STATISTICAL ANALYSIS PLAN

Protocol Number:	SGN33A-005
Version:	5 04-Dec-2017
Protocol Title:	A randomized, double-blind phase 3 study of vadastuximab talirine (SGN-CD33A) versus placebo in combination with azacitidine or decitabine in the treatment of older patients with newly diagnosed acute myeloid leukemia (AML)
Sponsor:	Seattle Genetics, Inc. 21823 30th Drive SE Bothell, WA 98021, USA

APPROVAL SIGNATURES

Product:	Vadastuximab talirine
Protocol Number:	SGN33A-005
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The individuals signing below have reviewed and approve this statistical analysis plan.

[redacted]

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LIST OF ABBREVIATIONS

ADI	absolute dose intensity
AE	adverse event
AML	acute myeloid leukemia
ANC	absolute neutrophil count
ATA	antitherapeutic antibodies
CBC	complete blood count
CI	confidence interval
CR	morphologic complete remission
CRc	composite complete remission (CR+CRi)
CRi	morphologic complete remission with incomplete blood count recovery
CRF	case report form
CSR	clinical study report
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EOT	end of treatment
HMA	hypomethylating agents
HCT-CI	hematopoietic cell transplantation-comorbidity index
IDI	intended dose intensity
IDMC	independent data monitoring committee
ITT	intent-to-treat
LFS	leukemia-free survival
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mLFS	morphologic leukemia-free state
MRC	Medical Research Council
MRD	minimal residual disease
MRU	medical resource utilization
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OS	overall survival
PRO	Patient reported outcome
PD	pharmacodynamic
PK	pharmacokinetic
PT	preferred term
RDI	relative dose intensity
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
TRM	treatment related mortality
TTCR	time to complete remission

1 INTRODUCTION

This document outlines the statistical methods to be implemented within the scope of Protocol SGN33A-005, entitled "A randomized, double-blind phase 3 study of vadastuximab talirine (SGN-CD33A) versus placebo in combination with azacitidine or decitabine in the treatment of older patients with newly diagnosed acute myeloid leukemia (AML)". Results of the proposed analyses will become the basis of the clinical study report (CSR) for this protocol.

The purpose of this plan is to provide specific guidelines from which the analysis will proceed. All planned analyses specified in this document will be performed. Any changes to this plan, in the form of "post hoc" or "data driven" analyses will be identified as such in the final CSR. Any changes will either be reflected in amendments to this plan before the database lock or specifically documented in the CSR.

Due to safety concerns raised by the IDMC, the study was terminated early prior to the formal interim analyses planned in the protocol. Final analysis will be performed based on 240 patients randomized into the study by the time enrollment was closed. This SAP reflects the proposed analyses for the abbreviated CSR.

2 STUDY OBJECTIVES

2.1 Primary Objective

- To compare the composite complete remission (CRc) rate (morphologic complete remission [CR] and morphologic CR with incomplete hematologic recovery [CRi]) between treatment arms
- To compare overall survival (OS) between treatment arms

2.2 Secondary Objectives

- To compare the minimal residual disease-negative remission (MRD-negative CRc) rate between treatment arms
- To evaluate the duration of remission in the 2 treatment arms
- To evaluate event-free survival (EFS) in the 2 treatment arms
- To evaluate leukemia-free survival (LFS) in the 2 treatment arms
- To evaluate the safety profiles in the 2 treatment arms
- To evaluate the time to response in the 2 treatment arms
- To evaluate the 30- and 60-day mortality rates in the 2 treatment arms

2.3 Additional Objectives

- To evaluate the treatment effect of vadastuximab talirine compared to the control group on the change in patient reported outcomes (PRO) and medical resource utilization (MRU)
- To assess the incidence of antitherapeutic antibodies (ATA)
- To assess exploratory markers of clinical outcome and the pharmacodynamics (PD) of vadastuximab talirine in combination with a hypomethylating agent (HMA)

3 STUDY ENDPOINTS

3.1 Primary Endpoint

- CRc rate
- OS

3.2 Secondary Endpoints

The secondary endpoints are:

- MRD-negative CRc rate
- Duration of remission
- EFS
- LFS
- Type, incidence, severity, seriousness, and relatedness of adverse events
- Laboratory abnormalities
- Time to CR or CRi (TTCR)
- Mortality rates at Day 30 and Day 60 post the first study treatment

3.3 Additional Endpoints

- Change from baseline in PRO
- MRU based on the number of medical care encounters
- Incidence of ATA to vadastuximab talirine
- Biomarkers of pharmacodynamic effects
- Exploratory markers of clinical activity

4 STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, phase 3 study designed to compare the CRc rate and OS between patients treated with HMA plus vadastuximab talirine (experimental arm) versus patients treated with HMA plus placebo (comparator arm).

Patients will be randomized in a 1:1 manner to one of the study arms, stratified by cytogenetic risk, Eastern Cooperative Oncology (ECOG) performance status, HMA, and age. Investigators may select either HMA (azacitidine or decitabine). Response will be assessed by bone marrow examination and complete blood count (CBC) conducted between Day 22 to 28 of even-numbered cycles until CR or CRi. The response assessment window may be up to Day 42 in the event of a delay in the start of the next cycle of treatment. After CR/CRi, response assessment will be performed by CBC surveillance. In addition, bone marrow examination will be conducted according to the following schedule:

- 2 cycles after initial confirmation of CR or CRi
- At the time of conversion from CRi to CR
- At the time of suspected relapse
- End of treatment (EOT), if not performed within the previous 4 weeks

Patients may continue on study treatment until progression, leukemic recurrence, or unacceptable toxicity, whichever comes first. Patients who achieve stable disease or better should receive a minimum of 4 cycles of study treatment. Progression is defined after 4 or more cycles of treatment as either a >25% absolute rise in the percent of bone marrow blast from baseline (or a proportional increase of >25% in patients with baseline bone marrow blasts >75%) or appearance of new extramedullary disease. Patients who fulfill the criteria for progression but who are still deriving clinical benefit in the opinion of the investigator may continue on study treatment.

After discontinuation of study treatment, patients who have not experienced progression or leukemic recurrence will continue to be assessed for response by CBC surveillance every 2 months through 24 months after EOT, and every 4 months thereafter, until initiation of another anticancer treatment (excluding stem cell transplant and maintenance therapy in the absence of relapse), progression, or leukemic recurrence, whichever comes first. For all patients, survival status follow up will take place every 2 months (or more frequently as needed to support analysis of the study endpoints) after EOT until death or study closure, whichever comes first.

Safety, including SAEs and early mortality, will be monitored over the course of the study by an Independent Data Monitoring Committee (IDMC).

5 ANALYSIS SETS

5.1 Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set will include all randomized patients. Patients will be included in the treatment group assigned at randomization regardless of the actual treatment received.

5.2 Modified Intent-to-Treat Analysis Set

The modified intent-to-treat (mITT) analysis set will include all patients from the ITT analysis set who receive any dose of blinded study treatment (vadastuximab talirine or placebo) or HMA. Patients will be included in the treatment group assigned at randomization regardless of the actual treatment received.

5.3 Safety Analysis Set

The safety analysis set will include all patients who receive any dose of blinded study treatment (vadastuximab talirine or placebo) or HMA. Treatment group will be determined using the actual treatment received, regardless of the randomization treatment assignment. Patients receiving any dose of vadastuximab talirine will be grouped into the experimental arm. Patients who do not receive vadastuximab talirine but receive any dose of HMA will be grouped into the comparator arm.

6 STATISTICAL CONSIDERATIONS

6.1 General Principles

Descriptive statistics (mean, median, standard deviation, minimum and maximum) will be used to summarize continuous variables. Frequencies and percentages will be used to summarize categorical variables. The median survival time will be estimated using the Kaplan-Meier method; the associated confidence interval (CI) will be calculated based on the complementary log-log transformation (Collett 1994).

Unless otherwise specified, all statistical tests will be performed using a two-sided alpha of 0.05. Confidence intervals will be calculated at a two-sided 95% level. Multiplicity adjustment for alpha level is discussed in Section 6.7.

Any analysis not described in this plan will be considered exploratory, and will be documented in the CSR as a post hoc analysis or a change to the planned analysis.

To comply with regulatory electronic submission guidelines, listings of all clinical data will be submitted as electronic data sets. To facilitate data review for the study report, only pertinent data listings will be created and attached to the appendix of the CSR.

All statistical tables, listings, and figures will be produced using SAS®, version 9.3 or more recent. Other statistical software, if used, will be described in the CSR.

6.2 Determination of Sample Size

There are 2 primary endpoints for this study: CRc rate and OS. To maintain strong control of the type I error rate at 0.05, a fallback procedure proposed by Wiens will be used in the testing of the primary endpoints, with an alpha of 0.01 pre-assigned to CRc rate and an alpha of 0.04 pre-assigned to OS (Wiens 2005).

The sample size was calculated based on maintaining 90% power to test both primary endpoints and to account for 2 planned interim analyses for OS, one futility analysis at 30% and one interim efficacy analysis at 60% of the targeted number of OS events, using the O'Brien-Fleming method.

For the primary endpoint of CRc rate, at least 308 patients are required to provide 90% power to detect an improvement in CRc rate from 20% to 40% using a chi-square test at a significance level of 0.01.

For the primary endpoint of OS, approximately 354 OS events are required to provide 90% power to detect a hazard ratio of 0.70 (12.9 months median OS in the experimental arm [vadastuximab talirine plus HMA] versus 9 months for the comparator arm [placebo plus HMA]) using a log-rank test at a 2-sided alpha of 0.04.

To provide adequate power for both primary endpoints, a total of 540 patients will be randomized in a 1:1 ratio to either the experimental arm or the comparator arm, assuming an accrual period of 26 months with a slower rate of accrual for the first 6 months, a 12-month follow-up from the last patient enrolled to the final analysis of OS (after approximately 354 OS events have occurred), and a 5% yearly drop-out rate.

EAST (Version 6.3) was used to calculate and validate the sample size.

6.3 Randomization and Blinding

This is a randomized, double-blind, placebo-controlled, comparative study that will enroll approximately 540 patients in a 1:1 manner.

Randomization will be stratified by:

- Cytogenetic risk per revised UK Medical Research Council (MRC) classification (intermediate versus adverse)
- ECOG performance status (0–1 versus 2)
- HMA (azacitidine versus decitabine)
- Age (<75 years versus ≥75 years)

Fixed block randomization will be performed centrally using a system that will assign a unique patient randomization number. The actual treatment assignment will remain blinded. Randomization procedures are detailed in the Study Manual.

6.4 Data Transformations and Derivations

Age as entered in the CRF will be used for any calculations and analyses, if available. If age is not available, age in years will be calculated with the SAS INTCK function using consent date and birth date.

Study Day will be calculated as (Date of Visit [or Event] – Date of Randomization + 1) for dates on or after randomization. For dates prior to randomization, Study Day will be calculated as (Date of Visit [or Event] – Date of Randomization).

Other time variables based on two dates (e.g., Start Date and End Date) will be calculated as (End Date – Start Date + 1) (in days) unless otherwise specified in the planned analysis section.

The following unit conversion will be implemented unless otherwise specified:

Months = Days / 30.4375

Years = Days / 365.25

Baseline values used in all analyses will be the most recent non-missing measurement prior to the first dose of study treatment (HMA or blinded study drug). For patients who did not receive any study treatment, baseline is the last non-missing measurement on study.

At baseline, if both bone marrow biopsy and aspirate results are available, the biopsy result will be used as the baseline bone marrow blasts. The only exception will be if the biopsy result is blasts <20% and the patient was qualified for the study based on the aspirate result (blasts ≥20%), then the aspirate result will be used as the baseline bone marrow blasts.

The EOT date will be the date the EOT visit is performed, or 30 days after the last dose of any study treatment if an EOT visit is not performed.

For efficacy analysis, if the response is determined to be progression or disease relapse, the earliest date of the bone marrow examination or CBC (within a 14 day window from the bone marrow examination) that supports the overall response assessment at a given visit will be the response assessment date. For any other responses (CR, CRi, mLFS, partial response, anti-leukemic effect, and stable disease), the latest date of the bone marrow examination or CBC (within a 14 day window from the bone marrow examination) that supports the overall response assessment at a given visit will be the response assessment date.

6.5 Handling of Dropouts and Missing Data

Missing data will not be imputed unless otherwise specified. Missing AE dates will be imputed while calculating duration of events and treatment emergent status. Missing subsequent anticancer therapy start date will be imputed while deriving time-to-event endpoints as applicable (see Appendix A and B for imputation details). Missing data in PRO assessment will be handled according to the questionnaire's standard guidelines. Patients with a missing value for a variable other than response or time-to-event endpoints (e.g., CRc

rate and OS) will be excluded from the analysis of that endpoint. Censoring rules will be applied in the analysis of time-to-event endpoints as detailed in Section 7.5.

6.6 Multicenter Studies

There are multiple centers in this study, however it is not anticipated that any center will accrue enough patients to warrant an analysis by center.

6.7 Multiple Comparison/Multiplicity

To maintain strong control of the Type I error rate at 0.05, the fallback procedure proposed by Wiens will be used in the testing of primary endpoints, with an alpha of 0.01 pre-assigned to CRc rate and an alpha of 0.04 pre-assigned to OS (Wiens 2005). If the test for the CRc rate is statistically significant, then the alpha of 0.01 will be re-allocated to OS, and the test for OS will be performed at a 2-sided alpha of 0.05. If the test for the CRc rate is not statistically significant, then the test for OS will be performed at a 2-sided alpha of 0.04.

The parallel gatekeeping principle will be used to control the overall type I error rate of 0.05 (Dmitrienko 2011). The primary endpoints, CRc rate and OS (family 1), will be the gatekeepers for testing the secondary endpoint of MRD-negative CRc rate (family 2). If at least one of the primary endpoints is statistically significant, then a statistical test will be performed for the MRD-negative CRc rate. If both CRc rate and OS are statistically significant, then MRD-negative CRc rate will be tested at an overall alpha of 0.05. If only one of the 2 primary endpoints is statistically significant, then MRD-negative CRc rate will be tested at the corresponding alpha level of the significant primary endpoint. If the tests for both CRc rate and OS are not statistically significant, then the p-value of the test for MRD-negative CRc rate will still be calculated but considered descriptive.

Two formal interim analyses for OS are planned. The test significance level for OS at the interim analysis will be adjusted based on the actual number of OS events observed at each interim analysis according to the O'Brien-Fleming spending function.

Due to safety concerns raised by the IDMC, the study was terminated early prior to the first interim analysis planned in the protocol. Final analysis will be performed based on 240 patients randomized into the study by the time enrollment was closed. All efficacy analysis will be descriptive in nature and no multiple testing procedure will be applied.

6.8 Examination of Subgroups

As exploratory analyses, subgroup analyses may be conducted for selected endpoints (see Section 7). Subgroups may include but are not limited to the following:

- ECOG performance status (0–1, 2)
- Cytogenetic risk by MRC (adverse, intermediate/unknown)
- HMA
- Age (<75, ≥75 years old)

- Age (<80, ≥80 years old)
- Gender
- Race
- Geographic region (North America/Australia, Western Europe/Israel, Eastern Europe, Asia)
- Type of AML (de novo AML, secondary AML)
- AML subtype (AML with recurrent genetic abnormalities, AML with myelodysplasia-related changes, AML with therapy-related myeloid neoplasms, AML not otherwise specified)
- Underlying myelodysplasia (yes, no)
- Prior hematological disorder (yes, no)
- Mutational abnormalities (NPM1+, NPM1-)
- Medically unfit for intensive therapy (yes, no)
- Baseline bone marrow blast percentage (20% - 30%, >30%)
- Baseline bone marrow blast percentage (20% - 50%, >50%)
- Baseline WBC (≤5,000, >5,000/μL)
- Baseline WBC (<10,000, ≥10,000/μL)
- Baseline WBC (<15,000, ≥15,000/μL)
- Remission status (CRc, non-responders)
- MRD-negative remission status (MRD-negative CRc, MRD-positive CRc, non-responders)
- Charlson Comorbidity Index (low, moderate, high)
- Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI; low, intermediate, high)
- Wheatley Risk group (good, standard, poor)
- European ALMA score (favorable, intermediate, unfavorable)
- Treatment-related mortality (TRM) score (low, intermediate, high)

6.9 Covariates

Stratified analyses specified in Section 7.5 will include adjustment for the stratification factors as recorded at randomization. Selected baseline values may be used as covariates in the exploratory analysis of efficacy endpoints.

6.10 Timing of Analyses

Due to safety concerns raised by the IDMC, the study was terminated early prior to the formal interim analyses planned in the protocol. Final analysis will be performed based on 240 patients randomized into the study by the time enrollment was closed.

7 PLANNED ANALYSES

7.1 Disposition

Patient enrollment and disposition will be summarized by treatment group and total using the ITT analysis set. The table will present the number and percentage of patients who were randomized, received study drug, received treatment per randomization assignment, and in follow-up visits. The number and percentage of patients who discontinued treatment will be summarized by the primary reason for treatment discontinuation. The number and percentage of patients who discontinued the study will be summarized by the primary reason for study discontinuation.

The number and percentage of patients randomized in each country and at each site will be summarized by treatment group and total. Disposition data will be listed by patient using the ITT analysis set.

7.2 Demographic and Baseline Characteristics

Demographics and baseline characteristics, including age, gender, ethnicity, race, height, weight, and ECOG score will be listed and summarized; summaries will be presented by treatment group and total using the ITT analysis set.

Disease specific characteristics, including time from initial AML diagnosis, baseline bone marrow blast percentage, baseline WBC, AML subtype, prior hematologic disorder, cytogenetic risk group, mutational abnormalities, Wheatley risk group, European ALMA score, TRM score, Charlson comorbidity index and HCT-CI, will be summarized by treatment group and total using the ITT analysis set. In addition, the number and percentage of patients who receive at least one prior anticancer therapy for hematological disorder will be summarized.

Reasons for enrollment and reasons patients are medically unfit to receive intensive therapy will be summarized by treatment group and total using the ITT analysis set.

The stratification factors entered at the time of randomization and the actual strata at baseline for each patient will be presented in a listing.

7.3 Protocol Deviations

Important protocol deviations (defined as protocol violations by Seattle Genetics) are those that represent a divergence from the protocol that could have a significant effect on the integrity of the study data, or on the subject's rights, safety, or welfare. Important protocol deviations also include exemptions to the study inclusion/exclusion criteria and will be

summarized by category. A list of patients with important protocol deviations will be presented.

7.4 Treatment Administration

Treatment administration will be summarized by treatment group using the safety analysis set. Summary statistics for duration of therapy (weeks), number of cycles per patient, and the number and percentage of patients who were treated at each cycle will be presented. In addition, the cumulative dose, number of doses, average dose per cycle, absolute dose intensity (ADI) and relative dose intensity (RDI) will be described for the blinded study treatment. The number and percentage of patients whose blinded study treatment dose was ever modified will be summarized by modification type (delay, reduction, unplanned dose adjustment), cycle and overall (i.e., overall drug administrations for a patient) for each treatment group. The number and percentage of doses that were modified may also be summarized. Kit errors will be listed.

Duration of therapy is defined as time from the first dose of study drug to the earliest of the following:

- Day 28 of the last treatment cycle
- EOT visit
- Date of death
- Last contact date if the patient is still on treatment at the time of the analysis

Person-time exposure for a treatment group will be calculated by adding the duration of therapy of all patients from the same treatment group.

Intended Dose Intensity (IDI) is defined as the intended dose of drug (e.g., mcg/kg) per unit of time. IDI will be calculated in 2 ways, with and without accounting for the dose modification intended by the investigator.

Absolute Dose Intensity (ADI) is defined as the actual dose (e.g., mcg/kg) per unit of time that the patient received over the entire treatment period. For the purpose of calculating ADI, treatment period is defined as time from the first dose of study drug to Day 28 of the last treatment cycle.

Relative Dose Intensity (RDI) is defined as the absolute dose intensity over the intended dose intensity.

RDI = ADI/IDI * 100.

Cycle length will be calculated as the interval between Day 1 of 2 consecutive cycles. Cycle length will not be calculated for the last treatment cycle of each patient. The number and percentage of patients with cycle length ≥5 weeks will be summarized by cycle and treatment group.

7.5 Efficacy Analyses

All efficacy analyses will be descriptive in nature and will be presented using the ITT analysis set.

7.5.1 Primary Endpoint

7.5.1.1 Composite Complete Remission (CRc) Rate

CRc rate is defined as the proportion of patients achieving CR or CRi prior to the start of subsequent anticancer therapy or stem cell transplant. Patients whose disease response cannot be assessed will be considered non-responders in the calculation of CRc rate. The CRc rate and the 2-sided 95% CI will be summarized by treatment group.

7.5.1.2 Overall Survival (OS)

Overall survival (OS) is defined as the time from randomization to death due to any cause. Specifically,

OS = Date of death – Date of randomization + 1.

For a patient who is not known to have died by the end of study follow up, observation of OS is censored on the date the patient was last known to be alive (i.e., date of last contact). Patients lacking data beyond the day of randomization will have their survival time censored on the date of randomization (i.e., OS duration of 1 day).

Specifically, censored OS will be calculated as:

Censored OS = max(1, last contact date - date of randomization + 1),

The Kaplan-Meier method will be used to estimate OS. Kaplan-Meier curves depicting OS in the two arms will be generated. Additionally, the median OS, and survival rates at 30 days, 60 days, 3 months and every 3 months thereafter to the end of the follow-up period will be reported. The associated two-sided 95% CIs will be calculated.

Subgroup analysis of OS will be performed by the stratification factors and may be performed for the subgroups specified in Section 6.8.

7.5.2 Secondary Endpoints

7.5.2.1 Minimum Residual Disease-Negative CRc Rate

MRD-negative CRc rate is defined as the proportion of patients achieving both morphologic remission (CR or CRi) and MRD-negative status prior to the start of subsequent anticancer therapy or stem cell transplant. Patients whose morphologic response or MRD status cannot be assessed will be considered non-responders in the calculation of MRD-negative CRc rate. The MRD-negative CRc rate and the 2-sided 95% CI will be summarized by treatment group.

7.5.2.2 Duration of Remission

Duration of remission will be not analyzed given the limited follow-up of the study.

7.5.2.3 Event-Free Survival (EFS)

EFS will not be analyzed given the limited follow-up of the study.

7.5.2.4 Leukemia-Free Survival (LFS)

LFS will not be analyzed given the limited follow-up of the study.

7.5.2.5 Time to Complete Remission

Time to complete remission will not be analyzed given the limited follow-up of the study.

7.5.2.6 Mortality Rate

The 30-day mortality rate is defined as the proportion of patients who die within 30 days of randomization. The 60-day mortality rate is defined as the proportion of patients who die within 60 days of randomization. The 30-day and 60-day mortality rates and the associated 95% CIs will be summarized by treatment group. In addition, the cause of early mortality will be summarized by descending MedDRA preferred term and treatment group.

7.6 Safety Analyses

The safety analysis set will be used to summarize all safety endpoints.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 19.0 or higher).

Laboratory values will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE version 4.03 or higher).

Concomitant medications will be coded using the WHO Drug Dictionary (version: June 2015 or more recent).

7.6.1 Adverse Events

Adverse events (AEs) will be summarized by descending MedDRA preferred term (PT) unless otherwise specified. For incidence reporting, if a patient reports more than one AE that was coded to the same system organ class (SOC) or PT, the patient will be counted only once for that specific SOC or PT.

A treatment-emergent AE is defined as a newly occurring or worsening AE after the first dose of any study treatment. See Appendix C for details regarding treatment-emergent classification. Summaries of AEs will be provided by treatment group and total for the following:

- Pre-existing AEs
- All treatment-emergent AEs

- AEs related to blinded study treatment
- AEs related to azacitidine
- AEs related to decitabine
- Serious Adverse Events (SAEs)
- SAEs related to blinded study treatment
- SAEs related to azacitidine
- SAEs related to decitabine
- AEs leading to blinded study treatment dose delay
- AEs leading to azacitidine dose delay
- AEs leading to decitabine dose delay
- AEs leading to blinded study treatment dose reduction
- AEs leading to azacitidine dose reduction
- AEs leading to decitabine dose reduction
- AEs leading to overall treatment discontinuation
- AEs leading to blinded study treatment discontinuation
- AEs leading to azacitidine discontinuation
- AEs leading to decitabine discontinuation
- Grade 3 or higher treatment-emergent AEs
- Infusion-related reactions (within 24 hours of blinded study drug dose)
- Treatment-emergent AEs by SOC and PT
- Treatment-emergent AEs by SOC, PT, and maximum severity. At each SOC or PT, multiple occurrences of events within a patient are counted only once at the highest severity
- Grade 3 or higher treatment-emergent AEs by SOC and PT
- TEAEs with incidence ≥5% by SOC and PT
- SAEs with incidence ≥5% by SOC and PT

AEs in the categories below as defined by the Standardized MedDRA Queries (SMQs) or customized searches will be summarized by SOC, PT, and maximum severity. SAEs will be summarized by PT.

- Serious infection
- Bleeding
- Thrombocytopenia
- Neutropenia
- Anemia
- Hepatotoxicity
- Edema
- Pulmonary
- Cardiomyopathy
- Cardiac failure
- Myocardial infarction

All AEs, SAEs, grade 3 or higher treatment-emergent AEs, AEs leading to treatment discontinuation, and AEs with fatal outcome will be listed.

7.6.2 Clinical Laboratory Parameters

Clinical laboratory data (hematology and serum chemistry) will be summarized by treatment group and total. Summary statistics of actual value and change from baseline will be presented by scheduled visit. In addition, laboratory data will be summarized in shift tables comparing the baseline value to the worst post-baseline value by NCI CTCAE grade for each parameter.

All clinical laboratory data and NCI CTCAE grades will be presented in data listings. A separate listing of laboratory results with CTCAE grade 3 or higher will also be presented. Normal ranges will be documented and out-of-range values will be flagged.

Patients with the liver function test results (AST, ALT, ALP, and total bilirubin) meeting the Hy's law will be listed.

7.6.3 ECOG Performance Status

ECOG performance status will be summarized for each visit by treatment group and total. Shifts from baseline to the best and worst post-baseline scores will be tabulated.

7.6.4 Concomitant Medications

Concomitant medications will be summarized by the WHO Drug substance name by treatment group and total, and listed by patient.

The number and percentage of patients who receive myeloid growth factor as a concomitant medication and the reason for administration will be summarized by treatment group and total.

7.6.5 Deaths

The number of total deaths, deaths that occured within 30 days of last study treatment, and deaths that occured more than 30 days after last study treatment, as well as the relationship to disease, will be summarized by treatment group and total. In addition, cause of death will be identified by descending MedDRA preferred term (unless otherwise specified) and summarized by treatment group and total. Death information will be listed by patient.

7.7 Additional Analyses

7.7.1 Stem Cell Transplant

Patients who received stem cell transplant after study treatment discontinuation will be listed, including the reason patient became eligible for transplant, the level of match of the donor, time from last dose of blinded study treatment to transplant, and transplant conditioning regimens administered.

7.7.2 Pharmacokinetics

The observed plasma vadastuximab talirine ADC and SGD-1882 may be summarized with descriptive statistics at each PK sampling time point. Any additional PK and PK/PD analyses may be performed and presented in a separate report.

7.7.3 Antitherapeutic Antibody Incidence Rate

The antitherapeutic antibody (ATA) incidence rate is defined as the proportion of patients who develop ATA at any time during the study. The ATA incidence rate will be summarized by treatment group and total.

7.7.4 Biomarker Analyses

Biomarker assessments may be summarized using descriptive statistics. The relationship between biomarkers and efficacy and safety endpoints may be explored and presented in a separate report.

8 INTERIM ANALYSIS

Due to safety concerns raised by the IDMC, the study was terminated early prior to the formal interim analyses planned in the protocol. No interim analyses will be conducted. Final analysis will be performed based on 240 patients randomized into the study by the time enrollment was closed.

9 CHANGES FROM PLANNED ANALYSES

9.1 Changes from the Protocol

Not Applicable.

9.2 Changes from the Original SAP

9.2.1 Version 2 Changes

The SAP was updated to reflect changes in protocol amendment 2 and to add additional details to the analysis. Changes from version 1 are summarized below:

- Sec 2.2, 3.2, 5.2, 5.3, and 7.5.2.4: update per protocol amendment 2
    - Add "duration of remission" as secondary objective/endpoint
    - Add mITT analysis set and clarify the definition of safety analysis set
- Sec 6.2: clarify the 12-month follow-up is from the last patient enrolled to the final analysis of OS after approximately 334 deaths occurred.
- Sec 6.5 and Appendix B: add language or missing data handling for subsequent anticancer therapy start date
- Sec 6.8: add additional subgroups to allow subgroup analysis
- Sec 7.5 and 7.6: add additional details to efficacy and safety analysis and data presentation
- Sec 7.7.4 and 7.7.5: add additional analysis for subsequent anticancer therapy and stem cell transplant

9.2.2 Version 3 Changes

The SAP was updated to reflect changes in protocol amendment 3 and to add additional details to the analysis. Changes from version 2 are summarized below:

- Sec 2.1, 2.2, 3.1, 3.2, 7.5.1 and 7.5.2: update per protocol amendment 3 to change the CRc rate from a secondary endpoint to an independent primary endpoint and to clarify that the MRD-negative CRc rate will be compared between the treatment arms
- Sec 6.2, 6.7, 6.10, and 8: update the sample size, multiplicity strategy, timing of the analysis, and interim analysis to account for 2 independent primary endpoints
- Sec 6.8: add additional subgroups to allow subgroup analysis
- Sec 7.4: add additional details for the calculation of duration of therapy
- Sec 7.6.1: add analysis for AEs of special interest (i.e., hepatobiliary AEs)
- Sec 7.6.3: add analysis for vital sign measurements
- Sec 7.7.5: add analysis for SOS/VOD

9.2.3 Version 4 Changes

The study was terminated early due to safety concerns raised by the IDMC. The SAP was updated to include only analyses required for the abbreviated CSR. Changes from version 3 are summarized below:

- Sec 6.7: Clarify that all efficacy analyses will be descriptive in nature and no multiple testing procedure will be applied
- Sec 6.10: Clarify that no interim analysis will be conducted and final analysis will be based on 240 patients randomized into the study by the time enrollment was closed
- Sec 7.1: Remove the summary of screen failed patients
- Sec 7.5: Remove all efficacy analyses other than the descriptive summary of CRc rate, OS, MRD-neg CRc rate, and early mortality rate
- Sec 7.6.1: Add additional summary of AEs of special interest
- Sec 7.6.2: Add additional summary to evaluate the extent of neutropenia
- Sec 7.7: Remove the analyses of PRO endpoints, transfusion, MRU, and subsequent therapy
- Sec 8: Clarify that no interim analysis will be conducted and final analysis will be based on 240 patients randomized into the study by the time enrollment was closed

9.2.4 Version 5 Changes

The SAP was updated to remove analyses that are limited by data availability as a result of early study termination. Changes from version 4 are summarized below:

- Sec 6.8: Remove subgroup analysis by FLT3 and ELN risk group
- Sec 7.2: Remove ELN risk group from disease characteristics summary
- Sec 7.4: Remove dose intensity summary for HMA because azacitidine and decitabine were administered according to package inserts
- Sec 7.6.2: Remove the exploratory analyses of laboratory results
- Sec 7.6.5: Remove the summary of growth factor cumulative dose
- Remove the vital signs listing

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APPENDIX A: IMPUTATION OF PARTIALLY MISSING ADVERSE EVENT DATES

The algorithm below should be used to impute pre-existing condition and adverse event (AE) start dates for which only partial information is known. For ease of reading, both pre-existing conditions and AEs will be referred to as AE for the remainder of this document. The algorithm should be applied to every AE record on a record by record basis. AE start dates should be imputed before imputation of AE condition end date in all cases. The AE condition end date should only be used in the imputation of the AE start date if it a full known date.

AE day and month are missing

If the year is the same as the year of first dose of investigational agent and the onset period and/or onset time indicate that the start of the AE was pre-dose:

> AE start date will be imputed as the minimum of (AE condition end date*, day prior to first dose of investigational agent)

If the year is the same as the year of first dose of investigational agent and the onset period and/or onset time indicate that the start of the AE was post-dose:

> AE start date will be imputed as the minimum of (AE condition end date*, first dose date of investigational agent)

If the year is before the year of first dose of investigational agent:

> AE start date will be imputed as the minimum of (AE condition end date*, December 31st see example 2 below)

If the year is after the year of first dose of investigational agent:

> AE start date will be imputed as the minimum of (AE condition end date*, January 31st see example 2 below)

AE month only is missing

Treat day as missing and replace both month and day according to the above procedure

AE day only is missing

If the month/year is the same as the month/year of first dose of investigational agent and the onset period and/or onset time indicate that the start of the AE was pre-dose:

> AE start date will be imputed as the minimum of (AE condition end date*, day prior to first dose of investigational agent)

If the month/year is the same as the month/year of first dose of investigational agent and the onset period and/or onset time indicate that the start of the AE was post-dose:

> AE start date will be imputed as the minimum of (AE condition end date*, first dose date of investigational agent)

If the month/year is before the month/year of first dose of investigational agent:

AE start date will be imputed as the minimum of (AE condition end date*, last day of the month)

If the month/year is after the month/year of first dose of investigational agent:

AE start date will be imputed as the minimum of (AE condition end date*, last day of the month)

* only use condition end date if known and full end date is available.

The following algorithm should be used to impute AE condition end dates. The AE records for a condition/event should be sorted by the imputed start dates then record position (order of entry into the eCRF). After sorting, if any condition end date month/year is greater than any subsequent record end date month/year, then change the imputed start day only to end of month. Repeat as necessary.

After sorting the AE records, apply the following rules to partial or missing AE condition end dates:

For all records excluding the last chronological record for a condition/event

AE condition end date will be imputed as the start date of the subsequent record

For the last chronological record for a condition/event

If outcome is "recovered/resolved", "recovered/resolved with sequelae", or "fatal" apply the following:

- If only year is provided for the end date and year is equal to the year of the last dose date:
  - AE condition end date will be imputed as the minimum of (last dose date + 30, death date, data extraction date, December 31st of the end date year)
- If only year is provided for the end date and year is not equal to the year of the last dose date:
  - AE condition end date will be imputed as the minimum of (death date, data extraction date, December 31st of the end date year)
- If month and year are provided for the end date:
  - AE condition end date will be imputed as the minimum of (death date, data extraction date, last day of the end date month/year)

If outcome is "recovering/resolving", "not recovered/resolved","unknown", or blank:

AE condition end date will not be imputed.

Example 1

AESPID 1: Condition/Event HEADACHE
First dose date 01JAN2012

Prior to imputation

Start date	Condition end date	Severity	Outcome	Onset
UNUNK2011	15APR2012	1	not recovered/not resolved	pre-ICF
15APR2012	UNMAY2012	2	recovering/resolving	post 1st dose
UNMAY2012	UNJUN2012	1	not recovered/resolved	post 1st dose
UNJUN2012	UNJUN2012	3	recovering/resolving	post 1st dose
UNJUN2012	10JUL2012	2	recovering/resolving	post 1st dose
10JUL2012	--	1	not recovered/not resolved	post 1st dose

Post imputation

Start date	Condition end date	Severity	Outcome
31DEC2011	15APR2012	1	not recovered/not resolved
15APR2012	31MAY2012	2	recovering/resolving
31MAY2012	30JUN2012	1	not recovered/not resolved
30JUN2012	30JUN2012	3	recovering/resolving
30JUN2012	10JUL2012	2	recovering/resolving
10JUL2012	--	1	not recovered/not resolved

Example 2 (highlights choice of last day of the month as opposed to the 1st or the 15th)

AESPID 4: Condition/Event NAUSEA
First dose date 01APR2012

Prior to imputation

Start date	Condition end date	Severity	Outcome	Onset
UNUNK2011	25APR2012	1	not recovered/resolved	pre-ICF
25APR2012	UNAPR2012	2	recovering/resolving	post 1st dose
UNAPR2012	04MAY2012	1	recovered/resolved	post 1st dose

Post imputation

Start date	Condition end date	Severity	Outcome
31DEC2011	25APR2012	1	not recovered/not resolved
25APR2012	31APR2012	2	recovering/resolving
31APR2012	04MAY2012	1	recovered/not resolved

APPENDIX B: IMPUTATION OF PARTIALLY MISSING SUBSEQUENT ANTICANCER THERAPY START DATE

The algorithm below should be used to impute subsequent anticancer therapy start dates for which only day is missing.

- If the month and year of the subsequent anticancer therapy start date is the same as the month and year of the response assessment date, and the response is a disease progression or relapse:
    - Subsequent anticancer therapy start date will be imputed as the date of response assessment.
- If the month and year of the subsequent anticancer therapy start date is the same as the month and year of the response assessment date, and the response is not a disease progression or relapse:
    - Subsequent anticancer therapy start date will be imputed as the first day of the month.

APPENDIX C: DEFINITION OF THE TERM "TREATMENT-EMERGENT" WITH RESPECT TO AE CLASSIFICATION

The algorithm below should be used to determine whether an adverse event (AE) is classified as a treatment-emergent adverse event (TEAE). A TEAE is defined as any AE which is newly occurring or worsening in severity, where newly occurring means that the AE was not present at baseline. For ease of reading, both pre-existing conditions and AEs will be referred to as AEs for the remainder of this document. AE dates should be imputed in accordance with the algorithm detailed in Appendix A prior to determination of TEAE classification. Details of the TEAE classification are as follows:

1) Determine the first/earliest dose date/time of any study treatment (for combination studies this includes any component of the regimen)

2) Classify an AE as a baseline AE if it satisfies both of criteria a and b below:

    a) The onset period field is: "started before the signing of informed consent"; or "started after consent but before the first dose of any study treatment"; or, the onset period field is missing and the AE start date is prior to the first dose date of any study drug(step 1, above).

    b) The stop date satisfies either of i or ii below:

        i) The stop date is the same as or a later date than the first dose date of any study treatment

        ii) The stop date is missing with outcome equal to: recovering/resolving (this outcome may or may not be associated with a date); or not recovered/not resolved; or unknown.

        iii) Note: if the AE has no outcome or stop date provided it should be queried

    c) Note: If the event ended on Day 1 (the date of first dose of any study drug) it will be considered a baseline event.

3) Classify an AE as post-baseline if it meets either of criteria a or b below:

    a) The onset period of the AE is "started after the first dose of any study treatment"

    b) The onset period of the AE is missing and the AE start date is the same as or a later date than the first dose date of any study treatment

4) Compare post-baseline AEs to baseline AEs using the lower level term (LLT). **If the post-baseline AE meets any of the following criteria then classify it as a TEAE**:

    a) There is a baseline AE with the same LLT but the post-baseline AE has a greater CTC grade.

    b) There are no baseline AEs with a matching LLT for the post-baseline AE.

    c) The post-baseline AE is uncoded.