Statistical Analysis Plan

Sponsor:	Seattle Genetics, Inc.
Protocol No:	SGN33A-004
Version No./Date	Version 03/13-Apr-2017
Title	A phase 1/2 study of vadastuximab talirine (SGN-CD33A) in combination with azacitidine in patients with previously untreated International Prognostic Scoring System (IPSS) Intermediate-2 or High risk myelodysplastic syndrome (MDS)
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1.0 Introduction

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Seattle Genetics, Inc. Protocol SGN33A-004, entitled "A phase 1/2 study of vadastuximab talirine (SGN-CD33A) in combination with azacitidine in patients with previously untreated International Prognostic Scoring System (IPSS) Intermediate-2 or High risk myelodysplastic syndrome (MDS)". Results of the proposed analyses will become the basis of the final clinical study report (CSR) for this protocol.

This SAP should be read in conjunction with the study protocol and case report form (CRF). This version of the plan has been developed using the protocol dated 13 April, 2017 and CRF dated 29 August, 2017. Any further changes to the protocol or CRF may necessitate updates to the SAP.

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 clinical study report. Any changes will be reflected in amendments to this plan before the database lock, detailed below, or specifically documented in the clinical study report.

1.1 Changes from Protocol

Disposition will be presented by dose level and total, and will not be presented by cycles. The summary of duration of treatment gives information on cycles received, so disposition by cycles is not needed. Hematologic improvement was not able to be calculated as the required data components were not captured in the data.

2.0 Study Objectives

Primary Objective:

- To determine the recommended vadastuximab talirine dose in combination with azacitidine in the open-label Phase 1 Portion of study
- To compare the overall response rate (ORR = complete response + partial response [CR+PR]) between treatment arms in the randomized, double-blind, placebo-controlled Phase 2 Portion of study

Secondary Objectives:

- To evaluate the safety of the combination of vadastuximab talirine and azacitidine (Phase 1 and Phase 2 Portions)
- To compare the CR rate between treatment arms (Phase 2 Portion)
- To compare the hematologic improvement (HI) rate between treatment arms (Phase 2 Portion)
- To compare the duration of response (DOR) between treatment arms (Phase 2 Portion)
- To compare progression-free survival (PFS) between treatment arms (Phase 2 Portion)
- To compare the rate of transformation to acute myeloid leukemia (AML) between treatment arms (Phase 2 Portion)

- To compare the overall survival (OS) between treatment arms (Phase 2 Portion)

Exploratory Objectives:

- To assess the pharmacokinetics (PK) and pharmacodynamics of vadastuximab talirine (Phase 1 and Phase 2 Portions)
- To assess the incidence of antitherapeutic antibodies (ATAs) against vadastuximab talirine (Phase 1 and Phase 2 Portions)
- To assess exploratory biomarkers of clinical activity of vadastuximab talirine in combination with azacitidine (Phase 1 and Phase 2 Portions)
- To assess quality of life (QoL; Phase 2 Portion)

3.0 Study Design

3.1 Overall Study Design and Plan

This is a phase 1/2 study to evaluate the combination of vadastuximab talirine and azacitidine in subjects with previously untreated IPSS Intermediate-2 or High risk MDS. In the Phase 1 Portion of the trial, escalating doses of vadastuximab talirine will be evaluated in combination with azacitidine, and 1 dose will be selected for the randomized, double-blind, placebo-controlled Phase 2 Portion of the study, which is designed to compare the ORR between the 2 study arms.

3.1.1 Phase 1 Portion – Open-Label Dose Evaluation

Cohorts of 6 dose-limiting toxicity (DLT)-evaluable subjects will be enrolled in an open-label fashion to receive vadastuximab talirine in combination with azacitidine in 28-day cycles, starting at 5 mcg/kg vadastuximab talirine. DLT-evaluable population will include all Phase 1 subjects who have completed at least Cycle 1 of treatment (Cycle 1 of treatment is completed when the patient receives the first dose of azacitidine on Day 1 of Cycle 2) or discontinued study treatment because of adverse events (AEs) or for a safety-related reason before having had the opportunity to receive the first dose of azacitidine on Day 1 of Cycle 2. In the phase 1 Portion of the study, DLTs will be defined as posttreatment grade 4 neutropenia or grade 4 thrombocytopenia lasting >42 days from the start of therapy, in the absence of evidence of active MDS, or any grade 3 or higher non-hematologic toxicity that is clearly NOT resulting from underlying MDS or azacitidine, with the exception of:

a. Grade 3 allergic reaction, fatigue, asthenia, anorexia, or constipation

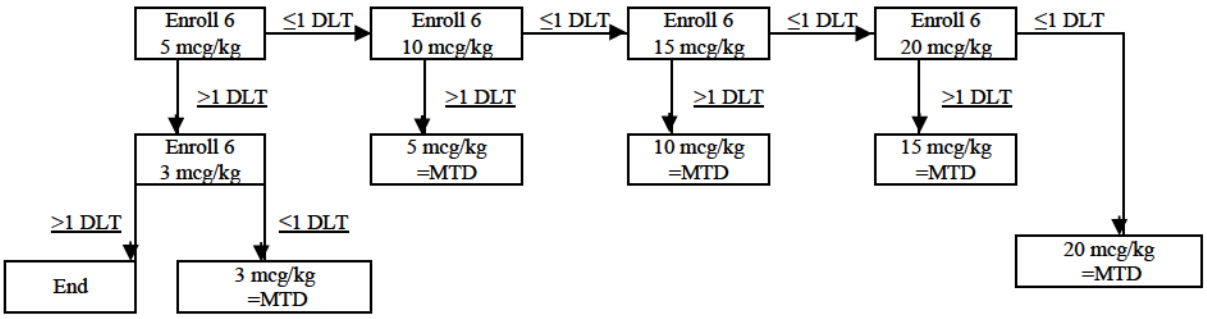
b. Grade 3 nausea, vomiting, or diarrhea not requiring tube feeding or total parenteral nutrition or hospitalization,

c. Febrile neutropenia (which resolves with appropriate treatment or marrow recovery), infection, bleeding, or other expected direct complications of cytopenias due to active MDS.

If 2 or more subjects in a 6-subject cohort have DLTs, that dose level will be considered to have exceeded the maximum tolerated dose (MTD). If 5 mcg/kg vadastuximab talirine in combination with azacitidine is considered tolerable (≤1 of 6 subjects experiences a DLT), a cohort of 6 DLT-evaluable subjects will receive 10 mcg/kg vadastuximab talirine and azacitidine. If 10 mcg/kg

vadastuximab talirine in combination with azacitidine is considered tolerable, a cohort of 6 DLT-evaluable subjects will receive 15 mcg/kg, and if 15 mcg/kg vadastuximab talirine in combination with azacitidine is considered tolerable, a cohort of 6 DLT-evaluable subjects will receive 20 mcg/kg. If 5 mcg/kg vadastuximab talirine in combination with azacitidine is not considered tolerable (>1 of 6 subjects experiences a DLT), a cohort of 6 DLT-evaluable subjects will receive 3 mcg/kg vadastuximab talirine and azacitidine. The dose escalation plan is presented in Figure 1.

Figure 1: Study Schematic – Phase 1 Portion



DLT = dose-limiting toxicity; MTD = maximum tolerated dose.

Azacitidine will be given on 7 days per cycle, either on the first 7 days or 5 days on/2 days off/2 days on; vadastuximab talirine will be given after azacitidine on the last day of azacitidine administration in each cycle. Response assessments (bone marrow examination and complete blood count [CBC]) will be conducted on Day 22-28 of even-numbered cycles until CR, then every 4 cycles thereafter. Subjects may continue on study treatment until disease progression, relapse, or unacceptable toxicity. After discontinuation of study treatment, subjects who have not experienced progression or relapse will continue to be assessed for response every 4 months through 24 months after the end of treatment (EOT) or until initiation of another anticancer treatment, progression, or relapse, whichever comes first. All subjects will be contacted for survival status every 2 months after EOT in follow up until death or study closure, whichever comes first. Safety will be monitored through the surveillance of AEs, laboratory test measures, physical examination findings, and concomitant medication records. An additional bone marrow examination will be conducted for research purposes for subjects in the Phase 1 Portion of the study only.

After 6 DLT-evaluable subjects have had the opportunity to complete at least Cycle 1 (Cycle 1 of treatment is completed when the patient receives the first dose of azacitidine on Day 1 of Cycle 2) of treatment in each planned dose cohort, the data will be aggregated and analyzed by a Safety Monitoring Committee (SMC) (Section 7.1). The SMC will comprise medical experts from Seattle Genetics or their designee and a group of the investigators involved in the Phase 1 Portion. Based on the evaluation of the data, including the incidence of DLT in each cohort, the SMC may recommend the dose of vadastuximab talirine for the Phase 2 Portion of the study at the time of the evaluation. If additional safety information is required to recommend a phase 2 dose, the SMC could recommend enrollment of up to 12 additional treated subjects to continue to evaluate the safety of the combination at vadastuximab talirine dose(s) of 3, 5, 10, or 20 mcg/kg.

3.1.2 Phase 2 Portion – Randomized, Placebo-Controlled

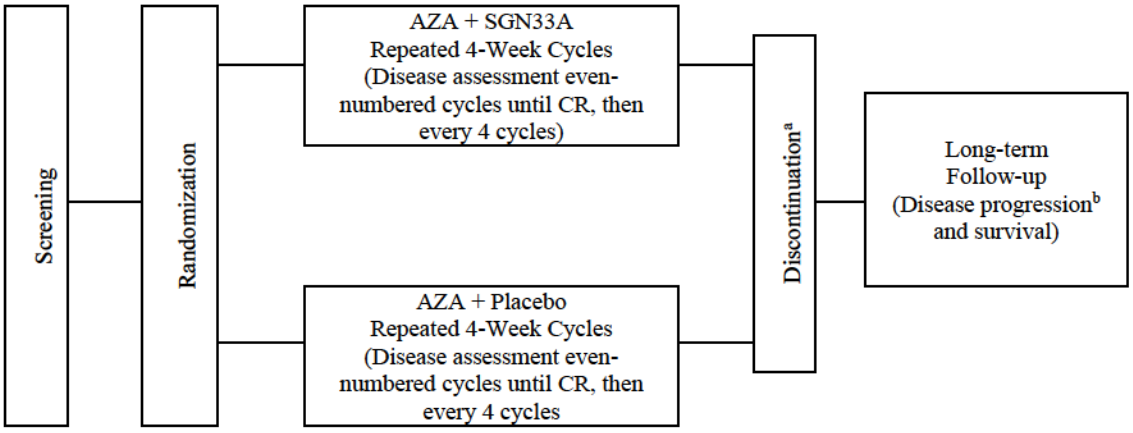
The study arms in the phase 2 portion include the following:

- Experimental arm: azacitidine in combination with vadastuximab talirine
- Comparator arm: azacitidine in combination with placebo

Subjects will be randomized in a 1:1 manner to one of the study arms above. Randomization will be stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1 or 2) and International Prognostic Scoring System (IPSS) score (Intermediate-2 vs High risk).

Subjects will receive vadastuximab talirine in combination with azacitidine in 28-day cycles, starting at the dose level of vadastuximab talirine determined in phase 1. Response assessments (bone marrow examination and CBC) will be conducted once between Day 22 and Day 29 of even-numbered cycles until CR, then every 4 cycles thereafter. Subjects may continue on study treatment until disease progression, relapse, or unacceptable toxicity. After discontinuation of study treatment, subjects who have not had progression or relapse will continue to be assessed for response every 4 months through 24 months after EOT or until initiation of another anticancer treatment, progression, or relapse, whichever comes first. All subjects will be contacted for survival status every 2 months after EOT in follow up until death or study closure, whichever comes first. Safety will be monitored through the surveillance of AEs, laboratory test measures, physical examination findings, and concomitant medication records. An Independent Data Monitoring Committee (IDMC) (Section 7.2) will also periodically assess the ongoing safety data and make recommendations to either continue evaluating the combination or to stop the study due to toxicity concerns. Figure 2 is a study schematic for the Phase 2 Portion.

Figure 2: Study Schematic – Phase 2 Portion



AZA = azacitidine; CR = complete response.

a Subjects may continue to receive repeated cycles of treatment until disease progression, relapse, unacceptable toxicity, or other discontinuation criteria are met.

b For subjects who discontinue without having experienced disease progression follow-up will include disease assessment (CBC and bone marrow) every 4 months for 24 months or until disease progression. Subjects will be followed every 2 months for survival until death or the end of the study.

Unblinding a subject's treatment assignment will be limited to emergency circumstances where knowledge of the treatment assignment would affect decisions regarding the management of the

subject. In the event of such an emergency circumstance, a formal unblinding procedure will be followed to allow the investigator to immediately access a subject's treatment assignment. Information on study treatment assignment should not be distributed to any other personnel involved in the clinical trial.

Please refer to Table 4 of the protocol for the full Schedule of Study Procedures and Assessments, Table 5 for the Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Assessments for the Phase 1 Portion and Table 6 for Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Assessments for the Phase 2 Portion.

3.2 Sample Size Considerations

Phase 1 Portion (minimum of 6 subjects per cohort): Six subjects are adequate to appropriately assess the safety profiles and DLT rates of differing dose levels of vadastuximab talirine in combination with azacitidine. If the true incidence rate of DLT is 10%, the probability of considering a dose level tolerable (ie, ≤1 of 6 subjects experiences a DLT) will be 88.6%. If the true incidence rate of DLT is 50%, the probability of considering a dose level tolerable will be 10.9%.

With this type of study design, the exact number of subjects needed to complete the Phase I Portion is unknown because it depends on the number of cohorts required to reach MTD. Approximately 24 subjects are expected to participate in the Phase 1 portion of this trial, assuming 4 dose-escalation cohorts of 6 subjects.

Phase 2 Portion (106 subjects): A sample size of 106 subjects will provide 85% power to detect a treatment difference in ORR, assuming an ORR of 30% for azacitidine alone vs 55% for the combination vadastuximab talirine with azacitidine, at a 2-sided 0.1 alpha level.

3.3 Study Duration

There will be approximately 35 sites enrolling subjects in this study. The estimated duration of study treatment through final primary analysis is approximately 51 months from enrollment of the first subject to completion of the last subject. All subjects will be contacted for survival status every 2 months after EOT in follow up until death or study closure, whichever comes first.

3.4 Randomization

During the Phase 2 Portion of the study, subjects will be randomized in a 1:1 manner to azacitidine with vadastuximab talirine and azacitidine with placebo. Randomization will be stratified by ECOG performance status (0 vs 1 or 2) and IPSS score (Intermediate-2 vs High risk).

4.0 Study Variables and Covariates

4.1 Primary Variable

The primary endpoint of the Phase 1 Portion of the study is to determine the recommended dose for the Phase 2 Portion, based upon the MTD.

The primary efficacy endpoint of the Phase 2 Portion of the study is the ORR, defined as the proportion of subjects who achieve any category of CR (CR and Marrow CR) or PR based on the 2006 International Working Group (IWG) criteria for MDS.

4.2 Secondary Variables

4.2.1 Efficacy

Secondary efficacy endpoints of the Phase 2 Portion of the study are the following:

- Complete response (CR) rate
- Hematologic improvement (HI) rate
- Duration of response (DOR)
- Progression-free survival (PFS)
- Rate of transformation to AML
- Overall survival (OS)

4.3 Other Variables

4.3.1 Pharmacokinetic and Antitherapeutic Antibody Assessments

- Estimates of selected PK parameters for plasma vadastuximab talirine and released SGD-1882
- Incidence of ATA

4.3.2 Biomarker Assessments

Biomarker assessments may include

- CD33 expression level
- Abundance of MDSC
- Characterization of leukocyte subpopulations in peripheral blood (peripheral blood mononuclear cells; PBMCs)
- Variation in sequence of CD33 and genes commonly mutated in MDS and hematologic malignancies
- Soluble CD33
- Abundance of a variety of cytokines
- Testing for Paroxysmal Nocturnal Hemoglobinuria (PNH) and human leukocyte antigen (HLA)-DR15

4.3.3 Safety

Safety assessments for both the Phase 1 Portion and the Phase 2 Portion of the study will consist of the following:

- Surveillance of AEs
- Laboratory test measures
- Physical examination findings
- Concomitant medication records.

4.3.4 Quality of Life

Quality of life for both the Phase 1 Portion and the Phase 2 Portion of the study will be assessed with the Quality of Life Questionnaire (QLQ)-C30 patient reported outcomes (PRO) tool at protocol-defined time points.

4.4 Predetermined Covariates and Prognostic Factors

Randomization will be stratified by ECOG performance status (0 vs 1 or 2) and IPSS score (Intermediate-2 vs High risk) to ensure some level of balance between treatment arms and these stratification factors will be used as covariates in statistical models for the primary analysis.

5.0 Definitions

Absolute Dose Intensity (ADI): is defined as the actual dose (µg/kg) per unit of time that the subject received over the entire treatment period. Actual time for the denominator will be calulcated separately for vadastuximab talirine and azacitidine as follows:

Vadastuxmab talirine: last day 1 dose date of azacitidine where vadastuximab talirine was received in that cycle +28 - first dose of any study drug

Azacitidine: last day 1 dose date of azacitidine +28 - first dose of any study drug

AEs Leading to Discontinuation of Study Drugs: are those indicated by "Reason for discontinuing treatment" of AE (linked by AE number) on the End of Treatment Summary page of the CRF.

Age (years): will be calculated with the SAS INTCK function using informed consent date and birth date.

ATA Incidence Rate: is defined as the proportion of patients that develop ATA at any time during the study.

Baseline: is defined as the most recent measurement prior to the first dose of any study treatment unless otherwise defined in a specific section of the SAP.

Complete Response: is defined as an answer of "Complete Remission" for the question "Response Assessment" in CRF form of "Response Assessment".

Concomitant Medication: is defined as any medication ongoing at the start of vadastuximab talirine or Placebo dosing or with a start date on or after the first dose date of any study treatment dose date up to 30 days post last dose or EOT whichever is longer. Medications with start and end dates before the first dose date of any study treatment may be concomitant if the medication is marked as ongoing. For medications with missing or partial start dates, a missing start date will be imputed with the first dose date of any study treatment, missing month and day for a partial start date will be imputed with January 1st, and missing day for a partial start date will be imputed with the first day of the month.

Days: The following unit conversion will be implemented unless otherwise specified:

Months = Days / 30.4375

Years =Days / 365.25.

Deaths: Subject deaths will be determined from End of Study CRF page (where reason for discontinuation is death) and from AE CRF page (where CTCAE grade is 5 or outcome is "fatal") and from the follow-up CRF page (where the answer to the question "Is the patient alive?" is "No"). The number of days between vadastuximab talirine or placebo last dose and death will be calculated as (date of death – last vadastuximab talirine or placebo dose date + 1).

Dose-Limiting Toxicity: see Section 3.1.1.

DLT Evaluable Subject: is defined as all Phase 1 subjects who have completed at least Cycle 1 of treatment (Cycle 1 of treatment is completed when the patient receives the first dose of azacitidine on Day 1 of Cycle 2), or discontinued study treatment because of AEs or for a safety-related reason (defined as AE, Investigator Decision, or Progressive Disease) before having had

the opportunity to receive the first dose of azacitidine on Day 1 of Cycle 2, or who experienced a DLT.

Duration of Response: is defined as the time from first observation of response (PR+CR/Marrow CR) to disease progression/relapse or death from any cause, whichever occurs first.

Duration of Treatment: is defined as time from the first dose of any study drug until 28 days after the last day 1 dose date, or until : last contact date if the patient is still on treatment at the time of the analysis.

Minimum(Last day 1 dose date + 27, death date, last contact date) – first dose date +1

Infusion Related Reactions AE: is defined for those AEs that have responses of "Yes" for the question "Were there any infusion-related reactions?" in the CRF forms "Treatment – Blinded Study Drug", "Treatment – Azacitidine", or "Treatment – Vadastuximab Talirine".

Hematologic Improvement: is defined in Table 1

Hematologic Improvement (HI) Rate: is defined in as the proportion of subjects with Erythroid response, Platelet response or Neutrophil response as defined in Table 1.

Table 1: International Working Group Response Criteria for Hematologic Improvement

Hematologic improvement*	Response criteria (responses must last at least 8 weeks)
Erythroid response (pretreatment[a], Hgb < 11 g/dL)	1. Hgb increase by ≥ 1.5 g/dL OR 2. Relevant reduction of units of red blood cell (RBC) transfusions by an absolute number of at least 4 RBC transfusions/8 weeks compared with the pretreatment transfusion number in the previous 8 weeks. Only RBC transfusions given for a Hgb of ≤ 9.0 g/dL pretreatment will count in the RBC transfusion response evaluation
Platelet response (pretreatment[a], Platelet < 100×10^9/L)	1. Absolute increase of ≥ 30×10^9/L for patients starting with > 20×10^9/L platelets; OR 2. Increase from < 20×10^9/L to > 20×10^9/L and by at least 100%
Neutrophil response (pretreatment[a], Neutrophil absolute < 1.0×10^9/L)	At least 100% increase and an absolute increase > 0.5×10^9/L
Progression or relapse after HI*	At least 1 of the following: At least 50% decrement from maximum response levels in granulocytes or platelets Reduction in Hgb by ≥ 1.5 g/dL Transfusion dependence

a Pretreatment counts averages of at least 2 measurements (not influenced by transfusions) ≥ 1 week apart.

b In the absence of another explanation, such as acute infection, repeated courses of chemotherapy, gastrointestinal bleeding, hemolysis, and so forth. It is recommended that the 2 kinds of erythroid and platelet responses be reported overall as well as by the individual response pattern.

Adapted from: Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood. 2006;108:419-425.

Marrow Complete Response: is defined as an answer of "Marrow Complete Remission" for the question "Response Assessment" in CRF form of "Response Assessment".

Objective Response Rate: is defined as the proportion of subjects with PR+CR/Marrow CR . Subjects who cannot be assessed for response will be counted as non-responders.

Pre-existing AE or Baseline AE: is defined as in Appendix 5.

Progression-Free Survival: PFS is defined as the time from first dose of study medication to first documentation of disease progression/relapse, or to death due to any cause, whichever occurs first. For subjects without disease progression/relapse or death on study, PFS will be censored at the time of the last on-study disease assessment demonstrating a lack of disease progression/relapse. If more than one date of progression is available, the earliest date will be used to determine PFS. Subjects who receive another antineoplastic therapy in the absence of documented progression will be censored at the time of receiving off-protocol therapy for

malignancy, EXCEPT that subjects who receive stem cell transplant in remission will continue to be followed for progression.

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

RDI = ADI / IDI *100.

Where IDI (intended dose intensity) is defined as the intended dose of drug (mg/kg) per unit of time.

Study Drug: The study drug is vadastuximab talirine (SGN-CD33A) for the study.

Serious AE (SAE): is defined as an answer of "Yes" for the question "Was this Serious" in CRF form of "Adverse Events and Pre-Existing Conditions".

Time Since Initial Diagnosis: is defined as

Date of first dose – date of initial MDS diagnosis + 1.

Transformation to AML: is defined as an answer of "Yes" for the question "Has the patient progressed to AML" in CRF form of "Follow-Up".

Treatment Arm, Actual

In the Phase 1 portion, the actual treatment arm will be the dose level of vadastuximab talirine the subject received in Cycle 1, regardless of the cohort in which they were enrolled.

In Phase 2 portion of the study, a subject's actual treatment arm (azacitidine in combination with vadastuximab talirine or azacitidine in combination with placebo) will be determined by whether the subject is administered vadastuximab talirine or placebo by merging the Treatment-Blinded Study Drug CRF data and the Medication Packs List using the Medication ID Number and the Kit Number. If a subject receives one or more dose of vadastuximab talirine, then the subject's actual treatment arm will be azacitidine in combination with vadastuximab talirine. If a subject receives only placebo, then the subject's actual treatment arm will be azacitidine in combination with placebo.

Treatment Arm, Randomized

In Phase 2 portion of the study, a subject's randomized treatment arm (azacitidine in combination with vadastuximab talirine or azacitidine in combination with placebo) will be the treatment arm associated with that subject's randomization number in the IXRS randomization schedule.

Treatment-Emergent AE (TEAE): All AEs reported after initiation of treatment and pre-existing conditions that worsen after initiation of treatment will be considered treatment-emergent AEs (TEAEs). See Appendix 4 and Appendix 5 for imputation of partial AE dates and detailed pre-existing AE rules, respectively. Unless otherwise specified, summaries of AEs will only include treatment-emergent events.

Treatment-Related-AE: is defined as an answer of "Yes" for the question "Was this related to Vadastuximab Talirine or Blinded Study Drug" in CRF form of "Adverse Events and Pre-Existing Conditions".

30-day Mortality Rate: is defined as the proportion of patients who die within 30 days from start of study therapy for Phase 1 and within 30 days from randomization for Phase 2.

60-day Mortality Rate: is defined as the proportion of patients who die within 60 days from start of study therapy for Phase 1 and within 60 days from randomization for Phase 2.

6.0 Analysis Sets

6.1 Intent-to-Treat Set

The intent-to-treat (ITT) set will include all subjects who are randomized in the Phase 2 Portion of the study. This set will be used for baseline and efficacy analyses. If the randomized treatment arm differs from the actual treatment at any drug administered periods for a given subject, that subject will be analyzed according to the randomized treatment arm.

6.2 Safety Set

The safety set will include all subjects who are enrolled and received at least 1 dose of study treatment (vadastuximab talirine, placebo or azacitidine) in both portions of the study. In the Phase 2 portion of the study, if the randomized treatment arm differs from the actual treatment, the subject will be analyzed according to the actual treatment arm. See Section 5 definitions of actual and randomized treatment arm.

6.3 DLT-Evaluable Set

The DLT-evaluable set will include all phase 1 subjects who completed at least Cycle 1 of treatment (Cycle 1 of treatment is completed when the patient receives the first dose of azacitidine on Day 1 of Cycle 2) or discontinued study treatment because of AEs or for a safety-related reason before having had the opportunity to receive the first dose of azacitidine on Day 1 of Cycle 2, or who had a DLT. Subjects in the DLT-evaluable set will be grouped by actual dose level.

6.4 Modified Intent-to-Treat Set

The modified intent-to-treat (mITT) set will include all ITT subjects who received at least 1 dose of study medication (azacitidine, vadastuximab talirine, or placebo) in the Phase 2 Portion of the study. Subjects will be grouped according to their randomized treatment group assignment regardless of the treatment they actually received.

7.0 Interim Analyses

No formal interim analyses for efficacy are planned for this study.

7.1 Safety Monitoring Committee

During the Phase 1 Portion of the study, the SMC will monitor the trial for safety and dose limiting toxicities (DLTs). Each dose cohort will be evaluated for DLTs prior to enrolling the subsequent cohort. Sufficient trends in safety or toxicity identified by the SMC may result in

enrollment suspension or study termination, as recommended by the SMC. The SMC may also recommend predetermined or intermediate dose levels for dose escalation and/or expansion for the Phase 2 portion of the study based on review of safety and efficacy data. In the event of a death or emergence of a life-threatening acute or chronic toxicity within the safety reporting period, enrollment to the study will be temporarily halted until the SMC convenes to review the aggregate safety data to determine if enrollment will resume, and the appropriate dose level moving forward. Additionally, the investigators and the PRA Medical Monitor will meet regularly (via teleconference, see section 7) to assess safety on an ongoing basis.

Meetings will be held approximately 1 week after the last patient completes the DLT period. The DLT period is defined as the time from start of study therapy in Cycle 1 through the start of day 1 of Azacitidine during Cycle 2, or the time at which a patient discontinues treatment due to study treatment-related toxicity prior to receiving Day 1 Cycle 2 treatment. This will occur for each dose escalation cohort that has been initiated and on an ad hoc basis as needed based on emerging safety data.

7.2 Independent Data Monitoring Committee

The IDMC will consist of 2 physicians and 1 statistician who are all external to Seattle Genetics, Inc. and free of any direct involvement with the conduct of this study beyond participation in the IDMC. The primary role of this IDMC will be to monitor safety data during the Phase 2 Portion of this study.

Details of the safety reviews will be provided in the IDMC charter.

8.0 Data Review

8.1 Data Handling and Transfer

Data handling and transfer specifications will be stated and conducted according to the Data Management Plan (DMP).

8.2 Data Screening

Beyond the data review and cleaning built into the PRA DMP, the PRA programming of analysis datasets, and TFLs provides additional data review.

Review of a TFL dry run on the nearly finalized database will allow for further data review prior to finalization. The dry run TFLs will be discussed with the sponsor in a data review meeting to identify any final data issues and seek corrections prior to database lock. The PRA statistician and the sponsor must approve database lock.

9.0 Statistical Methods

There are two phases to this study. The primary objective of the Phase 1 Portion of the study is to determine the recommended vadastuximab talirine dose in combination with azacitidine. All analyses in the Phase 1 Portion of the study will be descriptive. There will be no formal inferential analyses performed for the Phase 1 Portion of the study.

The Phase 2 Portion of the study will use inferential statistics to explore the efficacy of vadastuximab talirine dose in combination with azacitidine. All inferential analyses will compare the effect of vadastuximab talirine dose in combination with azacitidine to placebo in combination with azacitidine. Hypotheses will be two sided in nature and will be performed at the alpha = 0.1 level. Inferential statistics for continuous variables will include the estimate, the standard error (SE) of the estimate, and a 90% confidence interval. Estimates will be presented to 1 decimal more than original data. SE will be presented to 2 decimals more than original data.

Descriptive statistics (mean, median, standard deviations, minimum and maximum values) for continuous variables will be presented. Mean and median will be presented to 1 decimal more than original data. Standard deviation (SD) will be presented to 2 decimals more than original data. Minimum and maximum will match the decimal points in the original data. For categorical variables, summary measures will include the frequency and percentage (with 1 decimal place) of subjects in each category.

All data summaries and tabulations will be presented by dose level using the Safety set for the Phase 1 Portion of the analysis, and by treatment group for the ITT evaluable set for the Phase 2 Portion of the analysis set unless otherwise noted. For efficacy and exploratory analyses, further subgroup analyses are not planned.

All data summaries and tabulations will be prepared with SAS Version 9.1.4 or higher.

9.1 Subject Disposition

An accounting of study subject disposition will be tabulated by dose level and total, and the number of subjects in each analysis set will be summarized, i.e. all safety set and DLT-evaluable set for the Phase 1 Portion of the study. A similar analysis by treatment arm and total will be summarized for the ITT set, safety set, and efficacy evaluable set for the Phase 2 Portion of the study.

A tabulation of the number and percentage of subjects enrolled in the study (as defined by answering Yes to the eCRF question of "Will the patient be enrolled into the study?") at each site will be summarized by dose level and total for the Phase 1 and 2 Portion of the study.

Subjects who discontinue study treatment and subjects who withdraw from the study will be summarized by treatment arm and total along with reasons for discontinuation or withdrawal, along with number of subjects who are currently on study and on treatment. A summary table of follow up will be generated for the time from first dose to the time of last assessment, the time from end of treatment to the time of last assessment and the time from end of treatment to end of study. The summary will be presented for all enrolled subjects for the Phase 1 Portion summary and for the ITT set for the Phase 2 Portion.

A listing of subjects of the safety set for the Phase 1 Portion of the study and the ITT set for the Phase 2 Portion of the study who discontinued from the study and discontinued from the treatment will be presented including subjects' identifier, treatment center, the specific reason for discontinuation and/or for discontinuation of study treatment, the date of the last dose and the duration of treatment before discontinuation. A listing of subject eligibility and a listing of subject analysis sets will also be provided.

9.2 Protocol Deviations and Violations

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, treatment arm and/or dose level and total, and study portion. A listing of subjects with important protocol deviations will be presented.

9.3 Treatments

9.3.1 Extent of Study Drug Exposure

Phase 1 Portion Exposure

During the Phase 1 Portion of the study vadastuximab talirine will be administered every 4 weeks (after azacitidine on the last day of azacitidine administration) via IV at the assigned dose level (3 to 20 mcg/kg), based on the dose evaluation cohort.

Subjects will also receive azacitidine 75 mg/m^2 SC or IV (at the investigator's discretion) for 7 days (7 consecutive days or 5 days on/2 days off/2 days on), beginning on Day 1 of repeated 4-week cycles.

Phase 2 Portion Exposure

During the Phase 2 Portion of the study, subjects will be randomized to receive either vadastuximab talirine administered every 4 weeks (after azacitidine on the last day of azacitidine administration) via IV push at the dose determined in the Phase 1 Portion or placebo every 4 weeks (after azacitidine on the last day of azacitidine administration) via IV push.

All subjects will also receive azacitidine 75 mg/m^2 SC or IV (at the investigator's discretion) for 7 days (7 consecutive days or 5 days on/2 days off/2 days on), beginning on Day 1 of repeated 4-week cycles.

Treatment administration of both vadastuximab talirine and azacitidine will be summarized for both study phases by dose level using the safety set. The number and percentage of subjects whose dose was ever modified will be summarized by modification type, cycle and overall (i.e. over all drug administrations for a subject). Summary statistics related to duration of treatment and compliance will be presented as detailed below. For the continuous parameters, the mean, SD, median, minimum and maximum will be presented. The following summary statistics related to drug exposure will be calculated by dose level:

The number and percentage of subjects with at least 1 dose delayed, the number of doses delayed, at least 1 dose reduced, the number of doses reduced, the number of subjects with at least 1 dose unplanned adjustment and reasons for unplanned adjustment, and number of unplanned dose adjustments, the number of subjects with at least one infusion-related reaction, the number of infusion-related reactions, the number of subjects with a delayed hypersensitivity reaction, the number of delayed hypersensitivity reactions, the duration of treatment (weeks), the

number of doses received, the number of treatment cycles received (continuous summary), the number of subjects receiving 1, 2, 3, etc. cycles, the cumulative dose administered (µg/kg and total µg), the average dose per cycle (µg/kg and µg), absolute dose intensity (µg/kg), and relative dose intensity (%) will be presented.

A listing of intended dose regimen, intended dose, actual dose administered, and reasons for dose delayed, dose reduced, dose adjustment, and/or infusion-related reactions will be displayed.

9.3.2 Concomitant Medications

Other than the study drugs, any medication taken by subjects during the course of the study with a start date on or after the first dose of any study drug, start date prior to first dose date and end date after first dose date or marked as ongoing, will be considered concomitant. Medications stopped prior to the date of the first dose of any study drug will not be considered concomitant. Prior medications include all medications with a start date before the first day of treatment of any study drug and stopped prior to the date of first dose. Subjects in the safety set with multiple uses of a concomitant medication will be counted once for a given Anatomical-Therapeutic Chemical (ATC) and preferred name.

The number and percentage of subjects with each concomitant medication will be summarized by ATC class and preferred name for all treated subjects by planned dose level for each study portion. Preferred names will be presented in descending order of frequency in total.

Additionally, all medications will be listed by subject, displaying verbatim name, synonym (if applicable) and preferred name, indication, and start and stop dates.

9.4 Demographic and Baseline Characteristics

The number and percentage of subjects will be provided for Sex (male, female), race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other), ethnicity (Hispanic or Latino, Not Hispanic or Latino), ECOG performance status stratification category (0, 1 or 2), and IPSS stratification category (intermediate-2, high risk). Descriptive statistics will be provided for age (years), weight (kg), height (cm), and body surface area (BSA).

Baseline disease characteristics will be presented. The number and percentage of subjects will be provided for MDS Subtype (WHO 2008 Classification), cytopenias (hemoglobin count < 10 g/dL, absolute neutrophil count < 1500/µL, platelet count < 100,000/µL), blasts in the bone marrow (5-10%, 11-20%), cytogenetics (normal, all other abnormalities not valued as good or poor, 3 or more abnormalities or abnormal chromosome 7), IPSS classification (low, intermediate-1, intermediate-2, high), cytogenic category (very good, good, intermediate, poor, very poor), and IPSS-R category (very low, low, intermediate, high, very high) at baseline. Descriptive statistics will be provided for IPSS-R score, time since initial diagnosis, hemoglobin (g/dL), absolute neutrophil count ($x10^9$/L), platelets ($x10^9$/L), and bone marrow blasts (percent).

Prior cancer-related therapy data will be summarized as number and percentage for each therapy type (systemic therapy, radiotherapy) and current disease status of prior cancer (complete

remission, stable disease, active disease). In addition, the number and percentage of subjects with any prior therapy will be displayed.

Medical history will be summarized by count and percentage of subjects experiencing medical history events by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT).

Summaries will be presented by treatment group and study phase. Summaries for the Phase 1 Portion will be presented using the Safety Set. Summaries for the Phase 2 Portion will be presented using the ITT set.

By-subject listings include demographic and baseline characteristics, initial disease diagnosis, prior cancer-related therapy, and general medical history.

9.5 Efficacy Analyses

The primary endpoint of the Phase 2 Portion is ORR, and the study will be unblinded for analysis of ORR after all subjects have completed 6 cycles of therapy or have discontinued treatment for any reason before completing 6 cycles. Data collection for the secondary efficacy endpoints and the safety and other endpoints will continue in an unblinded or partially blinded fashion until all subjects have discontinued study treatment.

Primary and secondary endpoint analyses will be presented for the ITT set and the All Treated set for the Phase 2 Portion of the study. Summaries for the Phase 1 Portion of the study will be presented for the safety set.

9.5.1 Primary Efficacy Endpoint

Subjects will be assigned a response status based on assessments at each visit. The primary efficacy endpoint of the Phase 2 Portion of the study is ORR, defined as the proportion of subjects who achieve any category of CR (CR and Marrow CR) or PR based on the 2006 IWG criteria for MDS that are summarized in Appendix 18.6 of the protocol. ORR will be assessed during the on treatment period until EOT. Subjects who are not evaluable at any time during the treatment period will be considered non-responders.

The ORR will be summarized by treatment group and the treatment difference in ORR will be tested using a Cochran-Mantel-Haenszel (CMH) test stratified by randomization strata (ECOG status at baseline, that is, 0 vs 1 or 2 and IPSS category at baseline, that is, Intermediate-2 vs High risk). The 90% confidence interval for the treatment difference in ORR will be calculated.

ORR will be summarized descriptively, including 95% confidence intervals using the exact binomial method, by dose for the Safety set in the Phase 1 Portion of the study.

9.5.2 Secondary Efficacy Endpoints

The following analyses for the secondary endpoints will be performed for the Safety set for the Phase 1 Portion and ITT and EE set for the Phase 2 Portion of the study, respectively.

CR Rate, HI rate, and Rate of transformation to AML will be summarized descriptively by treatment arm or dose level. The corresponding 90% confidence intervals for the difference in rate between the 2 treatment arms will be provided for the 2 Portion of the study.

The number and percent of subjects with disease response of CR, Marrow CR, PR, stable disease [SD], PD or Relapse from CR / PR as collected on the Response Assessment CRF form will be presented at each visit by treatment arm or dose level.

Time-to-event variables (DOR, PFS, and OS) will be summarized descriptively using the Kaplan-Meier methodology using the SAS LIFETEST procedure. Medians and quartiles and their two sided 90% CI using the complementary log-log transformation method will be calculated, where possible. PFS probability at 3, 6, 9,…51 months with corresponding CIs will be reported. . Kaplan-Meier figures will be presented by treatment arm or dose level.

9.5.2.1 Duration of Response

DOR (for PR/CR and CR) is defined as the time from first observation of response (PR+CR/Marrow CR or CR/Marrow CR) to disease progression/relapse or death from any cause, whichever occurs first. Durations will be assessed in the ITT population with a PR or CR and calculated separately for subjects with CR/Marrow CR and those with PR+CR/Marrow CR combined. For subjects with a remission without subsequent disease progression/relapse or death on study, DOR will be censored at the time of the last disease assessment demonstrating a lack of disease progression/relapse. Subjects who receive another antineoplastic therapy in the absence of documented progression will be censored at the time of receiving off-protocol therapy for malignancy, EXCEPT that subjects who receive stem cell transplant in remission will continue to be followed for progression. Subjects who do not have a subsequent response assessment after their first observation of response will be censored at that date (day 1).

9.5.2.2 Progression-Free Survival

PFS is defined as the time from first dose of study medication to first documentation of disease progression/relapse, or to death due to any cause, whichever occurs first. For subjects without disease progression/relapse or death on study, PFS will be censored at the time of the last on-study disease assessment demonstrating a lack of disease progression/relapse. If more than one date of progression is available, the earliest date will be used to determine PFS. Subjects who receive another antineoplastic therapy in the absence of documented progression will be censored at the time of receiving off-protocol therapy for malignancy, EXCEPT that subjects who receive stem cell transplant in remission will continue to be followed for progression. Subjects who do not have a post-baseline response assessment after will be censored at baseline (day 1).

9.5.2.3 Overall Survival

OS is defined as the time from first dose of study medication to death due to any cause. For subjects not known to have died at the end of the study, OS will be censored at the time the subject was last known to be alive (including follow-up data).

9.5.3 Other Efficacy Endpoints

9.5.3.1 Quality of Life

The QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales (Physical functioning, Role functioning, Emotional functioning, Cognitive functioning, Social functioning), three symptom scales (Fatigue, Nausea and vomiting, Pain), a global health status / QoL scale, and six single items (Dyspnoea, Insomnia, Appetite loss, Constipation, Diarrhoea, Financial difficulties). Each of the multi-item scales includes a different set of items – no item occurs in more than one scale.

The QLQ-C30 is collected at Cycle 1, Day 1 pretreatment. This will be the baseline measure. The questionnaire is collected on Day 1 of even-numbered cycles thereafter.

All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level.

Thus a high score for a functional scale represents a high / healthy level of functioning, a high score for the global health status / QoL represents a high QoL, but a high score for a symptom scale / item represents a high level of symptomatology / problems.

The principle for scoring these scales is the same in all cases:

1. Estimate the average of the items that contribute to the scale; this is the raw score.

2. Use a linear transformation to standardize the raw score, so that scores range from 0 to 100; a higher score represents a higher (“better”) level of functioning, or a higher (“worse”) level of symptoms.

SAS coding of the scoring procedure is presented in the scoring manual page 54 of the manual.

Data from the QLQ-C30 will be scored as recommended by the European Organization for Research and Treatment of Cancer and summarized descriptively for the functional scales, symptom scales, individual items, and the global health status. Normalized scores and their changes from baseline will be summarized for functional scales, symptom scales, individual items, and the global health status.

9.5.3.2 Pharmacokinetics and Immunogenicity

Blood samples for PK and ATA assessments will be collected at the time points outlined in Table 4 and 5 in the protocol. Sensitive, qualified assays will be used to measure concentrations of antibody-drug conjugate (ADC) (vadastuximab talirine) and SGD-1882 in plasma and ATA in serum. Remaining PK samples will be archived for possible analysis of SGN-CD33-related species. The assays will include enzyme-linked immunosorbent assays (ELISA) and liquid chromatography/tandem mass spectrometry assays, as well as other assays if further characterization is required. A qualified electrochemiluminescence assay will be used to assess ATA.

Estimates of selected PK parameters (vadastuximab talirine ADC and SGD-1882) and incidence of ATA to vadastuximab talirin will be summarized by phase and treatment arm or dose level.

9.5.3.3 Biomarkers

Biomarker assessments may include CD33 expression level, abundance of myeloid-derived suppressor cells (MDSC), characterization of leukocyte subpopulations in peripheral blood mononuclear cells (PBMC), variation in sequence of CD33 and genes commonly mutated in MDS and hematologic malignancies, soluble CD33, abundance of a variety of cytokines, and testing for paroxysmal nocturnal hemoglobinuria (PNH) and HLA-DR15 at protocol-specified time points. Methods of analysis may include flow cytometry, ELISA, deoxyribonucleic acid (DNA), and ribonucleic acid (RNA) sequencing. Biomarker results may be defined and presented in a separate report.

9.5.4 Methods for Handling Dropouts and Missing Data

With the exception of time-related endpoints, missing observations will generally be treated as missing at random and will not be imputed, unless otherwise noted.

For time-related endpoints, DOR and PFS will follow Table 2 below:

Table 2: Kaplan-Meier Analysis Rules

Situation	Date of Progression or Censoring	Outcome
No baseline and/or post-baseline disease assessment	Date of first dose	Censored
No documented progression	Date of last adequate response assessment (or Study Day 1 in the absence of a post-baseline response assessment)	Censored
PD documented during or between scheduled visits	Date of response assessment demonstrating PD	Event
New subsequent cancer therapy initiated prior to documented progression	Start date of new subsequent cancer therapy	Censored
Death before first PD assessment	Date of death	Event
Death between response assessment visits	Date of death	Event

For concomitant medication dates, see Section 5 for imputation rules. For missing or partial start and stop adverse event dates, see Appendix 4 for imputation rules.

Note that the actual value for date (not imputed) will be presented in all data listings and imputed dates will be used for derivations only.

9.5.5 Multiplicity

No adjustments for multiple testing will be utilized for any analyses.

9.5.6 Pooling of Sites

No pooling of sites will be used in any analyses.

9.6 Safety Analyses

Safety data will be summarized for the safety set separately for Phase 1 and Phase 2 Portions by treatment arm or dose level. For the Phase 2 Portion of the trial summaries will be by actual treatment received. Actual treatment for the Phase 2 Portion of the trial is defined as follows:

- Any subject who receives at least one dose of vadastuximab talirine will be assigned an "actual" treatment of vadastuximab talirine.
- Subjects who only receive azacitidine for the duration of the trial will be assigned an "actual" treatment of azacitidine.

9.6.1 Adverse Events

9.6.1.1 Dose Limiting Toxicities

The incidence of DLTs will be summarized using the DLT evaluable set. The number and percentage of subjects experiencing a DLT and not experiencing a DLT will be presented for each dose level for the DLT evaluable set.. The DLTs observed will be summarized by dose level and by MedDRA PT. DLTs will also be summarized by category of NCI CTCAE (version 4.03) grade by SOC and PT.

9.6.1.2 Adverse Events and Serious Adverse Events

AEs will be summarized by descending frequency of MedDRA PT unless otherwise specified. For incidence reporting, if a subject reports more than one AE that was coded to the same SOC or PT, the subject will be counted only once for that specific SOC or PT. See Section 5 for definition of pre-existing AEs, TEAEs, related AEs, SAEs, infusion-related reaction AEs and AEs leading to vadastuximab talirine treatment discontinuation. All the AEs summarized in tables are TEAEs, except related AEs or unless otherwise indicated. All AEs will be coded by SOC, MedDRA PT, and severity grade using NCI CTCAE. All recorded AEs will be included in the data listings.

A summary table of number and percent of the following AE categories will be provided by treatment or dose level and total as follows:

- Pre-existing AEs
- All TEAEs
- TEAEs related to vadastuximab talirine or placebo
- TEAEs related to azacitidine treatment
- TEAEs with outcome of death
- Treatment-emergent SAEs
- Treatment-emergent SAEs related to vadastuximab talirine or placebo
- Treatment-emergent SAEs related to azacitidine treatment

- TEAEs leading to dose delay of vadastuximab talirine or placebo treatment
- TEAEs leading to dose delay of azacitidine treatment
- TEAEs leading to dose interruption (full dose received) of vadastuximab talirine or placebo treatment
- TEAEs leading to dose interruption (full dose received) of azacitidine treatment
- TEAEs leading to dose being stopped early (full dose not received) of vadastuximab talirine or placebo treatment
- TEAEs leading to dose being stopped early (full dose not received) of azacitidine treatment
- TEAEs leading to dose reduction of vadastuximab talirine or placebo treatment
- TEAEs leading to dose reduction of azacitidine treatment
- TEAEs leading to treatment discontinuation
- Treatment-emergent SAEs leading to treatment discontinuation
- Vadastuximab Talirine -related TEAEs leading to treatment discontinuation
- Azacitidine -related TEAEs leading to treatment discontinuation
- Grade 3-5 TEAEs
- Grade 3-5 vadastuximab talirine or placebo treatment-related TEAEs
- Grade 3-5 azacitidine treatment-related TEAEs
- Infusion-related reaction TEAEs

All the above categories of AEs as well as TEAEs that started during infusion and TEAEs that started within 24 hours post infusion will be displayed by descending frequency of PT by total. TEAEs will be summarized by SOC, PT by treatment or dose level, and total. TEAEs will also be summarized by SOC, PT, maximum severity, treatment or dose level, and total. The listings include subjects with TEAE leading to treatment discontinuation. All AEs (including non-treatment-emergent events) recorded on the CRF will be listed.

9.6.1.3 Deaths and Serious Adverse Events

The number of total deaths (see definition in Section 5), deaths that occur within 30 days of last vadastuximab talirine treatment, and deaths that occur more than 30 days after last vadastuximab talirine treatment as well as the relationship to disease will be summarized by treatment or dose level and total.. The number and percentage of subjects who died will be summarized by category of disease related or not. They will be also summarized in the same way and stratified by death date within or after 30 days of last vadastuximab talirine dose.

The 30-day and 60-day mortality rates (see definition in Section 5) and the associated 90% CIs will be summarized by treatment group.

Death information will be listed by subject. Additionally, listings of AEs leading to death and SAEs will be generated.

9.6.2 Laboratory Data

Hematology laboratory parameters include white blood cell count, red blood cell count, hemoglobin, hematocrit and platelets, and the differential includes: neutrophils, lymphocytes, monocytes, eosinophils, and basophils.

The chemistry tests includes: Albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), calcium, creatinine, chloride, ferritin, lactate dehydrogenase (LDH), phosphorus, potassium, sodium, total bilirubin, uric acid and lipase, amylase~~, and hemoglobin A1c (at screening only)~~ and Creatinine Clearance as estimated by the central lab as-Glomerular Filtration Rate.

Inflammatory serologies include: C-reactive protein (CRP), C3, and C4.

Specialty autoimmune serologies include: Anti-neutrophil cytoplasmic antibodies (ANCA), anti-double-stranded DNA (anti-dsDNA), quantitative immunoglobulins (IgM, IgG, IgA), rheumatoid factor (RF), antinuclear antibodies (ANA), and Direct Coomb's.

Laboratory data values will be converted to standard units by conversion programming. A list of Standard units used to present laboratory data is provided in Appendix 2.

Where laboratory values are categorized into NCI CTCAE version 4.03 grades, the categories are defined according to the criteria available on the following website:

http://evs.nci.nih.gov/ftp1/CTCAE/About.html

NCI CTCAE grades will be applied for the following lab parameters (given in Appendix 3). Laboratory measurements that are within their institutional limits of normal and are not graded as 1-4, per the CTCAE, will be summarized as "Grade 0," which is defined as normal.

Hematology: White blood cell (WBC) count with 5-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), red blood cell count, platelet count, hemoglobin, and hematocrit.

Chemistry: Albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), calcium, creatinine, chloride, ferritin, lactate dehydrogenase (LDH), phosphorus, potassium, sodium, total bilirubin, uric acid, lipase, and amylase).

Clinical laboratory data (hematology, complete blood count [CBC] with differential, serum chemistry, inflammatory serologies, and specialty autoimmune serologies) will be presented graphically (mean and standard deviation) for selected laboratory tests, by treatment or dose level and scheduled visit. Summary statistics may be tabulated where appropriate. The worst post-baseline NCI CTCAE v4.03 will be presented by treatment or dose level and total for each laboratory test. Subjects with at least one on-study measurement for each laboratory parameter will be included, regardless of whether or not a baseline assessment is present.

Laboratory results and NCI CTCAE grades for hematology, and serum chemistry will be presented in data listings. Normal ranges will be documented and out-of-range values will be flagged by subject listings of grade 3 or higher abnormal lab results. Continuous summaries will be presented by clinical laboratory results, clinical visit, treatment group or dose level and study portion for actual results and changes from baseline. A shift table from baseline to worst observed post-baseline measure will also be presented.

9.6.3 ECOG Performance Status

Shifts from baseline to the best and worst post-baseline score will be tabulated by treatment or dose level.

A by-subject listing of ECOG performance status will be generated.

9.6.4 Physical Examinations, Electrocardiogram, and Other Observations Related to Safety

Clinically significant findings observed during physical examinations will be recorded on the AE and pre-existing condition CRFs. No analyses for physical examinations will be performed.

By-subject listings of weight, height , electrocardiogram (ECG) results, and subsequent cancer-related therapies will be generated.

10.0 Validation

PRA seeks to ensure the quality of the results provided for the study in the form of TFLs, and the derived datasets used in their creation, through the following processes:

The entire set of TFLs will be checked for completeness and consistency prior to its delivery to the client by the lead analysis programmer, the lead statistician, and a senior level statistician, or above, who is not a member of the project team.

The PRA validation process will be repeated any time TFLs are redelivered using different data. Execution of this validation process will be documented through the study Table of Programs that will be provided to Seattle Genetics at study conclusion.

Appendix 1 Glossary of Abbreviations

Glossary of Abbreviations:	
ADC	Antibody-drug Conjugate
ADI	Absolute Dose Intensity
AE	Adverse event
ALP	Alkaline Phosphatase
ALT	Aminotransferase
AML	Acute Myeloid Leukemia
ANA	Antinuclear Antibodies
ANCA	Anti-neutrophil Cytoplasmic Antibodies
AST	Aspartate Aminotransferase
ATA	Antitherapeutic Antibodies
ATC	Anatomical-Therapeutic Chemical
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMH	Cochran-Mantel-Haenszel
CR	Complete Response
CRF	Case Report Form
CRP	C-reactive Protein
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting Toxicity
DNA	Deoxyribonucleic Acid
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ELISA	Enzyme-linked Immunosorbent Assays
EOT	End of Treatment
HI	Hematologic Improvement
IDMC	Independent Data Monitoring Committee

IPSS	International Prognostic Scoring System
ITT	Intent to Treat
IWG	International Working Group
LDH	Lactate Dehydrogenase
MDS	Myelodysplastic Syndrome
MDSC	Myeloid-Derived Suppressor Cells
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PFS	Progression Free Survival
PK	Pharmacokinetic
PNH	Paroxysmal Nocturnal Hemoglobinuria
PR	Partial Response
PRO	Patient Reported Outcome
PT	Preferred Term
QoL	Quality of Life
QLQ	Quality of Life Questionnaire
RDI	Relative Dose Intensity
RF	Rheumatoid Factor
RNA	Ribonucleic Acid
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SD	Standard Deviation
SE	Standard Error
SMC	Safety Monitoring Committee
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event

TFL	Tables, Listings, and Figures
WBC	White Blood Cell

Appendix 2 Laboratory Standard Units

Laboratory Test	Conventional Units
Alanine Transaminase	U/L
Albumin	g/L
Alkaline Phosphatase	U/L
Amylase	U/L
Aspartate Transaminase	U/L
Basophils	10^9/L
Bilirubin (Total)	umol/L
Blood Urea Nitrogen	mmol/L
Calcium	mg/dL
Chloride	mmol/L
Creatinine	umol/L
Eosinophils	10^9/L
Ferritin	pmol/L
Gamma-glutamyltransferase	U/L
GFR	ml/min
Glucose	mg/dL
Hematocrit	Ratio
Hemoglobin	g/dL
Hemoglobin A1C	%
International normalized ratio	%
Lactate Dehydrogenase	U/L
Lipase	U/L
Lymphocytes	10^9/L
Magnesium	mg/dL
Monocytes	10^9/L
Total Neutrophils	10^9/L
Partial Thromboplastin Time	seconds
Phosphorous	mmol/L
Platelets	10^9/L
Potassium	mmol/L
Prothrombin Time	seconds
Sodium	mmol/L
Uric Acid	mmol/L
White Blood Cells	10^9/L
Red Blood Cells	10^{12}/L

Appendix 3 CTCAE v4.03 Grading for Laboratory Values and QTc

CTCAE v4.03 SOC	CTCAE v4.03 Term	Grade 1	Grade 2	Grade 3	Grade 4
Investigations	White blood cell decreased	<LLN - 3000/mm^3; <LLN - 3.0 × 10^9/L	<3000 - 2000/mm^3; <3.0 - 2.0 × 10^9/L	<2000 - 1000/mm^3; <2.0 - 1.0 × 10^9 /L	<1000/mm^3; <1.0 × 10^9/L
Investigations	White blood cell increased (leukocytosis)	-	-	>100,000 mm^3	Clinical manifestations of leucostasis; urgent intervention indicated
Blood and lymphatic system disorders	Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated
Investigations	Lymphocyte count decreased	<LLN - 800/mm^3; <LLN - 0.8 x10^9 /L	<800 - 500/mm^3; <0.8 - 0.5 × 10^9 /L	<500 - 200/mm^3; <0.5 - 0.2 × 10^9 /L	<200/mm^3; <0.2 × 10^9 /L
Investigations	Lymphocyte count increased	-	>4000 - 20,000 mm^3	>20,000 mm^3	-
Investigations	Neutrophil count decreased	<LLN - 1500/mm^3; <LLN - 1.5 × 10^9/L	<1500 - 1000/mm^3; <1.5 - 1.0 × 10^9/L	<1000 - 500/mm^3; <1.0 - 0.5 × 10^9/L	<500/mm^3; <0.5 × 10^9/L
Investigations	Platelet count decreased	<LLN - 75,000/mm^3; <LLN - 75.0 × 10^9/L	<75,000 - 50,000/mm^3; <75.0 - 50.0 × 10^9/L	<50,000 - 25,000/mm^3; <50.0 - 25.0 × 10^9/L	<25,000/mm^3; <25.0 × 10^9/L
Metabolism and nutrition disorders	Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated
Investigations	Alkaline phosphatase increased	>ULN - 2.5 × ULN	>2.5 - 5.0 × ULN	>5.0 - 20.0 × ULN	>20.0 × ULN
Investigations	Alanine aminotransfera	>ULN - 3.0 × ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 × ULN

CTCAE v4.03 SOC	CTCAE v4.03 Term	Grade 1	Grade 2	Grade 3	Grade 4
	se increased				
Investigations	Aspartate aminotransferase increased	>ULN - 3.0 × ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 × ULN
Investigations	Blood bilirubin increased	>ULN - 1.5 × ULN	>1.5 - 3.0 × ULN	>3.0 - 10.0 × ULN	>10.0 × ULN
Investigations	GGT increased	>ULN – 2.5 x ULN	>2.5 - 5.0 × ULN	>5.0 - 20.0 × ULN	>20.0 × ULN
Investigations	Hemoglobin increased	Increase in >0-2 gm/dl above ULN or above baseline if baseline is above ULN	Increase in >2-4 gm/dl above ULN or above baseline if baseline is above ULN	Increase in >4 gm/dl above ULN or above baseline if baseline is above ULN	-
Investigations	INR increased	>1-1.5 x ULN; >1-1.5 times above baseline if on anticoagulation	>1.5-2.5 x ULN; >1.5-2.5 times above baseline if on anticoagulation	>2.5 x ULN; >2.5 times above baseline if on anticoagulation	-
Investigations	Prolonged PTT	>ULN - 1.5 × ULN	>1.5 – 2.5 × ULN	>2.5 × ULN; hemorrhage	-
Metabolism and nutrition disorders	Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences
Metabolism and nutrition disorders	Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life-threatening consequences

CTCAE v4.03 SOC	CTCAE v4.03 Term	Grade 1	Grade 2	Grade 3	Grade 4
Investigations	Creatinine increased	>1 - 1.5 × baseline; >ULN - 1.5 × ULN	>1.5 - 3.0 × baseline; >1.5 - 3.0 × ULN	>3.0 baseline; >3.0 - 6.0 × ULN	>6.0 × ULN
Metabolism and nutrition disorders	Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 - 500 mg/dL; >13.9 - 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Metabolism and nutrition disorders	Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life-threatening consequences; seizures
Metabolism and nutrition disorders	Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L; life-threatening consequences
Metabolism and nutrition disorders	Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; life-threatening consequences
Metabolism and nutrition disorders	Hypophosphatemia	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 - 1.0 mg/dL; <0.6 - 0.3 mmol/L	<1.0 mg/dL; <0.3 mmol/L; life-threatening consequences
Metabolism and nutrition disorders	Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences
Metabolism and nutrition disorders	Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences
Metabolism and nutrition disorders	Hyponatremia	<LLN - 130 mmol/L	-	<130 - 120 mmol/L	<120 mmol/L; life-threatening consequences
Metabolism and nutrition disorders	Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences
Metabolism and nutrition disorders	Hyperuricemia	>ULN – 10 mg/dl (0.59 mmol/L) without physiologic	-	>ULN - 10 mg/dl (0.59 mmol/L) with physiologic consequences	>10 mg/dl ; >0.59 mmol/L; life-threatening consequences

CTCAE v4.03 SOC	CTCAE v4.03 Term	Grade 1	Grade 2	Grade 3	Grade 4
		consequences			
Electrocardiogram QT corrected interval prolonged		QTc 450 - 480 ms	QTc 481 - 500 ms	QTc >= 501 ms	

Appendix 4 Imputation of Partially Unknown 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/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/resolved	post 1st dose

Post imputation

Start date	Condition end date	Severity	Outcome
31DEC2011	15APR2012	1	not recovered/resolved
15APR2012	31MAY2012	2	recovering/resolving
31MAY2012	30JUN2012	1	not recovered/resolved
30JUN2012	30JUN2012	3	recovering/resolving
30JUN2012	10JUL2012	2	recovering/resolving
10JUL2012	--	1	not recovered/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/resolved
25APR2012	31APR2012	2	recovering/resolving
31APR2012	04MAY2012	1	recovered/resolved

Appendix 5 Treatment Emergent Adverse Event Programming Guide

Term	Standard Definition
Treatment emergent	Any newly occurring or worsening AE, where newly occurring means an AE that was not present at baseline. Eg, if the patient had a grade 1 headache at baseline that resolved and later had another grade 1 headache, that second headache would NOT be considered a TEAE. See below for more algorithm details. Where: 1. Get first dose date/time of any study treatment (the earliest of Azacitidine or vadastuximab talirine/placebo) 2. Define baseline AEs as AEs with: • an onset period of ("started before the signing of informed consent", or "started after consent but before the first dose of any study treatment". If the onset period of the AE is missing, then look for AE start date < first dose date (from 1). If AE start date is missing, use AE start date imputation rule. **<AND>** • a stop date that is: ➢ ≥ first dose date **<OR>** ➢ missing with outcome equal to ▪ recovering/resolving (this outcome may or may not have a date with it), or ▪ not recovered/not resolved, or ▪ unknown ▪ *Note: AEs with no outcome and missing stop dates should be queried.* • Note: If the event ended on Day 1 (the day of first dose) it will be considered a baseline event. 3. Define post-baseline AEs as AEs with an onset period of ("started after the first dose of any study treatment". If the onset period of the AE is missing, then look for AE start date >= first dose date (from 1). If AE start date is missing, use AE start date imputation rule. 4. Compare post-baseline AEs to baseline AEs using lower level term (LLT). • If terms match from baseline to post-baseline: ➢ Compare CTC grades. If post-baseline CTC grade is > baseline CTC grade, then TEAE=YES. If post-baseline CTC grade is <= Baseline CTC grade, then TEAE=NO. • If there are no matching terms from baseline to post-baseline, then TEAE=Yes.

	• If post-baseline AEs are uncoded, then TEAE = Yes. NOTE: if TEAE = 1 or . then include in output, i.e. only exclude TEAE= 0 for "Treatment-emergent" outputs.