichever occurs first, or the End of Trial.

A safety analysis will be performed in the first 10 subjects in each arm after the completion of at least 1 cycle of treatment. An independent Data Monitoring Committee will be established to evaluate safety. Following the initial DMC data review meeting, the DMC will meet approximately every 6 months per DMC charter (or more often if requested by the DMC Chairman) to assess safety data. Details are outlined in the DMC charter.

The study schematic is presented in [Section 17.1](#) while the table of events is presented in [Section 17.2](#).



## 4.2. Study Endpoints

### 4.2.1. Primary Efficacy Endpoint

The primary endpoint is:

- PFS measured as time from randomization to progression according to RECIST 1.1 (based on Investigator assessment) or death due to any cause, whichever occurs first.

### 4.2.2. Secondary Efficacy Endpoints

The secondary endpoints are:

- Number (%) of subjects with Stable Disease (SD) for  $\geq 18$  weeks, complete response (CR) or partial response (PR) (DCR).
- Overall survival.
- Number (%) of subjects who achieve an objective CR or PR (ORR).
- Safety endpoints include the incidence of treatment-emergent adverse events (TEAEs), serious TEAEs, Grade 3-4 TEAEs, TEAEs of special interest, and laboratory abnormalities and other safety parameters.

### 4.2.3. Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are:

- Exploratory efficacy as measured by irPFS, irDCR, and irORR based on Investigator assessment using irRECIST.
- Measures of the tumor-associated immune state, [REDACTED]
- [REDACTED]
- DNA analyses, gene expression and soluble factors in blood.

## 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 histology (non-squamous vs squamous). Approximately 90 subjects will be randomized to one of two treatment arms in a 1:1 ratio. A permuted-block randomization method will be employed. Subjects will receive one of the following treatments based on the randomization assignment:

- Arm A: CC-486 300 mg administered orally daily on days 1-14 plus pembrolizumab 200 mg administered as a 30-minute IV infusion on day 1 of a 21-day cycle, or

- Arm B: Placebo administered orally daily on days 1-14 plus pembrolizumab 200 mg administered as a 30-minute IV infusion on day 1 of a 21-day cycle

CC-486 and matching placebo will be double blind whereas pembrolizumab will be open-label. CC-486 and pembrolizumab are designated as IPs.

#### 4.4. Sample Size Determination

The primary goal of this study is to provide estimates of the difference in efficacy and safety between CC-486 plus pembrolizumab and pembrolizumab plus placebo.

Approximately 90 subjects will be randomized 1:1 to receive CC-486 plus pembrolizumab or pembrolizumab plus placebo. The primary analysis will be conducted when 70 PFS events occur.

Selected hypothetical scenarios are presented in [Table 2](#) with confidence interval and power estimates, when approximately 70 PFS events have occurred.

[Table 2](#) demonstrates the hypothetical power of testing the null hypothesis  $H_0: \lambda_T / \lambda_C = 1$ , against the two sided alternative  $H_A: \lambda_T / \lambda_C \neq 1$ , assuming that time to PFS events in both treatment arms follow exponential distributions, and  $\lambda_C$  is the monthly hazard rate of the survival distribution in the control arm, and  $\lambda_T$  is the monthly hazard rate of the survival distribution in the experimental arm (CC-486+pembrolizumab).

**Table 2: Hypothetical Power and Resulting Two-sided 90% CI of Hazard Ratio**

Combo Treatment Median PFS (month)	5.5	5.0	4.6
Total PFS events	74	75	76
Power (%) w/two-sided $\alpha=0.10$ <sup>1</sup>	82.4	71.7	59.4
HR with [two-sided 90% CI]	0.55 [0.38,0.81]	0.60 [0.41,0.88]	0.65 [0.45,0.95]

<sup>1</sup> These calculations assume the median PFS in pembrolizumab alone is 3.0 months ([Garon, 2014](#)). And lost to follow-up (to assess PFS events) rate is 10% at the end of study

The power calculations are conducted with East 5.4.

## 5. GENERAL STATISTICAL CONSIDERATIONS

Programming, statistical analysis, and reporting will be conducted according to the following conventions.

### 5.1. Reporting Conventions

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

- Listings will include both the randomized treatment and actual treatment;
- Data from all study centers will be combined for analysis;
- All stratified efficacy analyses will use the stratification factors including histology (non-squamous vs squamous);
- P-values will be rounded to 4 decimal places. P-values  $<0.00005$  will be presented as ' $<0.0001$ ' and p-values  $\geq 0.9995$  will be presented as ' $>0.9999$ ';
- Confidence intervals (CIs) will be presented as 2-sided 90% CIs unless otherwise specified;
- 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, median, Standard Deviation (STDEV), minimum, and maximum for continuous variables;
- All mean and median 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;
- All percentages will be rounded to one decimal place. The number and percentage of responses will be presented in the form XX (XX%), where the percentage is in the parentheses;
- All laboratory data will be reported using standard international (SI) units;
- All listings will be sorted for presentation in order of randomized treatment arm, study center, subject, and date of procedure or event. Subjects who are enrolled but not randomized will be listed as a non-randomized group before randomized subjects;
- All analysis and summary tables will have the analysis population sample size (i.e., number of subjects);
- The day of the first dose of any study drug will be defined as Day 1;
- Baseline is defined as the last non-missing value on or before the first dose date of administration of CC-486/placebo, unless specified otherwise. 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 will be used as the baseline. For lab values with equal or missing CTC grade on the same date, the average of these values will be used as the baseline. For subjects who were not

treated, the baseline will be the last non-missing assessment value taken on the day of or before the randomization or Cycle 1 Day 1, whichever is later.

- SAS Version 9.2 (or higher) will be the statistical software package used to produce all other data summaries, listings, graphs, and statistical analyses.

## 5.2. Calculation of Treatment Start Dates, Cycles, and Treatment End date

The treatment start date will be calculated as follows:

- The day of the first dose of any study drug will be defined as Day 1.

The treatment end date will be calculated as follows:

- For subjects who discontinue prior to the clinical cutoff date, treatment end date of individual drug is the date of treatment discontinuation from treatment disposition form in the eCRF.
- For subjects who are still on treatment at the time of study closure or clinical cutoff, treatment end date of CC-486 is the last non-missing dose date of CC-486+7.
- Treatment end date of pembrolizumab is the last non-missing dose date of pembrolizumab+20.
- The treatment end date of the investigational product (IP) would be the latest of the two individual drug end dates.

Cycle dates will be calculated as follows:

- Each cycle starts with the date of the first dose date of the cycle, and the last day of the cycle is the day before the first dose date of subsequent cycle. In by-cycle analyses, assessments taken pre-dose on Day 1 of a given cycle (e.g., laboratory measures) will be grouped with the previous cycle.
- For the last cycle, the last day of the cycle is 21 days after Day 1 of the last cycle, the treatment discontinuation date on the electronic case report form (eCRF) EOT page, or study cut-off date, whichever is earlier.
- The cycle number and the day with a cycle for each date of interest, e.g., AE start date, will be calculated based on the cycle window set by the start and end dates of the study medication.

## 5.3. Analysis Populations

### 5.3.1. Intent-to-Treat Population/Full Analysis Set

The Intent-to-Treat (ITT) population includes all subjects who are randomized. All efficacy analyses will be based on the ITT population, unless otherwise specified. The efficacy analyses will be performed according to treatment assigned at randomization.

### **5.3.2. Safety Population**

The safety population includes all subjects who are randomized and receive at least one dose of study drug. If a subject receives study drug other than the subject's randomized treatment assignment, then the subject is assigned to the treatment arm reflecting the treatment that the subject actually received during the study. All safety analyses will be based on the Safety population, unless otherwise specified.

### **5.3.3. Efficacy Evaluable Population**

The efficacy evaluable (EE) population is defined as ITT subjects who meet protocol requirements (meet eligibility criteria and have at least one valid tumor assessment at baseline) and are evaluated for tumor assessment after receiving at least one dose of study treatment. Selected efficacy analysis (e.g., PFS, OS, and ORR) will be performed using the EE population.

### **5.3.4. PK Population**

The pharmacokinetic population will include all randomized subjects who have evaluable concentration data to determine the pharmacokinetic parameters from at least one dose of CC-486. The evaluable subjects in the pharmacokinetic population will be included in the pharmacokinetic data analysis.

### **5.3.5. Biomarker Population**

The biomarker analysis population will include all randomized subjects who received at least 1 dose of IP, provided consent for exploratory biomarker studies, and had at least 1 predose biomarker tissue collected and deemed of adequate quality for biomarker analysis.

## 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.

Subject disposition (analysis of population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent for both treatment and follow-up phases for ITT population.

Reasons for treatment discontinuation will be summarized for the study drug (CC-486 or Placebo) and pembrolizumab separately, for all subjects with the following categories. The number and percentage of subjects who are in the survival follow-up, lost to survival follow-up, or died at the time of analysis will also be presented.

- Death
- Adverse events
- Pregnancy
- Progressive disease
- Withdrawal by Subject
- Non-compliance with study drug
- Lost to follow-up
- Study terminated by sponsor
- Transition to commercially available treatment
- Physician Decision
- Symptomatic deterioration
- 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
- Progressive disease
- Withdrawal by Subject
- Non-compliance with study drug

- Lost to follow-up
- Study terminated by sponsor
- Transition to commercially available treatment
- Physician Decision
- Symptomatic deterioration
- Protocol violation
- Other

Number of subjects randomized by strata and number of subjects randomized by country and site will be summarized. Listings will be provided for subjects who are screened but not enrolled, randomized but not treated, and for discontinued subjects with reason for treatment discontinuation.

## 7. PROTOCOL DEVIATIONS/VIOLATIONS

The protocol deviations/violations will be 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 efficacy evaluable population. Events that could trigger exclusion from the EE population include inclusion/exclusion criteria violations, failure to take any study drug as assigned, randomization errors, and 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 deviations/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

Subject's age (years), height (cm), weight (kg), Body Mass Index (BMI) and Body Surface Area (BSA) at baseline will be summarized descriptively. Sex, race, ethnicity and reproductive status 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:  $\text{BMI (kg/m}^2\text{)} = \text{weight in kg} / (\text{height in m})^2$ .

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

### 8.2. Baseline Characteristics

The following baseline characteristic will be summarized by frequency counts, by treatment arm and overall:

- ECOG performance status at baseline (0, 1);
- Disease stage at primary diagnosis (Ia, Ib, IIa, IIb, IIIa, IIIb, IV, Unknown);
- Disease stage at baseline (Ia, Ib, IIa, IIb, IIIa, IIIb, IVa, IVb, Unknown);
- Histology (squamous cell carcinoma, adenocarcinoma);
- Current sites of metastasis;
- Number of metastatic sites.

### 8.3. Cancer History and Baseline Lesion Status

The following items will be summarized for cancer diagnosis:

- The time from specimen collection date to first dose date in months, defined as  $(\text{first dose date} - \text{specimen collection date} + 1) / 30.4375$
- Tissue type (archival tissue, fresh tumor biopsy [surgical, core needle, other])
- Most current recurrence/progression (month) as defined as  $(\text{first dose date} - \text{most recent recurrence/progression specimen collection date} + 1) / 30.4375$
- Number of target/non-target lesions
- Method of assessment for target/non-target lesions
- Sum of target lesion diameters

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

## **8.4. Medical History**

A summary of medical and surgical history will be presented by MedDRA (Version 19.0) system and organ class (SOC) and preferred term (PT).

## **8.5. Prior Therapy**

### **8.5.1. Prior Anti-Cancer Therapy**

#### **8.5.1.1. Prior Systemic Anti-Cancer Therapy**

Prior systemic therapies (e.g. chemotherapy) will be coded to therapeutic drug classes and generic drug names using the World Health Organization (WHO) drug dictionary. The duration, the number of cycles (if known), and the best response will all be presented in a listing. A summary table will also be provided.

#### **8.5.1.2. 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 type of radiotherapy (External Beam Location, Radio-Immuno Therapy, Brachytherapy, Other) and each site of radiation therapy will be presented.

#### **8.5.1.3. Prior Surgeries**

The number and percentage of subjects who had any prior surgery will be presented. Prior surgeries will be listed.

## **8.6. Prior and Concomitant Medications**

Medications reported on the Prior and Concomitant medications eCRF pages will be coded to therapeutic drug classes and generic drug names using the WHO drug dictionary version WHODRUG ENHANCED 01 MARCH 2016.

### **8.6.1. Prior Medications**

Prior medications are defined as all medications that were started before Day 1 of Treatment. 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 for the Treatment Period are defined as medications that were initiated before the first dose of study drug and continued during the study treatment, or initiated on/after the date of the first dose of study drug and within 28 days after the date of treatment discontinuation.

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

CELGENE PROPRIETARY INFORMATION

## 9. STUDY TREATMENTS AND EXTENT OF EXPOSURE

Study treatment and extent of exposure summaries will be provided based on the safety population. Descriptive statistics will be provided for treatment duration, number of cycles, cumulative dose, dose intensity, and relative dose intensity by treatment arm. Dose reduction/interruption will also be summarized.

### 9.1. Treatment Duration

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

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

Each cycle starts with the date of the first dose date of the cycle and the last day of the cycle is the day before the first dose date of subsequent cycle.

For clinical cutoff, the last day of pembrolizumab will be Day 1 of the last cycle plus 20 days or last dose of treatment plus 20 days, whichever comes first. For CC-486, the last day will be Day 1 of the last cycle plus 20 days or last dose of treatment plus 7 days, whichever comes first. Treatment duration specific to a drug will follow the rules described above, respectively for each drug. Treatment duration specific to a treatment arm combination will be the maximum of the two end dates from the same arm.

Descriptive statistics will be provided for treatment duration and total number of cycles for each arm, i.e. the CC-486 plus pembrolizumab and the pembrolizumab plus placebo arms. Descriptive statistics will also be provided for number of doses received for both CC-486 and pembrolizumab separately.

### 9.2. Cumulative Dose

Cumulative dose will be computed separately for CC-486, pembrolizumab and placebo. Cumulative dose for pembrolizumab is defined as the sum of all actual doses, defined as the values entered on the dose assigned field on the dosing eCRF, taken across the Treatment Period in  $\text{mg}/\text{m}^2$ . 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. Similarly, the cumulative dose for placebo 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 safety subjects.

### 9.3. Dose Intensity

Dose intensity during the treatment is defined as the cumulative dose divided by the treatment duration in weeks. Dose intensity will be calculated separately for CC-486 and pembrolizumab.

Dose intensities will be calculated as follows:

- Dose intensity for pembrolizumab ( $\text{mg}/\text{m}^2/\text{wk}$ ) = [cumulative dose for pembrolizumab in  $\text{mg}/\text{m}^2$ ] / [treatment duration in weeks].

- Dose intensity for CC-486 (mg/ wk) = [cumulative dose for CC-486 in mg] / [treatment duration in weeks].

Dose intensity will be presented by drug for the Treatment Period of the study for the treated population.

#### 9.4. Relative Dose Intensity

Relative dose intensity by week is the dose intensity divided by the protocol weekly dose, expressed as a percentage. Relative dose intensity will be calculated separately for CC-486 and pembrolizumab.

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

The original protocol weekly doses for CC-486:

- CC-486: 1400 mg /wk (300 mg each day on days 1 to 14 of each 21 day cycle)

The original protocol weekly doses for pembrolizumab:

- Pembrolizumab: 66.67 mg/wk (200 mg on day 1 of a 21-day cycle).

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

#### 9.5. Dose Reduction/Interruption

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

In addition, for CC-486, dose interruption is defined as a zero dose given on one or more days on which the protocol -specified dose is non-zero. Consecutive zeros are counted as one interruption. Dose interruption for pembrolizumab will be defined similarly.

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

- Number of cycles and doses administered;
- Number and percentage of subjects with at least 1 dose reduction, number of dose reductions, and reasons (Per Protocol, adverse event, or other) for reduction;

Number and percentage of subjects with at least one dose interruption, number of dose interruptions will be presented.

## 10. EFFICACY ANALYSIS

All efficacy evaluations will be conducted using the ITT population. Supportive analysis of the primary and key secondary efficacy endpoints using the EE population will be conducted for the final analysis. Data listings will be provided for all endpoints.

### 10.1. Multiplicity

There is no multiplicity adjustment on the efficacy endpoints. The statistical tests will not be formally performed.

### 10.2. Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is progression-free survival (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 or have not died as of the data cutoff date will be censored at the time of the last radiologic assessment where the subject was documented to be progression-free prior to the data cutoff date. In the event that a new anti-cancer therapy is initiated for a subject prior to documented progression (or death), the subject will be censored at the time of the last radiologic assessment where the subject was documented to be progression-free prior to the new anti-cancer therapy. Subjects with a single missing radiologic assessment prior to a visit with documented disease progression (or death) will be analyzed as a PFS event at the time of the radiologic assessment that shows progression or death (whichever is earlier). Subjects with two or more consecutive 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 or more consecutive missing visits. The PFS censoring rule is further illustrated in [Table 3](#).

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 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 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 new anticancer therapy will not result in censoring for this analysis.

**Table 3: Censoring Rules for PFS**

<b>Value of Progression-free Survival Date (ADT)</b>	<b>Censored (Y,N)</b>	<b>Derivation</b>
ADT = min(death date, progression date)	N	If a subject died or had disease progression, and the time interval between the death date/progression date and the previous tumor assessment date with progression-free response or the randomization date is less than or equal to <b>91</b> days.
ADT = the last progression-free assessment date/ randomization date	Y	If a subject died or had disease progression, and the time interval between the death date/progression date and the previous tumor assessment date with progression-free response or the randomization date is greater than <b>91</b> days.
ADT = the last tumor assessment date/randomization date	Y	If a subject did not die or have progression, and did not receive any subsequent anticancer chemotherapy. If there was no post-baseline tumor assessment, then ADT = the randomization date.
ADT = the last tumor assessment date on or prior to start of subsequent chemotherapy/randomization date	Y	If a subject did not die or have progression on or prior to start of subsequent anticancer chemotherapy, or a subject died/progressed after the start of sequent anticancer chemotherapy. If there was no post-baseline tumor assessment, then ADT = the randomization date.
ADT = the last tumor assessment date on or prior to date of surgery or start of radiotherapy/randomization date	Y	If a subject did not die or have progression on or prior to date of surgery or start of curative radiotherapy, or a subject died/progressed after the date of surgery or start of radiotherapy. If there was no post-baseline tumor assessment, then ADT = the randomization date.
ADT = the last tumor assessment date on or prior to treatment discontinuation date/randomization date	Y	If a subject did not die or have progression on or prior to the date of treatment discontinuation due to symptomatic deterioration, or a subject died/progressed after the date of treatment discontinuation due to symptomatic deterioration. If there was no post-baseline tumor assessment, then ADT = the randomization date.

ADT = analysis date; N = no; Y = yes.  
Note: Progression-free response refers to a response that was neither progressive disease (PD) nor un-evaluable (UE).

The final analysis for PFS will be conducted when a total of approximately 70 PFS events occur, all disease progression and death events that occurred on or prior to the projected clinical cutoff date will be included.

The survival distribution of PFS will be estimated using the Kaplan-Meier method, the median PFS including two-sided 90% confidence interval (CI) for each treatment arm will be provided. The survival distributions for two treatment arms will be compared using the stratified log-rank test, and the p-value will be provided. The stratification factors will be histology (non-squamous vs squamous). The associated hazard ratio (HR) and two-sided 90% confidence interval will be estimated by using stratified Cox proportional hazard model with treatment, and strata (i.e. histology) as model covariate. Kaplan-Meier curves will be provided by treatment arm and strata.

The number and percent of subjects surviving without progression will be provided for every 8 weeks 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 90% confidence interval from the Cox model with stratification factors):

- 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 efficacy evaluable population.

### 10.3. Analyses of Secondary Efficacy Endpoints

The secondary efficacy endpoints will be analyzed based on ITT population except otherwise specified.

#### 10.3.1. Overall Survival (OS)

Overall survival (OS) is defined as the duration (in months) between randomization and death from any cause:

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

Subjects who are still alive at the end of the study will be censored at the last contact date or clinical cutoff, whichever is earlier. The last contact date is the date of the last record in the database for that subject, or if the subject is dead, the last known date the subject was alive from the follow-up assessment, AE record or date of discontinuation record. The OS analysis may also be conducted at the time when 70 deaths occur, in addition to when the primary analysis is performed.

Median of overall survival including two-sided 90% CI for each treatment group will be calculated. The hazard ratio and a two-sided 90% CI will be estimated using Cox proportional hazard model with treatment, and all stratification factors in the model. The Kaplan-Meier curve for survival will be presented for each strata and treatment group. Median time to censoring for



those who are still alive at the cutoff date will also be provided. The analysis will be based on the ITT population.

### 10.3.2. Overall Response Rate (ORR)

The number and percentage of those with a tumor response of partial response (PR), or complete response (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 17.4.4. If there is more than one CT scan within a relative day range, the best response will be counted.

Overall response rate (ORR) 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. The ORR will be presented for each treatment group and strata. The 90% Clopper-Pearson confidence interval of the response rates will be provided. A two-sided 90% CI of the Response rate differences between CC-486 plus pembrolizumab and pembrolizumab plus placebo, with each stratum and overall will be provided. The p-value from a CMH test with stratification factors, if cell size is sufficiently large, will be reported to indicate the strength of association of the relative treatment effect.

The analysis will be based on the ITT population and will be repeated based on the EE population as a sensitivity analysis.

### 10.3.3. Disease Control Rate (DCR)

Disease Control rate (i.e., percent of subjects who have stable disease (SD) or complete response (CR) or partial response (PR) compared with baseline, where baseline is the last CT scan obtained prior to or on Day 1 of Treatment) over the Treatment Period is a secondary efficacy endpoint. When SD is believed to be best response, it must meet the minimum duration of 18 weeks from randomization. The DCR will be presented for each treatment group and strata. The 90% Clopper-Pearson confidence interval of the response rates will be provided. A two-sided 90% CI of the Response rate differences between CC-486 plus pembrolizumab and pembrolizumab plus placebo arm, with each stratum and overall will be provided. The analysis will be based on the ITT population.

### 10.3.4. Time to response

Time to response is defined as the time from the first dose date to the first occurrence of confirmed response (CR or PR). Time to response will be summarized with descriptive statistics.

Only subjects with a CR or PR as a best overall confirmed response will be included in this analysis. The analysis will be based on the ITT population.

### 10.3.5. Duration of response

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

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

The duration of response will be analyzed using the Kaplan-Meier method. The median time (including 2-sided 90% CI) will be summarized for each treatment arm; the associated hazard ratio with two-sided 90% confidence interval may be estimated using Cox proportional hazard model ([Cox, 1972](#)). The analysis will be based on the ITT population.

#### **10.4. Analyses of Exploratory Efficacy Endpoint**

Exploratory endpoint, irORR, assessed by Investigator according to irRECIST will be analyzed in a manner similar to the analysis described in [Section 10.3](#).

#### **10.5. Assessing Study Center Effect and Treatment-by-Center Interaction**

This study is a multicenter study and has approximately 40 study sites to enroll approximately 90 subjects. However, since the site is not part of the efficacy model, no site effect will be assessed.

## 11. SAFETY ANALYSIS

The purpose of this section is to describe the safety analyses for the Treatment Period of the study. Adverse events and laboratory values will be analyzed based on the safety population, per treatment arm and for treatment-related TEAEs or TEAEs with action taken, also by specific drug.

### 11.1. 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 start of study drug through 30 days after the last dose of study drug. In addition, any serious AE with an onset date more than 30 days after the 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 19.0.

Treatment-related TEAE will be summarized for each treatment arm. 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. TEAEs with a missing relationship will be presented in the summary table as a relationship category of “treatment-related”.

The incidence of TEAEs will be summarized for each treatment arm by MedDRA SOC and PT in a descending order of frequency of SOC and PT within each SOC based on the combination arm. If a subject experiences multiple AEs under the same SOC or PT, then the subject will be counted only once for that SOC or PT.

The toxicity of AEs will be graded 1 to 5 according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. For all other AEs not described in the CTCAE criteria, the toxicity 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. 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). In addition, AEs with a missing intensity will be presented in the summary table as an intensity category of “Missing.”

Deaths during the study will be summarized by cause categories. AEs regarded as primary cause of deaths, as reported on CRF, will also be summarized by SOC and PT. For both types of summaries, on-treatment (within 30 days after the last dose of study treatment) and post-treatment deaths will be summarized separately.

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

- All TEAEs;
- TEAEs reported as treatment-related;
- Serious TEAEs;

- Treatment-related serious TEAEs;
- All TEAEs with grade 3-4;
- Treatment-related grade 3-4 TEAEs;
- TEAEs leading to death;
- Treatment-related TEAEs leading to death;
- TEAEs leading to dose discontinuation;
- All TEAEs by CTCAE grade as well as grade 1-2 vs. grade 3-4 ;
- All death within 30 days of last dose with cause of death.

Listings for the corresponding summary tables will be presented separately. Non-treatment-emergent AEs will also be listed.

## 11.2. Adverse Events of Special Interest

The following TEAEs of special interest for CC-486 based on risk definitions (search criteria) as outlined in the Vidaza RMP (risk management plan) currently approved at the time of data cut-off will be summarized by treatment arm:

- Myelosuppression (neutropenia, thrombocytopenia, anemia, general myelosuppression);
- Hemorrhagic events;
- Infections;
- Renal failure;
- Hepatic failure;
- Ischemic colitis;
- Interstitial lung disease;
- Cardiac events (cardiac failure, cardiac arrhythmias, and myocardial infarction);
- Anxiety, confusional state, insomnia;
- Other psychiatric disorders;
- Tumor lysis syndrome.

The following TEAEs of special interest for pembrolizumab based on risk definitions (search criteria) as outlined in the pembrolizumab IB will be summarized by treatment arm:

- Adrenal insufficiency
- Colitis
- Hematologic

- Hepatic
- Hyperthyroidism
- Hypophysitis
- Hypothyroidism
- Infusion reactions
- Myasthenic syndrome
- Myositis
- Pancreatitis
- Pericarditis
- Pneumonitis
- Nephritis
- Skin
- Thyroiditis
- Type 1 diabetes mellitus
- Uveitis
- Vasculitis

The AE of special interest may be reviewed during the study at each MedDRA upgrade or protocol.

### **11.3. Clinical Laboratory Evaluations**

Clinical laboratory values from the central laboratories will be graded according to NCI CTCAE version 4.0 for applicable tests. The worst grade during the treatment period will be summarized by treatment arm. Frequency distributions for shift from baseline to the worst grade during treatment period will be presented by treatment arm. Normal ranges will be used to determine the categories of High, Low, and Normal for lab tests that have no severity grade.

Listings of clinical laboratory data from central laboratory with abnormal flags will be provided by subjects and tests. Listings will also be provided for the local laboratory data.

#### **11.3.1. Hematology**

Hemoglobin, hematocrit, red blood cell count and morphology, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell count with absolute and differential and percent (neutrophils, lymphocytes, monocytes, eosinophils, basophils, and bands), platelet count, reticulocytes, erythrocyte sedimentation rate, international normalized ratio, prothrombin time, partial thromboplastin time will be collected in hematology panel. Additional laboratory samples may be collected as clinically indicated.

In order to investigate the maximal degree of myelosuppression, the NCI CTCAE grade for hemoglobin, leukocytes, lymphocytes, neutrophils and platelets will be summarized by the worst grade in each treatment cycle and by the worst grade overall (i.e., any time after first dose of study drug). The number and percentage of subjects with each NCI CTCAE grade will be presented. A shift table representing the shift from the baseline grade to the worst grade will be provided for each of these laboratory tests.

Treatment group differences in each laboratory parameter with respect to the NCI CTCAE grades will be summarized by the frequency distribution of subjects with the grades.

All laboratory parameters will be summarized by descriptive statistics within each treatment arm, as appropriate.

### **11.3.2. Clinical Chemistry**

Serum chemistry panel includes sodium, potassium, bicarbonate, calcium, magnesium, phosphorus, blood urea nitrogen, serum creatinine and clearance, uric acid, glucose, lactic dehydrogenase, total protein, albumin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase, total, direct and indirect bilirubin, fibrinogen, ferritin. Additional laboratory samples may be collected as clinically indicated.

Hepatic and renal function will be summarized using the NCI CTCAE grade for ALT (SGPT), AST (SGOT), albumin, total bilirubin, creatinine, potassium, and sodium. The number and percentage of subjects that have each NCI CTCAE grade will be summarized using the worst grade for each cycle and overall. A shift table representing the shift from the baseline grade to the worst grade will be provided for each of these laboratory tests.

Treatment group differences in each laboratory parameter with respect to the NCI CTCAE grades will be summarized by the frequency distribution of subjects with the grades.

All laboratory parameters will be summarized by descriptive statistics within each treatment arm, as appropriate.

### **11.4. Vital Sign Measurements**

Vital signs (Weight, Temperature, Systolic and Diastolic Blood Pressure, Pulse and Respiratory rate) will be recorded at screening and on Day 1 of each cycle and EOT. Vital sign data will be listed.

### **11.5. Physical Examination**

Physical Examination will be recorded in source documentation (i.e. not collected on CRF) only and hence no table and listings will be produced.

### **11.6. Electrocardiograms**

Triplicate 12-lead ECGs will be recorded at screening and EOT and will be assessed locally. The 12-lead ECGs (12-lead at 25 mm/sec reporting rhythm, ventricular rate, PR-interval, QRS complex, QT interval, and QTc interval) will be performed after the subject has been in the supine position for at least 5 minutes. Shift from baseline to most abnormal post-baseline

qualitative assessment of ECG abnormality (i.e., ‘Normal’, ‘Abnormal, not clinically significant’, and ‘Abnormal, clinically significant’) will be displayed in cross-tabulations by treatment.

### **11.7. ECOG Performance Status**

The Eastern Cooperative Oncology Group (ECOG) score runs from 0 to 5, with 0 denoting perfect health and 5 death. ECOG performance status (PS) scores will be assessed and reported on the appropriate eCRF at screening, Day 1 of each cycle and at EOT. A shift table representing the shift from the baseline to the worst post-baseline ECOG PS scores will be provided for each treatment cycle and overall.

### **11.8. Pregnancy test**

A by-subject listing of pregnancy test and results will be provided for all female subjects of childbearing potential.

## 12. PHARMACOKINETIC ANALYSES

For the first 10-12 subjects randomized to each Arm, blood samples for CC-486 PK assessment will be collected on Day 1 of Cycle 1 and Cycle 2 prior to the dose administration of CC-486/placebo, known as predose, and over the 8-hour period following each dose administration of CC-486/placebo at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, and 8 hours post-dose.

Validated high-performance liquid chromatography/tandem mass spectrometric method (LC-MS/MS) will be used for azacitidine plasma concentration analysis.

### 12.1. Plasma concentrations

By-subject listing of pharmacokinetic blood sample collection times as well as derived sampling time deviations will be provided. CC-486 plasma concentrations will be summarized using descriptive statistics (N, arithmetic mean, standard deviation, standard error, minimum, median, maximum, percent coefficient of variation, geometric mean, and geometric percent coefficient of variation) for each cycle, if/when appropriate. Concentrations that are below the limit of quantitation (BLQ) will be treated as zero for the computation of descriptive statistics. Missing concentrations and concentrations from blood samples collected more than  $\pm 10\%$  of nominal time will be omitted from the calculation of descriptive statistics.

Individual subject concentration-time data and mean concentration-time data for each cycle will be graphically presented on linear and semi-logarithmic scales.

Following single dose administration, predose samples that are BLQ or missing will be assigned a numerical value of zero for the calculation of AUC. Any anomalous concentration values observed at predose will be identified in the clinical study report (CSR) and used for the computation of AUC. Pharmacokinetic parameters will be computed if the anomalous value is not greater than 5% of the  $C_{max}$ . If the anomalous value is greater than 5% of  $C_{max}$ , the computed pharmacokinetic parameters for the given subject will be dropped from the pharmacokinetic analysis.

Any other BLQ concentrations will be assigned a value of zero if they precede quantifiable samples in the initial portion of the profile. A BLQ value that occurs between quantifiable data points, especially prior to  $C_{max}$ , will be evaluated to determine if an assigned concentration of zero makes sense, or if reanalysis or exclusion of the data is warranted. Following  $C_{max}$ , BLQ values embedded between 2 quantifiable data points will be treated as missing when calculating AUC. BLQ values occurring at the end of the collection interval (after the last quantifiable concentration) will be treated as missing data. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration curve, these quantified values will be excluded from the pharmacokinetic analysis by assigning them a value of missing, unless otherwise warranted by the concentration-time profile. For the purpose of analysis, these trailing BLQ values may be designated as zero in the dataset if the pharmacokinetic program used to do the analysis (such as WinNonlin®) will treat trailing zero values as missing when calculating AUC.

Actual sampling times will be used in the calculations of pharmacokinetic parameters that will be derived using noncompartmental (NCA) methods with Phoenix™ WinNonlin® Professional



Version 6.3, or higher, [REDACTED] Graphics may be prepared with SAS Version 9.1, or higher; or Excel 2007, or higher; Phoenix™ WinNonlin® Professional 6.3, or higher; or S-Plus 8.2., or higher [REDACTED].

## 12.2. PK Parameter

The following PK parameters will be calculated for CC-486:

- $AUC_{inf}$  Area under the plasma concentration-time curve from Time 0 extrapolated to infinity, calculated as  $[AUC_t + C_t/\lambda_z]$ .  $C_t$  is the last quantifiable concentration. No AUC extrapolation will be performed with unreliable  $\lambda_z$ . If AUC %Extrap is  $\geq 25\%$ ,  $AUC_{inf}$  will not be reported
- $AUC_t$  Area under the plasma concentration-time curve from Time 0 to the time of the last quantifiable concentration, calculated by linear trapezoidal method when concentrations are increasing and the logarithmic trapezoidal method when concentrations are decreasing.
- $C_{max}$  Maximum observed plasma concentration, obtained directly from the observed concentration versus time data.
- $T_{max}$  Time to  $C_{max}$ , obtained directly from the observed concentration versus time data.
- $t_{1/2}$  Terminal phase half-life in plasma, calculated as  $[(\ln 2)/\lambda_z]$ .  $t_{1/2}$  will only be calculated when a reliable estimate for  $\lambda_z$  can be obtained.
- CL/F Apparent total clearance, calculated as  $[Dose/AUC_{inf}]$ .
- $V_z/F$  Apparent volume of distribution, calculated as  $[(CL/F)/\lambda_z]$ .

### 12.3. PK Analyses

By-subject listing of pharmacokinetic parameters will be provided. The pharmacokinetic parameters will also be summarized using descriptive statistics (N, arithmetic mean, standard deviation, standard error, minimum, median, maximum, percent coefficient of variation, geometric mean, and geometric percent coefficient of variation) for each treatment. Also, when appropriate, graphical representations (i.e., scatter plots, box plots, etc) may be used to visualize the results. In addition, two-sided 90% confidence intervals (CIs) for the geometric means will also be provided.

A linear mixed effects model will be performed on the log-transformed PK parameters  $AUC_{inf}$  and  $C_{max}$  (ANOVA). Other PK parameters, such as  $AUC_t$ , may also be tested. Included in the model will be cycle of visit as fixed effects and subject as the random effect. The 90% CIs for the mean of the difference (test - reference) on the log-scale will be calculated, and the back-transformed 90% CIs for the geometric mean of the ratio (test/reference) will be provided. Note: test = CC-486 co-administered with pembrolizumab during Cycle 2; reference = CC-486 alone during Cycle 1 (see Protocol Section 5 for details). For  $T_{max}$ , a non-parametric statistical method will be used to compare the median  $T_{max}$  between treatments.  $T_{lag}$  (lag time in absorption) will also be tested, if observed.

As a sensitivity analysis, a paired T-test on the PK parameters of the same patient between cycles of visit will also be conducted.

### **13. BIOMARKER ANALYSES**

Tumor, blood and serum will be collected to explore the hypothesized mechanism of CC-486 priming to pembrolizumab efficacy, and potentially identify biomarkers to predict patients that would benefit from this therapeutic regimen. Fresh tumor biopsy is the preferred tissue for these analyses; however archival formalin fixed, paraffin embedded (FFPE) blocks may be provided instead. Blood, serum and saliva will also be collected at time point detailed in the schedule of events. Biomarker analyses will be performed separately. Details of these analyses will be outlined in a separate document.

## **14. INTERIM ANALYSIS**

### **14.1. General Information**

An independent Data Monitoring Committee will be established and will include medical oncologists and a statistician, all of whom are not otherwise involved in the study conduct. During the course of the study, the DMC will review the safety data regularly. The DMC will offer recommendations based on periodic evaluations of comparative safety data, in accordance with criteria outlined in the DMC Charter. An independent statistician will prepare the reports to the DMC members for each scheduled meeting. Details will be provided in the DMC charter.

## **15. CHANGES TO THE STATISTICAL ANALYSES SECTION OF THE PROTOCOL**

An efficacy evaluable population was added to examine the effect of adherence to protocol requirement. The efficacy evaluable (EE) population is defined as ITT subjects who meet protocol requirements (either meet eligibility criteria and/or have at least one valid tumor assessment at baseline) and are evaluated after receiving at least one dose of study treatment.

The protocol states that exploratory endpoints such as irPFS, irORR, and irDCR assessed by Investigator according to irRECIST will be analyzed. In this SAP, irORR is the only exploratory endpoint that will be analyzed using statistical methods described for similar secondary endpoint.

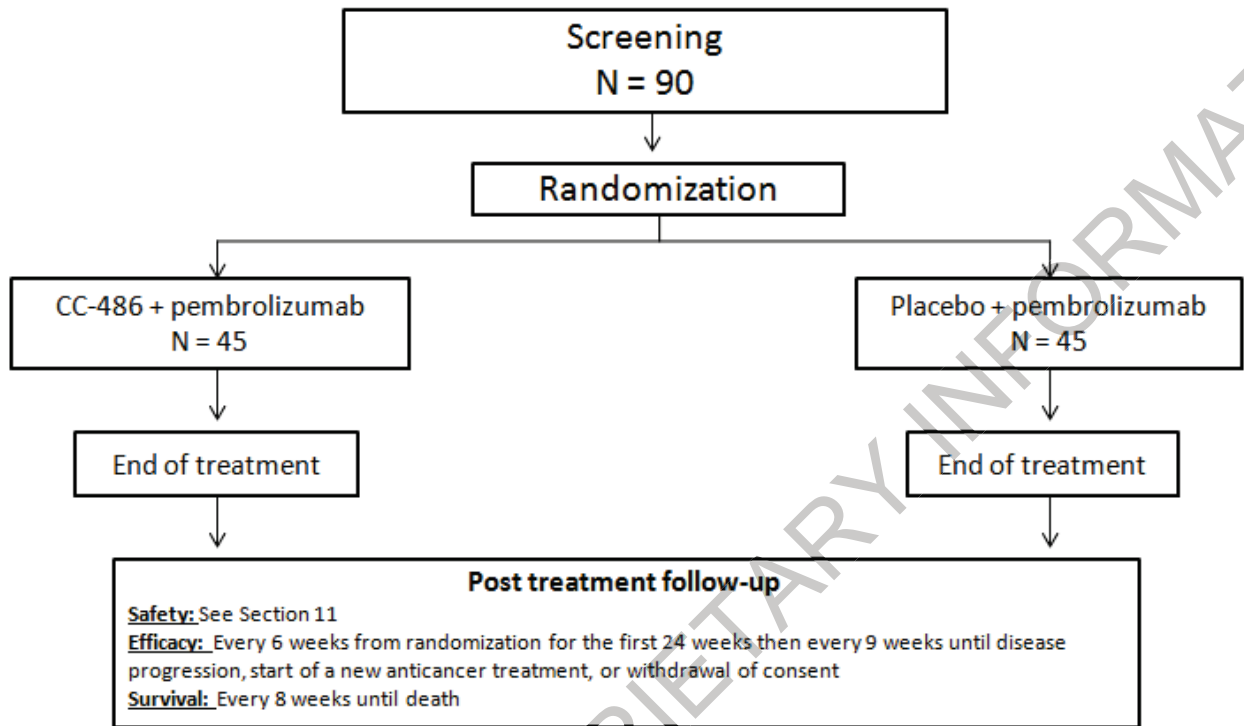
In Protocol Section 10.6.3, subgroup analyses on the efficacy variables OS, PFS, and DCR were described. These subgroup analyses will not be performed in this SAP.

## 16. REFERENCES

Cox, DR. Regression Models and Life-Tables. Journal of the Royal Statistical Society. Series B  
Garon EB, Leighl NB, Rizvi NA, et al. Safety and clinical activity of pembrolizumab in previously treated patients (pts) with non-small cell lung cancer (NSCLC) [abstract]. In: Proceedings of the 2014 ASCO Annual Meeting; 2014 May 30-Jun 3; Chicago, IL. J Clin Oncol. 32:5s, 2014 (suppl; abstr 8020).

## 17. APPENDICES

### 17.1. Study Schematic



**17.2. Table of Events**

Events	Screening Period	Treatment Period <sup>a</sup>						Follow-up Period
	Screening	Cycle 1		Cycle 2		Subsequent cycles		
Day	-21 to -1	1 <sup>b</sup>	14	1	14	1	EOT	Disease Progression/Survival
Informed consent	X							
Demographics	X							
Prior cancer history	X							
Prior cancer therapies <sup>c</sup>	X							
Complete medical history	X							
Prior/ concomitant medication evaluation <sup>d</sup>	X (≤ 28d from screening)	Continuous, until 28 days after last dose						
Prior/ concomitant procedures evaluation <sup>e</sup>	X (≤ 28d from screening)	Continuous, until 28 days after last dose						
Inclusion/exclusion criteria	X							
IRT registration	X							
IRT randomization		X <sup>f</sup>						
Adverse event evaluation	Continuous after informed consent signature. See Section <b>Error! Reference source not found.</b> for additional details on AE reporting timeframe							
Physical examination (source documented only)	X	X		X		X	X	



Events	Screening Period	Treatment Period <sup>a</sup>						Follow-up Period
	Screening	Cycle 1		Cycle 2		Subsequent cycles		
Day	-21 to -1	1 <sup>b</sup>	14	1	14	1	EOT	Disease Progression/ Survival
Weight	X	X		X		X	X	
Height	X							
Vital signs	X	X		X		X	X	
ECOG performance status	X	X		X		X	X	
Hematology laboratory <sup>g</sup>	X	X	X	X	X	X	X	
Coagulation <sup>h</sup>	X							
HBV and HCV serologies (HBsAg, HBeAg, HBsAb, HBeAb, HBcAb, HCVAb)	X						X	
Chemistry laboratory <sup>i</sup>	X	X	X	X	X	X	X	
Lipid panel <sup>j</sup>	X					Every 4 <sup>th</sup> cycle	X	
Thyroid test	X					X Cycle 3 Day 1 then every 6 weeks		
Urinalysis <sup>k</sup>	X	X		X		X	X	

Events	Screening Period	Treatment Period <sup>a</sup>						Follow-up Period
	Screening	Cycle 1		Cycle 2		Subsequent cycles		
Day	-21 to -1	1 <sup>b</sup>	14	1	14	1	EOT	Disease Progression/ Survival
Serum $\beta$ -hCG (for all FCBP) <sup>l</sup>	X							
Serum or Urine $\beta$ -hCG (for all FCBP) <sup>l</sup>	X (w/in 72 hours)	X		X		X	X	
PK blood draws sampling (See Section <b>Error!</b> <b>Reference source not found.</b> for timepoints)		X		X				
Tumor biopsy for Biomarker Analyses	X (Mandatory – archival or fresh tumor collection)				X (Optional)			
Blood for Biomarker DNA Analyses		X		X				
Blood for Biomarker RNA Analyses		X		X			X	
Serum for Biomarker Analyses		X		X		X <sup>m</sup>	X	
Saliva for Germline DNA Analysis		X						

Events	Screening Period	Treatment Period <sup>a</sup>						Follow-up Period
	Screening	Cycle 1		Cycle 2		Subsequent cycles		
Day	-21 to -1	1 <sup>b</sup>	14	1	14	1	EOT	Disease Progression/ Survival
Tumor evaluation (CT/MRI)	X	RECIST 1.1 algorithm: Every 6 weeks ( $\pm$ 5 days) from randomization for the first 24 weeks then every 9 weeks until disease progression (for exceptions refer to Section <b>Error! Reference source not found.</b> ) or start of a new anticancer treatment, or withdrawal of consent  The irRECIST will be evaluated as exploratory efficacy assessment. For additional details, see Sections <b>Error! Reference source not found.</b> , <b>Error! Reference source not found.</b> and <a href="#">Appendix B</a> , Section <b>Error! Reference source not found.</b>						
Bone Scan		Only if clinically indicated						
CT Scan of the Head or Brain MRI	X	Only if clinically indicated						
Administer CC-486/placebo		Daily on Days 1-14						
Administer pembrolizumab		X <sup>n</sup>		X		On Day 1 only		
IP accountability		X		X		X	X	
Survival follow-up							Every 8 weeks (+/- 5 days)	
Anticancer therapy since IP discontinuation							At every survival follow-up visit	

Abbreviations:  $\beta$ -hCG = beta human chorionic gonadotropin; C1D1 = Cycle 1 Day 1; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EOT = End of Treatment; FCBP = females of child bearing potential; IP = investigational product; irRECIST = immune-related Response Evaluation Criteria in Solid Tumors; IRT = interactive response technology; MRI = magnetic resonance imaging; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors

<sup>a</sup> All visits have a  $\pm$  2-day window, except Cycle 1 Day 1 which must occur within 21 days from Informed Consent Form signature, and survival follow-up which has a  $\pm$ 5-day window.

<sup>b</sup> Cycle 1 Day 1 evaluations can be omitted if Screening evaluations are performed within 72 hours of Cycle 1 Day 1.

<sup>c</sup> Prior cancer therapies include surgery, radiation, systemic or any other therapy (eg, hormonal, locoregional) for the subject's cancer

<sup>d</sup> Prior/concomitant medication evaluation  $\leq$  28 days before screening through 28 days after last dose.

<sup>e</sup> Prior/concomitant procedures evaluation  $\leq$  28 days before screening through 28 days after last dose.

<sup>f</sup> Prior to receiving first dose.

<sup>g</sup> Hematology includes complete blood count (CBC) with differential, including but not limited to red blood cell (RBC) count, hemoglobin, hematocrit, white blood cell (WBC) count with differential (neutrophil count including lymphocyte, monocyte, eosinophil, basophil counts and bands), absolute neutrophil count (ANC), and platelet count. ANC should be measured with automated count where available.

<sup>h</sup> Coagulation tests, including prothrombin time (PT), partial thromboplastin time (PTT), activated partial thromboplastin time (aPTT) and international normalized ration (INR)

<sup>i</sup> Chemistry includes (but is not limited to) sodium, potassium, calcium, phosphorus, chloride, magnesium, bicarbonate, blood urea nitrogen (BUN) or urea, serum creatinine, fasting glucose, uric acid, albumin, total protein, alkaline phosphatase, lactate dehydrogenase, total bilirubin (indirect and direct), aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT)

<sup>j</sup> Lipid Panel parameters include total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides

<sup>k</sup> Urinalysis (a urine dipstick may be used) at screening and D1 of each cycle if abnormal at baseline.

<sup>l</sup> Serum  $\beta$ -hCG (for all FCPB) performed at screening; remaining pregnancy tests may be serum or urine at the Investigator's discretion. Pregnancy testing (for all FCPB) must be done within 72 hours prior to the first administration of IP and prior to dosing on Day 1 of every cycle. If the serum screening pregnancy test is performed  $>$  72 hours before first dose, a serum or urine pregnancy test should be performed (Investigator's discretion). The subject may not receive IP until the Investigator has verified that the result of the pregnancy test is negative.

<sup>m</sup> Day 1 of Cycle 3 and every third cycle thereafter (C6D1, C9D1, C12D1)

<sup>n</sup> On Cycle 1 Day 1, pembrolizumab will be administered after the 6 hour CC-486 PK sample collection. For all subsequent pembrolizumab administration, pembrolizumab will be co-administered with CC-486.

### 17.3. Handling of Dates

Dates will be stored as numeric variables in the SAS analysis files and reported in DDMMYYYY 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 (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.

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

#### 17.3.1. Calculation Using Dates

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

- Study days after the start day of study drug will be calculated as the difference between the date of interest and the first date of dosing of study drug (e.g, CC-486) plus 1 day. The generalized calculation algorithm for relative day is the following:
  - If TARGET DATE  $\geq$  DRUG START DATE then STUDY DAY = (TARGET DATE – DRUG START DATE) + 1;

- Else use  $\text{STUDY DAY} = \text{TARGET DATE} - \text{DRUG START DATE}$ .

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

- Age (expressed in days) is calculated:  $\text{AGE} = \text{CONSENT} - \text{DATE of BIRTH} + 1$ . In practice, age will be transformed to years by dividing the difference by 365.25 days, then truncating.
  - Preference is for using calculated age from clinical database. When not available, calculated age from CRF or IVRS may be used
  - Partial birth date: impute missing day as 15<sup>th</sup> of the month; impute as 01-July for missing month; 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:

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

## 17.4. Date Imputation Guideline

### 17.4.1. Impute Missing Adverse Events/ Prior or Concomitant Medications

#### Incomplete Start 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.
- 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, month, and year*

- No imputation is needed; the corresponding AE will be included as TEAE.

**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 the incomplete stop date is **prior to** the year of the last dosing date or prior to 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.

### **17.4.1. Adverse Events**

Partially missing AE start dates will be imputed in the ADaM 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.

### **17.4.2. 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 ADaM 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.

### **17.4.3. Medical History**

Partially missing medical history start dates will be imputed in the ADaM dataset for medical history (for the purposes of calculating durations of PsA and psoriasis). 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.



**17.4.4. Tumor Response Visit Window**

Relative Day Ranges for the CT-Scans

Study Week	Relative Weeks From Randomization	Relative Days From Randomization
6	6	2 - 63
12	12	64 - 105
18	18	106 - 147
24	24	148 - 203
33	33	204 - 266
42	42	267 - 329
51	51	330 - 392
60	60	393 - 455
69	69	456 - 518
78	78	519 - 581
87	87	582 - 644
96	96	645 - 707
105	105	708 - 770
114	114	770 - 833