STATISTICAL ANALYSIS PLAN

Phase 1 Study of SGI-110 in Patients with Acute Myeloid Leukemia

NCT Number: NCT02293993
PRT NO.: 343-14-001
Version Date: 15 February 2018 (Version 3.0)

Phase 1 Study of SGI-110 in Patients with Acute Myeloid Leukemia

Statistical Analysis Plan

Protocol No.: 343-14-001

Confidential

Otsuka Pharmaceutical Co., Ltd.

Version 3.0: 2018/02/15

Table of Contents

List of Abbreviations and Definition of Terms

List of Abbreviations

Abbreviation	Expansion
AE	Adverse event
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
AMLSG	Acute myeloid leukemia study group
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
Cr	Creatinine
CR	Complete remission
CRi	Complete remission with incomplete blood count recovery
CRp	Complete remission with incomplete platelet recovery
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram, electrocardiography
ECOG	Eastern Cooperative Oncology Group
IMP	Investigational medicinal product
LINE-1	Long interspersed nucleotide element-1
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NE	Not evaluable
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PR	Partial response
PS	Performance status
PT	Preferred term
QTcF interval	QT interval as corrected by Fridericia's formula
RBC	Red blood cell
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
TEAE	Treatment-emergent adverse event
WHO-DD	World Health Organization Drug Dictionary

1 Introduction

This statistical analysis plan (SAP) describes the methods of summary/analysis or assessment of the data collected in this trial. This SAP was prepared based on protocol version 8 (Protocol No.: 343-14-001) prepared on 13 Oct 2017.

The analysis methods for the pharmacokinetic (PK) evaluation are not described in this SAP, as a PK analysis plan will be prepared as a separate document. By-subject listings are not included in this SAP unless stated otherwise.

2 Trial Objectives

Primary objective:

To evaluate the tolerability of SGI-110 when administered subcutaneously to Japanese patients with acute myeloid leukemia (AML)

Secondary objectives:

- To perform PK evaluation of plasma SGI-110 and decitabine
- To evaluate efficacy (complete remission rate, composite complete remission rate, overall remission rate, overall survival, composite complete remission duration)
- To evaluate safety through observed adverse events (AEs) and examinations

Exploratory objective:

To perform pharmacodynamics (PD) evaluation of the extent of deoxyribonucleic acid (DNA) hypomethylation

3 Trial Design

This is a phase 1, multicenter, open-label study to evaluate the tolerability of SGI-110 in Japanese patients with relapsed or refractory AML after undergoing standard therapy or Japanese patients with AML aged 65 years or older who are not eligible for standard chemotherapy.

This trial consists of a screening period, dose limiting toxicity (DLT) evaluation period, and withdrawal examination. Subjects who complete investigational medicinal product (IMP) administration and all observations during the DLT evaluation period, and who do not have any apparent progression of AML, will be permitted to continue treatment with IMP following the DLT evaluation period if they wish. The primary evaluation data for Cohorts 1, 2, and 4 will have a cut-off date of 31 May 2016 and the primary evaluation data for Cohort 3 will have a cut-off date of 30 Nov 2017. The period up until the data cut-off will be defined as the primary evaluation part. This will be followed by an extended treatment part to assess long-term safety, which will include those subjects on IMP treatment who have consented to participate in the extended treatment part. Transition from the primary evaluation part to the extended treatment part will take place at the start of the next course after the data cut-off.

Administration of the IMP will be started in Cohort 1 (36 mg/m^2 in 5-day regimen) and 3 subjects will receive the IMP in this cohort. If none of the 3 subjects has a DLT during the DLT evaluation period, the study will proceed to the next cohort. If one of the 3 subjects experiences a DLT, 3 additional subjects will be enrolled and DLTs will be evaluated in a total of 6 subjects. The study will proceed to the next cohort only if no more than one of the 6 subjects has a DLT. If the number of subjects exhibiting a DLT within a cohort is $\geq 2/3$ or $\geq 2/6$, there will be no dose escalation.

In Cohort 2 (60 mg/m^2 in 5-day regimen) and Cohort 4 (90 mg/m^2 in 5-day regimen), DLTs will be assessed in the same manner. However, even if none of the first 3 subjects enrolled has a DLT, a total of 6 subjects will be enrolled in each of Cohorts 2 and 3 of which the dose has been determined as the recommended dose for a next phase study.

Based on the occurrence of DLTs, the tolerability at the recommended dose for a next phase study will be confirmed in Japanese subjects as well.

The sponsor will review safety data obtained from the previous cohort(s) and judge the transition to the next cohort, including selection of a cohort to proceed to, based on the advice of the Independent Data Monitoring Committee.

If the number of subjects exhibiting DLT within a cohort is ≥ 2/3 or ≥ 2/6, then there will be no transition to the next cohort, and the maximum tolerated dose (MTD) will be determined as follows:

≥ 2/3 or ≥ 2/6 subjects with DLT	MTD
In Cohort 1	< 36 mg/m^2 in 5-day regimen
In Cohort 2	36 mg/m^2 in 5-day regimen
In Cohort 4	60 mg/m^2 in 5-day regimen

If the incidence of DLT does not reach either ≥ 2/3 or ≥ 2/6 in any of the cohorts in the table above, the MTD will not be determined in this study. For Cohort 3 (60 mg/m^2 in 10-day regimen), DLT will be evaluated but the MTD of 10-day regimen will not be determined from the incidence of DLT.

The DLT evaluation period will be from the start of administration in Course 1 to the examination scheduled for Day 29 of Course 1. However, for subjects who have postponed the start of IMP administration scheduled for Day 1 of Course 2 (extended treatment period), the DLT evaluation period will last until the start of IMP administration in Course 2.

Subjects will be hospitalized for treatment during Course 1. Subjects will be required to remain hospitalized until the examination scheduled for Day 29 of Course 1 if they complete the trial in Course 1 (until the withdrawal examination if they are withdrawn during Course 1) and until the start of IMP administration in Course 2 if they proceed to the extended treatment period of Course 2 and the subsequent courses.

Dose-limiting toxicity shall be defined as any of the following AEs occurring during Course 1 for which there is a reasonable probability or possibility of a causal relationship with the IMP (being related to the IMP) if it cannot be reasonably explained by underlying disease, intercurrent illness, or concomitant medications. The severity of AEs will be graded in accordance with Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

- Non-hematologic toxicity of Grade 3 or higher, except for the following:
  - Nausea, vomiting, or diarrhea of Grade 3 that is controllable by optimal therapy
  - Grade 3 laboratory findings other than serum creatinine (Cr), bilirubin, aspartate aminotransferase (AST), or alanine aminotransferase (ALT), that are not associated with clinical manifestations
- Grade 4 thrombocytopenia that was not present at study entry and that is not resolved within 7 days

- Grade 4 neutropenia that was not present at study entry and that is not resolved within 7 days
- Febrile neutropenia*
  If the febrile neutropenia is not resolved or improved during the DLT evaluation period, it shall be defined as DLT. If the febrile neutropenia is resolved or improved during the DLT evaluation period, it shall be judged whether it is defined as DLT based on the background of the subject and through consultation with the Independent Data Monitoring Committee.
- Any AE that results in a delay of > 4 weeks in starting the next treatment course

*In this trial, febrile neutropenia is defined as a neutrophil count of < 500/μL accompanied by a fever of ≥ 38°C

The DLT evaluation period will be for the duration of Course 1. Subjects who complete IMP administration and all observations during the DLT evaluation period, and who do not have any apparent progression of AML, will be permitted to continue treatment with IMP following the DLT evaluation period if they wish.

4 Implementation of Planned Analyses

One interim analysis for cohort 1, 2 and 4 of this study will be take place that the data will be locked on 25Aug2017. And one final analysis for cohort 1, 2, 3 and 4 of this study will take place for final locked.

SAP will be fixed before lock of database.

After confirmation of which subjects are to be included in the statistical analyses and how to handle the data in the statistical analyses and discussion of how to deal with problems unexpected at the time of planning, final analysis will be done based on the SAP by using the final data.

5 Statistical Analysis Sets

5.1.1 Safety Analysis Set

The safety analysis set will include subjects who have received at least one dose of the IMP.

5.1.1.1 Dose-limiting Toxicity Analysis Set

The DLT analysis set will include subjects in whom tolerability has been assessed in Cohorts 1 to 4 (subjects who have received all doses and completed all assessments scheduled for the DLT evaluation period).

5.1.2 Efficacy Analysis Set

The efficacy analysis set will include subjects who have received at least one dose of the IMP and have data of the efficacy endpoints after the start of IMP administration.

5.1.3 Pharmacokinetic Analysis Set

The PK analysis set will include subjects whose plasma drug concentrations have been measured.

5.1.4 Pharmacodynamic Analysis Set

The PD analysis set will include subjects in whom the extent of DNA hypomethylation in long interspersed nucleotide element-1(LINE-1) has been measured.

6 Considerations for Data Analysis

6.1 Software

The following software (including versions) will be used in the analyses.

- SAS 9.4 (SAS Institute Inc.)

6.2 Data Conversion and Calculation

6.2.1 Conversion of Duration

1 month will be considered with 30 days for the analysis.

6.2.2 Time since Initial Diagnosis

Time since initial diagnosis will be calculated as [the date of first dose of IMP - date of diagnosis]. If the day is missing for date of diagnosis, the 15th of the month is used. If the month is missing, July 1 is used. If the year is missing, the date is left as missing.

6.2.3 Complete Remission Rate

Complete remission will be defined as follows.

- Complete remission (CR)

6.2.4 Composite Complete Remission Rate

Composite complete remission will be defined as follows.

- CR
- Complete remission with incomplete platelet recovery (CRp)
- Complete remission with incomplete blood count recovery (CRi)

6.2.5 Overall Remission Rate

Overall remission will be defined as follows.

- CR
- CRp
- CRi
- Partial response (PR)

The investigator or subinvestigator will evaluate response in each course in accordance with the response criteria in following table, which is based on the response criteria for AML treatment established by an international working group[1].

	Bone Marrow	Peripheral Blood
CR	• Blast cells < 5%	• Neutrophil count > 1,000/μL • Platelet count ≥ 100,000/μL • No blast cell • Transfusion independence
CRp	• Blast cells < 5%	• Neutrophil count > 1,000/μL • Platelet count < 100,000/μL • No blast cell • Red blood cell (RBC) transfusion independence
Morphologic CRi	• Blast cells < 5%	• Neutrophil count < 1,000/μL • No blast cell
PR	• Rate of decrease in blast cells in the bone marrow ≥ 50% and ratio of blast cells of 5% to 25%	• Neutrophil count > 1,000/μL • Platelet count ≥ 100,000/μL • No blast cell
Relapse	• Leukemia cells (blast cells) ≥ 5% in the bone marrow or presence of leukemia cells (blast cells) in the peripheral blood are manifested again after CR, CRi, or CRp has been achieved. • Leukemia cells with abnormal chromosomes are revealed again in chromosomal testing.	

6.2.6 Duration of Composite Complete Remission

Duration of composite complete remission (in number of days) is calculated from the first time a composite complete remission is observed to time of relapse defined as above table.

The duration of composite complete remission will be calculated to the last available time point in the case that relapse was not observed.

Duration of composite complete remission will be summarized for subjects who achieved complete remission during the study.

6.2.7 Overall Survival

Overall survival is defined as the number of days from the day the subject received the first dose of IMP to the date of death (regardless of cause).

Survival time will be censored on the last date of survival confirmation if a subject is alive or lost to follow-up.

6.3 Handling of Time Points

Data recorded at the time points specified in the case report form will be summarized for the respective time points. If data at the time of withdrawal or unspecified time points are within the acceptable time window specified in the protocol, they will be used as the data at that time point. If there are 2 or more data in a specific time window, the closest data to the scheduled visit date will be used for the analysis. If there are 2 data with same interval from the scheduled visit date, one before the scheduled visit date and the other after the scheduled visit date, the data from after the scheduled visit date will be used for the analysis. If 2 or more data are collected on the same date, the mean value of these data will be used for the analysis.

Baseline is defined as last available data before the first dose of IMP.

Time point of Cohort 3 vital sign data will be handled same as the time point of Cohorts 1, 2 and 4.

6.4 Handling of Missing Values and Outliers

No imputation of missing values or exclusion of outliers will be performed.

6.5 Significance Level and Confidence Coefficient

No significance level or confidence coefficient will be set, since statistical tests and interval estimations will not be performed.

6.5.1 Multiple Comparisons and Multiplicity

No multiple comparisons and multiplicity will be considered, since statistical tests will not be performed.

7 Disposition of Subjects

Subjects who gave informed consent will be used in the statistical analyses. Data will be summarized by cohort and overall (Cohorts 1, 2, and 4).

7.1 Disposition of Subjects

Subject disposition will be summarized. The frequency distribution (number of subjects and incidence rate [the same applies hereafter]) of subjects who gave informed consent, screen failures, subjects who were administered the IMP, subjects who completed course 1, and subjects who discontinued the study will be determined. In addition, the frequency distribution of study discontinuation will also be determined by primary reason for discontinuation.

Frequency distribution will be summarized for course 1 and on or after course 2. Only the subjects who continue IMP administration on or after course 2 will be included in the frequency distribution for on or after course 2.

7.2 Statistical Analysis Sets

The frequency distribution of subjects included or excluded in each analysis set will be determined for subjects who were administered the IMP.

8 Description of Analysis Datasets

The safety analysis set will be used in the statistical analyses. The following analyses will be performed by cohort and overall (Cohorts 1, 2, and 4).

8.1 Demographics and Baseline Characteristics

Demographic and other baseline characteristics are as follows;

1) Age (< 65 years, ≥ 65 and < 75 years, ≥ 75 years, calculated relative to date of informed consent)
2) Sex (Male, Female)
3) Height (cm)
4) Weight (kg)
5) Body surface area (m^2)
6) Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) (0, 1 or 2)
7) Diagnosis of AML
8) Time since initial diagnosis (calculated relative to date of first dose of IMP)
9) Hematopoietic stem cell transplantation history (Yes, No) and type of transplantation
10) De novo or secondary AML (De novo AML, secondary AML)
11) Prior radiotherapy history (Yes, No)
12) Chemotherapy history including induction therapy history and consolidation therapy history
13) Poor type category of Karyotype at screening (Better risk, Intermediate risk, Poor risk, Unknown)
14) Cytogenetic abnormalities (Yes, No, Unknown) and detail of abnormality
15) Extra medullary lesions found after diagnosis of AML (Yes, No)
16) Maximum proportion of blast cells (leukemic cells) in the bone marrow after diagnosis of AML
17) Baseline leukocytes (≥ 20.0×10^9/L, ≥ 2.0 and < 20.0×10^9/L, ≥ 1.0 and < 2.0×10^9/L, < 1.0×10^9 /L)
18) Baseline neutrophil (≥ 1.0×10^9/L, ≥ 0.5 and < 1.0×10^9/L, < 0.5×10^9/L)
19) Baseline platelets (≥ 50.0×10^9/L, ≥ 25.0 to < 50.0×10^9/L, < 25.0×10^9/L)

1) will be summarized with descriptive statistics in addition to categorical summary. 3), 4), 5), 8) and 16) will be summarized with descriptive statistics. Others will be summarized categorically.

In detail, poor-risk cytogenetics is defined based on the National Comprehensive Cancer Network (NCCN) Guidelines® (2014)[2] as follows:

Risk Status Based on Cytogenetics[1]

Risk Status	Cytogenetics
Better-risk	inv(16)[2,3] or t(16;16)[2] t(8;21)[2] t(15;17)
Intermediate-risk	Normal cytogenetics +8 alone t(9;11) Other non-defined
Poor-risk	Complex (≥3 clonal chromosomal abnormalities) Monosomal karyotype -5, 5q-, -7, 7q- 11q23 - non t(9;11) inv(3), t(3;3) t(6;9) t(9;22)[4]

[1] The molecular abnormalities included in this table reflect those for which validated assays are available in standardized commercial laboratories. Given the rapidly evolving field, risk stratification should be modified based on continuous evaluation of research data. Other novel genetic mutations have been identified that may have prognostic significance.

[2] Other cytogenetic abnormalities in addition to these findings do not alter better risk status.

[3] Paschka P, Du J, Schlenk RF, et al. Secondary genetic lesions in acute myeloid leukemia with inv(16) or t(16;16): a study of the German-Austrian AML study group (AMLSG). Blood 2013;121:170-177.

[4] For Philadelphia+ AML t(9;22), manage as myeloid blast crisis in chronic myeloid leukemia, with addition of tyrosine kinase inhibitors.

Source: NCCN Guidelines: Acute Myeloid Leukemia. Version 2.2014. NCCN.org.

8.2 Status of Trial Conduct

8.2.1 Investigational Medicinal Product Compliance

Not applicable.

8.2.2 Use of Medication Other Than Investigational Medicinal Product

Medications will be coded using World Health Organization Drug Dictionary (WHO-DD) version 01MAR2014.

The frequency distribution for the use of medications other than the IMP will be determined by therapeutic subgroup [Anatomical Therapeutic Chemical (ATC) level 2] and preferred term.

- Medications used before the start of IMP administration
- Medications used during the trial period (from the start of IMP administration to the end-of-trial assessment)

8.2.3 Number of Blood Transfusion

Frequency distribution of the number of subjects who received transfusion by the type of blood transfusion for each course including baseline will be summarized by cohort and overall (Cohorts 1, 2, and 4).

The number of blood transfusions (units/ month) over the treatment period will be calculated by the type of blood transfusion and subjects and will be summarized by cohort and overall (Cohorts 1, 2, and 4).

9 Safety Analysis

The safety analysis set or DLT evaluation analysis set will be used in safety analyses. The following analyses will be conducted by cohort and overall (Cohorts 1, 2, and 4) for subjects receiving IMP.

9.1 Extent of Exposure

Safety analysis set will be used for the analysis.

The following items will be tabulated.

- Frequency distribution of the number of IMP administrations on course 1.
- Frequency distribution of the number of IMP dosed subjects for each course
- Number of IMP administration courses for each subject will be summarized with descriptive statistics for the overall treatment period.

9.2 Primary Endpoints

DLT is the primary endpoint of this trial.

DLT evaluation analysis set will be used for the analysis.

- DLTs [preferred term (PT)] which observed on course 1 will be tabulated (number of subjects and incidence rate) by DLT criteria and Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and PT.

9.3 Secondary Endpoints

The safety analysis set will be used for the analysis.

9.3.1 Adverse Events

AEs will be coded using MedDRA version 20.0.

- The number of subjects and incidence will be summarized for all treatment-emergent AEs (TEAEs).
- The number of subjects and incidence will be summarized for all TEAEs by MedDRA SOC and PT.
- The number of subjects and incidence will be summarized for all TEAEs by MedDRA SOC, PT, and CTCAE grade. If a subject experiences the same TEAE 2 or more times, the most severe grade occurrence will be used for the analysis.
- The number of subjects and incidence will be summarized for all TEAEs by the timing of AE occurrence (in course 1, in or after course 2, and overall), MedDRA SOC and PT. AEs which had occurred in Course 1 and continued beyond course 2 will be included in “in or after course 2” category.

- TEAEs that DLTs and correspond to DLTs (preferred term) which were observed in course 1, in or after course 2, and overall will be tabulated (number of subjects and incidence rate). AEs which had occurred in Course 1 and continued beyond course 2 will be included in "in or after course 2" category.

Adverse drug reactions (TEAEs for which a causal relationship with the IMP are suspected adverse reaction) will be summarized in the same manner as above.

9.3.2 Death, Other Serious Adverse Events, CTCAE Grade 3 or above Adverse Events, and Other Significant Adverse Events

The following TEAEs will be summarized in the same manner as in first bullet of Section 9.3.1 Adverse Events. Also the following TEAEs, excluding TEAEs of grade ≥ 3, will be summarized in the same manner as in second bullet of Section 9.3.1 Adverse Events.

- Serious TEAEs
- TEAEs leading to death
- TEAEs leading to discontinuation in course 1, in or after course 2, and overall
- TEAEs of grade ≥ 3
- TEAEs leading to postponement of the start of the next course
- TEAEs leading to skipping of IMP administration

Adverse drug reactions (TEAEs for which a causal relationship with the IMP are suspected adverse reaction) will be summarized in the same manner as above.

9.3.3 Clinical Laboratory Tests

The following items will be tabulated by cohort and overall (Cohorts 1, 2, and 4) for hematological and biochemical tests performed at each time point.

- Descriptive statistics of the measured values
- Descriptive statistics of the change from baseline
- Shift tables comparing the baseline grade with last grade, worst grade through all courses and worst grade of each course categorized by CTCAE grade
- Shift tables comparing the baseline values with last value, worst value through all courses and worst value of each course by using the normality judgment (high, normal, low)

If the laboratory test parameter has both upper limit of normal and lower limit of normal, larger difference one from median of normal range will be taken as worst value.

The following item will be tabulated by cohort and overall (Cohorts 1, 2, and 4) for the urinalysis.

- Shift tables comparing the baseline values with last value, worst value through all courses and worst value of each course.

Also, some of laboratory test parameter will be figured by subject performed at each time point of course 1 and all courses.

- Line plots will be used to assess hemoglobin, red blood cell, white blood cell, neutrophil, lymphocytes and platelet.

9.3.4 Vital Signs and Body Weight

The following vital signs (blood pressure, pulse rate, body temperature) and body weight will be tabulated at each time point.

- Descriptive statistics of the measured values
- Descriptive statistics of the change from baseline

9.3.5 ECG (12-Lead ECG)

Electrocardiographic (ECG) assessment by site investigator will be used for the analysis.

The following items will be tabulated for heart rate, PR interval, RR interval, QRS interval, QT interval, and QT interval as corrected by Fridericia's formula (QTcF interval) at each time point.

- Descriptive statistics of the measured values
- Descriptive statistics of the change from baseline

The number of subjects and incidence of the following items will be tabulated by cohort for QTcF interval of last value and worst value (maximum value obtained after the start of IMP administration).

- Measured values will be classified as "greater than 450 ms", "greater than 480 ms", and "greater than 500 ms" for tabulation.
- Changes from baseline will be classified as "greater than 30 ms" and "greater than 60 ms" for tabulation.

The following item will be tabulated by cohort using the normality judgment (normal or abnormal) for the electrocardiogram at each time point.

- Shift table from baseline

9.3.6 ECOG PS

The following item will be tabulated for the ECOG PS at each time point.

- Frequency distribution of each ECOG PS score

9.3.7 Chest X-ray

The following item will be tabulated using the normality judgment (normal or abnormal) for the chest x-ray at each time point.

- Shift table from baseline

10 Efficacy Analysis

The efficacy analysis set will be used in efficacy analyses. The following analyses will be performed by cohort and overall (Cohorts 1, 2, and 4).

10.1 Complete Remission Rate, Composite Complete Remission Rate, Overall Remission Rate

The following analysis will be conducted by cohort and overall (Cohorts 1, 2, and 4).

- Distribution of remission in each course [CR, CRp, CRi, PR No response, progressive disease, and not evaluable (NE)]
- Distribution of the best overall remission: complete remission rate (CR), composite complete remission rate (CR + CRp + CRi), overall remission rate (CR + CRp + CRi + PR)

10.2 Duration of Composite Complete Remission

The following analysis will be conducted by cohort and overall (Cohorts 1, 2, and 4) for the subjects with composite complete remission.

- Summary of duration of composite complete remission using descriptive statistics.

10.3 Overall Survival

The following analysis will be conducted by cohort and overall (Cohorts 1, 2, and 4) in the efficacy analysis set. Also, same analysis will be conducted for responders, non-responders, and overall in efficacy analysis set. Responders will be defined as those subjects who meet the criteria of overall remission.

- Kaplan–Meier plots with median survival time

10.4 Adjustment for Covariates

No adjustment for covariates will be considered, since statistical tests and interval estimations will not be performed.

10.5 Subgroup Analysis

No subgroup analysis will be conducted, since the number of subjects in this study will be very limited.

11 Pharmacodynamic Analysis

The PD analysis set will be used for pharmacodynamics analyses. The following analyses will be performed by cohort and overall (Cohorts 1, 2, and 4).

11.1 DNA Methylation Inhibition

The following analysis will be conducted by cohort and overall (Cohorts 1, 2, and 4) for the subjects with the measurement of the degree of DNA methylation inhibition of LINE-1.

- Descriptive statistics of the DNA LINE-1 demethylation (defined as percent change from baseline in methylation value) at each time point. Also, line plots will be used to assess DNA LINE-1 demethylation [Mean ± Standard deviation (SD)] at each time point.
- Summary of the maximum DNA LINE-1 demethylation (defined as the largest percent decrease from baseline in methylation values within a subject between Day 8 and Day 29 of the first treatment course) using the descriptive statistics. Also, bar charts will be used to assess the maximum DNA LINE-1 demethylation within a subject between Day 8 and Day 29 of the first treatment course.
- Line plots of DNA LINE-1 demethylation will be produced for responders, non-responders, and overall in the pharmacodynamics analyses set. Responders will be defined as those subjects who meet the criteria of overall remission.

12 Rationale for Target Number of Subjects

For Cohorts 1, 2, and 4, tolerability will be evaluated in at least 3 subjects per cohort based on the Guidelines for Clinical Evaluation of Antimalignant Tumor Drugs. If DLTs are evaluated in 3 subjects in a cohort for the recommended dose and regimen, additional subjects will be enrolled for further safety evaluation in 6 subjects. For Cohort 3, tolerability will be evaluated in 6 subjects.

13 Changes From Analyses Planned in the Protocol

Categorization of urinalysis in shift tables was changed from CTCAE grade to qualitative value.

One interim analysis for cohort 1, 2 and 4 of this study will take place that the data will be locked on 25Aug2017.

Kaplan-Meier plots of overall survival with median survival time will be produced regardless of number of subjects in each cohort.

14 References

[1] Cheson BD, Bennett JM, Kopecky KJ, Büchner T, Willman CL, Estey EH, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol. 2003 Dec 15;21(24):4642-9.

[2] NCCN Guidelines: Acute Myeloid Leukemia. Version 2.2014. NCCN.org.