Protocol Title: A Phase 2, Multicenter, International, Single Arm Study to Assess The Safety And Efficacy Of Single Agent CC-486 (Oral Azacitidine) In Previously Treated Subjects With Locally Advanced Or Metastatic Nasopharyngeal Carcinoma

NCT Number: NCT02269943

Statistical Analysis Plan Date: 15 May 2017

DISCLOSURE

REDACTED STATISTICAL ANALYSIS PLAN

CC-486-NPC-001

A PHASE 2, MULTICENTER, INTERNATIONAL, SINGLE ARM STUDY TO ASSESS THE SAFETY AND EFFICACY OF SINGLE AGENT CC-486 (ORAL AZACITIDINE) IN PREVIOUSLY TREATED SUBJECTS WITH LOCALLY ADVANCED OR METASTATIC NASOPHARYNGEAL CARCINOMA

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STATISTICAL ANALYSIS PLAN

A Phase 2, Multicenter, International, Single Arm Study to Assess the Safety and Efficacy of Single Agent CC-486 (Oral Azacitidine) in Previously Treated Subjects with Locally Advanced or Metastatic Nasopharyngeal Carcinoma

STUDY DRUG: CC-486 (Oral Azacitidine)

PROTOCOL NUMBER: CC-486-NPC-001

DATE FINAL: 15 May 2017

Prepared by:

On behalf of
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SAP AUTHOR	[redacted] Printed Name and Title — Signature and Date
PROTOCOL TITLE	A Phase 2, Multicenter, International, Single Arm Study to Assess the Safety and Efficacy of Single Agent CC-486 (Oral Azacitidine) in Previously Treated Subjects with Locally Advanced or Metastatic Nasopharyngeal Carcinoma
INVESTIGATIONAL PRODUCT	CC-486 (Oral Azacitidine)
PROTOCOL NUMBER	CC-486-NPC-001
PROTOCOL VERSION, DATE	Amendment 3, 23 September 2016
SIGNATURE STATEMENT	By my signature, I indicate I have reviewed this SAP and find its contents to be acceptable.
Statistical Therapeutic Area Head Signature: *{See appended electronic signature page}* Printed Name: _____ Date: _____	
Lead Clinical Research Physician / Clinical Research Physician Signature: *{See appended electronic signature pag* Printed Name: [redacted] Date: [redacted]	
Lead Product Safety Physician Signature: *{See appended electronic signature page}* Printed Name: _____ Date: _____	

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Lead Product Safety Physician

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Printed Name _____ Date _____

Lead Product Safety Physician

Signature *{See appended electronic signature page}*

Printed Name _____ Date _____

1. LIST OF ABBREVIATIONS

Table 1: Abbreviations and Specialist Terms

AE	adverse event
AUC	area under the curve
BE	Biomarker Evaluable
BLQ	below the limit of quantitation
BSA	body surface area
C1D1	Cycle 1, Day 1
C2D1	Cycle 2, Day 1
CI	confidence interval
Cmax	maximum drug concentration
CpG	C-phosphate-G (cytosine and guanine separated by only one phosphate)
CR	complete response
CRF	case report form
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
EBV	Epstein-Barr virus
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	end of treatment
H-score	measurement of immunoreactivity via IHC
ICF	informed consent form
IP	investigational product
K-M	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities

MRI	magnetic resonance imaging
NCA	noncompartmental
NCI	National Cancer Institute
NPC	nasopharyngeal carcinoma
ORR	overall response rate
OS	overall survival
PD	pharmacodynamic
PET	positron emission tomography
PFS	Progression free survival
PK	pharmacokinetic
PO	oral(ly)
PR	partial response
PT	preferred term
Q1	first quartile
Q3	third quartile
QD	daily
RECIST	Response Evaluation Criteria in Solid Tumors
Rp	BRLF1 promoter
RT-PCR	real time-polymerase chain reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SI	International System of Units
SMQ	Standardized MedDRA Query
SOC	system organ class
STDEV	standard deviation
TEAE	treatment-emergent adverse event
TIL	tumor infiltrating lymphocyte
Tmax	time to Cmax

WHO	World Health Organization
Zp	BZLF1 promoter
Zta	EBV lytic protein

2. INTRODUCTION

This statistical analysis plan (SAP) describes the analyses and data presentations for Celgene's protocol CC-486-NPC-001 "A Phase 2, Multicenter, International, Single Arm Study to Assess the Safety and Efficacy of Single Agent CC-486 (Oral Azacitidine) in Previously Treated Subjects with Locally Advanced or Metastatic Nasopharyngeal Carcinoma", which was finalized on 11 July 2014 and subsequently amended on 1 October 2014 (Amendment 1), 03 April 2015 (Amendment 2), and 23 September 2016 (Amendment 3). It contains definitions of analysis populations, derived variables and statistical methods for the analysis of efficacy and safety.

These analyses include one pre-planned interim analysis, and a final analysis. The purpose of the SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches to any data analysis prior to database lock. This SAP 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.

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective is to evaluate the efficacy of CC-486 in subjects with nasopharyngeal carcinoma (NPC).

3.2. Secondary Objectives

The secondary objectives are to evaluate safety in all subjects and pharmacokinetics (PK) of CC-486 in a subset of subjects of Asian-Pacific Island ethnicity at experienced selected sites.

3.3. Exploratory Objectives

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a Phase 2, single arm, multicenter, international study to assess the safety and efficacy of single agent CC-486 (oral azacitidine) in previously treated subjects with locally advanced or metastatic NPC, who have progressed (clinically or radiographically) after having received 1 or 2 previous regimens, including a platinum-based chemotherapy. The primary endpoints are overall response rate (ORR) and progression-free survival (PFS).

Approximately 51 to 55 efficacy evaluable subjects will be enrolled according to Simon's optimal two-stage design; if the predefined activity is met (> 4 responses [complete response (CR)/partial response (PR)] out of the first 17 efficacy evaluable subjects based on independent radiological assessment), then the study will continue to enroll an additional 34 efficacy evaluable subjects. If ≤ 4 responses out of 17 are observed, then the study enrollment will be stopped. The Stage 1 decision will be based on ORR only, and the Stage 2 decision will be based on both ORR and PFS. Subjects who are not evaluable for efficacy will be replaced at the discretion of the sponsor. Subjects who are discontinued from study prior to the first tumor assessment for any reason other than for progressive disease are not evaluable and will be replaced. Subjects who progress prior to the end of Cycle 1 are not evaluable and will be replaced.

The study will consist of the following visits:

Screening Assessments: Screening evaluations will be performed for all subjects to determine study eligibility. These evaluations must be completed within 21 days of first dosing unless otherwise noted.

Treatment: Subjects meeting eligibility criteria must start treatment within 21 days of signing the informed consent form (ICF). For all subsequent visits, an administrative window of ± 2 days is permitted. Treatment cycles are 21 days in duration. All evaluations should be performed prior to dosing on the visit day, unless otherwise specified. CC-486 will be administered at a dose of 300 mg orally (PO) daily (QD) on Days 1to14 of a 21-day cycle. However, the first 6 subjects of Asian-Pacific Island ethnicity evaluable for safety will receive CC-486 at a dose of 200 mg orally QD on Days 1to14 of 21 days of Cycle 1; and if well-tolerated, and there are no safety concerns, subsequent subjects of Asian-Pacific Island ethnicity will be treated at the 300 mg QD on Days 1to14 of a 21-day cycle.

Response Assessment by Response Evaluation Criteria In Solid Tumors (RECIST) v 1.1: Response assessments (tumor evaluations) should be performed at screening within 28 days before the start of investigational product (IP), and every 6 weeks (± 5 days) from Cycle 1 Day 1 (C1D1) for the first 3 tumor evaluations and then every 9 weeks until disease progression, start of a new anticancer therapy, or withdrawal of consent from the entire study. Evaluation of response will be performed using RECIST v1.1.

An independent radiological assessment of responses will be conducted using RECIST v1.1.

Response assessments include computed tomography (CT) scan or magnetic resonance imaging (MRI) of the head and neck with supraclavicular node imaging, the chest and abdomen/pelvis,

neurological examination with facial nerve evaluation, and bone scans at baseline for all subjects. Bone scans will be repeated only if the subject is symptomatic or with known bone metastasis. The same mode of imaging for lesion evaluation at screening must be used consistently throughout the study.

All subjects with evidence of objective tumor response (CR or PR) should have the response confirmed with repeat assessments at the next scheduled scan, but after no less than 4 weeks. Response assessments must have occurred ≥ 6 weeks from Cycle 1 Day 1 to be considered as SD for a best response.

End of Treatment (EOT) Evaluation: An EOT evaluation should be performed for subjects who are withdrawn from treatment for any reason as soon as possible after the decision to permanently discontinue treatment has been made. Radiologic response assessment will be repeated only if required per the defined study imaging schedule.

Adverse Event (AE) Collection and Follow-up: Any AE that started after signing ICF and up to 28 days after the last dose of IP and those serious AEs (SAEs) made known to the Investigator at any time thereafter that are suspected of being related to IP will be collected.

Follow-up for Efficacy Endpoints: All subjects who discontinue treatment for reasons other than disease progression, start of new anticancer therapy, or withdrawal of consent from the entire study will be followed for tumor response assessments and subsequent anticancer therapies.

Follow-up for Survival: After the EOT visit, all subjects will be followed every 8 weeks (± 5 days) for survival until withdrawal of consent, death, or lost-to-follow up, whichever occurs first. Subsequent anticancer therapies should be collected at the same schedule. New anticancer therapy includes (but is not limited to) any systemic or local medication, surgery, radiation, or any other therapy intended to treat the subject's cancer.

Survival follow-up may be conducted by record review (including public records) and/or telephone contact with the subject, family, or the subject's treating physician.

Pharmacokinetics: A subset of enrolled subjects (Asian-Pacific island ethnicity only) at a selected number of experienced sites that have the ability to collect, process, and ship CC-486 PK samples will participate in PK sample collection. Six subjects of Asian-Pacific island ethnicity initially being administered 200 mg CC-486 on Days 1to14 of a 21-day cycle will be asked to participate in the PK sample collection at these selected sites. An additional 6 subjects of Asian-Pacific ethnicity will participate in the PK sampling if the dose is escalated to 300 mg in this population.

On each PK day (ie, Cycle 1 Days 1 and 14), subjects will ingest IP in the clinic after performing the required overnight fasting, if applicable taking antiemetic premedication (eg, odansetron), and completing the required pre-dose assessments (where applicable), with each dose being given at approximately the same time of day.

Blood samples for oral azacitidine PK assessment will be collected prior to each dose administration (pre-dose) and over the 8-hour period following each dose administration (0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, and 8 hours post-dose or similar schedule).

Biomarkers: Biomarkers will be assessed for Stage 1 subjects only.

4.1.1. Primary Endpoints

The primary endpoints are:

- ORR defined as the combined incidence of CR and PR, confirmed no less than 4 weeks after the criteria for response are first met, based on independent radiology assessment using RECIST v1.1, AND
- PFS measured as time from the start of the study treatment to progression, based on an independent radiology assessment of response using RECIST v1.1 or death (from any cause), whichever is earlier.

4.1.2. Secondary Endpoints

The secondary endpoints include:

- Overall survival (OS) defined as the time from first treatment to death by any cause.
- Disease control rate (DCR) defined as the combined incidence of CR and PR, confirmed no less than 4 weeks after the criteria for response are first met, and stable disease (SD) for ≥ 16 weeks from the date of first treatment, based on independent radiology assessment using RECIST v1.1.
- Safety to include the incidence of treatment-emergent AEs (TEAEs), SAEs, Grade 3-4 AEs, Grade 3 and higher AEs, AEs of special interest, and laboratory abnormalities and other safety parameters.
- PK of CC-486 in a subset of subjects of Asian-Pacific Island ethnicity at experienced selected sites.

4.1.3. Exploratory Endpoints

4.2. Stratification, Randomization and Blinding

Not applicable for this study.

4.3. Sample Size Determination

The sample size estimation is based on having sufficient sample in the Efficacy Evaluable Population (see Section 5.2.3) to show that the ORR is higher than 20% or median PFS is > 5 months. Simon's optimal two-stage design will be used (Simon, 1989). The null hypothesis that the true ORR is ≤ 20% or median PFS is ≤ 5 months will be tested against a one-sided alternative. In the first stage, 17 subjects will be accrued. If there are ≤ 4 responders among these 17 subjects, enrollment will be stopped. Otherwise, if there are > 4 responders, 34 additional

subjects will be accrued for a total of 51 subjects. Subjects who progress by the end of Cycle 1 are not evaluable for efficacy and will be replaced. This Phase 2 study will be considered positive if more than 14 responders are observed in 51 subjects or the hypothesis of median PFS ≤ 5 months (alternatively, the PFS rate at 5 months is ≤ 50%) is rejected. This design yields a marginal one-sided type I error rate of 5% and power of 85% when the true ORR is 40%. After the second stage (n = 51 subjects), the power for showing a median PFS of > 5 months is 80% (60%) when the true median PFS is about 8 (7) months.

5. GENERAL STATISTICAL CONSIDERATIONS

5.1. Reporting Conventions

- All tables will be presented by 'AP 200 mg', '300 mg', and 'Total', unless otherwise specified.
- Data from all study centers will be combined for analysis.
- P-values will be rounded to 4 decimal places. P-values that round to 0.0000 will be presented as '< 0.0001' and p-values that round to 1.000 will be presented as '> 0.9999'.
- Confidence intervals (CIs) will be presented as 2-sided 90% CIs unless specified differently in specific analyses.
- 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), first and third quartiles, minimum and maximum for continuous variables.
- All mean and quartile values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to 2 more decimal places than the measured value.
- All percentages will be rounded to 1 decimal point. The number and percentage of responses will be presented in the form XX (XX.X), where the percentage is in the parentheses.
- All analysis and summary tables will have the analysis population sample size (ie, number of subjects) in the column heading.
- All listings will be sorted for presentation in order of study site, subject identification and date of procedure or event.
- The day of the first dose of study drug will be defined as Day 1.
- 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 the subsequent cycle; The cycle number for each date of interest, eg, AE, will be calculated based on the cycle window set by its start and end dates. If a date is on or after start date of cycle i and before start date of cycle (i+1), the corresponding cycle number will be "i".
- For the last cycle, the last day of the cycle is the treatment discontinuation date on the case report form (CRF) EOT page or the Day 1 of the last cycle + 20, whichever is earlier.
- In by-cycle analyses, assessments taken pre-dose on Day 1 of a given cycle (eg, laboratory measures) will be grouped with the previous cycle.

- Baseline value will be defined as the last non-missing value before the first dose of study drug is administered; for subjects who were not treated, the baseline will be the assessment value taken on the Screening visit.
- Partial dates will be imputed based on the rules specified in Section 18.3.
- All laboratory data will be reported using International System of Units (SI).
- Summaries of the most severe toxicity grade in clinical laboratory in each treatment cycle and most severe grade post-baseline overall and shifts from baseline to most severe toxicity grade post-baseline overall will include all scheduled and unscheduled assessments. A similar approach will be used for summaries of Eastern Cooperative Oncology Group (ECOG) performance status.
- For safety parameters, the Final Evaluation will be defined as the last on-treatment value, which is the last non-missing assessment on or prior to the last dose date + 28 days or the treatment discontinuation date, whichever is later.
- SAS® Version 9.2 (or higher) will be the statistical software package used to produce all data summaries, listings, graphs, and statistical analyses.

5.2. Analysis Populations

5.2.1. Enrolled Population

The Enrolled Population includes all subjects who were enrolled to the study.

5.2.2. Safety Population

The Safety Population includes all subjects who received at least 1 dose of IP.

5.2.3. Efficacy Evaluable Population

The Efficacy Evaluable Population includes all subjects who meet all eligibility criteria, and EITHER

1. Received at least 2 cycles of IP at any dose intensity and discontinued treatment for progressive disease, OR
2. Received at least 4 cycles of IP at any dose intensity and have baseline and at least two post-screening tumor assessments.

Subjects receiving the 200 mg dose will be efficacy evaluable for response if they meet the defined criteria. Subjects not eligible for the Efficacy Evaluable Population will be replaced at the discretion of the sponsor.

5.2.4. Pharmacokinetic Population

The PK Population includes a subset of enrolled subjects of Asian-Pacific Island ethnicity at experienced selected sites who have evaluable pharmacokinetic data from at least 1 dose of IP.

6. SUBJECT DISPOSITION

Analysis population allocation will be summarized. The number and percentage of subjects who are treated and discontinued the treatment and the number and percentage of subjects who discontinued the study will be presented for the enrolled population. Each reason for treatment discontinuation and each reason for study discontinuation collected on the CRF will be summarized in the subject disposition table.

The number and percentage of subjects who died, and the number of subjects who are in survival follow-up or lost to survival follow-up at the time of analysis will also be presented in the subject disposition table.

The number and percentage of subjects eligible or not eligible for the study, enrolled under each protocol amendment, and treated by site will be summarized.

Listings will be provided for screen failures with reason for screen failure, discontinued subjects with reason for treatment discontinuation or reason for study discontinuation included.

7. PROTOCOL DEVIATIONS/VIOLATIONS

Protocol deviations and violations will be identified and assessed periodically by the clinical research physician or designee following institution standard operational procedures. Prior to database lock, a final review and categorization of protocol violations or deviations will be performed by the study team. The protocol violations will be summarized using frequency tabulations for the enrolled population.

A listing of subjects with protocol deviations or violations will also be provided.

8. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographics and baseline characteristics will be summarized for the Enrolled Population, unless otherwise specified. Individual subject listings will be provided to support the summary tables.

8.1. Demographics and Baseline Characteristics

Age (years), height (cm), weight (kg), body surface area (BSA) (m^2), and vital signs at baseline will be summarized by sample size, mean, median, STDEV, minimum, and maximum values. Age category (< 65 years, ≥ 65 years and < 75 years, and ≥ 75 years), sex, race, ethnicity, ECOG performance status at baseline, and electrocardiogram (ECG) overall interpretation at baseline will be summarized by number and percentage of subjects in each category. Descriptive summary statistics for EBV-DNA (by real time-polymerase chain reaction [RT-PCR])) at baseline will be provided.

Age will be calculated as follows: Age = Maximum Integer ≤ ([Date of Informed Consent – Date of Birth +1] / 365.25).

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

8.1.1. Cancer History

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

- Cancer diagnosis
- Current cancer type (locally advanced, metastatic)
- Stage at initial diagnosis (0, I, II, III, IVA, IVB, IVC)
- TNM Classification at initial diagnosis: T category (TX, T0, Tis, T1, T2, T3, T4), N category (NX, N0, N1, N2, N3, N3a, N3b), M category (M0, M1)
- Best response to prior therapy (CR, PR, SD, progressive disease, unknown, not applicable)

Time from initial diagnosis to first dose and time from most recent recurrence/ progression to first dose will be summarized descriptively.

8.2. Medical History

A summary of relevant medical history will be presented by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) for the safety population.

8.3. Prior Therapies/Surgeries

Any prior therapy will be collected at screening. Prior systemic anticancer therapies or other anticancer therapies will be coded to therapeutic drug classes and generic drug names using the

World Health Organization (WHO) drug dictionary. Prior cancer surgeries will be coded by MedDRA.

The number and percentage of subjects who had any prior radiation therapies, prior cancer surgeries, and prior systemic or other anticancer therapies will be presented for the safety population. Descriptive statistics (eg, the time from end of prior therapy/surgery to first dose date in months) may also be provided, if needed. The therapies/surgeries with the same sequence/regimen number will be counted as one prior therapy/surgery. For subjects who had prior systemic anticancer therapies or other anticancer therapies, the incidence by coded therapeutic drug class and generic drug name will be provided in the summary table. The summary table of incidence of prior cancer surgeries will also be provided.

8.4. Prior and Concomitant Medications

Medications reported on the Prior and Concomitant Medications CRF page will be coded to therapeutic drug classes and generic drug names using the WHO drug dictionary and will be summarized for the safety population. The Anatomical Therapeutic Chemical coding scheme of the WHO drug dictionary will be used to group medications into relevant categories for these tabulations. Individual listing of prior and concomitant medications will be provided to support the tables.

8.4.1. Prior Medications

A prior medication will be any medication started prior to the date of the first dose of study drug. A summary will be presented showing the number and percentage of subjects who took prior medications by therapeutic drug class and generic drug name, as well as the number and percentage of subjects that took any prior medication.

8.4.2. Concomitant Medications

Concomitant medication is defined as a medication that was either 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 of the last dose of study drug.

A summary will be presented showing the number and percentage of subjects who took concomitant medications by WHO therapeutic drug class and generic drug name, as well as the number and percentage of subjects who took any concomitant medications.

8.5. Concomitant Procedures/Surgeries

A concomitant procedure/surgery is defined in a manner similar to the concomitant medication above. A summary will be presented showing the number and percentage of subjects who had concomitant procedures/surgeries by SOC and PT.

9. STUDY TREATMENTS AND EXTENT OF EXPOSURE

Study treatment and extent of exposure summaries will be provided based on the safety population. Treatment duration, dose exposure, number of cycles, number of doses, cumulative dose, dose intensity, average daily dose, relative dose intensity, dose reduction, and dose interruption, number of subjects dosed at each cycle and maximum number of cycles received per subject will be summarized. Individual subject listings of exposure to study drug will be provided. Column headers will be displayed as follows: 'AP 200 mg', '300 mg', and 'Total'.

9.1. Treatment Duration

The treatment start date is the date of the first dose of study drug and the treatment end date is the date of the last non-missing dose of study drug.

Treatment duration (in days) is calculated as (the treatment end date – the treatment start date + 1). Summary statistics for treatment duration (in days) will be provided. Descriptive statistics will be provided for the total number of treatment cycles subjects received and for the number of doses received.

9.2. Dose Exposure

Dose exposure (days) for overall is defined as the total number of actual days on CC-486 (dose > 0 mg) during treatment phase.

9.3. Cumulative Dose

Cumulative dose is defined as the sum of all administered doses in mg during the treatment period across all cycles.

9.4. Dose Intensity

Dose intensity reported in mg/day will be calculated as the cumulative dose divided by the treatment duration in days which is defined in Section 9.1 above.

9.5. Average Daily Dose

Average daily dose (mg/day) is defined as the cumulative dose of study drug divided by the dose exposure.

9.6. Relative Dose Intensity

Relative dose intensity will be calculated as the dose intensity divided by the protocol daily dose x 100. The protocol daily dose is defined as 300*14/21 mg/day for subjects who received CC-486 at a starting dose of 300 mg daily. For the first 6 Asian-Pacific Island ethnicity subjects evaluable for safety who received CC-486 at a starting dose of 200 mg, the protocol daily dose is defined as 200*14/21 mg/day.

Descriptive statistics for the cumulative dose (mg), dose intensity (mg/day), relative dose intensity, as well as a frequency summary of subjects within each relative dose intensity categories (≥ 90%, < 90% to 80%, < 80% to 70%, and < 70%) will be provided.

9.7. Dose Reduction, Interruption and Overdose

Dose reduction is defined as a non-zero dose administered after the Cycle 1 Day 1 (C1D1) dose which is at a lower dose level than the dose the subject received at the previous dosing day.

Dose interruption occurs if the record of actual administered dose is zero except as required by the protocol. Consecutive zeros are counted as one interruption.

Overdose, as defined for this protocol, refers to the treatment CC-486 only. On a per dose basis, an overdose is defined as any amount over the protocol-specified dose of CC-486 assigned to a given subject, regardless of any associated AEs or sequelae.

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

Dose reduction, interruption and overdose will be summarized as follows:

- Number and percentage of subjects with at least one dose reduction, reasons for each reduction, and frequency of reductions
- Summary statistics (sample size, mean, median, STDEV, first and third quartiles, minimum, and maximum) for time to first reduction
- Number and percentage of subjects with at least 1 dose interruption, reasons for each interruption and frequency of interruption
- Number and percentage of subjects who had > 5 days of dose interruption due to AE, and had ≥ 14 days of dose interruption due to AE
- Summary statistics (sample size, mean, median, STDEV, first and third quartiles, minimum, and maximum) for time to first interruption and total days of interruption

10. EFFICACY ANALYSIS

All efficacy results will be summarized for the efficacy evaluable population. If Stage 2 is conducted, analyses will be performed for PFS and OS in addition to ORR. Column headers will be displayed as follows: 'AP 200 mg', '300 mg', and 'Total'.

10.1. Multiplicity

There is no multiplicity adjustment for the efficacy endpoints.

10.2. Analysis of the Efficacy Endpoints

The primary efficacy endpoints are ORR and PFS.

Overall response rate is defined as the combined incidence of CR and PR, confirmed no less than 4 weeks after the criteria for response are first met, based on independent radiology assessment using RECIST version 1.1. After the enrollment of 51 patients, if more than 14 responders are observed, the null hypothesis (ORR ≤ 20%) will be rejected, the true ORR will be concluded to be > 20%, The point estimate and two-sided 90% CI of ORR will be provided using the Clopper-Pearson method (Clopper, 1934).

Progression-free survival will be based on independent radiology assessed response using RECIST v1.1. Progression-free survival is defined as the time from the date of start of the study treatment to the date of disease progression or death (any cause) on or prior to the data cut-off date for the statistical analysis, whichever occurs earlier. Subjects who do not have disease progression or have not died as of the data cut-off date will be censored at the time of the last radiologic assessment prior to the data cut-off date. In the event that a new anticancer therapy is initiated for a subject prior to documented progression, 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 initiation of the new anticancer 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). Subjects with ≥2 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 ≥2 consecutive missing visits.

The Kaplan-Meier (K-M) method will be used to estimate PFS distribution, and the medians with two-sided 90% CIs will be reported. Since the study did not enter the second stage, no hypothesis testing will be conducted for PFS. The K-M estimates of PFS rates at each 2-month interval will be provided. Kaplan-Meier curves for PFS will be presented.

Disease control rate, a secondary efficacy endpoint, is defined as CR and PR, confirmed ≥ 4 weeks after the criteria for response are first met, and SD ≥16 weeks from the first treatment, based on independent radiology assessment using RECIST v1.1. The point estimate and two-sided 90% CI of DCR will be provided using the Clopper-Pearson method (Clopper, 1934).

Overall survival, another secondary efficacy endpoint, is defined as the time from first treatment to death of any cause. Subjects who did not die by the end of study or the clinical data cut-off date will be censored on the last-known-to-be-alive date or the clinical cut-off date, whichever is earlier.

The survival distribution of OS will be estimated using K-M method. The median including two-sided 90% CI will be provided. The survival rates will be provided at each 2-month interval. Kaplan-Meier curves for OS will also be presented.

10.3. Analyses of Other Evidence of Anti-cancer Activities

The number and percentage of subjects who received any anticancer therapy post-treatment will be summarized overall and by therapy categories. The time from study treatment discontinuation to the earliest date of anticancer therapy initiation will be summarized descriptively. Listings will be provided for each posttreatment anticancer therapy category.

10.4. Eastern Cooperative Oncology Group Performance Status

A by-subject ECOG listing will be provided.

11. SAFETY ANALYSIS

All safety analyses will be conducted based on the safety population. Descriptive statistics will be provided by treatment dose and for total safety population.

11.1. Adverse Events

Adverse events will be analyzed in terms of TEAEs which are defined as any AE that begins or worsens on or after the start of study drug through 28 days after the last dose of study drug. All AEs will be coded using MedDRA version 19 or higher.

A treatment-related TEAE is defined as a TEAE which was reported as "Suspected" on the CRF. Adverse events with a missing relationship will be treated as "treatment-related."

The incidence of TEAE will be summarized by MedDRA SOC and PT. Severity of AEs will be graded 1 to 5 according to the CTCAE Version 4.0 or higher. For all other AEs not described in the CTCAE, severity will be assessed by the investigator as mild (Grade 1), moderate (Grade 2), severe (Grade 3), life-threatening (Grade 4) or death (Grade 5).

Tables summarizing the number and percentage of subjects experiencing TEAEs by treatment dose and for total safety population will be generated for each of the following:

- All TEAEs by SOC and PT
- All TEAEs by SOC
- All TEAEs by PT
- All TEAEs by Preferred term with Incidence of >5%
- All TEAEs by onset cycle
- Treatment-related TEAEs
- TEAEs of Grade 3 or 4
- Treatment-related TEAEs Grade 3 or 4
- All TEAEs by maximum CTCAE grade
- Treatment-related TEAEs by maximum CTCAE grade
- Serious TEAEs
- All serious TEAEs by Preferred term with Incidence of >5%Treatment-related serious TEAEs
- All treatment-related serious TEAEs by Preferred term with Incidence of >5%
- TEAEs with action of study drug withdrawn
- Treatment-related TEAEs with action of study drug withdrawn
- TEAEs with action of study drug dose reduced

- Treatment-related TEAEs with action of study drug dose reduced
- TEAEs with action of study drug dose interrupted
- Treatment-related TEAEs with action of study drug dose interrupted
- TEAEs with outcome of death
- Treatment-related TEAEs with outcome of death
- All deaths within 28 days of last dose with cause of death
- TEAEs for the following baseline subgroups (provided the number of subjects is sufficient):
  - Age (< 65 years, 65 years to < 75 years, ≥ 75 years)
  - Sex

For summaries by severity, if a subject experiences the same AE more than once with different toxicity grades, the event with the maximum grade will be tabulated in "by maximum grade" tables. If a subject experiences multiple occurrences of AEs under the same SOC and/or PT, the subject will be counted only once for that SOC and/or PT. In addition, AEs with a missing intensity will be presented in the summary table with an intensity category of "Missing."

Listings will be prepared that include the verbatim term, PT, and SOC as well as full details of all AEs for subjects in the safety population.

Separate listings will also be prepared for serious TEAEs, TEAEs leading to death, and TEAEs resulting in discontinuation of IP. All deaths will be listed with the cause of death collected on the Death CRF page.

11.2. Adverse Events of Special Interest

11.2.1. AE of Special Interest

The selected AEs of special interest refers to a group of terms/PTs from one or more SOCs relating to a defined medical condition or area of interest. The following AEs of Special Interest are based on risk definitions (search criteria) as outlined in the Vidaza RMP currently approved at the time of data cut-off date:

- Myelosuppression (neutropenia, thrombocytopenia, anemia, general myelosuppression)
- Haemorrhagic events
- Infections
- Renal failure
- Hepatic failure
- Ischemic colitis
- Interstitial lung disease

- Tumor lysis syndrome
- Cardiac disorders (cardiac failure, cardiac arrhythmias and myocardial infarction)
- Anxiety, confusion, insomnia
- Other psychiatric disorders

After review of the data, there may be other AEs of special interest identified. The following summaries will be provided for TEAEs included in the above-mentioned AEs of special interest:

- All TEAEs
- TEAEs of Grade 3 or 4
- Serious TEAEs
- TEAEs leading to study drug withdrawal
- TEAEs leading to study drug dose reduction
- TEAEs leading to study drug dose interruption
- TEAEs leading to death

Additional safety analyses may be performed by specific parameters (eg, time to occurrence), if warranted.

11.2.2. Dose Limiting Toxicity

Dose limiting toxicity (DLT) is defined in the protocol and will be evaluated only for the first 6 subjects of Asian-Pacific Island ethnicity evaluable for safety (receiving 200 mg QD of CC-486). A summary table of DLTs will be presented including number and percentage of subjects having DLT.

A flag for DLTs may be added to selected listings of AEs as appropriate.

11.3. Clinical Laboratory Evaluations

Clinical laboratory values will be graded according to CTCAE version 4.0 for applicable tests. Normal ranges will be used to determine the categories high, low, and normal for laboratory tests. Listings will be provided for all clinical lab evaluations with normal ranges included.

11.3.1. Hematology, Chemistry, Urinalysis, and Coagulation

The laboratory values will be graded using CTCAE v4.0 for applicable tests as follows:

- Hematology: red blood cell count, hemoglobin, hematocrit, white blood cell count, absolute neutrophil count, absolute lymphocytes, absolute monocytes, absolute eosinophils, absolute basophils, and platelets.
- Chemistry: sodium, potassium, calcium, magnesium, phosphorus, blood urea nitrogen, creatinine, uric acid, glucose, lactate dehydrogenase, total protein, albumin, alkaline phosphatase, bilirubin (total and direct), aspartate aminotransferase/serum glutamic oxaloacetic transaminase, alanine aminotransferase.

For laboratory values that fall outside the grade criteria of CTCAE v4.0 for laboratory tests listed above, a Grade of 0 will be assigned.

For hematology and chemistry, the number and percentage of subjects that have each CTCAE grade will be summarized using the most severe grade overall during the treatment for each of the applicable tests. A shift table representing the shift from the baseline grade to the most severe grade during treatment will be provided for all applicable laboratory tests listed above. For coagulation, a listing will be provided. The onset day of nadir across all cycles, the analyte value at nadir, and the change from baseline to analyte value at nadir will be summarized descriptively.

11.3.2. Epstein-Barr Virus-DNA measurements

Epstein-Barr Virus DNA (by RT-PCR) in serum will be measured at baseline and on Day 1 of all cycles. Results and change from baseline will be summarized by cycle for the safety population using descriptive statistics (sample size, mean, median, STDEV, minimum, and maximum values). A by-subject listing will be provided.

11.4. Vital Sign Measurements

For vital signs, a shift table from baseline to worst post-baseline will be displayed for temperature, systolic and diastolic blood pressure and pulse by normal range categories (low/normal/high). Normal ranges given in Table 2 will be used to determine the categories low, normal and high. A by-subject listing will be provided.

Table 2: Normal Ranges of Vital Sign Measurements

Test	Normal Range (Unit)
Diastolic Blood Pressure	60, 90 (mmHg)
Systolic Blood Pressure	100, 140 (mmHg)
Pulse	60, 100 (beats per minute)
Temperature	[35, 38] (°C)

11.5. Physical Examination

Any findings from physical examination before the start of study drug will be documented as medical history on the medical history CRF page and any findings after the start of study drug will be documented as AEs on CRF. Therefore, there will be no separate analysis for physical examination.

11.6. Electrocardiograms

The 12-lead ECG overall investigator interpretation will be documented at screening and EOT visits.

The shift of overall interpretation ('normal', 'abnormal, not clinically significant' and 'abnormal, clinically significant') from baseline to the final evaluation on treatment will be displayed in cross–tabulations.

A by-subject listing of ECG data will be provided.

12. PHARMACOKINETICS ANALYSIS

12.1. Plasma concentrations

A by-subject listing of PK blood sample collection times, derived sampling time deviations, and azacitidine concentrations will be provided. Azacitidine plasma concentrations will be summarized using descriptive statistics (number of subjects, arithmetic mean, STDEV, minimum, median, maximum, percent coefficient of variation, geometric mean, and geometric percent coefficient of variation) for each dose level/cycle/day, 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 ± 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 dose level/cycle/day will be graphically presented on linear and semi-logarithmic scales.

12.2. Pharmacokinetic Parameters

Following single dose administration, predose samples that are BLQ or missing will be assigned a numerical value of zero for the calculation of PK parameters. Any anomalous concentration values observed at predose will be identified in the clinical study report. Pharmacokinetic parameters will be computed if the anomalous value is ≤ 5% of the maximum drug plasma concentration (C_{max}). If the anomalous value is > 5% of C_{max}, the computed PK parameters for the given subject will be excluded from the PK descriptive statistics.

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 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 PK parameters. Below the limit of quantitation 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 PK 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 PK program used to do the analysis (such as WinNonlin®) will treat trailing zero values as missing when calculating PK parameters.

Actual sampling times will be used in the calculations of pharmacokinetic parameters, which will be derived using noncompartmental methods with Phoenix™ WinNonlin® Professional Version 6.3, or higher, . Graphics may be prepared with SAS Version 9.2, or higher; or Excel 2007, or higher; Phoenix™ WinNonlin® Professional 6.3, or higher; or S-Plus 8.2., or higher

The following PK parameters will be calculated for azacitidine:

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from Time 0 extrapolated to infinity, calculated as $[AUC_t + Ct/\lambda_z]$. C_t is the last quantifiable concentration. No AUC extrapolation will be performed with unreliable λ_z. If AUC %Extrap is $\geq$ 25%, AUC_{inf} will not be reported
AUC_{0-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 vs. 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 λ_z can be obtained.
CL/F	Apparent total clearance, calculated as $[dose/AUC_{inf}]$.
Vz/F	Apparent volume of distribution, calculated as $[(CL/F)/\lambda_z]$.

The following PK parameters for azacitidine will be calculated for diagnostic purposes and listed, but they will not be summarized:

λz	Apparent terminal rate constant, calculated by linear regression of the terminal portion of the log-concentration versus time curve in plasma. Visual assessment will be used to identify the terminal linear phase of the concentration versus time profile. A minimum of 3 data points will be used for calculation. λz will not be estimated if the terminal phase of the log-concentration versus time profile does not exhibit a linear decline phase, or if the regression coefficient < 0.8.
λ_z lower	Lower limit of time (hours) included in the calculation of λ_z.
λ_z N	Number of data points used in the calculation of λ_z.
λ_z upper	Upper limit of time (hours) included in the calculation of λ_z.
Rsq	Regression coefficient for calculation of λ_z.
%AUC Extrap	Percentage of AUC_∞ due to extrapolation from the last quantifiable time point to infinity.

12.3. Pharmacokinetic Analyses

A by-subject listing of PK parameters will be provided. The PK parameters will also be summarized using descriptive statistics (number of subjects, arithmetic mean, STDEV, minimum, median, maximum, percent coefficient of variation, geometric mean, and geometric percent coefficient of variation) for each dose level/cycle/day. Also, when appropriate, graphical representations (egscatter plots, box plots) may be used to visualized the results.

13. BIOMARKER AND CORRELATION ANALYSES

No biomarker and correlation analysis will be done due to limited tumor biopsy data collected.

14. QUALITY OF LIFE ANALYSIS

Not applicable for this study.

15. INTERIM ANALYSIS

One interim analysis will be performed for Stage 1 according to Simon's optimal two-stage design based on efficacy evaluable population.

The ORR will be monitored by Celgene study team according to Simon's optimal two-stage design based on the efficacy evaluable population. The interim analysis will be performed using the data collected by the cutoff date for the interim analysis. The cutoff date is defined as the date when there are more than 4 responders observed in Stage 1 of Simon's two-stage design. If at Stage 1 the predefined activity is met (> 4 responses [CR or PR] out of the first 17 efficacy evaluable subjects based on independent radiological assessment), then the study will continue to enroll an additional 34 subjects. If ≤ 4 responses out of 17 are observed, then the study enrollment will be stopped. All subjects enrolled prior to the cutoff date will be included in the interim analysis and all data up to the cutoff date will be summarized or listed.

The following summary tables and listings will be provided for the Stage 1 interim analysis:

- Analysis populations
- Demographic and baseline characteristics for the enrolled population
- Cancer history for the enrolled population
- ORR based on independent radiology assessment for the efficacy evaluable population
- ORR based on investigator assessment for the efficacy evaluable population
- Treatment exposure and dose modification for the safety population
- Incidence of TEAEs by MedDRA SOC and PT for the safety population
- Incidence of TEAEs leading to dose discontinuation for the safety population
- Incidence of TEAEs with outcome of death for the safety population
- Incidence of Grade 3 or 4 TEAEs by MedDRA SOC and PT for the safety population
- Incidence of serious TEAEs by MedDRA SOC and PT for the safety population
- Incidence of TEAEs of Special Interest by MedDRA SOC and PT for the safety population

- Listing of subject eligibility
- Listing of demographics and baseline characteristics
- Listing of cancer history
- Listing of dosing
- Listing of tumor assessment
- Listing of tumor response
- Listing of adverse events
- Listing of deaths
- PK and biomarker analysis provided there are sufficient data

The above related data for the Stage 1 interim analysis will be cleaned and the detailed data cleaning plan will be documented in the data management plan.

16. CHANGES TO THE STATISTICAL ANALYSES SECTION OF THE PROTOCOL

'Enrolled Population' is defined in SAP.

17. REFERENCES

Eisenhauer EA, Therasse P, Boqaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009; 45:228-47.

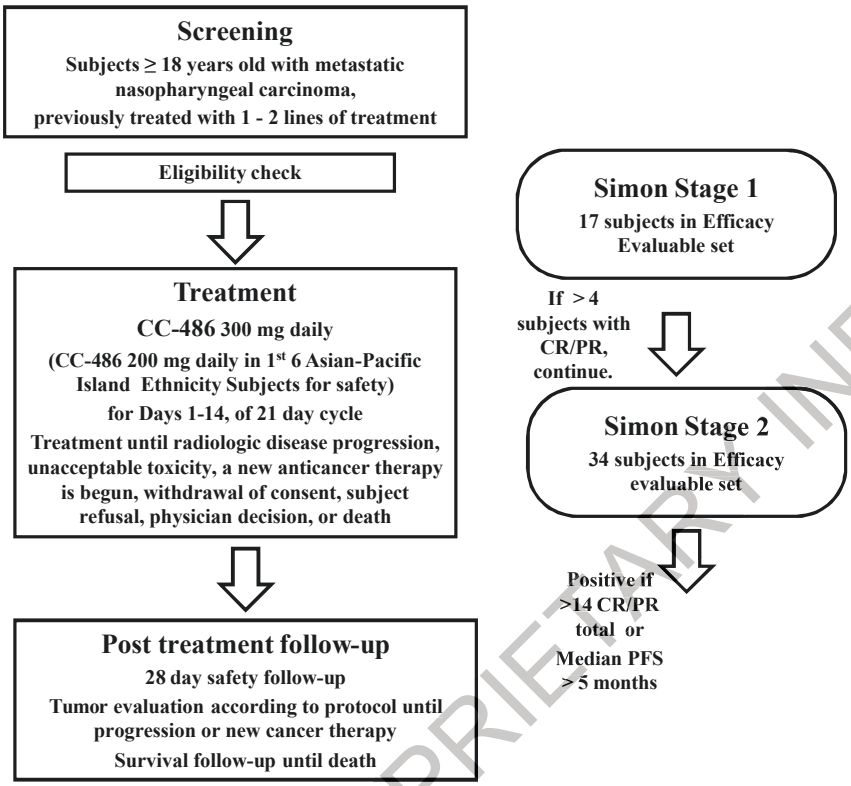
Du Bois D, Du Bois E. A formula to estimate the approximate surface area if height and weight be known. Arch Int Med. 1917, 17(6), 863-71.

Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials. 1989;10:1-10.

Clopper C, Pearson E S. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934;26:404–413.

18. APPENDICES

18.1. Study schematic



18.2. Handling of Dates

Dates will be stored as numeric variables in the SAS analysis files and reported in DDMMMYYYY format (eg, 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 (ND) in the database. Procedure dates will not be imputed.
- **Log Dates** are dates recorded in the CRF data logs. Specifically, they are the start and end dates for AEs 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

17.2 (eg, for duration or cycle assignment). 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 and disease progression. In most cases they are derived either from a milestone (e.g., the survival date is derived from the death date), or a procedure date (e.g., the disease progression date is derived from the date of the tumor scan that was used to determine disease 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.

18.3. Date Imputation Guideline

18.3.1. Impute Missing Adverse Events/ Prior or Concomitant Medications/Procedures

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.

18.3.2. Impute Missing Prior Therapy Dates or Cancer Diagnosis Date

When necessary for analysis purposes, the diagnosis dates or prior therapy dates without a specific day of the month given (ie, JAN2008) will be assigned the 15th day of the month and dates without a specific day or month (ie, 2008) will be assigned the 30th day of June to complete the date. If the above imputation inappropriately results in a diagnosis date or prior therapy date on or after the first dose date, then the incomplete date will be assigned to the day prior to first dose date.

18.3.3. 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.

18.3.4. 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.

18.3.5. Medical History

Partially missing medical history start dates will be imputed in the derived dataset for medical history. The 15th of the month will be used to impute a partially missing start date that has only the day missing, and June 30th will be used to impute a partially missing start date that has both the month and day missing.

18.3.6. Birth Date

Partially missing birth date will be imputed in the derived dataset. Missing day will be imputed by 15th of the month, missing month will be imputed by July and missing year will result in missing age.