STUDY PROTOCOL

SY-1425-201

Protocol Title: A Biomarker-Directed Phase 2 Trial of SY-1425, a Selective Retinoic Acid Receptor Alpha Agonist, in Adult Patients with Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS)

Protocol Number: SY-1425-201

Phase: 2

Study Drug: SY-1425 (tamibarotene), azacitidine, and daratumumab

IND number: 129755

EudraCT number: 2017-000783-14

Date of Protocol: 31 August 2022 (Amendment 7)

Version History

Amendment 6: *29 March 2019 – France only*

Amendment 5: *25 April 2018*

Amendment 4: *25 September 2017 – USA Only*

Amendment 3: *07 July 2017*

Amendment 2: *20 March 2017*

Amendment 1: *23 August 2016*

Original: *18 March 2016*

Sponsor: Syros Pharmaceuticals, Inc.
35 CambridgePark Drive, 4th Floor
Cambridge, MA 02140
USA

Not for Distribution – Do Not Copy

INVESTIGATOR PROTOCOL APPROVAL

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to principles of Good Clinical Practice and local regulations and requirements.

Institution/Clinic: _____

Principal Investigator

Print Name: _____

Signature: _____

Date (mm/dd/yyyy): _____

SPONSOR PROTOCOL APPROVAL

I have read this protocol and I approve the design of this study:

[redacted] _____ _____ [redacted]

Date

Syros Pharmaceuticals

CONTACT INFORMATION

Sponsor: Syros Pharmaceuticals, Inc.
35 CambridgePark Drive, 4th Floor
Cambridge, MA 02140
USA

PROTOCOL SYNOPSIS

Study Title:

A Biomarker-Directed Phase 2 Trial of SY-1425, a Selective Retinoic Acid Receptor Alpha Agonist, in Adult Patients with Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS)

Protocol Number:

SY-1425-201

Phase:

2

Name of Study Drugs:

SY-1425, azacitidine, and daratumumab

Study Population:

- Relapsed and/or refractory non-acute promyelocytic leukemia (APL) acute myeloid leukemia (AML) patients who have failed to achieve a complete remission (CR) or partial remission (PR) following standard induction therapy, or have relapsed after any duration of CR or PR
- Relapsed and/or refractory higher-risk Myelodysplastic Syndrome (MDS) (High/Very High Risk, as defined by the Revised International Prognostic Scoring System [IPSS-R]) patients that have failed to achieve a CR or PR, or any hematologic improvement (HI, per International Working Group [IWG] 2006 criteria) after standard therapy with hypomethylating agents (eg, azacitidine, decitabine), or have relapsed after any duration of CR, PR, or HI
- Newly diagnosed, treatment-naïve non-APL AML patients who, at the time of study entry, are unlikely to tolerate standard intensive chemotherapy due to age, performance status, or comorbidities. (Referred to as Newly Diagnosed Unfit AML)
- Transfusion dependent lower-risk MDS patients without the del 5q abnormality who are refractory to erythropoietin treatment or unlikely to respond to erythropoietin (EPO) treatment (EPO >500). (Referred to as Transfusion Dependent Lower-Risk MDS). Lower-risk MDS: Very Low/Low/Intermediate Risk, as defined by IPSS-R. Red blood cell (RBC) transfusion dependent anemia defined as no 8 consecutive weeks without RBC transfusions within the 16 weeks prior to study entry, or ≥4 RBC transfusions within the 8 weeks prior to study entry.

Number of Patients:

Approximately 162 response evaluable patients will be enrolled into 6 arms:

- Arm 1 (n = ~ 25 biomarker positive patients): Relapsed and/or refractory non-APL AML patients and relapsed and/or refractory higher-risk MDS patients.
- Arm 2A (n = ~ 25 biomarker positive patients) and Arm 2B (n = ~ 50 patients; ~ 25 biomarker positive and ~ 25 biomarker negative): Newly diagnosed, treatment-naïve non-APL AML patients who, at the time of study entry, are unlikely to tolerate standard intensive chemotherapy due to age, performance status, or comorbidities. Arm assignment is determined by Investigator choice of treatment.
  - Patients in Arm 2A will receive SY-1425 as a single agent
  - Patients in Arm 2B will receive SY-1425 in combination with azacitidine
- Arm 3 (n = ~ 25 biomarker positive patients): Transfusion dependent lower-risk MDS patients without the del 5q abnormality who are refractory to erythropoietin treatment or unlikely to respond to erythropoietin treatment (EPO > 500 mU/mL).
- Arm 4 (n = ~ 12 biomarker positive patients): Relapsed and/or refractory non-APL AML patients, relapsed and/or refractory higher-risk MDS patients.
- Arm 5 (n = ~ 25 biomarker positive patients): Relapsed and/or refractory non-APL AML patients who will receive SY-1425 in combination with azacitidine.

Biomarker positive patients are defined as patients positive for the RARA super-enhancer associated biomarker and/or the IRF8 biomarker. Arms 1, 2A, 2B, 3, and 5 will include approximately 20 patients who are positive for the *RARA* super-enhancer associated biomarker. There is no minimum requirement for *RARA* super-enhancer associated biomarker patients in Arm 4.

Study Objectives:

Primary Objectives

- Characterize the clinical activity of SY-1425 in biomarker positive patients by the overall response rate (ORR) in patients in Arms 1, 2A, 2B, and 5, and by the transfusion independence rate (TIR) in patients in Arm 3
- Characterize the safety and tolerability of the combination of SY-1425 and daratumumab in Arm 4

Secondary Objectives

- Characterize the clinical activity of SY-1425 in patients positive for the *RARA* super-enhancer associated biomarker by the ORR in Arms 1, 2A, 2B, and 5, and by TIR in Arm 3

- Characterize the clinical activity of SY-1425 in patients positive for the IRF8 biomarker and negative for the *RARA* super-enhancer associated biomarker by the ORR in Arms 1, 2A, 2B, and 5, and by TIR in Arm 3
- Characterize the clinical activity of the combination of SY-1425 and azacitidine by the ORR in patients in Arm 2B
- Characterize the clinical activity of the combination of SY-1425 and daratumumab by ORR in Arm 4
- Characterize the clinical activity by patients in Arms 1, 2A, 2B, 3, 4, and 5, based on event-free survival (EFS), relapse-free survival (RFS), duration of response (DOR), overall survival (OS), hematologic improvement (HI)
- For all patients, evaluate the requirement for supportive measures secondary to cytopenias
- Characterize the safety and tolerability of SY-1425 as a single agent in Arms 1, 2A, and 3, in combination with azacitidine in Arms 2B and 5.
- Characterize the pharmacokinetics (PK) of SY-1425 after single and multiple doses

Exploratory Objectives

- Assess factors associated with the ORR, including but not limited to arm and diagnosis, prior treatment, *RARA* super-enhancer associated biomarker and/or IRF8 biomarker status, dehydrogenase/reductase (SDR family) member 3 (DHRS3) induction, myeloid differentiation, induction of CD38 expression and other potential predictors of success including genotype and mutation status
- Evaluate changes in Health-Related Quality of Life (HRQOL)
- Establish PK/PD relationships based on PD markers in leukemic cells from repeat peripheral blood samples
- Characterize the PK of daratumumab in combination with SY-1425
- Characterize the relationship between SY-1425 activity and baseline tumor biomarker levels, and levels over time (RARα mRNA or IRF8 mRNA)
- Characterize clinical activity of SY-1425 administered as a single agent and in combination with azacitidine or daratumumab by time-to-response
- Characterize expression of myeloid differentiation markers, including CD38, over time
- Explore the potential role of additional gene or protein alterations (e.g. expression or mutation) in sensitivity and/or resistance to SY-1425 using multiplex platform(s)

Study Design:

This is a Phase 2, multi-center, open-label study exploring the activity of SY-1425 in patients with relapsed or refractory non-APL AML, or higher-risk MDS, newly diagnosed treatment-naïve patients with non-APL AML, who are unlikely to tolerate standard intensive

chemotherapy at the time of study entry, and patients with transfusion dependent, lower-risk MDS. All patients must be evaluated for the *RARA* super-enhancer associated biomarker or the associated IRF8 biomarker at the time of the study screening evaluation, as determined in peripheral blood using an investigational assay. Patients will accrue to each of the six arms based on diagnosis (AML, MDS), prior treatment (relapsed/refractory, newly diagnosed treatment-naïve unfit AML patients), risk group (higher-risk MDS, lower-risk MDS transfusion dependent), and Investigator choice of treatment (SY-1425 single agent, or in combination with azacitidine or daratumumab). SY-1425 will be administered at 6 mg/m^2/day orally (PO) in two divided doses, which corresponds to the dose approved in Japan for use of tamibarotene in patients with relapsed/refractory APL. SY-1425 will be given on a 28-day treatment cycle.

- Arms 1, 2A, and 3: SY-1425 will be administered as a single agent and dosing will be continuous.
- Arms 2B and 5: Azacitidine will be administered at 75 mg/m^2 (intravenously or subcutaneously) on Days 1 through 7, daily, of a 28-day cycle. SY-1425 will be administered at 6 mg/m^2/day PO in two divided doses on Days 8 through 28 of a 28-day cycle.
- Arm 4: SY-1425 will be administered at 6 mg/m^2/day PO in two divided doses on a 28-day treatment cycle. Dosing will be continuous, beginning with a 7-day lead-in, and then administered on a 28-day treatment cycle. Daratumumab will be administered at a dose of 16 mg/kg starting on Cycle 1 Day 1 weekly for 8 weeks (8 doses total), followed by dosing every 2 weeks for 16 weeks (8 doses total), followed by dosing every 4 weeks until progression or intolerance.

The dose of SY-1425 may be increased due to unsatisfactory response as early as C2D1 and again at C3D1 in consultation with the Sponsor. SY-1425 doses may be increased for AML and higher-risk MDS patients to 9 mg/m^2/day if a CR/CRi is not achieved at the C2D1 response assessment. The dose may be increased one additional dose level to 12 mg/m^2/day if a CR/CRi is not achieved at the C3D1 response assessment. Doses may be increased for lower-risk MDS patients to 9 mg/m^2/day at C2D1 if the patient has not reduced their transfusion requirements by 50% after 4 weeks (C2D1). The dose may be increased one level to either 9 or 12 mg/m^2/day after Week 8 (C3D1) for lower-risk MDS patients who have not achieved transfusion independence but who have achieved a minor erythroid response.

Patients will be treated with single agent SY-1425, or SY-1425 in combination with azacitidine or daratumumab to determine activity, to establish the safety profile of SY-1425 in patients with AML and MDS, to explore the hypothesis that patients with the *RARA* super-enhancer associated biomarker or the associated IRF8 biomarker at baseline are responsive to single agent SY-1425 or SY-1425 in combination, to establish the pharmacokinetic/ pharmacodynamic (PK/PD) relationships, and to evaluate the relationship between the activity of single agent SY-1425 or SY-1425 in combination, and baseline level of RARA and IRF8 biomarkers.

In AML and higher-risk MDS patients, response will be measured by changes from baseline in peripheral blood counts and bone marrow aspirates. Bone marrow aspirates will be collected to measure response on Day 1 of Cycles 2, 3 (if CR/CRi was not achieved on C2D1), and 4,

followed by every third cycle, with additional bone marrow aspirates analyzed as clinically indicated based upon changes in peripheral blood counts, or when it is needed to establish either CR or disease progression. Bone marrow aspirate pathology slides (smears) used to assess response should be retained at the sites for up to 5 years or until Sponsor approval to discard samples is provided, whichever is sooner, to support the potential for future analyses.

In lower-risk MDS patients, response will be measured by changes from baseline in transfusion requirements and peripheral blood counts, which will be evaluated at each study visit.

Patients may continue to receive study treatment until experiencing unacceptable toxicity, disease progression/relapse, decision to pursue post-remission therapy other than SY-1425 single agent, or SY-1425 in combination with azacitidine or daratumumab, or the Investigator determines it is in the best interest of the patient to discontinue treatment. Newly diagnosed AML patients enrolled in Arm 2A who achieve a CR/CRi or PR while on SY-1425 single agent treatment and then relapse, or who fail to achieve a CR/CRi or PR after completing at least 4 cycles of SY-1425 single agent treatment, are eligible to receive SY-1425 in combination with azacitidine.

Lower-risk MDS patients will be withdrawn from the study at week 24 if they do not have at least a minor erythroid response defined as either a 50% decrease in transfusion requirements or a 50% improvement in hemoglobin concentration per the response criteria, defined as a hemoglobin increase $\geq$ 0.75g/dL. Lower-risk MDS patients who in the opinion of the Investigator are receiving clinical benefit, but do not meet the minor erythroid response criteria can remain on study with Sponsor approval. Lower-risk MDS patients who continue past week 24 will continue to receive treatment until erythroid relapse (loss of erythroid response), disease progression, or unacceptable toxicity.

An end of treatment (EoT) visit will be conducted for all AML and higher-risk MDS patients within 30 days of the last dose of study drug, but prior to the start of any subsequent therapies to monitor for safety and resolution of adverse events (AEs). For lower-risk MDS patients, the EoT visit will also be the end of study visit which will be conducted 30 days after the last dose of study drug. All AML and higher-risk MDS patients will be followed every 3 months for survival for up to 2 years and patients who are withdrawn prior to relapse will also follow-up for event free survival (EFS).

However, following implementation of Amendment 7, assessments will be performed per institutional standard of care for patients enrolled in Arm 2B or Arm 5. Aside from serious adverse event (SAE), adverse event of special interest, and Pregnancy and Birth Event collection (via the pharmacovigilance safety database) for patients still receiving study drug in Arm 5, the study procedures and data collection outlined in Table 3 will be considered as guidance and will no longer be required for the study or entered into the electronic data capture system. Patients in Arm 5 may continue to receive study drug until experiencing unacceptable toxicity, disease progression/relapse, decision to pursue post-remission therapy other than SY-1425 in combination with azacitidine, or the Investigator determines it is in the best interest of the patient to discontinue treatment.

Inclusion Criteria:

1. Patients must be at least 18 years of age.
2. Patients must have:
   a. Relapsed and/or refractory non-APL AML that has failed to achieve a CR or PR following standard induction therapy, or has relapsed after any duration of CR or PR
      i. Patients must have measurable disease with bone marrow blasts ≥5% at screening.
   b. Relapsed and/or refractory higher-risk MDS (High / Very High Risk, as defined by the Revised International Prognostic Scoring System (IPSS-R)) patients that have failed to achieve a CR or PR, or any HI (per IWG 2006 criteria) after standard therapy with hypomethylating agents (eg, azacitidine, decitabine), or have relapsed after any duration of CR or PR or HI
      i. Patients must have measurable disease with bone marrow blasts >5% at screening.
   c. Newly diagnosed, treatment-naïve non-APL AML in patients who, at the time of study entry are unlikely to tolerate standard intensive chemotherapy due to age, performance status, or comorbidities based on at least one of the following criteria (Ferrara et al, 2013):
      i. Age ≥ 75-years-old
      ii. Eastern Cooperative Oncology Group (ECOG) Performance Status of 3
      iii. Cardiac history of congestive heart failure (CHF) or documented ejection fraction (EF) ≤ 50%
      iv. Pulmonary disease with DLCO ≤ 65% or FEVI ≤ 65%
      v. Creatinine clearance ≥ 30 mL/min to < 45 mL/min
      vi. Hepatic impairment with total bilirubin > 1.5 to ≤ 3.0 x upper limit of normal (ULN)
      vii. Any other comorbidity that the Investigator judges to be incompatible with intensive chemotherapy, and reviewed and approved by the Sponsor prior to enrollment
   d. Transfusion dependent lower-risk MDS without the del 5q abnormality, in patients refractory to erythropoietin treatment or unlikely to respond to EPO treatment (EPO >500).
      i. Lower-risk MDS: Very Low /Low / Intermediate Risk, as defined by IPSS-R.
      ii. Red blood cell (RBC) transfusion dependent anemia defined as no 8 consecutive weeks without RBC transfusions within the 16 weeks prior to study entry, or ≥4 RBC transfusions within the 8 weeks prior to study entry.

iii. Refractory to or ineligible for ESAs is defined as RBC-Transfusion Dependence despite ESA treatment of ≥40,000 units/week recombinant human erythropoietin for 8 weeks or an equivalent dose of darbepoetin (150 µg/week) or serum EPO level >500 mU/mL in patients not previously treated with ESAs.

3. Patients must be evaluated for the *RARA* super-enhancer associated biomarker or IRF8 biomarker as measured by RT-qPCR with a centralized test of peripheral blood at the time of study screening.
   a. Patients in arms 1, 2A, 3, 4, and 5 must be positive for the biomarker as defined by a predetermined cutoff to be eligible for enrollment.
4. Must be amenable to serial bone marrow aspirates and peripheral blood sampling during the study.
5. ECOG Performance Status (PS) of 0, 1 or 2. For newly diagnosed AML patients < 75 years of age, ECOG 0 to 3; for ≥ 75 years of age, ECOG 0 to 2.
6. Adequate organ function as defined by:
   a. Total bilirubin ≤ 1.5 x the upper limit of normal (ULN), unless suspected to have Gilbert's disease. For newly diagnosed AML patients < 75 years of age, total bilirubin ≤ 3.0 x ULN; for ≥ 75 years of age, total bilirubin ≤ 1.5 x ULN.
   b. ALT and AST ≤ 3 x ULN or ≤ 5 x ULN if documented liver infiltration with leukemia cells.
   c. Serum creatinine ≤ 2.0 x ULN or calculated creatinine clearance ≥ 45 mL/min based on the Cockroft-Gault GFR estimation. For newly diagnosed AML patients < 75 years of age, creatinine clearance ≥ 30 mL/min; for ≥ 75 years of age, creatinine clearance ≥ 45 mL/min.
7. Discontinued use of chemotherapy, radiation therapy, or growth factors for at least 2 weeks prior to first study treatment, with the exception of hydroxyurea.
8. No investigational agents within 2 weeks prior to first study treatment.
9. No strong inducers of CYP3A4 (see Appendix 5) within 2 weeks prior to first study treatment.
10. Resolved acute effects of any prior AML/MDS therapy to baseline or ≤ Grade 1 CTCAE severity.
11. Serum/urine pregnancy test (for females of childbearing potential) that is negative at screening and immediately prior to initiation of treatment (first dose).
12. Willingness and ability to comply with the scheduled study visits, treatment plans, laboratory tests and other procedures.
13. Fully-executed, signed and dated Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approved informed consent document.

Exclusion Criteria:

1. APL (M3 subtype of AML) or patients with a t(9:22) cytogenetic translocation.
2. Hyperleukocytosis (leukocytes ≥ 25 x 10^9/L) at study entry. These patients may be treated with hydroxyurea according to routine practice, and enroll in the study when the leukocyte count falls below 25 x 10^9/L.
3. Patients known to be refractory to platelet or packed red cell transfusions per Institutional Guidelines, or a patient who refuses blood product support.
4. Prior treatment with ATRA or systemic retinoid for the treatment of hematologic malignancy.
5. **Arm 4 only** – Prior or concurrent exposure to daratumumab or other CD38 therapies
6. **Arm 4 only** – Subject has either of the following:
   a. Known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) <50% of predicted normal. Note that FEV1 testing is required for subjects suspected of having COPD and subjects must be excluded if FEV1 is <50% of predicted normal.
   b. Known moderate or severe persistent asthma within the past 2 years (see Appendix 8), or uncontrolled asthma of any classification. Note that subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed to participate in the study.
7. Patients with other active malignancy (not including basal cell carcinoma, non-melanoma skin cancer, cervical carcinoma in situ, localized prostate cancer treated with hormone therapy). Patients with history of other cancers should be free of disease for at least 2 years.
8. Patients with hypertriglyceridemia defined as >1000 mg/dL (CTCAE v4.03 Grade 4).
9. Any clinically significant cardiac disease including one of the following currently or in the previous 6 months: myocardial infarction, unstable cardiac function due to unstable angina or congestive heart failure, congenital long QT syndrome, torsades de pointes or clinically-significant ventricular arrhythmias.
10. QTc interval >480 msec based on triplicate ECG readings using the Fridericia (QTcF), with the exception of patients with Right Bundle Branch Block or Left Bundle Branch Block.
11. Patients with an active, life-threatening or clinically-significant uncontrolled systemic infection.
12. Patients with known active uncontrolled central nervous system (CNS) leukemia.
13. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) related illness or hepatitis B or hepatitis C infection.

a. **Arm 4 only**: Patients with resolved infection (ie, patients who are HBsAg negative but positive for antiHBs or antiHBc) must also be screened using PCR measurement of HBV DNA levels. Patients who are PCR positive for HBV will be excluded.

b. **Arm 4 only**: Patients with serologic findings suggestive of HBV vaccination (antiHBs positivity as the only serologic marker) AND a known history of prior HBV vaccination do not need to be tested for HBV DNA by PCR.

14. Known malabsorption syndrome or other condition that may impair absorption of study medication (eg, gastrectomy).
15. Major surgery within 4 weeks prior to starting study treatment.
16. Patients taking Vitamin A supplements (>10,000 IU/d) unless discontinued prior to first dose of study drug, or having hypervitaminosis A.
17. Concurrent treatment with any investigational or approved oncology agents (unless specified in the protocol, such as hydroxyurea) or herbal preparations.
18. **Arm 4 only**: Known allergies, hypersensitivity, or intolerance to mannitol, corticosteroids, monoclonal antibodies or human proteins, or their excipients, or known sensitivity to mammalian-derived products.
19. **Arm 4 only**: Vaccination with live attenuated vaccines within 4 weeks of first study drug administration.
20. Current illicit drug or alcohol abuse.
21. Other severe acute or chronic medical condition such as refractory congestive heart failure, pulmonary disease associated with dyspnea at rest or requiring oxygen therapy, kidney dialysis, liver cirrhosis (Child B or C), or psychiatric condition or laboratory abnormality that may increase the risk to the patient associated with study participation or investigational product administration or which may interfere with the interpretation of study results or, in the judgment of the Investigator, would make the patient inappropriate for entry into this study.
22. Pregnant females; breastfeeding females; and males and females of childbearing potential not willing to use two highly effective methods of birth control, one being barrier method. Intrauterine devices and birth control pills are not barrier methods, but are highly effective especially when combined with a barrier method (eg, latex condom or a diaphragm or cervical cap) while taking study drug (SY-1425, azacitidine and daratumumab) and continuing contraception use for at least 90 days after the last dose of study drug. Men/women should not donate sperm or ova during this timeframe.

    a. Non-childbearing potential is defined as menopausal for at least 2 years or documented oophorectomy.

Study Endpoints:

Primary Endpoints

- ORR for biomarker positive patients with AML or higher-risk MDS (Arms 1, 2A, 2B, 5)

- TIR for patients with lower-risk MDS (Arm 3)
- Safety and tolerability of SY-1425 in combination with daratumumab assessed by the type and frequency of AEs and SAEs using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 4.03, as well as changes in clinically significant clinical laboratory values, electrocardiogram (ECG) parameters and vital sign measurement (Arm 4)

Secondary Endpoints

- ORR for AML or higher-risk MDS patients positive for the *RARA* super-enhancer associated biomarker (Arms 1, 2A, 2B, and 5)
- TIR for lower-risk MDS patients positive for the *RARA* super-enhancer associated biomarker (Arm 3)
- Response rate (ORR + TIR) for patients positive for the IRF8 biomarker and negative for the *RARA* super-enhancer associated biomarker treated with SY-1425 as a single agent (Arms 1, 2A, and 3)
- ORR for AML or higher-risk MDS patients positive for the IRF8 biomarker and negative for the *RARA* super-enhancer associated biomarker (Arms 1, 2A, 2B, and 5)
- TIR for lower-risk MDS patients positive for the IRF8 biomarker and negative for the *RARA* super-enhancer associated biomarker (Arm 3)
- ORR for AML patients who are treated with SY-1425 in combination with azacitidine (Arm 2B)
- ORR for AML or higher-risk MDS patients treated with SY-1425 in combination with daratumumab (Arm 4)
- Clinical activity as measured by EFS, RFS, DOR, OS, and HI in Arms 1, 2A, 2B, 4, and 5
- Clinical activity as measured by DOR and HI in Arm 3
- Proportion of patients requiring supportive measures secondary to cytopenias, as measured by changes in transfusion rates, incidence and duration of growth factor support and antibiotics use, and number of hospitalizations associated with febrile neutropenia and/or thrombocytopenic bleeding
- Characterize the safety and tolerability of SY-1425 as a single agent and in combination with azacitidine by assessing the type and frequency of AEs and SAEs using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 4.03, as well as changes in clinically significant clinical laboratory values, electrocardiogram (ECG) parameters and vital sign measurements (Arms 1, 2A, 2B, 3, and 5)
- PK parameters of SY-1425, as single agent and in combination with azacitidine or daratumumab, after single and multiple doses by performing PK analysis to define

time to maximum concentration (t_{max}), C_{max}, minimum plasma concentration (C_{min}), AUC, total body clearance (CL/F) and half-life ($t_{1/2}$), where the data permits

Exploratory Endpoints

- Sensitivity analyses to the primary endpoint to predict ORR or TIR across all patients by arm, diagnosis type, prior therapy, *RARA* super-enhancer associated biomarker and/or IRF8 biomarker status; DHRS3 induction, peripheral blood myeloid differentiation markers, induction of CD38 expression, genotype and mutation status
- Changes in Health-Related Quality of Life (HRQOL)
  - AML/higher-risk MDS patients (Arms 1, 2A, 2B, 4, and 5): Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu) questionnaire
  - Lower-risk MDS patients (Arm 3): Functional Assessment of Cancer Therapy-Anemia (FACT-An) questionnaire
- Establish PK/PD relationships by performing analysis of PD biomarkers (DHRS3 and myeloid differentiation markers) in leukemic cells from repeat peripheral blood samples and assessing any changes over time
- PK parameters for daratumumab in combination with SY-1425, including maximum concentration (C_{max}) and minimum concentration (C_{min}; trough concentration)
- Characterize the relationship between SY-1425 activity and baseline expression, and expression over time of messenger RNA (mRNA) expression of RARA and IRF8 biomarkers by correlating baseline biomarker mRNA expression levels of RARα and IRF8 with ORR, EFS, RFS, DOR, OS, and HI Rate
- Estimate of median time-to-response
- Evaluate changes in expression of myeloid differentiation markers, including CD38, over time
- Analysis of additional genes or proteins using multiplex platforms

Statistical Methods:

For each of Arms 1, 2A, 2B (biomarker positive subset), 3 and 5, an exact 2-sided 90% confidence interval will be calculated for the ORR (Arms 1, 2A, 2B, 5) or TIR (Arm 3). Success for Arms 1, 2A and 3 (n=25 each) is achieved if the lower bound of the confidence interval excludes 5%. Assuming a 25% response rate for SY-1425 as a single agent, the power for each of these arms of this study is 90.4%. Arm 2B has two subgroups defined by biomarker status (n=25 each). Success for the biomarker positive subgroup in Arm 2B is achieved if the lower bound of the confidence interval excludes 20%. Assuming a 45% response rate for the combination of SY-1425 and azacitidine in biomarker positive patients, the power for this subgroup of Arm 2B of the study is 86.6%. Success for Arm 5 (n=25) is achieved if the lower bound of the confidence interval excludes 10%. Assuming a 30% response rate for the

combination of SY-1425 and azacitidine in relapsed and/or refractory biomarker-positive AML patients, the power for Arm 5 of this study is 80.7%.

Success for the entire Arm 2B population is achieved if the lower bound of the confidence interval excludes 20%. Assuming a 38% response rate for the combination of SY-1425 and azacitidine in the entire Arm 2B population, the power for the secondary endpoint of Arm 2B of the study is 84.6%.

The primary endpoint of Arm 4 is safety and tolerability of SY-1425 in combination with daratumumab. The sample size is not based on any hypothesis testing but is appropriate for studies of this type with a primary focus on safety.

No adjustment for multiple hypothesis testing across arms will be made.

ORR is defined as:

- AML: ORR as determined by the investigator based on the rate of CR/CRi/CRh. MLFS, and PR, per the revised IWG AML criteria (Cheson et al, 2003, Bloomfield et al, 2018).
- Higher-risk MDS: ORR as determined by the Investigator per the revised IWG AML criteria (Cheson et al, 2003) or modified IWG MDS criteria (Cheson et al, 2006). Response is based on the rate of CR/CRi, PR, and HI. CR includes marrow CR.

TIR is defined as:

- Lower-risk MDS: TIR, defined as the proportion of patients who achieve transfusion independence defined as 8 consecutive weeks of RBC transfusion independence.

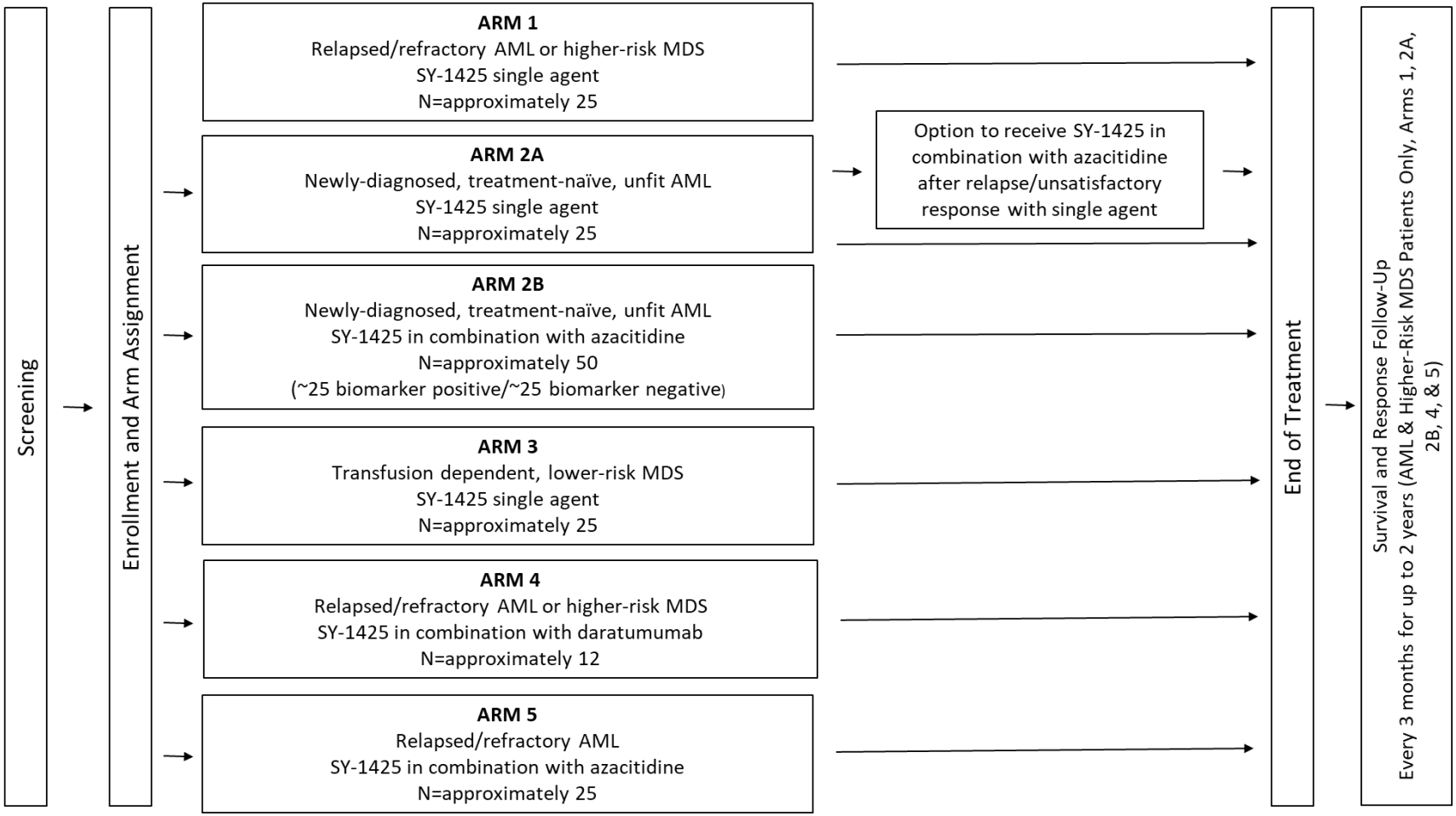
Clinical activity of SY-1425, as single agent and in combination with azacitidine or daratumumab, as measured by EFS, RFS, DOR, OS, and HI in AML and higher-risk MDS patients.

- EFS: defined as time from first treatment until date of documentation of disease relapse following CR/CRi, or death, whichever occurs first. If the patient does not achieve a CR, EFS is defined as the point of progression or death, whichever occurs first.
- RFS: defined as time from first objective documentation of CR/CRi (including CRh/MLFS for AML patients) or PR until the date of first objective documentation of disease relapse or death due to any cause, whichever occurs first.
- DOR: defined as time from first date of response (CR/CRi [including CRh/MLFS for AML patients]), PR, or HI for MDS patients - if best response) until date of relapse.
- OS: defined as time from first treatment until death from any cause.
- HI Rate: defined according to the modified IWG response criteria for MDS (Cheson et al, 2006) as the proportion of patient with a response (lasting at least 8 weeks) after first treatment.

Clinical activity of SY-1425 as measured by DOR and HI in transfusion dependent lower-risk MDS patients.

- DOR is defined as the time from first date of response (HI or transfusion independence) until date of relapse.
- HI is defined according to the modified IWG response criteria for MDS (Cheson et al, 2006) as response (lasting at least 8 weeks) after first treatment.

Figure 1: Study Schematic



Abbreviations: AML = acute myeloid leukemia; MDS = Myelodysplastic Syndrome.
NOTE: Each of Arms 1, 2A, 2B, 3, and 5 will include approximately 20 patients who are positive of the *RARA* super-enhancer associated biomarker

Table 1: Schedule of Events (Arms 1, 2A, and 3)

	Screening (a)	**Cycle 1**				**Cycles 2-4**		**Cycles 5+ (b)**	**Post Dose Adjustment Visit (c)**	**End of Treatment (EoT) (d)**	**Post- treatment Follow-up (AML & HR MDS Only)**
Study Day (D/d)	Within 30 days of dosing	D1	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±2d)	D15 (±2d)	D1 (±2d)	Within 8-15 days of dose adjustment	Within 30 days of last dose (d)	Every 3 mo. post EoT (±14 d) (e)
Baseline Documentation – All Patients											
Informed Consent	X										
Eligibility Review	X										
Medical History	X										
Demographics	X										
Height	X										
Weight (f)	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status	X	X				X		X		X	
Physical Exam	X	X	X	X	X	X	X	X	X	X	
Safety Labs/Measurements – All Patients											
Hematology (g)	X	X	X	X	X	X	X	X	X	X	
Serum Chemistries (g)	X	X	X	X	X	X		X	X	X	
Coagulation (g)	X	X		X		X		X		X	
Triglycerides and Total Cholesterol (g)	X	X		X		X		X	X	X	
Urinalysis (g)	X	X								X	
Pregnancy Test (h)	X	X				X		X		X	
Triplicate ECG (i)	X	X		X		X				X	

Table 1: Schedule of Events (Arms 1, 2A, and 3)

	Screening (a)	**Cycle 1**				**Cycles 2-4**		**Cycles 5+ (b)**	**Post Dose Adjustment Visit (c)**	**End of Treatment (EoT) (d)**	**Post- treatment Follow-up (AML & HR MDS Only)**
Study Day (D/d)	Within 30 days of dosing	D1	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±2d)	D15 (±2d)	D1 (±2d)	Within 8-15 days of dose adjustment	Within 30 days of last dose (d)	Every 3 mo. post EoT (±14 d) (e)
Vital Signs	X	X	X	X	X	X	X	X	X	X	
Clinical Assessments – All Patients											
Adverse Event Monitoring (j)	X	X	X	X	X	X	X	X	X	X	
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	
Red Blood Cell and Platelet Transfusions Recorded (k)	X	X	X	X	X	X	X	X	X	X	
Dosing Compliance/ Diary Review		X	X	X	X	X	X	X	X	X	
Study Treatment											
SY-1425		Continuous Dosing							X		
Clinical Assessments – AML & Higher-Risk MDS Patients Only											
HRQOL (FACT-Leu)	X	X				C4 only				X	
Subsequent Therapies (l)											X
EFS and Overall Survival Follow-Up										X	X
Clinical Assessments – Lower-Risk MDS Patients Only											
HRQOL (FACT-An)	X	X				C4 only				X	

Table 1: Schedule of Events (Arms 1, 2A, and 3)

	Screening (a)	**Cycle 1**				**Cycles 2-4**		**Cycles 5+ (b)**	**Post Dose Adjustment Visit (c)**	**End of Treatment (EoT) (d)**	**Post- treatment Follow-up (AML & HR MDS Only)**
Study Day (D/d)	Within 30 days of dosing	D1	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±2d)	D15 (±2d)	D1 (±2d)	Within 8-15 days of dose adjustment	Within 30 days of last dose (d)	Every 3 mo. post EoT (±14 d) (e)
EPO Levels (m)	X										
Specialty Lab Assessments – All Patients											
Peripheral blood *RARA* Super-Enhancer Associated Biomarker Assessment and IRF8 biomarker (n)	X										
ChIP-Sequencing (o)	X										
Blood sample for biomarker research (p)	X										
Pharmacokinetics (q)		X		X		X			X		
Blood Sample for ADME PGx (r)		X									
Blood Sample for Pharmacodynamics (s)		X		X						X	
Peripheral Blood for CD38 & Myeloid Marker Immunophenotyping (t)		X	X	X		X		Every 3rd Cycle		X	
Blood Sample for Resistance Mechanism										X	
Cytogenetics and Mutational Analysis (u)	X									X	

Table 1: Schedule of Events (Arms 1, 2A, and 3)

	Screening (a)	Cycle 1				Cycles 2-4		Cycles 5+ (b)	Post Dose Adjustment Visit (c)	End of Treatment (EoT) (d)	Post- treatment Follow-up (AML & HR MDS Only)
Study Day (D/d)	Within 30 days of dosing	D1	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±2d)	D15 (±2d)	D1 (±2d)	Within 8-15 days of dose adjustment	Within 30 days of last dose (d)	Every 3 mo. post EoT (±14 d) (e)
Specialty Lab Assessments – AML& Higher-Risk MDS Patients Only											
Bone Marrow Aspirate for Eligibility	X										
Bone Marrow Aspirate for Response Assessment (v)						X		Every 3rd Cycle		X	
Immunophenotyping (w)	X					X		Every 3rd Cycle			

Abbreviations: ADME = absorption, distribution, metabolism, and excretion; AML = acute myeloid leukemia; BSA = body surface area; ChIP = chromatin immunoprecipitation; CR = complete remission; CRi = complete remission, morphologic, with incomplete blood count recovery; D/d = day(s); ECOG = Eastern Cooperative Oncology Group; EoT = end of treatment; ECG = electrocardiogram; EFS = event-free survival; EPO = erythropoietin; FACT-An = Factual Assessment of Cancer Therapy-Anemia; FACT-Leu = Factual Assessment of Cancer Therapy-Leukemia; HRQOL = Health Related Quality of Life; IRF8 = Interferon Regulatory Factor 8; MDS = Myelodysplastic Syndrome; PD = pharmacodynamic; PGx = pharmacogenomics; PK = pharmacokinetic; RARA = retinoic acid receptor alpha; SAE = serious adverse event.

(a) Screening assessments must be performed within 30 days of study drug administration. Screening assessments may also occur on Day 1 prior to dosing.
(b) Cycle 5 schedule should be followed for all subsequent cycles.
(c) If a patient has an SY-1425 dose modification (decrease or increase) to a new dose level (as defined in Section 8.4), a dose adjustment visit must be performed within 8-15 days of the dose adjustment. This visit can be combined with another scheduled visit if it is scheduled to occur within that window.
(d) An EoT visit for AML and Higher-Risk MDS patients should occur within 30 days of the last dose of study drug, but prior to any subsequent therapies. For Lower-Risk MDS patients the EoT visit will also be the end of study visit and should occur 30 days after the last dose of study drug (+/- 5 days).
(e) AML and Higher-Risk MDS patients will enter post-treatment follow-up. Visits should occur every 3 months post EoT for response assessment and overall survival. These visits may be conducted by phone. Follow-up visit window is +/- 14 days.
(f) Weight will be measured at each visit. Weight will be used to calculate BSA to determine dosing requirements. BSA used for dosing calculations should be updated if the weight changes more than 15%.
(g) Safety laboratory assessments are outlined in Section 7.2 of the protocol and will be performed locally.
(h) A pregnancy test (urine or serum) must be completed for women of child bearing potential during screening, on Day 1 of each cycle visit, and at EoT.
(i) ECG on Cycle 1 Day 1 must be performed prior to dosing. All other ECGs can be taken at any time during the study visit. All ECGs will be done as triplicate 12-lead ECGs.
(j) SAEs will be captured from the time of signing of the Informed Consent Form through 30 days after last dose of study drug, and non-serious AEs from the time of first dose of study drug through 30 days after last dose of study drug.

(k) All transfusions received by the patient from 16 weeks prior to enrollment until the EoT visit will be recorded.
(l) Subsequent therapies will be recorded for 3 months after the last dose of study drug.
(m) Low-risk MDS patients in Arm 3 only.
(n) Peripheral blood sample will be sent to a central lab for assessment of *RARA* super-enhancer associated biomarker and IRF8 biomarker at screening to confirm eligibility. Other associated *RARA* pathway genes will also be analyzed.
(o) All patients will have a peripheral blood sample collected at screening for ChIP-sequencing analysis to be performed at a central lab (assuming sufficient material is available at time of sample processing).
(p) For U.S. only: All patients will have a whole blood sample collected at screening (same collection time as the biomarker assessment) for additional biomarker research.
(q) All patients will have PK sampling on Day 1 of Cycle 1 at 2-4 hours, and 5-8 hours post dose, and on Day 15 of Cycle 1 and Day 1 of Cycles 2, 3, and 4 at two time points at least two hours apart. A subset of approximately 15 patients, sufficient to obtain PK evaluable results from at least 10 patients, will have more intensive sampling [pre-dose (0h), and 0.5, 1, 2, 4, 6, 8 hours post-dose] on Day 1 and Day 15 of Cycle 1, and will have sparse sampling on Day 1 of Cycles 2, 3, and 4 at two time points at least 2 hours apart. If a patient's SY-1425 dose is modified to a different dose level (see Section 8.4) during the course of the study, PK sampling should occur within 8-15 days of the dose adjustment following the same schedule as Cycle 1 Day 1 (either intensive or sparse depending on which PK sampling schedule originally enrolled under).
(r) Absorption, distribution, metabolism, excretion PGx sample to be taken pre-dose.
(s) Peripheral blood will be collected in all patients on Day 1 of Cycle 1 pre-dose and 5-8 hours post-dose, on Day 15 of Cycle 1, and at EoT visit to determine changes in RNA including dehydrogenase/reductase (SDR family) member 3 (DHRS3). This sample should be collected in the same procedural timeframe as the corresponding PK sample.
(t) Peripheral blood collected for central analysis of CD38 and myeloid marker immunophenotyping on Days 1 (pre-dose), 8 and 15 of Cycle 1; Day 1 of Cycles 2, 3, 4, followed by every third cycle (7, 10, 13, etc); and EoT. Collected only for patients enrolled under Amendment 4 or a subsequent protocol amendment.
(u) Cytogenetics and mutational analysis will be performed at screening and at the EoT visit. Cytogenetics and mutational analyses will be performed locally. These analyses are performed on bone marrow for AML and Higher-Risk MDS patients, and on peripheral blood for Lower-Risk MDS patients.
(v) Bone marrow aspirates will be collected to assess response in AML and Higher-Risk MDS patients on Day 1 of Cycles 2, 3, 4, followed by every third cycle (7, 10, 13, etc.), and as clinically indicated. If a patient achieved a CR/CRi at Cycle 2 Day 1, the Cycle 3 Day 1 bone marrow aspirate is not required. A bone marrow aspirate should be collected to confirm relapse which will be recorded as an end of treatment sample and will be used for cytogenetics assessment. For patients enrolled in Arm 2A, an unscheduled bone marrow aspirate may be required to support eligibility to receive treatment with SY-1425 in combination with azacitidine after relapse/unsatisfactory response with single agent SY-1425.
(w) Bone marrow aspirate samples will be collected for immunophenotyping to measure myeloid differentiation markers and will be analyzed locally at screening and when aspirates are performed to assess response [see footnote (v), above]. Immunophenotyping may also be performed when clinically indicated on peripheral blood to measure myeloid differentiation markers.

Table 2: Schedule of Assessment (Central Laboratory Sampling) (Arms 1, 2A, and 3)

Study Visit	**Biomarker & ChIP Sequencing Samples**	**Pharmacokinetic Sampling – Choose Appropriate Schedule Below Based Upon Enrollment**		**ADME PGx Sample**	**Pharmacodynamics Sample**	**CD38 & Myeloid Marker Immunophenotyping (a)**	**Resistance Mechanism**
		Non-Intensive Pharmacokinetics Sample	***Intensive Pharmacokinetics Cohort Sample***				
Screening	3 blood samples collected any time during visit (b)						
Cycle 1 Day 1 (c)		• 2-4 hours post-dose • 5-8 hours post-dose	• pre-dose (0h) (c) • 0.5 hours post-dose (± 15 mins) • 1 hour post-dose (± 15 mins) • 2 hours post-dose (± 15 mins) • 4 hours post-dose (± 30 mins) • 6 hours post-dose (±30 mins) • 8 hours post-dose (±30 mins)	• Pre-dose (c)	• Pre-dose (c) • 5-8 hours post dose	• Collected any time during visit (d)	
Cycle 1 Day 8						• Collected any time during visit (d)	

Table 2: Schedule of Assessment (Central Laboratory Sampling) (Arms 1, 2A, and 3)

Study Visit	Biomarker & ChIP Sequencing Samples	Pharmacokinetic Sampling – Choose Appropriate Schedule Below Based Upon Enrollment		ADME PGx Sample	Pharmacodynamics Sample	CD38 & Myeloid Marker Immunophenotyping (a)	Resistance Mechanism
		Non-Intensive Pharmacokinetics Sample	*Intensive Pharmacokinetics Cohort Sample*				
Cycle 1 Day 15 (c)		• 2 post-dose samples at least 2 hours apart	• pre-dose (0h) (c) • 0.5 hours post-dose (± 15 mins) • 1 hour post-dose (± 15 mins) • 2 hours post-dose (± 15 mins) • 4 hours post-dose (± 30 mins) • 6 hours post-dose (± 30 mins) • 8 hours post-dose (± 30 mins)		• A postdose sample to be collected at any time point during the visit	• Collected any time during visit (d)	
Cycle 2 Day 1		• 2 post-dose samples at least 2 hours apart	• 2 post-dose samples at least 2 hours apart			• Collected any time during visit (d)	
Cycle 3 Day 1		• 2 post-dose samples at least 2 hours apart	• 2 post-dose samples at least 2 hours apart			• Collected any time during visit (d)	
Cycle 4 Day 1		• 2 post-dose samples at least 2 hours apart	• 2 post-dose samples at least 2 hours apart			• Collected any time during visit (d)	
Cycle 7 Day 1 and every 3rd cycle thereafter						• Collected any time during visit (d)	

Table 2: Schedule of Assessment (Central Laboratory Sampling) (Arms 1, 2A, and 3)

Study Visit	Biomarker & ChIP Sequencing Samples	Pharmacokinetic Sampling – Choose Appropriate Schedule Below Based Upon Enrollment		ADME PGx Sample	Pharmacodynamics Sample	CD38 & Myeloid Marker Immunophenotyping (a)	Resistance Mechanism
		Non-Intensive Pharmacokinetics Sample	*Intensive Pharmacokinetics Cohort Sample*				
Within 8-15 days of a dose adjustment (c)		• 2 post-dose samples at least 2 hours apart	• pre-dose (0h) (c) • 0.5 hours post-dose (± 15 mins) • 1 hour post-dose (± 15 mins) • 2 hours post-dose (± 15 mins) • 4 hours post-dose (± 30 mins) • 6 hours post-dose (± 30 mins) • 8 hours post-dose (± 30 mins)				
End of Treatment					• 1 sample collected any time during visit	• Collected any time during visit (d)	• Collected any time during visit

Abbreviations: ChIP = chromatin immunoprecipitation; mins = minutes; 0h = zero hour; PGx = pharmacogenomics

(a) Collected only for patients enrolled under Amendment 4 or a subsequent protocol amendment.

(b) For patients screened in France, only 2 samples will be collected.

(c) For Cycle 1 Day 1 for all patients, and Cycle 1 Day 15 and post-dose adjustment visits for patients in the intensive PK cohort, the morning dose of SY-1425 must be administered in clinic to allow for collection of the pre-dose (0 hour) samples.

(d) Refer to the Lab Manual for details on number of collection tubes

Table 3: Schedule of Events (Arms 2B, and 5, and Patients in Arm 2A who receive SY-1425 in Combination with Azacitidine After Relapse/Unsatisfactory Response with Single Agent SY-1425)

	Screening (a)	**Cycle 1 28 days**					**Cycles 2-4 cycle = 28 days**				**Cycles 5+** (b) **cycle = 28 days**		**Post Dose Adjustment Visit** (c)	**End of Treatment (EoT)** (d)	**Post-Treatment Follow-up** (e)
Study Day (D/d)	Within 30 days of dosing	D1	D2-7	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±2d)	D2-7	D8 (±2d)	D15 (±2d)	D1 (±2d)	D2-7 (±2d)	Within 8-15 days from dose adjustment	Within 30 days of last dose (d)	Every 3 months post EoT (±14 days)
Baseline Documentation															
Informed Consent	X														
Eligibility Review	X														
Medical History	X														
Demographics	X														
Height	X														
Weight (f)	X	X		X	X	X	X		X	X	X		X	X	
ECOG Status	X	X					X				X			X	
Physical Exam	X	X		X	X	X	X		X	X	X		X	X	
Safety Labs/Measurements															
Hematology (g)	X	X		X	X	X	X		X	X	X		X	X	
Serum Chemistries (g)	X	X		X	X	X	X				X		X	X	
Coagulation (g)	X	X		X			X		X		X			X	
Triglycerides & Total Cholesterol (g)	X	X			X		X				X		X	X	
Urinalysis (g)	X	X												X	
Pregnancy Test (h)	X	X					X				X			X	
Triplicate ECG (i)	X			X		X			X					X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Table 3: Schedule of Events (Arms 2B, and 5, and Patients in Arm 2A who receive SY-1425 in Combination with Azacitidine After Relapse/Unsatisfactory Response with Single Agent SY-1425)

	Screening (a)	**Cycle 1 28 days**					**Cycles 2-4 cycle = 28 days**				**Cycles 5+ (b) cycle = 28 days**		**Post Dose Adjustment Visit (c)**	**End of Treatment (EoT) (d)**	**Post-Treatment Follow-up (e)**
Study Day (D/d)	Within 30 days of dosing	D1	D2-7	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±2d)	D2-7	D8 (±2d)	D15 (±2d)	D1 (±2d)	D2-7 (±2d)	Within 8-15 days from dose adjustment	Within 30 days of last dose (d)	Every 3 months post EoT (±14 days)
Clinical Assessments															
AE Monitoring (j)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
RBC & Platelet Transfusions Recorded (k)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dosing Compliance/ Diary Review				X	X	X	X		X	X	X		X	X	
HRQOL (FACT-Leu)	X	X					C4 only							X	
Subsequent Therapies (l)															X
EFS and Overall Survival Follow-Up														X	X
Study Treatments															
SY-1425				Continuous dosing, Days 8-28 of each Cycle											
Azacitidine		X	X (m)				X	X (m)			X	X (m)			

Table 3: Schedule of Events (Arms 2B, and 5, and Patients in Arm 2A who receive SY-1425 in Combination with Azacitidine After Relapse/Unsatisfactory Response with Single Agent SY-1425)

	Screening (a)	**Cycle 1 28 days**					**Cycles 2-4 cycle = 28 days**				**Cycles 5+ (b) cycle = 28 days**		**Post Dose Adjustment Visit (c)**	**End of Treatment (EoT) (d)**	**Post-Treatment Follow-up (e)**
Study Day (D/d)	Within 30 days of dosing	D1	D2-7	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±2d)	D2-7	D8 (±2d)	D15 (±2d)	D1 (±2d)	D2-7 (±2d)	Within 8-15 days from dose adjustment	Within 30 days of last dose (d)	Every 3 months post EoT (±14 days)
Specialty Laboratory Assessments															
Peripheral blood (*RARA* Super-Enhancer Assoc. & IRF8 Assessment) (n)	X													X	
Molecular analysis (o)	X														
Blood sample for biomarker research (p)	X						C2 only							X	
Pharmacokinetics (q)				X		X			X				X		
Blood Sample for ADME PGx (r)		X													
Blood Sample for Pharmacodynamics (s)		X		X		X								X	
Blood Sample for Resistance Mechanism														X	
Cytogenetics and Mutational Analysis (t)	X													X	
Bone Marrow Aspirate for Eligibility	X														
Bone Marrow Aspirate for Response Assessment (u)							X				Every 3rd Cycle			X	
MRD (v, w)	X						X				Every 3rd Cycle				

Abbreviations: ADME = absorption, distribution, metabolism, excretion; AE = adverse event; AESI = adverse event of special interest; BSA = body surface area; CR = complete remission; CRi = complete remission, morphologic, with incomplete blood count recovery; D/d = day(s); ECOG = Eastern Cooperative Oncology Group; ECG = electrocardiogram; EFS = event-free survival; EoT = end of treatment; HRQOL = Health Related Quality of Life; IRF8 = Interferon Regulatory Factor 8; PD = pharmacodynamic; PGx = pharmacogenomics; PK = pharmacokinetic; RBC = red blood cell; RARA = retinoic acid receptor alpha; SAE = serious adverse event.

(a) Screening assessments must be performed within 30 days of study drug administration, and may occur on Day 1 prior to dosing. Screening assessments are not required for patients in Arm 2A who receive SY-1425 in combination with azacitidine after relapse/unsatisfactory response with single agent SY-1425.

(b) Cycle 5 schedule should be followed for all subsequent cycles. **Following implementation of Amendment 7, assessments will be performed per institutional standard of care for patients enrolled in Arm 5. Aside from SAE, AESI, and Pregnancy and Birth Event collection (via the pharmacovigilance safety database) for patients still receiving study drug in Arm 5, the study procedures and data collection outlined in Table 3 will be considered as guidance and will no longer be required for the study or entered into the electronic data capture system.**

(c) If a patient has an SY-1425 dose modification (decrease or increase) to a new dose level (as defined in Section 8.4), a dose adjustment visit must be performed within 8-15 days of the dose adjustment. This visit can be combined with another scheduled visit if it is scheduled to occur within that window.

(d) An EoT visit should occur within 30 days of the last dose of study drug and prior to any subsequent therapies.

(e) Patients will enter post-treatment follow-up. Visits should occur every 3 months post EoT for response assessment and overall survival. These visits may be conducted by phone. Follow-up visit window is ±14 days. **Following implementation of Amendment 7, no further collection of post-treatment follow-up data will occur for patients enrolled in Arm 2B or Arm 5; patient follow-up should continue per institutional standard of care.**

(f) Weight will be used to calculate BSA to determine dosing requirements. BSA used for dosing calculations should be updated if the weight changes more than 15%.

(g) Safety laboratory assessments are outlined in Section 7.2 and will be performed locally.

(h) A pregnancy test (urine or serum) must be performed for women of childbearing potential during screening, on Day 1 of each cycle, and at EoT.

(i) ECG on Cycle 1 Day 8 must be performed prior to dosing. All other ECGs can be taken at any time during the study visit. All ECGs will be done as triplicate 12-lead ECGs.

(j) SAEs will be captured from the time of signing of the informed consent through 30 days after last dose of any study drug, and non-serious AEs from the time of first dose of any study drug through 30 days after last dose of any study drug. **Following implementation of Amendment 7, see footnote (b) for safety event collection instructions for patients still receiving study drug in Arm 5.**

(k) All transfusions received by the patient from 16 weeks prior to enrolment until the EoT visit will be recorded.

(l) Subsequent therapies will be recorded for 3 months after the last dose of study drug **or until implementation of Amendment 7 for patients enrolled in Arm 2B or Arm 5**.

(m) If dosing on Days 6 and 7 is not possible due to logistical limitations, these doses may be delayed to Days 8 and 9.

(n) Peripheral blood samples will be sent to a central lab for assessment of *RARA* super-enhancer associated biomarker and IRF8 biomarker at screening. Other associated *RARA* pathway genes will also be analyzed.

(o) All patients will have peripheral blood sample collected at screening for biomarker sequencing analysis to be performed at a central lab (assuming sufficient material is available at time of sample processing).

(p) For U.S. only: All patients will have a whole blood sample collected at screening (same collection time as the biomarker assessment) for additional biomarker research.

(q) All patients will have PK sampling on Day 8 of Cycle 1 at 2-4 hours and at 5-8 hours post-dose. PK sampling also on Day 22 of Cycle 1, and on Day 8 of Cycles 2, 3, and 4 at two time points at least 2 hours apart. If a patient's SY-1425 dose is modified to a different dose level (see Section 8.4) during the course of the study, PK sampling should occur within 8-15 days of dose adjustment following the same schedule as Cycle 1 Day 8. PK sampling is not required for patients in Arm 2A who receive SY-1425 in combination with azacitidine after relapse/unsatisfactory response with single agent SY-1425.

(r) Absorption, distribution, metabolism, excretion PGx sample to be taken Cycle 1 Day 1 pre-dose. PGx sample is not required for patients in Arm 2A who receive SY-1425 in combination with azacitidine after relapse/unsatisfactory response with single agent SY-1425.

(s) Peripheral blood will be collected in patients in Arms 2A and 2B on Day 1 of Cycle 1 pre-dose, on Day 8 of Cycle 1 pre-dose and 5 to 8 hours post-dose, on Day 22 of Cycle 1, and at EoT visit to determine changes in RNA including dehydrogenase/reductase (SDR family) member 3 (DHRS3). This sample should be collected in the same procedural timeframe as the corresponding PK sample. PD sampling is not required for patients in Arm 2A who receive SY-1425 in combination with azacitidine after relapse/unsatisfactory response with single agent SY-1425.

(t) Cytogenetics and mutational analysis will be performed at screening and at the EoT visit. Cytogenetics and mutational analyses will be performed locally.

(u) Bone marrow aspirates will be collected to assess morphologic response and minimal residual disease on Day 1 of Cycles 2, 3, 4, followed by every third cycle (7, 10, 13, etc.), and as clinically indicated. If a patient achieved a CR/CRi at Cycle 2 Day 1, the Cycle 3 Day 1 bone marrow aspirate is not required. A bone marrow aspirate should be

collected to confirm relapse which will be recorded as an end of treatment sample and will be used for cytogenetics assessment. Bone marrow aspirate smears should be archived for potential future analysis.

(v) Baseline assessment of immunophenotype by multiparameter flow cytometry

(w) MRD should be measured when a patient has responded with a CR, per local practice.

Table 4: Schedule of Assessment (Central Laboratory Sampling) (Arms 2B and 5)

Study Visit	Biomarker & Sequencing	Pharmacokinetics Sample	ADME PGx	Pharmacodynamics (Arm 2B Only)	Resistance Mechanism
Screening	blood samples collected any time during visit (a)				
Cycle 1 Day 1			• Pre-dose	• Pre-dose	
Cycle 1 Day 8 (b)		• 2 post-dose samples at least 2 hours apart		• Pre-dose (b) • 5-8 hours post dose	
Cycle 1 Day 22		• 2 post-dose samples at least 2 hours apart		• A post-dose sample to be collected at any time point during the visit	
Cycle 2 Day 1	blood samples collected any time during visit				
Cycle 2 Day 8		• 2 post-dose samples at least 2 hours apart			
Cycle 3 Day 8		• 2 post-dose samples at least 2 hours apart			
Cycle 4 Day 8		• 2 post-dose samples at least 2 hours apart			
Within 8-15 days of a dose adjustment		• 2 post-dose samples at least 2 hours apart			
End of Treatment (c)	blood samples collected any time during visit			• Collected any time during visit	• Collected any time during visit

Abbreviations: ADME = absorption, distribution, metabolism, and excretion; PGx = pharmacogenomics.

(a) For patients screened in France, only 2 samples will be collected.

(b) For Cycle 1 Day 8, the morning dose of SY-1425 must be administered in clinic to allow for collection of the pre-dose (0 hour) sample.

(c) Following implantation of Amendment 7, an End of Treatment Visit and the associated assessments will not be required for patients enrolled in Arm 5.

Table 5: Schedule of Events (Arm 4)

	Screening (a)	**SY-1425 Lead-In** D -7 to -1		**Cycle 1**				**Cycle 2**				**Cycles 3-6**		**Cycles 7+ (b)**	**Post Dose Adjustment Visit (c)**	**End of Treatment (EoT) (d)**	**Post-treatment Follow-up**
Study Day (D/d)	Within 30 days of dosing	D -7	D -4	D1	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±1d)	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±2d)	D15 (±2d)	D1 (±2d)	Within 8-15 days of dose adjustment	Within 30 days of last dose (d)	Every 3 mo. post EoT (±14 d) (e)
Baseline Documentation																	
Informed Consent	X																
Eligibility Review	X																
Medical History	X																
Demographics	X																
Height	X																
Weight (f)	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status	X			X				X				X		X		X	
Physical Exam	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Safety Labs/Measurements																	
Hematology (g)	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum Chemistries (g)	X	X		X	X	X	X	X				X		X	X	X	
Coagulation (g)	X	X				X		X				X		X		X	
Triglycerides and Total Cholesterol (g)	X	X				X		X				X		X	X	X	
Urinalysis (g)	X	X														X	

Table 5: Schedule of Events (Arm 4)

	Screening (a)	**SY-1425 Lead-In** D -7 to -1		**Cycle 1**				**Cycle 2**				**Cycles 3-6**		**Cycles 7+ (b)**	**Post Dose Adjustment Visit (c)**	**End of Treatment (EoT) (d)**	**Post-treatment Follow-up**
Study Day (D/d)	Within 30 days of dosing	D -7	D -4	D1	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±1d)	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±2d)	D15 (±2d)	D1 (±2d)	Within 8-15 days of dose adjustment	Within 30 days of last dose (d)	Every 3 mo. post EoT (±14 d) (e)
Pregnancy Test (h)	X	X		X				X				X		X		X	
Pulmonary Function Testing (i)	X																
Blood Group and Type Assessment, and Indirect Antiglobulin Test (IAT) (j)		X															
Triplicate ECG (k)	X	X	X					X				C3 & C4 only				X	
Vital Signs (l)	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical Assessments																	
Adverse Event Monitoring (m)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Red Blood Cell and Platelet Transfusions (n)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dosing Compliance/ Diary Review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Table 5: Schedule of Events (Arm 4)

	Screening (a)	**SY-1425 Lead-In** D -7 to -1		**Cycle 1**				**Cycle 2**				**Cycles 3-6**		**Cycles 7+ (b)**	**Post Dose Adjustment Visit (c)**	**End of Treatment (EoT) (d)**	**Post-treatment Follow-up**
Study Day (D/d)	Within 30 days of dosing	D -7	D -4	D1	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±1d)	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±2d)	D15 (±2d)	D1 (±2d)	Within 8-15 days of dose adjustment	Within 30 days of last dose (d)	Every 3 mo. post EoT (±14 d) (e)
HRQOL (FACT-Leu)	X			X								C4 only				X	
Subsequent Therapies (o)																	X
EFS and Overall Survival Follow-Up																X	X
Study Treatment																	
SY-1425		Continuous Dosing													X		
Pre-infusion Medications (p)				X	X	X	X	X	X	X	X	X	X	X			
Daratumumab				X	X	X	X	X	X	X	X	X	X	X			
Post-infusion Medications (q)				X	X	X	X	X	X	X	X	X	X	X			
Specialty Lab Assessments																	
Peripheral blood *RARA* Super-Enhancer Associated Biomarker Assessment and IRF8 biomarker (r)	X																

Table 5: Schedule of Events (Arm 4)

	Screening (a)	**SY-1425 Lead-In** D -7 to -1		**Cycle 1**				**Cycle 2**				**Cycles 3-6**		**Cycles 7+ (b)**	**Post Dose Adjustment Visit (c)**	**End of Treatment (EoT) (d)**	**Post-treatment Follow-up**
Study Day (D/d)	Within 30 days of dosing	D -7	D -4	D1	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±1d)	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±2d)	D15 (±2d)	D1 (±2d)	Within 8-15 days of dose adjustment	Within 30 days of last dose (d)	Every 3 mo. post EoT (±14 d) (e)
Blood sample for biomarker research (s)	X																
SY-1425 Pharmacokinetics (t)		X	X												X		
Daratumumab Pharmacokinetics (u)				X	X												
Blood Sample for ADME PGx (v)		X															
Blood Sample for Pharmacodynamics (w)		X			X											X	
Peripheral Blood for CD38 & Myeloid Marker Immunophenotyping (x)		X	X	X	X	X		X				C3 & C4 only		Every 3rd Cycle		X	
Blood Sample for Resistance Mechanism																X	
Cytogenetics and Mutational Analysis (y)	X															X	

Table 5: Schedule of Events (Arm 4)

	Screening (a)	**SY-1425 Lead-In** D -7 to -1		**Cycle 1**				**Cycle 2**				**Cycles 3-6**		**Cycles 7+ (b)**	**Post Dose Adjustment Visit (c)**	**End of Treatment (EoT) (d)**	**Post-treatment Follow-up**
Study Day (D/d)	Within 30 days of dosing	D -7	D -4	D1	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±1d)	D8 (±1d)	D15 (±1d)	D22 (±1d)	D1 (±2d)	D15 (±2d)	D1 (±2d)	Within 8-15 days of dose adjustment	Within 30 days of last dose (d)	Every 3 mo. post EoT (±14 d) (e)
Bone Marrow Aspirate for Eligibility	X																
Bone Marrow Aspirate for Response Assessment (z)								X				C3 & C4 only		Every 3rd Cycle		X	
Immunophenotyping (aa)	X							X				C3 & C4 only		Every 3rd Cycle			

Abbreviations: ADME = absorption, distribution, metabolism, and excretion; AML = acute myeloid leukemia; BSA = body surface area; CR = complete remission; CRi = complete remission, morphologic, with incomplete blood count recovery; D/d = day(s); ECOG = Eastern Cooperative Oncology Group; EoT = end of treatment; ECG = electrocardiogram; EFS = event-free survival; EPO = erythropoietin; FACT-Leu = Factual Assessment of Cancer Therapy-Leukemia; HRQOL = Health Related Quality of Life; IRF8 = Interferon Regulatory Factor 8; MDS = Myelodysplastic Syndrome; PD = pharmacodynamic; PGx = pharmacogenomics; PK = pharmacokinetic; RARA = retinoic acid receptor alpha; SAE = serious adverse event.

(a) Screening assessments must be performed within 30 days of study drug administration. Screening assessments may also occur on Day -7 prior to dosing.
(b) Cycle 7 schedule should be followed for all subsequent cycles.
(c) If a patient has an SY-1425 dose modification (decrease or increase) to a new dose level (as defined in Section 8.4), a dose adjustment visit must be performed within 8-15 days of the dose adjustment. This visit can be combined with another scheduled visit if it is scheduled to occur within that window.
(d) An EoT visit should occur within 30 days of the last dose of study drug, but prior to any subsequent therapies.
(e) Patients will enter post-treatment follow-up. Visits should occur every 3 months post EoT for response assessment and overall survival. These visits may be conducted by phone. Follow-up visit window is +/- 14 days.
(f) Weight will be used to calculate BSA to determine dosing requirements. BSA used for SY-1425 dosing calculations should be updated if the weight changes more than 15%. Daratumumab dose will be calculated based on the patient's weight at Cycle 1 Day 1 rounded to the nearest kilogram. The dose of daratumumab will remain constant throughout the study unless the patient's weight changes more than 10%.
(g) Safety laboratory assessments are outlined in Section 7.2 of the protocol and will be performed locally. Based on emerging safety information for daratumumab, patients enrolled into Arm 4 prior to the Syros administrative letter dated 26 December 2018 who had been receiving daratumumab for less than 6 months as of that date, an HBV serology test should be performed at the next scheduled visit. Patients with resolved infection (ie, patients who are HBsAg negative but positive for antiHBs or antiHBc)

should also have HBV DNA PCR test performed. The Sponsor should be consulted to determine the clinical management of patients who are either seropositive for HBV (defined by a positive test for HBsAg) or PCR positive for HBV.

(h) A pregnancy test (urine or serum) must be completed for women of child bearing potential during screening, on Day -7 (pre-dose), on Day 1 of each cycle visit, and at EoT.

(i) For patients with COPD, FEV1 should be measured. Symptom and disease directed exams should be performed as clinically indicated during the treatment phase.

(j) ABO, Rh and IAT will be assessed. A wallet card with the patient's blood type and IAT will be provided to patients.

(k) ECG on Day -7 must be performed prior to dosing. All other ECGs can be taken at any time during the study visit. All ECGs will be done as triplicate 12-lead ECGs.

(l) Vital signs (blood pressure, temperature, pulse) measured in sitting position. On Cycle 1 Day 1: before the start of daratumumab infusion; at 0.5, 1, 1.5, 2, 3.5 hours after the start of the infusion; at the end of the infusion; 0.5 and 1 hour after the end of the infusion. For all other infusions, vital signs will be measured before infusion starts and at the end of the infusion.

(m) SAEs will be captured from the time of signing of the Informed Consent Form through 30 days after last dose of any study drug, and non-serious AEs from the time of first dose of any study drug through 30 days after last dose of any study drug.

(n) All transfusions received by the patient from 16 weeks prior to enrollment until the EoT visit will be recorded.

(o) Subsequent therapies will be recorded for 3 months after the last dose of study drug.

(p) Administer pre-infusion medications approximately 1 to 3 hours before daratumumab infusion. One hour prior to infusion is preferred, however, PO pre-infusion medications may be administered within 3 hours before the infusion. Includes acetaminophen (650-1000 mg), antihistamine (diphenhydramine 25-50 mg, or equivalent), methylprednisolone (100 mg or equivalent for the first 2 doses, and 60 mg for all subsequent doses in the absence of infusion related reactions in the first 2 doses), and a leukotriene inhibitor (bronchospasm prophylaxis is optional with first dose on Cycle 1 Day 1 only for patients considered at risk for bronchospasm). See Section 8.2.3.2.1.

(q) All subjects will receive oral methylprednisolone (20 mg or equivalent) on the 2 days following all daratumumab infusions (beginning the day after the infusion). In the absence of infusion related AEs after the first 3 infusions, post-infusion corticosteroids should be administered per investigator discretion. Post-infusion medications may also include antihistamine (diphenhydramine 25-50 mg, or equivalent), leukotriene inhibitor, short-acting β2 adrenergic receptor agonist (e.g. salbutamol aerosol), and control medications for lung disease (e.g. inhaled corticosteroids ± long-acting β2 adrenergic receptor agonists for patients with asthma; long-acting bronchodilators such as tiotropium or salmeterol ± inhaled corticosteroids for patients with COPD). See Section 8.2.3.2.2.

(r) Peripheral blood sample will be sent to a central lab for assessment of *RARA* super-enhancer associated biomarker and IRF8 biomarker at screening to confirm eligibility. Other associated *RARA* pathway genes will also be analyzed.

(s) All patients will have a whole blood sample collected at screening (same collection time as the biomarker assessment) for additional biomarker research.

(t) SY-1425 PK: All patients will have PK sampling pre-dose (0h), and 0.5, 1, 2, 4, 6, 8 hours post-dose on Days -7 and -4. If a patient's SY-1425 dose is modified to a different dose level (see Section 8.4) during the course of the study, PK sampling should occur within 8-15 days of the dose adjustment following the same schedule as Day -7.

(u) Daratumumab PK: All patients will have PK sampling on Cycle 1 Day 1 prior to infusion (0h) and prior to the end of infusion (5-10 mins before end of infusion), and on Cycle 1 Day 8 prior to infusion (0h).

(v) Absorption, distribution, metabolism, excretion PGx sample to be taken pre-dose.

(w) Peripheral blood will be collected in all patients on Day -7 pre-dose and 5-8 hours post-dose, on Day 8 of Cycle 1, and at EoT visit to determine changes in RNA including dehydrogenase/reductase (SDR family) member 3 (DHRS3). This sample should be collected in the same procedural timeframe as the corresponding PK sample.

(x) Peripheral blood collected for central analysis of CD38 and myeloid marker immunophenotyping on Days -7 (pre-dose) and -4; Days 1, 8 and 15 of Cycle 1; Day 1 of Cycles 2, 3, 4, followed by every third cycle (7, 10, 13, etc); and EoT. For timepoints on days on which daratumumab is administered, collection is performed prior to daratumumab dosing.

(y) Cytogenetics and mutational analysis will be performed at screening and at the EoT visit. Cytogenetics and mutational analyses will be performed locally.

(z) Bone marrow aspirates will be collected to assess response on Day 1 of Cycles 2, 3, 4, followed by every third cycle (7, 10, 13, etc.), and as clinically indicated. If a patient achieved a CR/CRi at Cycle 2 Day 1, the Cycle 3 Day 1 bone marrow aspirate is not required. A bone marrow aspirate should be collected to confirm relapse which will be recorded as an end of treatment sample and will be used for cytogenetics assessment

(aa) Bone marrow aspirate samples will be collected for immunophenotyping to measure myeloid differentiation markers and will be analyzed centrally at screening and when aspirates are performed to assess response [see footnote (y), above]. Immunophenotyping may also be performed locally when clinically indicated on peripheral blood and/or bone marrow aspirate to measure myeloid differentiation markers.

Table 6: Schedule of Assessment (Central Laboratory Sampling) (Arm 4)

Study Visit	Biomarker Samples	Pharmacokinetic Sampling		ADME PGx Sample	Pharmacodynamics Sample	CD38 & Myeloid Marker Immunophenotyping	Resistance Mechanism	Immunophenotyping (Bone Marrow Aspirate)
		SY-1425 PK	Daratumumab PK					
Screening	2 blood samples collected any time during visit (a)							Within 30 days of dosing
SY-1425 Lead-In Day -7 (b)		• pre-dose (0h) (b) • 0.5 hours post-dose (± 15 mins) • 1 hour post-dose (± 15 mins) • 2 hours post-dose (± 15 mins) • 4 hours post-dose (± 30 mins) • 6 hours post-dose (±30 mins) • 8 hours post-dose (±30 mins) (c)		• Pre-dose (b)	• Pre-dose (b) • 5-8 hours post dose	• Collected pre-dose (b), (d)		
SY-1425 Lead-In Day -4 (b)		• pre-dose (0h) (b) • 0.5 hours post-dose (± 15 mins) • 1 hour post-dose (± 15 mins) • 2 hours post-dose (± 15 mins) • 4 hours post-dose (± 30 mins) • 6 hours post-dose (±30 mins) • 8 hours post-dose (±30 mins) (c)				• Collected any time during visit (d)		

Table 6: Schedule of Assessment (Central Laboratory Sampling) (Arm 4)

Study Visit	Biomarker Samples	Pharmacokinetic Sampling		ADME PGx Sample	Pharmacodynamics Sample	CD38 & Myeloid Marker Immunophenotyping	Resistance Mechanism	Immunophenotyping (Bone Marrow Aspirate)
		SY-1425 PK	Daratumumab PK					
Cycle 1 Day 1			• Prior to daratumumab infusion (0h) • Prior to the end of daratumumab infusion (5-10 mins before end of infusion)			• Collected prior to daratumumab dosing (d)		
Cycle 1 Day 8			• Prior to daratumumab infusion (0h)		• A post-dose sample to be collected at any time point during the visit	• Collected prior to daratumumab dosing (d)		
Cycle 1 Day 15						• Collected prior to daratumumab dosing (d)		
Cycle 2 Day 1						• Collected prior to daratumumab dosing (d)		Bone marrow aspirate sample collected
Cycle 3 Day 1						• Collected prior to daratumumab dosing (d)		Bone marrow aspirate sample collected
Cycle 4 Day 1						• Collected prior to daratumumab dosing (d)		Bone marrow aspirate sample collected
Cycle 7 Day 1 and every 3rd cycle thereafter						• Collected prior to daratumumab dosing (d)		Bone marrow aspirate sample collected

Table 6: Schedule of Assessment (Central Laboratory Sampling) (Arm 4)

Study Visit	Biomarker Samples	Pharmacokinetic Sampling		ADME PGx Sample	Pharmacodynamics Sample	CD38 & Myeloid Marker Immunophenotyping	Resistance Mechanism	Immunophenotyping (Bone Marrow Aspirate)
		SY-1425 PK	Daratumumab PK					
Within 8-15 days of a dose adjustment (b)		• pre-dose (0h) (b) • 0.5 hours post-dose (± 15 mins) • 1 hour post-dose (± 15 mins) • 2 hours post-dose (± 15 mins) • 4 hours post-dose (± 30 mins) • 6 hours post-dose (± 30 mins) • 8 hours post-dose (± 30 mins) (c)						
End of Treatment					• 1 sample collected any time during visit	• Collected any time during visit (d)	• 1 sample collected any time during visit	

Abbreviations: mins = minutes; 0h = zero hour; PGx = pharmacogenomics

(a) For patients screened in France, only 2 samples will be collected.

(b) For Days -7 and -4, and post-dose adjustment visits, the morning dose of SY-1425 must be administered in clinic to allow for collection of the pre-dose (0 hour) samples.

(c) Collection of the 8 hour post-dose samples may be omitted due to logistical issues and patient hardship when necessary.

(d) Refer to Lab Manual for details on number of collection tubes

TABLE OF CONTENTS

SPONSOR PROTOCOL APPROVAL 3
CONTACT INFORMATION 4
PROTOCOL SYNOPSIS 5
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 50
1. BACKGROUND 53
1.1. Acute Myeloid Leukemia and Myelodysplastic Syndrome 53
1.2. SY-1425 53
1.2.1. Preclinical Data 54
1.2.1.1. Mechanism of Action 54
1.2.1.2. Safety Pharmacology, Toxicology, and Pharmacokinetic Studies 54
1.2.2. Clinical Experience 56
1.3. Azacitidine 59
1.3.1. Rationale for Combination of SY-1425 and Azacitidine 59
1.4. Daratumumab 60
1.4.1. Rationale for Combination of SY-1425 and Daratumumab 61
1.5. Study Rationale 61
2. OBJECTIVES 63
2.1. Primary 63
2.2. Secondary 63
2.3. Exploratory 63
3. STUDY ENDPOINTS 65
3.1. Primary 65
3.2. Secondary 65
3.3. Exploratory Endpoints 66
4. STUDY DESIGN 67
5. STUDY POPULATION 70
5.1. Number of Patients 70
5.2. Duration of Study 70
5.3. Inclusion Criteria 71
5.4. Exclusion Criteria 73
6. STUDY CONDUCT 76

6.1. General Instructions 76
6.2. Study Procedures by Time Point 76
6.3. Premature Discontinuation 76
7. DESCRIPTION OF STUDY PROCEDURES 78
7.1. Baseline Documentation 78
7.1.1. Informed Consent 78
7.1.2. Eligibility Review 78
7.1.3. Medical History 78
7.1.4. Demographics 78
7.1.5. Height 78
7.1.6. Weight 78
7.1.7. ECOG Performance Status 78
7.1.8. Physical Examination 78
7.2. Safety and Laboratory Assessments 79
7.2.1. Hematology 79
7.2.2. Serum Chemistries 79
7.2.3. Coagulation 79
7.2.4. Triglycerides and Total Cholesterol 79
7.2.5. Urinalysis 79
7.2.6. Pregnancy Test 79
7.2.7. Electrocardiograms 79
7.2.8. Vital Signs 80
7.2.9. Pulmonary Function Testing (Arm 4 Only) 80
7.2.10. Blood Group and Type Assessment, and Indirect Antiglobulin Test (Arm 4 Only) 80
7.3. Clinical Assessments 81
7.3.1. Adverse Event Monitoring 81
7.3.2. Prior, Concomitant, and Subsequent Medication Review 81
7.3.3. Blood Product Transfusions 81
7.3.4. Erythropoietin Levels – Lower-Risk MDS Patients Only 81
7.3.5. Dosing Compliance/Diary Review 81
7.3.6. Health Related Quality of Life 81

7.3.7. Event Free Survival and Overall Survival - AML and Higher-Risk MDS Patients Only....82
7.4. Specialty Laboratory Assessments....82
7.4.1. RARα and IRF8 biomarker assessments....82
7.4.2. Development of Future Companion Diagnostic....82
7.4.3. Identification of Additional Biomarkers of Response to SY-1425....82
7.4.4. Identification of Resistance Mechanisms for SY-1425....82
7.4.5. Bone Marrow Sample Collection - AML and Higher-Risk MDS Patients Only....82
7.4.5.1. Bone Marrow Aspirate for Response Assessment (AML and Higher-Risk MDS Patients Only)....83
7.4.5.2. Immunophenotyping (AML and Higher-Risk MDS Patients Only)....83
7.4.5.3. CD38 and Myeloid Marker Immunophenotyping (Central Analysis)....83
7.4.6. Pharmacokinetics....84
7.4.7. ADME Pharmacogenomics....84
7.4.8. Pharmacodynamics....85
7.4.9. Additional Exploratory Biomarker Analysis....85
7.5. Amendment 7 Study Procedure Changes....85
8. STUDY DRUG MANAGEMENT....87
8.1. Allocation to Treatment....87
8.2. Study Drug Administration....87
8.2.1. SY-1425....87
8.2.2. Azacitidine....88
8.2.3. Daratumumab....88
8.2.3.1. Daratumumab Preparation....88
8.2.3.2. Daratumumab Administration....88
8.3. Reference/Control Therapy....91
8.4. Recommended Dose Modifications....91
8.4.1. SY-1425 Guidelines....91
8.4.1.1. Dose Increases....91
8.4.1.2. Dose Reductions....92
8.4.1.3. Non-Hematologic Adverse Events....92
8.4.1.4. Hematologic Adverse Events:....93

8.4.1.5. Discontinuation of Therapy Due to Treatment-Related Toxicity 93
8.4.1.6. Alternative Dosing Regimens 93
8.4.2. Azacitidine Guidelines 93
8.4.2.1. Dose Adjustments Based on Hematology Laboratory Values 93
8.4.2.2. Dose Adjustments Based on Serum Electrolytes and Renal Toxicity 94
8.4.3. Dose Delay Guidelines for Patients Receiving SY-1425 in Combination with Azacitidine 94
8.4.4. Daratumumab Guidelines 95
8.4.4.1. Daratumumab Cycle Delay 95
8.4.4.2. Daratumumab Interruption or Missed Doses 96
8.4.4.3. Dose Delay Guidelines for Patients Receiving SY-1425 in Combination with Daratumumab 96
8.5. Study Drug Dosing Compliance 96
8.5.1. SY-1425 96
8.5.2. Azacitidine 97
8.5.3. Daratumumab 97
8.6. Study Drug Storage and Drug Accountability 97
8.6.1. SY-1425 97
8.6.2. Azacitidine 97
8.6.3. Daratumumab 97
8.7. Concomitant Medications 98
8.7.1. Cytotoxic or Investigational Therapy 98
8.7.2. Other Agents Targeting CD38 (Arm 4 Only) 98
8.7.3. Oral Hydroxyurea 98
8.7.4. Antibacterial, Antifungal, and Antiviral 98
8.7.5. Hematopoietic Growth Factors 98
8.7.6. Platelet Transfusions 98
8.7.7. Red Blood Cell Transfusions 99
8.7.8. Moderate and Strong Inhibitors and Strong Inducers of CYP3A4 99
8.7.9. Antifibrinolytic 99
8.7.10. Retinoic Acid Syndrome 99
8.7.11. Multivitamin and Supplements 99
8.7.12. Antacids and Proton pump inhibitors 99

8.8. Description of SY-1425 100
8.8.1. Drug Substance 100
8.8.2. Drug product 100
8.8.3. Drug Product Precautions 101
8.9. Description of Azacitidine 101
8.10. Description of Daratumumab 101
9. ADVERSE EVENTS 102
9.1. Definition of an Adverse Event 102
9.2. Definition of a Serious Adverse Event 102
9.3. Procedures for Eliciting, Recording, and Reporting Adverse Events 103
9.3.1. Eliciting and Recording Adverse Events 103
9.3.2. Adverse Event Relationship Assessment 103
9.3.3. Adverse Event Severity Assessment 104
9.4. Specific Instructions for Recording Adverse Events on the eCRF 104
9.4.1. Diagnosis Versus Signs and Symptoms 104
9.4.2. Adverse Events Occurring Due to Other Events 104
9.4.3. Persistent of Recurrent Adverse Events 105
9.4.4. Disease Under Study 105
9.4.5. New Cancers 105
9.5. Reporting of Serious Adverse Events 105
9.6. Reporting of Adverse Events of Special Interest 106
9.7. Pregnancy and Birth Events Procedures 106
9.8. Overdose 107
9.9. Clinical Laboratory Changes 107
9.10. Reporting of Serious Adverse Events to Institutional Review Boards/Ethics Committees 108
9.11. Reporting of Serious Adverse Events to Regulatory Authorities 108
10. STATISTICS 109
10.1. General Procedures 109
10.2. Analysis Populations 109
10.3. Determination of Sample Size 109
10.4. Statistical Analysis 110

10.4.1. Demographic and Baseline Characteristics 110
10.4.2. Analysis of Efficacy 110
10.4.2.1. Primary Endpoints 110
10.4.3. Secondary Endpoints 111
10.4.4. Exploratory Endpoints 112
10.4.5. Analysis of Safety 113
10.4.5.1. Adverse Events 113
10.4.5.2. Laboratory Determination 113
10.4.5.3. Other Safety Data 113
10.5. Interim Analysis 114
10.6. Pharmacokinetics 114
10.7. Pharmacodynamics 114
11. ETHICS AND RESPONSIBILITIES 115
11.1. Good Clinical Practice 115
11.2. Ethical Conduct of the Study 115
11.3. Informed Consent 115
11.4. Records Management 115
11.5. Source Documentation 116
11.6. Study Drug Accountability 116
11.7. Auditing and Monitoring 116
11.8. Study Report and Publications 116
11.9. Study Discontinuation 116
11.10. Confidentiality 117
12. REFERENCES 118
13. APPENDICES 121
APPENDIX 1. NAMES OF STUDY PERSONNEL 122
APPENDIX 2. ECOG PERFORMANCE STATUS 123
APPENDIX 3. CRITERIA FOR DETERMINATION OF MDS IPSS-R RISK CATEGORY 124
APPENDIX 4. IWG RESPONSE CRITERIA TABLE FOR AML, MDS AND HEMATOLOGIC IMPROVEMENT 125
APPENDIX 5. CYP3A INHIBITORS/INDUCERS 129
APPENDIX 6. FACT-AN QOL 130

APPENDIX 7. FACT-LEU QOL.....133
APPENDIX 8. ASTHMA GUIDELINES 136
APPENDIX 9. THE FAMILY OF ANTIHISTIMINE MEDICATIONS 140
APPENDIX 10. CONVERSION TABLE FOR GLUCOCORTICOID DOSE.....141

LIST OF TABLES

Table 1: Schedule of Events (Arms 1, 2A, and 3) 19
Table 2: Schedule of Assessment (Central Laboratory Sampling) (Arms 1, 2A, and 3)....24
Table 3: Schedule of Events (Arms 2B, and 5, and Patients in Arm 2A who receive SY-1425 in Combination with Azacitidine After Relapse/Unsatisfactory Response with Single Agent SY-1425) 27
Table 4: Schedule of Assessment (Central Laboratory Sampling) (Arms 2B and 5)....32
Table 5: Schedule of Events (Arm 4) 33
Table 6: Schedule of Assessment (Central Laboratory Sampling) (Arm 4)....39
Table 7: List of Clinical APL Studies with Tamibarotene (SY-1425) 57
Table 8: Daratumumab Infusion Rates 89
Table 9: Dose Increases of SY-1425 91
Table 10: Dose Reductions of SY-1425 92
Table 11: Azacitidine Dose Adjustments Based on Nadir Counts 94
Table 12: Azacitidine Dose Adjustments Based on Nadir Counts and Cellularity 94
Table 13: Daratumumab Administration Schedule....96

LIST OF FIGURES

Figure 1: Study Schematic 18
Figure 2: Chemical Structure 100

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADME	Absorption, Distribution, Metabolism, and Excretion
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
APL	Acute Promyelocytic Leukemia
AST	Aspartate Aminotransferase
ATO	Arsenic Trioxide
ATRA	All-Trans Retinoic Acid
AUC	Area Under the Curve
ChIP	Chromatin Immunoprecipitation
CL/F	Total Body Clearance from Plasma
C_{max}	Maximum Plasma Concentration
C_{min}	Minimum Plasma Concentration
CNS	Central nervous system
COPD	Chronic Obstructive Pulmonary Disease
CR	Complete Remission; Complete Response
CRF	Case Report Form
CRi	CR, morphologic, with incomplete blood count recovery
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DHRS3	Dehydrogenase/reductase (SDR family) member 3
DOR	Duration of Response
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic data capture (system)
EFS	Event-Free Survival

Abbreviation	Definition
EoT	End of Treatment
EPO	Erythropoietin
EU	European Union
FACT-An	Factual Assessment of Cancer Therapy-Anemia
FACT-Leu	Factual Assessment of Cancer Therapy-Leukemia
FEV1	Forced Expiratory Volume in 1 Second
GCP	Good Clinical Practice
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HI	Hematologic Improvement
HIV	Human immunodeficiency virus
HRQOL	Health Related Quality of Life
IAT	Indirect Antiglobulin Test
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRF8	Interferon Regulatory Factor 8
IRB	Institutional Review Board
IPSS-R	Revised International Prognostic Scoring System
IRR	Infusion Related Reaction
IWG	International Working Group
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MPD	Myeloproliferative Disease
MRD	Minimal Residual Disease
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Overall Response Rate
OS	Overall Survival
PD	Pharmacodynamic
PDX	Patient Derived Xenograft

Abbreviation	Definition
PK	Pharmacokinetic
po/PO	By Mouth, Orally
PR	Partial remission
RARα	Retinoic Acid Receptor Alpha
RBC	Red Blood Cell
RFS	Relapse-free Survival
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SE	Super-enhancers
$t_{1/2}$	Half-life
t_{max}	Time to Maximum Concentration
ULN	Upper Limit of Normal
US	United States
WBC	White Blood Cell

1. BACKGROUND

1.1. Acute Myeloid Leukemia and Myelodysplastic Syndrome

Acute Myeloid Leukemia (AML) is the most common leukemia in adults (Ferrara and Schiffer, 2013) with an estimate of 20,830 new cases (4 new cases per 100,000) diagnosed in the United States (US) in 2015 (SEER data, 2016). Current treatment paradigms in younger patients (< 60 years) include induction regimens of standard cytotoxic chemotherapy (cytarabine and an anthracycline) and consolidation with additional chemotherapy and/or hematopoietic stem cell transplantation. While complete remission (CR) may be achieved initially in over 80% of patients, the 5-year overall survival is 35% to 40%. In older patients with AML (≥ 60 years), where the objectives of treatment are more commonly palliative, the use of hypomethylating agents may extend survival, but cure rates are very low. The estimated number of AML deaths in the US in 2015 was 10,460 with the percent of overall patients surviving 5 years reported at 25.9% (SEER data, 2016).

Myelodysplastic syndrome (MDS) is a heterogeneous hematopoietic disease commonly associated with bone marrow failure, peripheral blood cytopenias and associated complications of anemia, infection or hemorrhage, and progression to AML. The incidence of MDS is similar to that of AML, and is estimated at approximately 5 per 100,000, representing the most commonly diagnosed myeloid neoplasm in the US and Europe (Cogle et al, 2014). While MDS is generally a more indolent disease, early on lower-risk MDS patients commonly experience cytopenias with associated complications of anemia, infections, and/or bleeding. The prognosis of patients with later stage MDS is poor, and associated with low overall survival, similar to AML. Currently available therapies for MDS in the US include hypomethylating agents and lenalidomide which may limit the clinical impact of MDS. However, there remains unmet medical need for new agents that can extend survival and improve quality of life in patients with MDS (DeZern, 2015).

1.2. SY-1425

SY-1425 (tamibarotene) is an orally available, synthetic retinoid approved in Japan (Amnolake® Tablets) since April 2005 for the treatment of relapsed or refractory Acute Promyelocytic Leukemia (APL) whose disease is characterized by the presence of the t(15;17) translocation or expression of the PML-RARα gene. Tamibarotene was designed to be a more potent and selective retinoic acid receptor alpha (RARα) agonist with significantly improved *in vivo* pharmacologic properties compared to all-trans retinoic acid (ATRA), a component of the current first-line treatment of APL in the US. *In vitro*, tamibarotene is approximately 10-fold more potent than ATRA. It has a lower affinity for cellular retinoic acid binding protein, the overexpression of which is associated with resistance to ATRA, and is not subject to the predominant route of retinoid metabolism by Cyp26A1. These two features likely contribute to the sustained plasma levels of tamibarotene with repeated dosing. Furthermore, tamibarotene is a selective RARα agonist, whereas ATRA is a non-selective agonist of RARα, β and γ, and can isomerize *in vivo* to bind Retinoid X and peroxisome proliferator-activated receptors. This selectivity may provide SY-1425 a distinct and favorable safety, tolerability and efficacy profile.

1.2.1. Preclinical Data

1.2.1.1. Mechanism of Action

SY-1425 is a potent and selective small molecule agonist of the RARα. Retinoic acid receptors are transcription factors that act as transcriptional repressors in the unbound state and as transcriptional activators when bound by an agonist ligand. As previously described in the context of APL with the t(15;17) PML-RARα translocation, RARα agonist binding relieves pathogenic repression of myeloid differentiation, enabling normalization of myelopoiesis and terminal differentiation of tumor cells.

Super-enhancers (SEs) have recently been identified as exceptionally large clustered enhancer regions in the human genome, which are densely occupied by transcription factors, cofactors and chromatin regulators. They have been implicated in directing gene expression programs that define cell identity and also regulate oncogenes important in the pathogenesis of cancer. Syros has used genome wide profiling of AML patient samples to identify a SE at the *RARA* gene locus regulating expression of the *RARA* gene in a subset of non-APL AML primary patient samples. This SE leads to upregulation of RARα mRNA levels and defines a novel subset of AML that Syros found to be uniquely responsive to SY-1425 *in vitro* and *in vivo*. In non-APL AML cell lines, SY-1425 inhibited the proliferation of cells containing the *RARA* SE and high RARα transcript levels, but not in those without. Furthermore, in these sensitive cell lines genes consistent with promotion of differentiation were upregulated in response to SY-1425, similar to the RARα agonist response in APL. In patient-derived xenograft (PDX) models, tumor growth was inhibited and survival prolonged in those containing high levels of RARα mRNA expression but not in PDX models whose tumor cells contained low levels of RARα mRNA. These PDX models with high levels of RARα mRNA also demonstrated an increase in differentiated cell number and diversity, with a reduction of blasts in both peripheral blood and bone marrow with SY-1425 treatment. A similar correlation was made with the SE strength and mRNA levels of Interferon Regulatory Factor 8 (IRF8) which is a downstream nuclear effector of the interferon pathway known to have cross talk with RARα signaling.

These studies indicate that RARα mRNA levels and mRNA levels for other RARα pathway-associated genes, such as IRF8, may be potential biomarkers for response to SY-1425. Analysis of a public mRNA expression data set derived from MDS patient samples further indicates that similar to AML, MDS contains a subpopulation of patients with significantly elevated mRNA for RARα. Moreover, SE analysis has confirmed that MDS patient cells contain a *RARA* SE of comparable magnitude to those in AML, thus extending the potential for SY-1425 therapeutic use to MDS.

These data lead to the hypothesis that the presence of a SE at the *RARA* gene and concomitant high levels of RARα mRNA expression (along with the RARα pathway associated gene IRF8) in AML and MDS patients predicts for response to SY-1425 treatment.

1.2.1.2. Safety Pharmacology, Toxicology, and Pharmacokinetic Studies

The nonclinical safety assessment indicated that the activity and toxicity profile of tamibarotene is qualitatively similar to other retinoids, a class for which there is extensive nonclinical and clinical experience. No novel toxicities have been identified for tamibarotene. In addition, the

hematopoietic effects noted with tamibarotene appear to be less than those observed with other retinoids suggesting that tamibarotene may be better tolerated.

A battery of safety pharmacology studies was conducted for the evaluation of the potential effects of tamibarotene on the nervous, respiratory, cardiovascular, renal and gastrointestinal systems in mice, rats and/or dogs. No major pharmacologic effects were identified in the safety pharmacology studies.

In single dose studies with tamibarotene, the maximum tolerated nonlethal dose was 200 mg/kg and ≥100 mg/kg in the rat and dog, respectively. The LD50 in the rat was calculated to be ~342 mg/kg.

A series of genotoxicity studies were conducted with tamibarotene. Tamibarotene was negative for mutagenicity in a bacterial revertant mutation assay and negative for clastogenicity in an *in vivo* mouse micronucleus assay. Tamibarotene was positive for clastogenicity in a Chinese Hamster Lung cell assay at the highest concentration tested (86 μg/mL) without S9 activation but negative in the presence of S9 metabolic activation.

Repeat oral dose toxicity studies have been conducted for up to 26 and 39 weeks in rats and dogs, respectively, at doses up to 0.4 mg/kg/day. The duration of the chronic toxicity studies is sufficient to support the proposed duration of dosing in the Phase 2 clinical trial. The spectrum of toxicities observed with tamibarotene are similar to other retinoids. Test article-related effects were noted in bone, testes, vaginal and uterine epithelium, gastrointestinal tract, skin and mucocutaneous junctions. Clinical pathology alterations included effect on white blood cell (WBC) differential (increased neutrophils), serum proteins and liver enzymes. Similar findings have been described in humans, supporting the appropriateness of rat and dog for the evaluation of tamibarotene. As anticipated with retinoids, tamibarotene exhibited reproductive toxicity including teratogenicity.

The pharmacokinetic profile of tamibarotene, including absorption, distribution, metabolism, and excretion, has been evaluated primarily in rats and dogs following single and repeat dose oral and/or IV studies in which radiolabeled drug was administered. Pharmacokinetics in rats and dogs suggest that absorption following oral administration is relatively rapid in both species with time of maximum concentration (t_{max}) in the 1-2 hour range. The oral absorption in male rat was estimated as 67%. Plasma radioactivity levels at maximum plasma concentration (C_{max}), area under the curve (AUC) and 24 hours after dosing suggested accumulation from Day 1 to Day 7 of dosing. Whole body autoradiography studies in rats showed peak tissue radioactivity concentrations were observed within 1 hour post-dose for the majority of tissues and decreased over the 168 hours post-dose. The greatest concentration of radioactivity at 1 hour after dosing was observed in the liver, which was approximately 12 times higher than in the plasma. Levels of radioactivity in the adrenals, small intestine, kidney, duodenum, stomach, esophagus, Harderian gland, and brown fat were approximately 1.4 to 4.3 times higher than the levels in the plasma. Placental transfer of tamibarotene-related material was observed in pregnant rats with fetal liver showing the highest level of radioactivity.

Protein binding was extensive in the rat, dog, and human plasma with binding ≥ 98.7%. Protein binding appeared to be independent of concentration and was also determined to be reversible. Tamibarotene was predominantly bound to serum albumin in the dog and human plasma with lesser amounts bound to γ-globulins (dog and human) and human α_1-acid glycoprotein.

The *in vitro* studies suggest that there was a low to negligible potential for drug-drug interactions based on protein-binding characteristics.

In vitro metabolism studies of tamibarotene conducted with human liver microsomes demonstrated extensive metabolism of the parent compound and the generation of two major metabolites, M-3 (6-hydroxy-tamibarotene) and M-4 (7-hydroxy-tamibarotene). The data also suggest that tamibarotene is unlikely to alter the pharmacokinetic (PK) profile of concomitantly administered drugs that are metabolized by CYP enzymes, but that the PK profile of tamibarotene may be altered by CYP3A4 inhibitors and inducers.

The predominant moiety in the plasma of rats and dogs was the parent compound. There are potentially two major metabolic pathways in the rat. For the first potential major pathway, tamibarotene undergoes 6- or 7-hydroxylation to yield the related hydroxy-tamibarotene (M-3 or M-4). The hydroxylated tamibarotene is subsequently converted to oxo-tamibarotene (M-5 or M-7). For the second potential major pathway, tamibarotene undergoes hydrolysis of the carboxamide bond to yield tetrahydro-tetramethyl-naphthylamine and terephthalic acid. Taurine conjugates of tamibarotene, M-3, and M-4 (M-6, M-1, and M-2, respectively) are also formed. Excretion patterns following oral administration of radiolabeled tamibarotene were comparable for rats and dogs, with the primary route of excretion in the feces and the majority of the radioactive dose being excreted within the first 24 hours after dosing. Data generated in bile duct-cannulated rats dosed intraduodenally with bile from treated rats indicated that tamibarotene and its metabolites underwent extensive enterohepatic recirculation. Lacteal secretion of tamibarotene-related material was observed in rat with milk:plasma ratios of between 13- and 94-fold. Unchanged tamibarotene was the major drug-related component in milk, with small amounts of M-6 and tetrahydro-tetramethyl-naphthylamine also detected.

1.2.2. Clinical Experience

Table 7: List of Clinical APL Studies with Tamibarotene (SY-1425) lists the previous oncology clinical studies of tamibarotene in patients with APL; all have been completed.

Table 7: List of Clinical APL Studies with Tamibarotene (SY-1425)

Study Identifier	Indication	Dose/regimen	Design	Patients Enrolled (N)
Tobita et al. (1997)	APL, relapsed after ATRA	6 mg/m^2/day induction for up to 8 weeks	P2 efficacy and safety, open-label single arm	25 (24 evaluable)
TOS-80T-003 Study (2002)	APL (relapsed and treatment naïve)	6 mg/m^2/day induction for up to 8 weeks	Ph2 PK, efficacy, and safety, open-label single arm	42 (41 safety-evaluable, 39 efficacy-evaluable)
Shinagawa et al. (2014)	APL in remission after consolidation (Maintenance)	6 mg/m^2/day for 14 days every 3 months for 2 years	Ph3 randomized controlled vs ATRA	347, including 134 randomize to maintenance with tamibarotene
Sanford et al. (2015)	APL relapsed after ATRA and ATO	6 mg/m^2/day induction and for up to six cycles of consolidation (every other month) for 1 year.	Ph2 efficacy and safety, single arm, open-label	14
Wang et al. (2015)	Relapsed APL	6 mg/m^2/day	Ph3 randomized open-label, tamibarotene/ATO vs ATRA/ATO	71, including 35 treated with tamibarotene

In Japan, the recommended dose of tamibarotene for the treatment of patients with relapsed/refractory APL is 6 mg/m^2/day administered as divided doses after breakfast and dinner. Approximately 1400 patients were treated with tamibarotene in clinical trials and in the post marketing approval setting. The Japanese approval is based on data from two Phase 2 studies, the Koseisho study (Tobita et al, 1997) and the TOS-80T-003 study (Amnolake® label). In the two Phase 2 clinical studies conducted with tamibarotene, 63 efficacy evaluable APL patients, who were either naïve to treatment (5 patients) or who had relapsed following a complete response with ATRA (58 patients), received tamibarotene (6 mg/m^2/day; range 3 to 12 mg/m^2/day) for up to 8 weeks. Overall, 60% of patients had a complete response to treatment. The TOS-80T-003 study enrolled 42 Japanese patients with APL. Of 39 efficacy evaluable patients, 5 individuals were APL-treatment naïve and 34 had been treated previously with ATRA. Tamibarotene was also administered orally (PO) at a dose of 6 mg/m^2/day for eight weeks (range; 3 to 12 mg/m^2/day). The overall complete response rate in these patients was 61.5%. In patients who were in first relapse following ATRA therapy, the complete response rate was 81%, compared to those in second or more relapse who had a 31% complete response rate. Most of the adverse events (AEs) seen were mild and typical of this class of drugs and the incidence of AEs was similar across the dose range tested. AEs included dry skin, skin rash, headache, bone pain, fever and elevated blood tests for cholesterol, lipids (triglycerides), liver function enzymes and WBC counts. Retinoic Acid Syndrome was reported in three patients (7.3%). Thus, tamibarotene was shown to be safe, well tolerated and efficacious in the Japanese population with relapsed/refractory APL.

In the US, tamibarotene activity was evaluated by another sponsor in patients with relapsed or refractory APL following treatment with ATRA and arsenic trioxide (ATO). A Phase 2 trial was conducted at eight clinical sites in the US, Italy and Spain. A total of 14 patients, 12 of whom relapsed following ATRA and ATO and 2 of whom were refractory to ATRA and ATO and other chemotherapeutic agents, received treatment with tamibarotene (Sanford et al, 2015). Patients were dosed 6 mg/m^2 daily for 56 days for induction then every other month as consolidation therapy for 1 year. The overall response rate (ORR) was 64% (n=9), the rate of complete cytogenetic response was 43% (n=6) and the rate of complete molecular response was 21% (n=3). After induction, 5 (36%) patients achieved a CR, 4 (29%) achieved a CR with incomplete recovery of counts (CRi) and 5 (36%) had resistant disease. Six (43%) patients who achieved a CR (n = 3) or CRi (n = 3) achieved a complete cytogenetic response at a median time of 43 d after starting treatment (range 28–120 d). Seven of the 9 responders relapsed after a median of 4.6 months (range 1.6-26.8 months). The median event-free survival (EFS) was 3.5 months and the median overall survival was 9.5 months. Adverse events reported in greater than 20% of the patients included rash, infection, headache, diarrhea, neutropenia, insomnia, oropharyngeal pain, dry skin and syncope. All of these events were Grade 1 or 2 except for neutropenia (Grade 2-4). The overall response rate of CR + CRi was 64% (9/14) in this APL study and was consistent with that observed in the Japanese Phase 2 studies. It is also notable that these patients were more heavily pre-treated (median of two prior remissions and failure of both ATRA and ATO).

In China, a recent report (Wang et al, 2015) describes a phase 3, randomized, open-label, parallel-group, active-controlled, multicenter, study of 56 days treatment duration evaluating the efficacy and safety of 6 mg/m^2/day tamibarotene versus 25 mg/m^2/day ATRA, each in combination with ATO (0.15 mg/kg/day) in patients with relapsed APL. Patients were randomly assigned to ATRA + ATO (n=35) or tamibarotene + ATO (n=35). The CR rate was significantly higher in the tamibarotene + ATO group (80% vs. 54%; P = 0.022). The number who showed complete molecular remission was also significantly higher in the tamibarotene + ATO group (23% versus 3%), demonstrating a higher quality of remissions. The most commonly-reported adverse reactions included hypertriglyceridemia, hypercholesterolemia, rash, and elevation of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, in both groups. The tolerability observed in the study group was considered to be similar between groups. The only adverse finding reported to show an appreciable intergroup difference was leukocytosis, which occurred at a significantly lower frequency in the tamibarotene + ATO group than in the ATRA + ATO group, suggesting a reduced risk of RAS.

Tamibarotene was studied in APL maintenance therapy in comparison to ATRA (Shinagawa et al, 2014). Newly diagnosed APL patients in molecular remission at the end of consolidation therapy (n = 269 of 347 enrolled) were randomized to receive either tamibarotene (n = 134) at 6 mg/m^2 or ATRA (n = 135) at 45 mg/m^2 daily for 14 days every 3 months for 2 years. The relapse-free survival (RFS) rate was similar between treatments at 4 years (91% tamibarotene and 84% ATRA [p=0.095]). An analysis of patients with a high-risk of relapse (initial WBC $\geq$ 10.0 x 109/L) revealed a significant difference in RFS in favor of tamibarotene (87% tamibarotene versus 58% ATRA [p = 0.028]). Both treatments were generally well-tolerated, with most AEs considered mild or moderate. The most common drug-related events of grade 2 or greater in both arms were dyslipidemia, rash, increased AST/ALT and headache. Of these,

dyslipidemia and skin rash were more common in the tamibarotene arm. Discontinuations due to AE occurred in seven patients in the tamibarotene arm (skin rash in 5 patients; liver dysfunction, elevated triglycerides in 1 patient each) and four patients in the ATRA arm (nausea, headache, liver dysfunction and elevated triglycerides in 1 patient each). Overall, AEs seen with tamibarotene during extended maintenance therapy were similar to those reported in the previous Japanese APL registration studies.

Additional clinical trials have explored the activity of tamibarotene as single-agent treatment in advanced hepatocellular carcinoma (HCC) and in combination with paclitaxel/carboplatin in non-small cell lung cancer. Tamibarotene was studied in an open-label study in HCC (Kanai et al, 2014). Thirty-six patients enrolled and 31 received tamibarotene 8 or 12 mg/day. One patient achieved a partial response and seven achieved stable disease; disease control rate was 32%. Adverse events were experienced by all patients and were generally mild and consistent with those reported in other studies. Fourteen (14) of 31 patients (45%) experienced AEs considered drug-related and of grade 3-4. These AEs included increases in cholesterol, γ-GTP, AST or alkaline phosphatase, decrease in leukocytes, platelets or hemoglobin, thrombosis and rash. Serious adverse events (SAEs) included thrombosis of a limb (2 patients), pulmonary artery (2 patients) or portal vein (one patient). One patient died of interstitial lung disease. Tamibarotene was also studied in a Phase 2b clinical trial in patients with Stage IIIB (with pleural effusion) or Stage IV non-small cell lung cancer. Patients were treated with up to 6 cycles of paclitaxel plus carboplatin, plus either tamibarotene (6 mg/m^2/day) or placebo, followed by continuous treatment with either tamibarotene or placebo. The trial enrolled 145 non-small cell lung cancer patients. The study was terminated after a planned interim futility analysis, based on 127 efficacy evaluable patients with a median follow-up of 7.7 months, showed that the primary efficacy endpoint (improvement in PFS) would not be met. There were 38 deaths, including 19 due to disease progression (10 on the experimental arm, 9 on the control arm), 8 due toxicity (6 experimental, 2, control), and 11 with unknown causes (6 experimental, 5 control). The AE profile in 136 safety evaluable patients (73, tamibarotene + paclitaxel and carboplatin arm, 63 placebo + paclitaxel and carboplatin arm) showed a similar overall incidence of AEs (86.2% tamibarotene arm vs. 87.3% placebo arm). A higher incidence of ≥Grade 3 SAEs including thromboembolic events (6.9% vs. 1.6%) was reported in the tamibarotene vs. placebo arms, respectively. In general, the safety profile was consistent with the AE profile demonstrated in APL with single agent tamibarotene.

1.3. Azacitidine

Azacitidine is a pyrimidine analogue that exerts antineoplastic effects on abnormal hematopoietic bone marrow cells through multiple mechanisms including DNA hypomethylation. Cytotoxicity may also result from incorporation into DNA and RNA, with inhibition of DNA, RNA and protein synthesis. Azacitidine is approved in the US and European Union (EU) for MDS. Azacitidine is also approved for use in AML in the EU, and is widely accepted as standard of care for treatment of AML in the US.

1.3.1. Rationale for Combination of SY-1425 and Azacitidine

Azacitidine is an azanucleotide analog that is used in the treatment of myeloid malignancies (Derissen et al, 2013). As a hypomethylating agent, azacitidine works by inhibiting DNMT1

leading to depletion of methyl-cytosine in the DNA of the tumor cells (Derissen et al, 2006; Voso et al, 2014; Stresemann et al, 2008). Hypomethylation leads to the re-expression of genes associated with differentiation and growth arrest, contributing to its antineoplastic therapeutic effects. The RARα, encoded by the *RARA* gene, is a nuclear hormone receptor that acts as a transcriptional repressor when unbound by a ligand and as a gene activator when bound by an agonist (Niederreither and Dollé, 2008). While RARα is present in many tissues, it is especially important in the normal maturation of myeloid cells (Kastner et al, 2001). The tumor cells from the novel subset of AML defined by an *RARA* SE, leading to upregulated RARα expression, or high IRF8 expression are uniquely responsive to the RARα agonist, SY-1425. SY-1425 binds to RARα, and reprograms the tumor cells to express genes associated with myeloid differentiation and anti-proliferative responses. The loss of methyl-cytosine residues induced by azacitidine primes the tumor cells for reprogramming by SY-1425 thereby enhancing gene activation by SY-1425, which switches RARα from a repressive state to an activating state. Thus, the two agents may work cooperatively to promote terminal differentiation and decrease proliferation of the AML tumor cells, with the potential for increased clinical benefit.

In cell line models, the combination of azacitidine and SY-1425 showed synergistic anti-proliferative effects on the cells where a more than additive reduction in tumor cell growth was observed over a range of concentrations of each drug. Following up on this finding, SY-1425 and azacitidine were administered to a disseminated patient derived xenograft mouse model of RARA-high AML. Indeed, the combination demonstrated superior efficacy at reducing tumor burden, achieving deeper and prolonged CR, based on bone marrow and peripheral tumor cell reduction, as compared to the single agents. Mechanistic studies in AML cell line models have revealed that while azacitidine had moderate suppressive or activating effects on a broad set of genes, the addition of SY-1425 resulted in very strong and specific induction of RARα target genes. Furthermore, since both agents work with DNA interacting targets, it was hypothesized that the source of cell killing potentially originated from DNA damage. Indeed, the combination of SY-1425 with azacitidine or decitabine in cell line models resulted in emergent induction of DNA damage as detected by PARP cleavage and phosphorylation of H2A.X

As of 29 October 2018, SY-1425, in combination with azacitidine, in biomarker positive newly diagnosed unfit AML patients showed evidence of clinical activity with a high response rate and a rapid onset of responses. ORR was 63% (5/8) and the CR/CRi rate was 50% (4/8) with the majority of initial responses at C2D1. In biomarker-negative patients the ORR was 17% (1/6), with 1 CR observed; while these data were less mature, they preliminarily support the use of the RARA pathway activation biomarker(s) for patient selection. SY-1425 + azacitidine was generally well tolerated with no evidence for increased toxicities of the combination (Cook et al, 2018).

1.4. Daratumumab

Daratumumab is a human IgG1κ monoclonal antibody (mAb) that binds with high affinity to a unique epitope on CD38. It is a targeted immunotherapy that attacks tumor cells that overexpress CD38, a transmembrane glycoprotein, in a variety of hematological malignancies. Daratumumab induces lysis of CD38-expressing tumor cells by a wide spectrum of mechanisms including complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP), through activation of

complement proteins, natural killer (NK) cells, and macrophages, respectively (de Weers et al, 2011; Overdijk et al, 2015). Daratumumab is approved in the United States and European Union for use in multiple myeloma.

1.4.1. Rationale for Combination of SY-1425 and Daratumumab

CD38 expression in AML is considered to be generally low (CD38lo), but moderate in expression in a subset of patients (CD38dim) (Keyhani et al, 2000). CD38 induction in response to SY-1425 was observed by mRNA and FACS in RARA-high and IRF8-high cell line models of AML. In addition, AML patient samples showed similar rates of CD38 induction in response to ex vivo treatment with SY-1425 by FACS. Furthermore, ex vivo functional assays of normal human natural killer (NK) cell mediated killing of RARA-high AML cell lines showed that only the combination of SY-1425 and daratumumab, but neither agent on their own, could induce robust apoptosis of the AML cells and interferon gamma secretion of NK cells (indicative of NK cell activation.

The kinetics of induction showed that maximal levels of CD38 were achieved within 24 to 72 hours of SY-1425 ex vivo exposure. This provided a potential rationale to explore combination with a compound known to target CD38 and already approved in another hematology indication.

1.5. Study Rationale

Knowledge of underlying AML biology has increased significantly in the past two decades, with a focus on underlying cytogenetic and molecular aberrations (Grimwade et al, 2016), and dysregulated epigenetic mechanisms being associated with the pathogenesis of the disease (Wouters and Delwel, 2016). A recent approach to investigate transcriptional control of genes important in cancer identified an important role for the SE. SEs are exceptionally large clustered enhancer regions in the human genome, densely occupied by transcription factors, cofactors and chromatin regulators. They have been implicated in directing gene expression programs that define cell identity and also regulate oncogenes important in the pathogenesis of cancer (Hnisz et al, 2013). Syros' scientists have studied SEs and their contributions to the pathogenesis of AML, and identified a SE controlling the *RARA* gene locus in a subset of non-APL AML primary patient samples. They also found upregulation of RARα mRNA expression is associated with the SE at the *RARA* gene locus. This excess RARα expression allows the tumor to suppress differentiation by favoring the gene repression function of RARα in the absence of a concomitant increase of natural ligand. Upregulation of this *RARA* repressive circuit creates a *de novo* susceptibility for the tumor, by increasing sensitivity to SY-1425 a potent and selective RARα agonist. It was demonstrated that increased RARα mRNA expression correlated with increased sensitivity to SY-1425 *in vitro* and predicted response to SY-1425 in PDX models of AML. The mechanism of RARα-mediated differentiation block in the tumor and consequent response to SY-1425 is similar to that described with retinoids in APL, based on the presence of a specific pathogenic fusion gene, *PML-RARA*. These data, therefore, define a novel subset of AML, distinct from APL, that Syros found to be uniquely responsive to SY-1425 *in vitro* and *in vivo*. Furthermore, the existence of the SE at the *RARA* gene locus and upregulation of RARα mRNA expression has also been identified in a subset of patients with MDS. Since RARα mRNA and *RARA* SE strength are highly correlated, RARα mRNA levels and mRNA levels for pathway-

associated transcriptional complex partner genes, such as IRF8, can be used to quantify a biomarker in patients with AML and MDS for response to SY-1425.

The broad objectives of this clinical study conducted by Syros are to evaluate SY-1425 as single agent and in combination with azacitidine or daratumumab in patients with AML and MDS who are selected based on the presence of the *RARA* super-enhancer associated biomarker or IRF8 biomarker.

2. OBJECTIVES

2.1. Primary

The primary objectives are:

- Characterize the clinical activity of SY-1425 in biomarker positive patients by the overall response rate (ORR) in patients in Arms 1, 2A, 2B, and 5, and by the transfusion independence rate (TIR) in patients in Arm 3
- Characterize the safety and tolerability of the combination of SY-1425 and daratumumab in Arm 4

2.2. Secondary

The secondary objectives are:

- Characterize the clinical activity of SY-1425 in patients positive for the *RARA* super-enhancer associated biomarker by the ORR in Arms 1, 2A, 2B, and 5, and by TIR in Arm 3
- Characterize the clinical activity of SY-1425 in patients positive for the IRF8 biomarker and negative for the *RARA* super-enhancer associated biomarker by the ORR in Arms 1, 2A, 2B, and 5, and by TIR in Arm 3
- Characterize the clinical activity of the combination of SY-1425 and azacitidine by the ORR in patient in Arm 2B
- Characterize the clinical activity of the combination of SY-1425 and daratumumab by ORR in Arm 4
- Characterize the clinical activity by patients in Arms 1, 2A, 2B, 3, 4, and 5, based on event-free survival (EFS), relapse-free survival (RFS), duration of response (DOR), overall survival (OS), hematologic improvement (HI)
- For all patients, evaluate the requirement for supportive measures secondary to cytopenias
- Characterize the safety and tolerability of SY-1425 as a single agent in Arms 1, 2A and 3, in combination with azacitidine in Arms 2B and 5.
- Characterize the PK of SY-1425 after single and multiple doses

2.3. Exploratory

The exploratory objectives are:

- Assess factors associated with the ORR, including but not limited to arm and diagnosis, prior treatment, *RARA* super-enhancer associated biomarker and/or IRF8 biomarker status, dehydrogenase/reductase (SDR family) member 3 (DHRS3) induction, myeloid differentiation, induction of CD38 expression and other potential predictors of success including genotype and mutation status

- Evaluate changes in Health-Related Quality of Life (HRQOL)
- Establish PK/PD relationships based on PD markers in leukemic cells from repeat peripheral blood samples
- Characterize the PK of daratumumab in combination with SY-1425
- Characterize the relationship between SY-1425 activity and baseline tumor biomarker levels, and levels over time (RARα mRNA or IRF8 mRNA)
- Characterize clinical activity of SY-1425 administered as a single agent and in combination with azacitidine or daratumumab by time-to-response
- Characterize expression of myeloid differentiation markers, including CD38, over time
- Explore the potential role of additional gene or protein alterations (e.g. expression or mutation) in sensitivity and/or resistance to SY-1425 using multiplex platform(s)

3. STUDY ENDPOINTS

3.1. Primary

- ORR for biomarker positive patients with AML or higher-risk MDS (Arms 1, 2A, 2B, and 5)
- TIR for patients with lower-risk MDS (Arm 3)
- Safety and tolerability of SY-1425 in combination with daratumumab assessed by the type and frequency of AEs and SAEs using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 4.03, as well as changes in clinically significant clinical laboratory values, electrocardiogram (ECG) parameters and vital sign measurements (Arm 4)

3.2. Secondary

- ORR for AML or higher-risk MDS patients positive for the *RARA* super-enhancer associated biomarker (Arms 1, 2A, 2B and 5)
- TIR for lower-risk MDS patients positive for the *RARA* super-enhancer associated biomarker (Arm 3)
- Response rate (ORR +TIR) for patients positive for the IRF8 biomarker and negative for the *RARA* super-enhancer associated biomarker treated with SY-1425 as a single agent (Arms 1, 2A, and 3)
- ORR for AML or higher-risk MDS patients positive for the IRF8 biomarker and negative for the *RARA* super-enhancer associated biomarker (Arms 1, 2A, 2B, and 5)
- TIR for lower-risk MDS patients positive for the IRF8 biomarker and negative for the *RARA* super-enhancer associated biomarker (Arm 3)
- ORR for AML patients who are treated with SY-1425 in combination with azacitidine (Arm 2B)
- ORR for AML or higher-risk MDS patients treated with SY-1425 in combination with daratumumab (Arm 4)
- Clinical activity as measured by EFS, RFS, DOR, OS, and HI in Arms 1, 2A, 2B, 4, and 5
- Clinical activity as measured by DOR and HI in Arm 3
- Proportion of patients requiring supportive measures secondary to cytopenias, as measured by changes in transfusion rates, incidence and duration of growth factor support and antibiotics use, and number of hospitalizations associated with febrile neutropenia and/or thrombocytopenic bleeding
- Characterize the safety and tolerability of SY-1425 as a single agent and in combination with azacitidine by assessing the type and frequency of AEs and SAEs using National Cancer Institute (NCI) Common Terminology Criteria for Adverse

Events (CTCAE) v 4.03, as well as changes in clinically significant clinical laboratory values, electrocardiogram (ECG) parameters and vital sign measurements (Arms 1, 2A, 2B, 3, and 5)

- PK parameters of SY-1425, as single agent and in combination with azacitidine or daratumumab, after single and multiple doses by performing PK analysis to define time to maximum concentration (t_{max}), C_{max}, minimum plasma concentration (C_{min}), AUC, total body clearance (CL/F) and half-life ($t_{1/2}$), where the data permits

3.3. Exploratory Endpoints

- Sensitivity analyses to the primary endpoint to predict ORR or TIR across all patients by arm and diagnosis type, prior therapy, *RARA* super-enhancer associated biomarker and/or IRF8 biomarker status; DHRS3 induction, peripheral blood myeloid differentiation markers, induction of CD38 expression, genotype and mutation status
- Changes in Health-Related Quality of Life (HRQOL)
  - AML/higher-risk MDS patients (Arms 1, 2A, 2B, 4, and 5): Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu) questionnaire
  - Lower-risk MDS patients (Arm 3): Functional Assessment of Cancer Therapy-Anemia (FACT-An) questionnaire
- Establish PK/PD relationships by performing analysis of PD biomarkers (DHRS3 and myeloid differentiation markers) in leukemic cells from repeat peripheral blood samples and assessing any changes over time
- PK parameters for daratumumab in combination with SY-1425, including maximum concentration (C_{max}) and minimum concentration (C_{min}; trough concentration)
- Characterize the relationship between SY-1425 activity and baseline expression, and expression over time of messenger RNA (mRNA) expression of RARA and IRF8 biomarkers by correlating baseline biomarker mRNA expression levels of RARα and IRF8 with ORR, EFS, RFS, DOR, OS, and HI Rate
- Estimate of median time-to-response
- Evaluate changes in expression of myeloid differentiation markers, including CD38, over time
- Analysis of additional genes or proteins using multiplex platforms

4. STUDY DESIGN

This is a Phase 2, multi-center, open-label study exploring the activity of SY-1425 in patients with relapsed or refractory non-APL AML or higher-risk MDS, newly diagnosed treatment-naïve patients with non-APL AML who are unlikely to tolerate standard intensive chemotherapy at the time of study entry, and patients with transfusion-dependent lower-risk MDS without the del 5q- abnormality who are refractory to erythropoietin treatment or unlikely to respond to erythropoietin (EPO) treatment (EPO > 500).

All patients must be evaluated for the *RARA* super-enhancer associated biomarker or the associated IRF8 biomarker at the time of the study screening evaluation, as determined in peripheral blood using an investigational assay. Patients will accrue to each of the six arms based on diagnosis (AML, MDS), prior treatment (relapsed/refractory, newly diagnosed treatment-naïve unfit AML patients), risk group (higher-risk MDS, lower-risk MDS transfusion dependent), and Investigator choice of treatment (SY-1425 single agent, or in combination with azacitidine or daratumumab). SY-1425 will be administered at 6 mg/m^2/day orally (PO) in two divided doses, which corresponds to the dose approved in Japan for use of tamibarotene in patients with relapsed/refractory APL. SY-1425 will be given on a 28-day treatment cycle.

- Arms 1, 2A, and 3: SY-1425 will be administered as a single agent and dosing will be continuous.
- Arms 2B and 5: Azacitidine will be administered at 75 mg/m^2 (intravenously or subcutaneously) on Days 1 through 7, daily, of a 28-day cycle. SY-1425 will be administered at 6 mg/m^2/day PO in two divided doses on Days 8 through 28 of a 28-day cycle.
- Arm 4: SY-1425 will be administered at 6 mg/m^2/day PO in two divided doses. Dosing will be continuous, beginning with a 7-day lead-in, and then administered on a 28-day treatment cycle. Daratumumab will be administered at a dose of 16 mg/kg starting on Cycle 1 Day 1 weekly for 8 weeks (8 doses total), followed by dosing every 2 weeks for 16 weeks (8 doses total), followed by dosing every 4 weeks until progression or intolerance.

The dose of SY-1425 may be increased due to unsatisfactory response as early as C2D1 and again at C3D1 in consultation with the Sponsor. SY-1425 doses may be increased for AML and higher-risk MDS patients to 9 mg/m^2/day if a CR/CRi is not achieved at the C2D1 response assessment. The dose may be increased one additional dose level to 12 mg/m^2/day if a CR/CRi is not achieved at the C3D1 response assessment. Doses may be increased for lower-risk MDS patients to 9 mg/m^2/day at C2D1 if the patient has not reduced their transfusion requirements by 50% after 4 weeks (C2D1). The dose may be increased one level to either 9 or 12 mg/m^2/day after week 8 (C3D1) for lower-risk MDS patients who have not achieved transfusion independence but who have achieved a minor erythroid response.

Patients will be treated with single agent SY-1425, or SY-1425 in combination with azacitidine or daratumumab to determine activity, to establish the safety profile of SY-1425 in patients with AML and MDS patients, to explore the hypothesis that patients with the *RARA* super-enhancer associated biomarker or the associated IRF8 biomarker at baseline are responsive to single agent SY-1425 or SY-1425 in combination, to establish the pharmacokinetic/ pharmacodynamic

(PK/PD) relationships, and to evaluate the relationship between single agent SY-1425 or SY-1425 in combination activity and baseline RARA and IRF8 biomarkers.

In AML and higher-risk MDS patients, response will be measured by changes from baseline in peripheral blood counts and bone marrow aspirates. Bone marrow aspirates will be collected to measure response on Day 1 of Cycles 2, 3 (if CR/CRi was not achieved on C2D1), and 4, followed by every third cycle, with additional bone marrow aspirates analyzed as clinically indicated based upon changes in peripheral blood counts, or when it is needed to establish either CR or disease progression. Bone marrow aspirate pathology slides (smears) used to assess response should be retained at the site for up to 5 years or until Sponsor approval to discard samples is provided, whichever is sooner, to support the potential for future analyses.

In lower-risk MDS patients, response will be measured by changes from baseline in transfusion requirements and peripheral blood counts, which will be evaluated at each study visit.

Patients may continue to receive study treatment until experiencing unacceptable toxicity, disease progression/relapse, decision to pursue post-remission therapy other than SY-1425 single agent, or SY-1425 in combination with azacitidine or daratumumab, or the Investigator determines it is in the best interest of the patient to discontinue treatment. Newly diagnosed AML patients enrolled in Arm 2A who achieve a CR/CRi or PR while on SY-1425 single agent treatment and then relapse, or who fail to achieve a CR/CRi or PR after completing at least 4 cycles of SY-1425 single agent treatment, are eligible to receive SY-1425 in combination with azacitidine.

Lower-risk MDS patients will be withdrawn from the study at week 24 if they do not have at least a minor erythroid response defined as either a 50% decrease in transfusion requirements or a 50% improvement in hemoglobin concentration per the response criteria, defined as a hemoglobin increase $\geq$ 0.75 g/dL. Lower-risk MDS patients who in the opinion of the Investigator are receiving clinical benefit, but do not meet the minor erythroid response criteria can remain on study with Sponsor approval. Lower-risk MDS patients who continue past week 24 will continue to receive treatment until erythroid relapse (loss of erythroid response), disease progression, or unacceptable toxicity.

An end of treatment (EoT) visit will be conducted for all AML and higher-risk MDS patients within 30 days of the last dose of study drug, but prior to the start of any subsequent therapies to monitor for safety and resolution of adverse events (AEs). For lower-risk MDS patients, the EoT visit will also be the end of study visit which will be conducted 30 days after the last dose of study drug. All AML and higher-risk MDS patients will be followed every 3 months for survival for up to 2 years and patients who are withdrawn prior to relapse will also follow-up for event free survival (EFS).

However, following implementation of Amendment 7, assessments will be performed per institutional standard of care for patients enrolled in Arm 2B or Arm 5. Aside from SAE, adverse event of special interest (AESI), and Pregnancy and Birth Event collection (via the pharmacovigilance safety database) for patients still receiving study drug in Arm 5, the study procedures and data collection outlined in Table 3 will be considered as guidance and will no longer be required for the study or entered into the electronic data capture system (EDC). Patients in Arm 5 may continue to receive study drug until experiencing unacceptable toxicity, disease progression/relapse, decision to pursue post-remission therapy other than SY-1425 in

combination with azacitidine, or the Investigator determines it is in the best interest of the patient to discontinue treatment.

5. STUDY POPULATION

5.1. Number of Patients

Approximately 162 response evaluable patients will be enrolled into 6 arms:

- Arm 1 (n= ~ 25 biomarker positive patients): Relapsed and/or refractory non-APL AML patients and relapsed and/or refractory higher-risk MDS patients.
- Arm 2A (n= ~ 25 biomarker positive patients) and Arm 2B (n= ~ 50 patients; ~ 25 biomarker positive and ~ 25 biomarker negative): Newly diagnosed, treatment-naïve non-APL AML patients who, at the time of study entry, are unlikely to tolerate standard intensive chemotherapy due to age, performance status, or comorbidities. Arm assignment is determined by Investigator choice of treatment.
  - Patients in Arm 2A will receive SY-1425 as a single agent.
  - Patients in Arm 2B will receive SY-1425 in combination with azacitidine
- Arm 3 (n= ~ 25 biomarker positive patients): Transfusion dependent lower-risk MDS patients without the del 5q abnormality who are refractory to erythropoietin treatment or unlikely to respond to erythropoietin treatment (EPO >500 mU/mL).
- Arm 4 (n = ~ 12 biomarker positive patients): Relapsed and/or refractory non-APL AML patients, relapsed and/or refractory higher-risk MDS patients.
- Arm 5 (n = ~ 25 biomarker positive patients): Relapsed and/or refractory non-APL AML patients who will receive SY-1425 in combination with azacitidine.

Biomarker positive patients are defined as patients positive for the RARA super-enhancer associated biomarker and/or the IRF8 biomarker. Arms 1, 2A, 2B, 3 and 5 will include approximately 20 patients who are positive of the *RARA* super-enhancer associated biomarker. There is no minimum requirement for *RARA* super-enhancer associated biomarker patients in Arm 4.

Response evaluable patients will be defined as study patients receiving at least one complete cycle of study treatment, have completed at least one response assessment, and do not have any major protocol violations or are withdrawn from the study before completion of Cycle 1 because of documented disease progression (see Section 10.2).

Patients will be enrolled across approximately 20 centers in the US and Europe. A patient is considered enrolled upon receipt of first dose of any study drug.

5.2. Duration of Study

Patients may continue to receive study treatment until experiencing unacceptable toxicity, disease progression/relapse, decision to pursue post-remission therapy other than SY-1425 single agent, or SY-1425 in combination with azacitidine or daratumumab, or the Investigator determines it is in the best interest of the patient to discontinue treatment. Newly diagnosed AML patients enrolled in Arm 2A who achieve a CR/CRi or PR while on SY-1425 single agent treatment and then relapse, or who fail to achieve a CR/CRi or PR after completing at least 4 cycles of SY-1425 single agent are eligible to receive SY-1425 in combination with azacitidine.

Lower-risk MDS patients will be withdrawn from the study at week 24 if they do not have at least a minor erythroid response defined as either a 50% decrease in transfusion requirements or a 50% improvement in hemoglobin concentration per the response criteria, defined as a hemoglobin increase ≥ 0.75g/dL. Lower-risk MDS patients who in the opinion of the Investigator are receiving clinical benefit, but don't meet the minor erythroid criteria can remain on study with Sponsor approval. Lower-risk MDS patients who continue past week 24 will continue to receive treatment until erythroid relapse, disease progression, or unacceptable toxicity.

An EoT visit will be conducted for all AML and higher-risk MDS patients within 30 days of the last dose of study drug, but prior to the start of any subsequent therapies to monitor for safety and resolution of AEs. For lower-risk MDS patients, the EoT visit will also be the end of study visit which will be conducted 30 days after the last dose of study drug. All AML and higher-risk MDS patients will be followed every 3 months for survival for up to 2 years and patients who are withdrawn prior to relapse will also follow-up for event free survival.

However, following implementation of Amendment 7, assessments will be performed per institutional standard of care for patients enrolled in Arm 2B or Arm 5. Aside from SAE, AESI, and Pregnancy and Birth Event collection (via the pharmacovigilance safety database) for patients still receiving study drug in Arm 5, the study procedures and data collection outlined in Table 3 will be considered as guidance and will no longer be required for the study or entered into the EDC. Patients in Arm 5 may continue to receive study drug until experiencing unacceptable toxicity, disease progression/relapse, decision to pursue post-remission therapy other than SY-1425 in combination with azacitidine, or the Investigator determines it is in the best interest of the patient to discontinue treatment.

5.3. Inclusion Criteria

1. Patients must be at least 18 years of age.
2. Patients must have:
    a. Relapsed and/or refractory non-APL AML that has failed to achieve a CR or PR following standard induction therapy, or has relapsed after any duration of CR or PR
        i. Patients must have measurable disease with bone marrow blasts ≥5% at screening.
    b. Relapsed and/or refractory higher-risk MDS (High / Very High Risk, as defined by the Revised International Prognostic Scoring System (IPSS-R)) patients that have failed to achieve a CR or PR, or any HI (per IWG 2006 criteria) after standard therapy with hypomethylating agents (eg, azacitidine, decitabine), or have relapsed after any duration of CR or PR or HI
        i. Patients must have measurable disease with bone marrow blasts >5% at screening.
    c. Newly diagnosed, treatment-naïve non-APL AML in patients who, at the time of study entry are unlikely to tolerate standard intensive chemotherapy due to age, performance status, or comorbidities based on at least one of the following criteria (Ferrara et al, 2013):
        i. Age ≥ 75-years-old
        ii. Eastern Cooperative Oncology Group (ECOG) Performance Status of 3

iii. Cardiac history of congestive heart failure (CHF) or documented ejection fraction (EF) ≤ 50%

iv. Pulmonary disease with DLCO ≤ 65% or FEVI ≤ 65%

v. Creatinine clearance ≥ 30 mL/min to < 45 mL/min

vi. Hepatic impairment with total bilirubin > 1.5 to ≤ 3.0 x upper limit of normal (ULN)

vii. Any other comorbidity that the Investigator judges to be incompatible with intensive chemotherapy, and reviewed and approved by the Sponsor prior to enrollment

d. Transfusion dependent lower-risk MDS without the del 5q abnormality, in patients refractory to erythropoietin treatment or unlikely to respond to EPO treatment (EPO >500).

i. Lower-risk MDS: Very Low /Low / Intermediate Risk, as defined by IPSS-R.

ii. Red blood cell (RBC) transfusion dependent anemia defined as no 8 consecutive weeks without RBC transfusions within the 16 weeks prior to study entry, or ≥4 RBC transfusions within the 8 weeks prior to study entry.

iii. Refractory to or ineligible for ESAs is defined as RBC-Transfusion Dependence despite ESA treatment of ≥40,000 units/week recombinant human erythropoietin for 8 weeks or an equivalent dose of darbepoetin (150 μg/week) or serum EPO level >500 mU/mL in patients not previously treated with ESAs.

3. Patients must be evaluated for the *RARA* super-enhancer associated biomarker or IRF8 biomarker as measured by RT-qPCR as defined by a predetermined cutoff based on centralized testing of peripheral blood at the time of study screening.
   a. Patients in arms 1, 2A, 3, 4, and 5 must be positive for the biomarker to be eligible for enrollment.
4. Must be amenable to serial bone marrow aspirates and peripheral blood sampling during the study.
5. ECOG Performance Status (PS) of 0, 1 or 2. For newly diagnosed AML patients < 75 years of age, ECOG 0 to 3; for ≥ 75 years of age, ECOG 0 to 2.
6. Adequate organ function as defined by:
   a. Total bilirubin ≤ 1.5 x the upper limit of normal (ULN), unless suspected to have Gilbert's disease. For newly diagnosed AML patients < 75 years of age, total bilirubin ≤ 3.0 x ULN; for ≥ 75 years of age, total bilirubin ≤ 1.5 x ULN.
   b. ALT and AST ≤ 3 x ULN or ≤ 5 x ULN if documented liver infiltration with leukemia cells

c. Serum creatinine ≤ 2.0 x ULN or calculated creatinine clearance ≥ 45 mL/min based on the Cockroft-Gault GFR estimation. For newly diagnosed AML patients < 75 years of age, creatinine clearance ≥ 30 mL/min; for ≥ 75 years of age, creatinine clearance ≥ 45 mL/min.

7. Discontinued use of chemotherapy, radiation therapy, or growth factors for at least 2 weeks prior to first study treatment, with the exception of hydroxyurea.
8. No investigational agents within 2 weeks prior to first study treatment.
9. No strong inducers of CYP3A4 (see Appendix 5) within 2 weeks prior to first study treatment.
10. Resolved acute effects of any prior AML/MDS therapy to baseline or ≤ Grade 1 CTCAE severity.
11. Serum/urine pregnancy test (for females of childbearing potential) that is negative at screening and immediately prior to initiation of treatment (first dose).
12. Willingness and ability to comply with the scheduled study visits, treatment plans, laboratory tests and other procedures.
13. Fully-executed, signed and dated Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approved informed consent document.

5.4. Exclusion Criteria

1. APL (M3 subtype of AML) or patients with a t(9:22) cytogenetic translocation.
2. Hyperleukocytosis (leukocytes ≥25 x 10^9/L) at study entry. These patients may be treated with hydroxyurea according to routine practice, and enroll in the study when the leukocyte count falls below 25 x 10^9/L.
3. Patients known to be refractory to platelet or packed red cell transfusions per Institutional Guidelines, or a patient who refuses blood product support.
4. Prior treatment with ATRA or systemic retinoid for the treatment of hematologic malignancy.
5. **Arm 4 only** – Prior or concurrent exposure to daratumumab or other CD38 therapies
6. **Arm 4 only** – Subject has either of the following:
   a. Known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) <50% of predicted normal. Note that FEV1 testing is required for subjects suspected of having COPD and subjects must be excluded if FEV1 is <50% of predicted normal.
   b. Known moderate or severe persistent asthma within the past 2 years (see Appendix 8), or uncontrolled asthma of any classification. Note that subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed to participate in the study.
7. Patients with other active malignancy (not including basal cell carcinoma, non-melanoma skin cancer, cervical carcinoma in situ, localized prostate cancer treated with hormone

therapy). Patients with history of other cancers should be free of disease for at least 2 years.

8. Patients with hypertriglyceridemia defined as >1000 mg/dL (CTCAE v4.03 Grade 4).
9. Any clinically significant cardiac disease including one of the following currently or in the previous 6 months: myocardial infarction, unstable cardiac function due to unstable angina or congestive heart failure, congenital long QT syndrome, torsades de pointes or clinically-significant ventricular arrhythmias.
10. QTc interval >480 msec based on triplicate ECG readings using the Fridericia (QTcF), with the exception of patients with Right Bundle Branch Block or Left Bundle Branch Block.
11. Patients with an active, life-threatening or clinically-significant uncontrolled systemic infection.
12. Patients with known active uncontrolled central nervous system (CNS) leukemia.
13. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) related illness or hepatitis B or hepatitis C infection.
    a. **Arm 4 only**: Patients with resolved infection (ie, patients who are HBsAg negative but positive for antiHBs or antiHBc) must also be screened using PCR measurement of HBV DNA levels. Patients who are PCR positive for HBV will be excluded.
    b. **Arm 4 only**: Patients with serologic findings suggestive of HBV vaccination (antiHBs positivity as the only serologic marker) AND a known history of prior HBV vaccination do not need to be tested for HBV DNA by PCR.
14. Known malabsorption syndrome or other condition that may impair absorption of study medication (eg, gastrectomy).
15. Major surgery within 4 weeks prior to starting study treatment.
16. Patients taking Vitamin A supplements (>10,000 IU/d) unless discontinued prior to first dose of study drug, or having hypervitaminosis A.
17. Concurrent treatment with any investigational or approved oncology agents (unless specified in the protocol, such as hydroxyurea) or herbal preparations.
18. **Arm 4 only**: Known allergies, hypersensitivity, or intolerance to mannitol, corticosteroids, monoclonal antibodies or human proteins, or their excipients, or known sensitivity to mammalian-derived products.
19. **Arm 4 only**: Vaccination with live attenuated vaccines within 4 weeks of first study drug administration.
20. Current illicit drug or alcohol abuse.
21. Other severe acute or chronic medical condition such as refractory congestive heart failure, pulmonary disease associated with dyspnea at rest or requiring oxygen therapy, kidney dialysis, liver cirrhosis (Child B or C), or psychiatric condition or laboratory abnormality that may increase the risk to the patient associated with study participation or

investigational product administration or which may interfere with the interpretation of study results or, in the judgment of the Investigator, would make the patient inappropriate for entry into this study.

22. Pregnant females; breastfeeding females; and males and females of childbearing potential not willing to use two highly effective methods of birth control, one being barrier method. Intrauterine devices and birth control pills are not barrier methods, but are highly effective especially when combined with a barrier method (eg, latex condom or a diaphragm or cervical cap) while taking study drug (SY-1425, azacitidine and daratumumab) and continuing contraception use for at least 90 days after the last dose of study drug. Men/women should not donate sperm or ova during this timeframe.
    a. Non-childbearing potential is defined as menopausal for at least 2 years or documented oophorectomy.

6. STUDY CONDUCT

6.1. General Instructions

Patient enrollment is defined by when the first dose of study drug has been received by a patient. The contact information for Syros and designee(s), the Contract Research Organization (CRO), laboratory(s), and any other vendors for this study can be found in the study manual.

6.2. Study Procedures by Time Point

The study procedure schedule per visit is detailed in the Schedule of Events (Table 1, Table 3 and Table 5). Additional details may also be found in the study and laboratory manuals.

6.3. Premature Discontinuation

Patients can withdraw from study anytime at their request or they can be withdrawn by the Investigator or Sponsor for reasons of safety or compliance with study procedures.

Patients may be withdrawn from treatment if they are experiencing unacceptable toxicity or adverse event, disease progression, decision to pursue post-remission therapy other than SY-1425 single agent, or SY-1425 in combination with azacitidine or daratumumab, or if the Investigator determines it is in the best interest of the patient to discontinue treatment. Newly diagnosed AML patients enrolled in Arm 2A who achieve a CR/CRi or PR while on SY-1425 single agent treatment and then relapse, or who fail to achieve a CR/CRi or PR after completing at least 4 cycles of SY-1425 single agent are eligible to receive SY-1425 in combination with azacitidine. Patients may be replaced if they are not response evaluable (eg, withdraw from study prior to first response assessment, see Section 10.2).

Lower-risk MDS patients will be withdrawn from the study at week 24 if they do not have at least a minor erythroid response defined as either a 50% decrease in transfusion requirements or a 50% improvement in hemoglobin concentration per the response criteria, defined as a hemoglobin increase $\geq$ 0.75g/dL. Lower-risk MDS patients who in the opinion of the Investigator are receiving clinical benefit, but don't meet the minor erythroid criteria can remain on study with Sponsor approval. Lower-risk MDS patients who continue past week 24 will continue to receive treatment until erythroid relapse, disease progression, or unacceptable toxicity.

An EoT visit will be conducted for all AML and higher-risk MDS patients within 30 days of the last dose of study drug, but prior to the start of any subsequent therapies to monitor for safety and resolution of AEs. For lower-risk MDS patients, the EoT visit will also be the end of study visit which will be conducted 30 days after the last dose of study drug. All AML and higher-risk MDS patients will be followed every three months for survival for up to 2 years and patients who are withdrawn prior to relapse will also follow-up for EFS.

However, following implementation of Amendment 7, assessments will be performed per institutional standard of care for patients enrolled in Arm 2B or Arm 5. Aside from SAE, AESI, and Pregnancy and Birth Event collection (via the pharmacovigilance safety database) for patients still receiving study drug in Arm 5, the study procedures and data collection outlined in Table 3 will be considered as guidance and will no longer be required for the study or entered

into the EDC. Patients in Arm 5 may continue to receive study drug until experiencing unacceptable toxicity, disease progression/relapse, decision to pursue post-remission therapy other than SY-1425 in combination with azacitidine, or the Investigator determines it is in the best interest of the patient to discontinue treatment.

7. DESCRIPTION OF STUDY PROCEDURES

Following implementation of Amendment 7, assessments will be performed per institutional standard of care for patients enrolled in Arm 2B or Arm 5. Aside from SAE, AESI, and Pregnancy and Birth Event collection (via the pharmacovigilance safety database) for patients still receiving study drug in Arm 5, the study procedures and data collection outlined in Section 7 will be considered as guidance and will no longer be required for the study or entered into the EDC. See Section 7.5 for additional details.

7.1. Baseline Documentation

7.1.1. Informed Consent

All patients must provide written informed consent prior to any study-specific procedures being performed.

7.1.2. Eligibility Review

A review of all eligibility criteria will be performed on or before Cycle 1 Day 1 (Arms 1, 2A, 2B, 3, and 5) or Day -7 of the SY-1425 Lead-In (Arm 4), before enrolling a patient on the study.

7.1.3. Medical History

A complete medical history will be performed for each patient during the screening period. The history will include all prior therapies and patient's disease history. Concomitant therapies must also be recorded as outlined in Section 7.3.2.

7.1.4. Demographics

Date of birth, ethnicity, sex, and race will be recorded during the screening period.

7.1.5. Height

Height will be measured at screening only.

7.1.6. Weight

Weight will be measured as per the schedule of events. Weight will be used to calculate body surface area (BSA) dosing requirements. BSA used for SY-1425 dosing calculations should be updated if the weight changes more than 15%. For Arm 4, the dose of daratumumab should be recalculated if the patient's weight changes by more than 10%.

7.1.7. ECOG Performance Status

Eastern Cooperative Oncology Group (ECOG) Performance Status (Oken et al, 1982) will be assessed during screening and Day 1 of each cycle and at EoT visit.

7.1.8. Physical Examination

Patients will have a physical exam as per the schedule of events. This exam will be completed according to standard of care guidelines

7.2. Safety and Laboratory Assessments

Laboratory assessments will be drawn at the time points outlined in the schedule of events.

7.2.1. Hematology

Hemoglobin, platelets, WBC (leukocyte count including differential), neutrophils (absolute neutrophil count, [ANC] calculated from the leukocyte count and WBC differential count), lymphocytes, monocytes, eosinophils, basophils, and circulating blast counts will be captured according to the schedule of events.

7.2.2. Serum Chemistries

Sodium, potassium, chloride, bicarbonate (CO_2), blood urea nitrogen (BUN), creatinine, glucose, calcium, phosphorus, magnesium, uric acid, total protein, albumin, lactate dehydrogenase (LDH), alkaline phosphatase, total bilirubin, direct bilirubin, indirect bilirubin, AST, ALT, amylase, and lipase will be captured according to the schedule of events.

7.2.3. Coagulation

Prothrombin time (PT), international normalized ratio (INR), and activated partial prothrombin time (aPTT) will be captured according to the schedule of events.

7.2.4. Triglycerides and Total Cholesterol

Triglycerides and total cholesterol will be captured according to the schedule of events.

7.2.5. Urinalysis

Microscopic urinalysis including pH, specific gravity, protein, red and white blood cells, leukocyte esterase, and nitrate will be captured according to the schedule of events.

7.2.6. Pregnancy Test

Females of childbearing potential must have a negative serum or urine pregnancy test prior to starting study drug treatment and on Day 1 of each cycle and at EoT visit. For Arm 4, pregnancy testing will also be done pre-dose on Day -7 of the SY-1425 Lead-In.

7.2.7. Electrocardiograms

Triplicate 12-lead ECGs will be performed for all patients during screening and at EoT.

Patients enrolled in Arms 1, 2A and 3 will have also have triplicate ECGs performed on Cycle 1 Day 1 (pre-dose), Cycle 1 Day 15, Cycle 2 Day 1, Cycle 3 Day 1, and Cycle 4 Day 1.

Patients enrolled in Arms 2B and 5 will have also have triplicate ECGs performed on Cycle 1 Day 8 (pre-dose), Cycle 1 Day 22, Cycle 2 Day 8, Cycle 3 Day 8 and Cycle 4 Day 8.

Patients enrolled in Arm 4 will also have triplicate ECGs performed on Day -7 (pre-dose) and Day -4 of the SY-1425 Lead-In, Cycle 2 Day 1, Cycle 3 Day 1, and Cycle 4 Day 1.

7.2.8. Vital Signs

Vital signs will include blood pressure, body temperature, and heart rate. See schedule of events for time points.

Patients enrolled in Arm 4 will have vital signs monitored extensively on Cycle 1 Day 1 before, during (at 0.5, 1, 1.5, 2, 3.5 hours after the start of the infusion), and after (at the end of the infusion, and 0.5 and 1 hour after the end of the infusion) the first infusion of daratumumab. For all other infusions, vital signs will be measured before the start of the infusion and at the end of the infusion.

7.2.9. Pulmonary Function Testing (Arm 4 Only)

Patients enrolled in Arm 4 will have pulmonary function testing (PFT) performed at screening. For patients with COPD, FEV1 should be measured. Symptom and disease directed exams should be performed as clinically indicated during the treatment phase.

7.2.10. Blood Group and Type Assessment, and Indirect Antiglobulin Test (Arm 4 Only)

Blood Type, Rh, and Indirect Antiglobulin Test (IAT) should be done before the first dose of daratumumab. Subject RBC phenotyping (standard or extended) is an alternative option to the IAT test, if locally required. Either method must be completed prior to first daratumumab infusion.

Daratumumab interferes with the IAT, which is a routine pre-transfusion test performed to identify a patient's antibodies to minor antigens so that suitable donor blood can be given for transfusion. Daratumumab does not interfere with ABO/RhD typing. CD38 is expressed at very low levels on erythrocytes. Daratumumab binds to the CD38 on erythrocytes, which results in a positive IAT (Indirect Antiglobulin Test). This positive result masks the detection of antibodies to minor antigens and may prevent or delay blood banks from issuing donor blood for transfusion. This effect occurs during daratumumab treatment and for up to 6 months after treatment ends. Subjects will receive a patient identification wallet card for the study that includes the blood profile (ABO, Rh, and IAT or phenotyping) determined before the first infusion of daratumumab along with information on the IAT interference for healthcare providers/blood banks. Subjects are to carry this card throughout the treatment period and for at least 6 months after treatment ends. Blood banks can eliminate the daratumumab IAT interference with IAT by treating reagent RBCs with dithiothreitol (DTT) (Chapuy et al, 2015; Chapuy et al, 2016).

Possible methods for blood banks to provide safe RBCs for transfusion to subjects receiving daratumumab include:

a) Providing ABO/RhD compatible, phenotypically (standard or extended phenotyping) or genotypically matched units
b) Providing ABO/RhD compatible, K-negative units after ruling out or identifying alloantibodies using DTT-treated reagent RBCs

Uncrossmatched, ABO/RhD compatible RBC units should be administered if transfusion is needed emergently as per local blood bank practice.

Despite daratumumab binding to CD38 on erythrocytes, no indication of clinically significant hemolysis has been observed in daratumumab studies.

7.3. Clinical Assessments

7.3.1. Adverse Event Monitoring

Assessment of AEs, both serious and non-serious, will be monitored throughout the study. SAEs will be captured from the time of signing of the Informed Consent Form (ICF) through 30 days after last dose of any study drug, and non-serious AEs from the time of first dose of any study drug through 30 days after last dose of any study drug. AEs information will include the type, severity, timing, seriousness, and relatedness. All AEs will be recorded in the electronic case report form (eCRF). Refer to Section 9 for more details.

7.3.2. Prior, Concomitant, and Subsequent Medication Review

Prior AML and MDS related and all concomitant medications will be recorded from screening until EoT. All subsequent therapies for disease under study will be recorded for AML and higher-risk MDS patients until 3 months after the last dose of study drug. See Section 8.7 for more details.

7.3.3. Blood Product Transfusions

All transfusions (pRBCs, platelets, number of units, days of administration) will be recorded from 16 weeks prior to enrollment until the EoT visit.

7.3.4. Erythropoietin Levels – Lower-Risk MDS Patients Only

Lower-risk MDS patients capture EPO levels at screening.

7.3.5. Dosing Compliance/Diary Review

All patients will be instructed to maintain a dosing diary that records the time and number of SY-1425 tablets taken for each dosing interval in the study. This diary will be reviewed at each study visit for compliance.

7.3.6. Health Related Quality of Life

Patient reported health related quality of life (HRQOL) will be evaluated at screening, Cycle 1 Day 1, Cycle 4 Day 1, and at EoT to determine the impact of SY-1425 treatment. AML and Higher-Risk MDS patients will be evaluated using the Factual Assessment of Cancer Therapy-Leukemia (FACT-Leu) questionnaire (Appendix 7). Lower-Risk MDS patients will be evaluated using the Factual Assessment of Cancer Therapy-Anemia (FACT-An) questionnaire (Appendix 6). The FACT-Leu and FACT-An questionnaires are to be self-administered by the patient. The questionnaires should be completed by the patient prior to other clinical assessments being performed and should be reviewed by the site for completeness. If any questions were incomplete, the site should encourage the patient to complete any missing questions.

7.3.7. Event Free Survival and Overall Survival - AML and Higher-Risk MDS Patients Only

All AML and higher-risk MDS patients will be followed for survival for up to 2 years and patients who are withdrawn prior to relapse will also follow-up for event free survival.

7.4. Specialty Laboratory Assessments

7.4.1. RARα and IRF8 biomarker assessments

This study will be evaluating patients with AML and MDS for the presence of a biomarker based on the expression levels of RARα mRNA or IRF8 mRNA in peripheral blood mononuclear cells. The analysis will be determined based on peripheral blood collected during the screening procedures. Both biomarkers will be assessed as "biomarker positive" based on exceeding a predetermined cutoff using an investigational test, conducted at a central Clinical Laboratory Improvement Amendments (CLIA) registered laboratory.

7.4.2. Development of Future Companion Diagnostic

Peripheral blood samples collected from all screened patients may also be used to develop a future companion diagnostic for RARα and IRF8.

7.4.3. Identification of Additional Biomarkers of Response to SY-1425

In addition to evaluation of RARα mRNA and IRF8 mRNA, other mRNA levels for other RARα pathway associated genes such as CTNNB1 will also be explored.

Furthermore, chromatin immunoprecipitation (ChIP)-sequencing, RNA sequencing and DNA sequencing will be undertaken in patients where material is available. ChIP-sequencing will be used to evaluate the correlation between SE strength for *RARA*, *IRF8*, other super-enhancers in the malignant cells, and RNA expression levels of genes controlled by those SEs. RNA and DNA sequencing will be used to identify additional molecular alterations potentially associated with response to SY-1425.

7.4.4. Identification of Resistance Mechanisms for SY-1425

Resistance to ATRA in APL has been linked to both adaptive hypercatabolic response, resulting in reduction of effective ATRA exposure, and through mutations in the RARα ligand binding domain reducing the agonist potential of retinoids (Gallagher, 2002). RNA and DNA sequencing will be used in a blood sample collected at EoT to identify potential molecular alterations associated with resistance to treatment with SY-1425.

7.4.5. Bone Marrow Sample Collection - AML and Higher-Risk MDS Patients Only

Patients will have bone marrow aspirates collected during screening and on Day 1 of Cycles 2, 3 (if CR/CRi was not achieved on C2D1), and 4 with additional aspirates collected every third cycle starting with C7D1, and as clinically indicated based upon changes in peripheral blood counts, or when it is needed to establish either CR or disease progression. The sample collected upon relapse will represent the end of treatment collection.

Bone marrow aspirate samples will be analyzed locally at the clinical site to:

- Assess disease using the response criteria as outlined in Appendix 4.
- Analyze cytogenetics to determine karyotype (and IPSS-R score at screening) and disease response assessments
- Determine blast count
- Mutational analysis as routinely done by the clinical site (at screening and relapse)
- Immunophenotyping to measure myeloid differentiation markers as routinely done by the clinical site
  - Note: Patients enrolled in Arm 4 will have bone marrow aspirate analyzed for immunophenotyping at a central laboratory. Local analyses may also be performed if clinically indicated.
- MRD assessment per local practice in those patients who have achieved a CR

7.4.5.1. Bone Marrow Aspirate for Response Assessment (AML and Higher-Risk MDS Patients Only)

Assessment of disease will be determined using the response criteria as outlined in Appendix 4. Response will be measured by changes from baseline in peripheral blood counts and bone marrow aspirate. Bone marrow aspirates will be collected to measure response on Day 1 of Cycles 2, 3 (if CR/CRi was not achieved on C2D1), and 4, followed by every third cycle beginning on C7D1, with additional bone marrow aspirates analyzed as clinically indicated based on changes in peripheral blood counts, or when it is needed to establish either CR or disease progression.

7.4.5.2. Immunophenotyping (AML and Higher-Risk MDS Patients Only)

Bone marrow aspirate samples obtained at the time of screening, when bone marrow aspirates are collected to assess response, and upon relapse to be analyzed using local laboratories for changes in the expression of myeloid differentiation markers (eg, CD11b, CD13, CD15, CD33) as routinely done by the clinical site. Note: Patients enrolled in Arm 4 will have bone marrow aspirate analyzed for immunophenotyping at a central laboratory. Local analyses may also be performed if clinically indicated. Immunophenotyping may also be performed when clinically indicated on peripheral blood to measure myeloid differentiation markers.

7.4.5.3. CD38 and Myeloid Marker Immunophenotyping (Central Analysis)

Patients enrolled in Arms 1, 2A and 3 under Amendment 4 or a subsequent protocol amendment will have peripheral blood collected for central analysis of CD38 and myeloid marker immunophenotyping on Days 1 (pre-dose), 8 and 15 of Cycle 1; Day 1 of Cycles 2, 3, 4, followed by every third cycle beginning at Cycle 7 Day 1; and at EoT.

Patients enrolled in Arm 4 will have peripheral blood collected for central analysis of CD38 and myeloid marker immunophenotyping on Days -7 (pre-dose) and -4 of the SY-1425 Lead-In; Days 1, 8 and 15 of Cycle 1; Day 1 of Cycles 2, 3, 4, followed by every third cycle beginning at Cycle 7 Day 1; and at EoT. For timepoints on days on which daratumumab is administered, collection is performed prior to daratumumab dosing.

7.4.6. Pharmacokinetics

Blood samples will be taken to determine SY-1425 plasma concentrations. The time of dosing and sample collection, including hour and minutes, must be recorded. Details regarding the preparation, handling, and shipping of samples can be found in the study manual.

Patients enrolled in Arms 1, 2A and 3 will have sparse PK sampling on Day 1 of Cycle 1 at 2-4 hours, and 5-8 hours post dose, and on Day 15 of Cycle 1 and Day 1 of Cycles 2, 3, and 4 at two time points at least 2 hours apart.

A subset of approximately 15 patients enrolled in Arms 1, 2A and 3, sufficient to obtain PK evaluable results from at least 10 patients, will have more intensive sampling [pre-dose (0 hour), and 0.5, 1, 2, 4, 6, 8 hours post-dose] on Day 1 and Day 15 of Cycle 1, and will have sparse sampling on Day 1 of Cycles 2, 3, and 4 at two time points at least 2 hours apart.

For patients in Arm 2A who receive SY-1425 in combination with azacitidine after relapse/unsatisfactory response with single agent SY-1425, PK sampling is not required once initiating combination treatment.

Patients enrolled in Arms 2B and 5 will have sparse PK sampling on Day 8 of Cycle 1 at 2-4 hours and at 5-8 hours post-dose. PK sampling will also occur on Day 22 of Cycle 1, and on Day 8 of Cycles 2, 3 and 4 at two post-dose time points at least 2 hours apart.

Patients enrolled in Arm 4 will have SY-1425 PK sampling [pre-dose (0 hour), and 0.5, 1, 2, 4, 6, 8 hours post-dose] on Day -7 and Day -4 of the SY-1425 Lead-In. Patients enrolled in Arm 4 will also have daratumumab PK sampling on Cycle 1 Day 1 prior to infusion (0h) and prior to the end of infusion (5-10 minutes before end of infusion), and on Cycle 1 Day 8 prior to infusion (0h).

If a patient's SY-1425 dose is modified (increased or decreased) during the course of the study, PK sampling should occur within 8 to 15 days of the dose adjustment. Patients in the sparse PK sampling will have two samples taken at least 2 hours apart. Patients in the intensive PK sampling schedule will have more intensive sampling (pre-dose [0 hour], and 0.5, 1, 2, 4, 6 and 8 hours post-dose).

7.4.7. ADME Pharmacogenomics

A peripheral blood sample will be obtained on Cycle 1 Day 1 pre-dose (Arms 1, 2A, 2B, 3, and 5) or pre-dose on Day -7 of the SY-1425 Lead-In (Arm 4) and analyzed centrally for all patients to evaluate if absorption, distribution, metabolism, and excretion (ADME) genes contribute to inter-patient differences in the exposure of SY-1425.

For patients in Arm 2A who receive SY-1425 in combination with azacitidine after relapse/unsatisfactory response with single agent SY-1425, a pharmacogenomics sample is not required.

7.4.8. Pharmacodynamics

Peripheral blood will be collected and analyzed centrally in all patients. Patients enrolled in Arms 1, 2A and 3 will have sampling on Cycle 1 Day 1 (pre-dose (0 hour), and between 5-8 hours post dose), Day 15, and EoT visit for RNA analysis.

For patients in Arm 2A who receive SY-1425 in combination with azacitidine after relapse/unsatisfactory response with single agent SY-1425, PD sampling is not required once initiating the combination treatment.

Patients enrolled in Arm 2B will have sampling on Cycle 1 Day 1 (pre-dose), Cycle 1 Day 8 (pre-dose (0 hour), and between 5-8 hours post dose), Day 22, and EoT visit.

Patients enrolled in Arm 4 will have sampling on Day -7 of the SY-1425 Lead-In (pre-dose (0 hour), and between 5-8 hours post dose), Cycle 1 Day 8, and EoT visit.

DHRS3 (SDR family), a metabolic enzyme that is an important component of cellular maintenance of retinol homeostasis, will be included in the RNA analysis. The expression of this gene is tightly controlled in response to retinoic acid abundance. DHRS3 gene expression is most strongly induced by SY-1425 in AML cells harboring the *RARA* super-enhancer. However, there is also a significant upregulation in peripheral blood mononuclear cells, which may act as surrogate tissue for measuring SY-1425 response.

7.4.9. Additional Exploratory Biomarker Analysis

Any research blood sample remaining will be preserved and used to perform additional exploratory analysis focusing on furthering knowledge on either AML/MDS cancer or the compound SY-1425.

7.5. Amendment 7 Study Procedure Changes

Following implementation of Amendment 7, only the following study assessments will be required for patients in Arm 5 who are still receiving study drug:

- SAE collection (see Section 9.5 for reporting) is required for Amendment 7
- AESI collection (see Section 9.6) is required for Amendment 7
- Pregnancy and Birth Event collection (see Section 9.7 for reporting) is required for Amendment 7

Aside from SAE, AESI, and Pregnancy and Birth Event collection (via the pharmacovigilance safety database) for patients receiving study drug in Arm 5, the study procedures and data collection outlined in Table 3 will be considered as guidance only and will no longer be required for the study or collected in the EDC.

Rather than following the SoA (Table 3) for Arm 5 patients, approximately every 3 months the Investigator or designee will provide an update to the sponsor regarding the status of the patient and whether or not the patient continues to receive benefit from the study drug. Patients in Arm 5 may continue to receive study drug until experiencing unacceptable toxicity, disease progression/relapse, decision to pursue post-remission therapy other than SY-1425 in

combination with azacitidine, or the Investigator determines it is in the best interest of the patient to discontinue treatment (see Section 8.2.1).

In addition, no further collection of post-treatment follow-up data will occur for patients enrolled in Arm 2B or Arm 5; patient follow-up should continue per institutional standard of care.

See Section 8.5.1 for updated requirements regarding SY-1425 dosing compliance and Section 8.6.1 regarding SY-1425 drug accountability.

8. STUDY DRUG MANAGEMENT

8.1. Allocation to Treatment

All protocol specific requirements must be completed and documented prior to study drug administration. Following determination that the patient meets all eligibility criteria, the Investigator or designee will enroll the patient according to procedures described in the study manual. Patients enrolled in Arms 1, 2A and 3 will receive SY-1425 as a monotherapy. Patients enrolled in Arms 2B and 5 will receive SY-1425 in combination with azacitidine. Newly diagnosed AML patients enrolled in Arm 2A who achieve a CR/CRi or PR while on SY-1425 single agent treatment and then relapse, or who fail to achieve a CR/CRi or PR after completing at least 4 cycles of SY-1425 single agent treatment are eligible to receive SY-1425 in combination with azacitidine. Patients enrolled in Arm 4 will receive SY-1425 in combination with daratumumab.

8.2. Study Drug Administration

8.2.1. SY-1425

SY-1425 will be supplied as 2 mg tablets. Each patient will receive 6 mg/m^2/day PO divided into two doses.

The dose of SY-1425 may be increased due to unsatisfactory response as early as C2D1 and again at C3D1 in consultation with the Sponsor. SY-1425 doses may be increased for AML and higher-risk MDS patients to 9 mg/m^2/day if a CR/CRi is not achieved at the C2D1 response assessment. The dose may be increased one additional dose level to 12 mg/m^2/day if a CR/CRi is not achieved at the C3D1 response assessment. Doses may be increased for lower-risk MDS patients to 9 mg/m^2/day at C2D1 if the patient has not reduced their transfusion requirements by 50% after 4 weeks (C2D1). The dose may be increased one level to either 9 or 12 mg/m^2/day after week 8 (C3D1) for lower-risk MDS patients who have not achieved transfusion independence but who have achieved a minor erythroid response.

Calculated doses will be rounded up to the nearest even number. For doses of 10 mg/day or 14 mg/day, for which the number of tablets daily is uneven (5 or 7 tablets), then the larger number (3 or 4 tablets, respectively) should be taken in the morning. Patients will be instructed to take the dose with a glass of water after their morning and evening meal. Tablets should not be crushed, broken or split. If a tablet is damaged (broken, crushed, split, etc.), the patient should record the information in the diary and bring the damaged tablet to the next study visit. Dosing should not be repeated if a patient vomits. A dose missed by greater than 4 hours should be skipped. SY-1425 will be given on a 28-day treatment cycle. For patients enrolled in Arms 1, 2A, 3 and 4, dosing will be continuous. For patients enrolled in Arms 2B and 5, SY-1425 will be administered on Days 8 through 28 of a 28-day cycle.

Patients may continue to receive study treatment until experiencing unacceptable toxicity, disease progression/relapse, decision to pursue post-remission therapy other than SY-1425 or the Investigator determines it is in the best interest of the patient to discontinue treatment. Newly diagnosed AML patients enrolled in Arm 2A who achieve a CR/CRi or PR while on SY-1425 single agent treatment and then relapse, or who fail to achieve a CR/CRi or PR after completing

at least 4 cycles of SY-1425 single agent treatment are eligible to receive SY-1425 in combination with azacitidine.

Lower-risk MDS patients will be withdrawn from the study at week 24 if they do not have at least a minor erythroid response defined as either a 50% decrease in transfusion requirements or a 50% improvement in hemoglobin concentration per the response criteria, defined as a hemoglobin increase ≥ 0.75g/dL. Lower-risk MDS patients who in the opinion of the Investigator are receiving clinical benefit, but do not meet the minor erythroid response criteria can remain on study with Sponsor approval. Lower-risk MDS patients who continue past week 24 will continue to receive treatment until erythroid relapse, disease progression, or unacceptable toxicity.

Following implementation of Amendment 7, patients in Arm 5 may continue to receive study drug until experiencing unacceptable toxicity, disease progression/relapse, decision to pursue post-remission therapy other than SY-1425 in combination with azacitidine, or the Investigator determines it is in the best interest of the patient to discontinue treatment.

8.2.2. Azacitidine

Azacitidine is commercially available as lyophilized powder in 100 mg single-dose vials. Each patient enrolled in Arms 2B and 5 will receive 75 mg/m^2 (intravenously or subcutaneously) on Days 1 through 7, daily of a 28-day cycle.

8.2.3. Daratumumab

Daratumumab supplied for IV infusion in this study is a colorless to yellow liquid and sterile concentrate of 20 mg/mL as a liquid vial. Each patient enrolled in Arm 4 will receive daratumumab 16 mg/kg starting on Cycle 1 Day 1 weekly for 8 weeks (8 doses total), followed by dosing every 2 weeks for 16 weeks (8 doses total), followed by dosing every 4 weeks until progression or intolerance.

8.2.3.1. Daratumumab Preparation

Infusion solution will be prepared as a 1,000-mL (first dose) or 500-mL (second and subsequent doses) dilution of daratumumab in sterile, pyrogen-free 0.9% NaCl. Preparation of infusion bags should be done on the day of the planned infusion. Daratumumab must be administered as an IV infusion given through a well-functioning IV catheter by using an infusion pump. The study drug must be filtered by using an inline filter (0.2 μM) during the infusion.

8.2.3.2. Daratumumab Administration

Daratumumab (16 mg/kg) will be administered as an IV infusion. Each subject's dose will be calculated based on the subject's weight at Cycle 1 Day 1 rounded to the nearest kilogram. The dose of daratumumab will remain constant throughout the study, unless the subject's weight changes more than 10% from Cycle 1 Day 1. All infusions will be planned as outpatient visits. Subjects will receive pre-infusion medications and post-infusion medications as detailed in the protocol (Sections 8.2.3.2.1 and 8.2.3.2.2 respectively).

The dilution volumes, initial infusion rates, and increment for the first, second, and subsequent doses are provided in Table 8. The first infusion, with a volume of 1,000 mL, takes

approximately 8 hours; the second and subsequent infusions, with volumes of 500 mL, take approximately 4 hours. The maximum infusion rate for all infusions is 200 mL/hour.

Table 8: Daratumumab Infusion Rates

	Dilution Volume	Initial Infusion Rate (first hour)	Incremental Increases in Infusion Rate[a]	Maximum Infusion Rate
First infusion	1000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Second infusion[b]	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent infusions[c]	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

a. Consider titration of the infusion rate only in the absence of infusion reactions.
b. Dilution volume of 500 mL should be used only if there were no Grade 1 (mild) or greater infusion reactions during the first 3 hours of the first infusion. Otherwise, continue to use a dilution volume of 1000 mL.
c. Use a modified initial rate for subsequent infusions (ie, third infusion onwards) only if there were no Grade 1 (mild) or greater infusion reactions during a final infusion rate of ≥100 mL/hr in the first two infusions. Otherwise, continue to use instructions for the second infusion.

As noted in Table 5, vital signs should be monitored extensively on Cycle 1 Day 1 before, during, and after the first infusion of daratumumab. For all other infusions, vital signs should be measured before the start of the infusion and at the end of the infusion. If a subject experiences any significant medical event, then the investigator should assess whether the subject should stay overnight for observation. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as a serious adverse event.

8.2.3.2.1. Daratumumab Pre-Infusion Medications

In an effort to prevent infusion related reactions, all subject will receive the following medications 1 to 3 hours prior to each study drug administration (1 hour prior to study drug administration is preferred):

- An antipyretic: paracetamol (acetaminophen) 650-1000 mg IV or PO
- An antihistamine: diphenhydramine 25-50 mg IV or PO, or equivalent. Avoid IV use of promethazine. (see Appendix 9 for list of antihistamines that may be used)
- A corticosteroid: methylprednisolone 100 mg IV or PO or equivalent for the first 2 doses and 60 mg for all subsequent doses (in the absence of IRR adverse events in the first 2 doses). Substitutions for methylprednisolone are allowed (refer to Appendix 10).
- A Leukotriene Inhibitor (optional) on Cycle 1 Day 1: montelukast 10 mg PO, or equivalent.

If necessary, all PO pre-infusion medications may be administered outside of the clinic on the day of the infusion, provided they are taken within 3 hours before the infusion

8.2.3.2.2. Daratumumab Post-Infusion Medications

In an effort to prevent delayed infusion-related reactions, all subjects will receive long- or intermediate-acting corticosteroids orally (20 mg methylprednisolone or equivalent in accordance with local standards) on the 2 days following all daratumumab infusions (beginning the day after the infusion).

In the absence of infusion-related AEs after the first 3 infusions, post-infusion corticosteroids should be administered per investigator discretion.

For subjects with a higher risk of respiratory complications (eg, subjects with mild asthma or subjects with COPD who have an FEV1 <80% at screening or developed FEV1 <80% during the study without any medical history) the following post-infusion medications should be considered:

- Antihistamine (diphenhydramine or equivalent)
- Leukotriene inhibitor (montelukast or equivalent)
- Short-acting β2 adrenergic receptor agonist such as salbutamol aerosol
- Control medications for lung disease (eg, inhaled corticosteroids ± long-acting β2 adrenergic receptor agonists for subjects with asthma; long-acting bronchodilators such as tiotropium or salmeterol ± inhaled corticosteroids for subjects with COPD)

In addition, these at-risk subjects may be hospitalized for monitoring for up to 2 nights after an infusion. If subjects are hospitalized, then their spirometry test (FEV1) should be performed before discharge. If these subjects are not hospitalized, then a follow-up telephone call should be made to monitor their condition within 48 hours after all infusions. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as a serious adverse event. Investigators may prescribe bronchodilators, H1-antihistamines, and corticosteroids that are deemed necessary to provide adequate supportive care in the event a bronchospasm occurs after subjects are released from the hospital/clinic. If an at-risk subject experiences no major infusion-related reactions, then these post-infusion medications may be waived after 4 doses at the investigator's discretion.

Any post-infusion medication will be administered after the infusion has completed.

8.2.3.2.3. Management of Daratumumab Infusion-Related Reactions (IRR)

Subjects should be carefully observed during daratumumab infusions. Trained study staff at the clinic should be prepared to intervene in case of any infusion reactions, and resources necessary for resuscitation must be available. Attention to staffing should be considered when multiple subjects will be dosed at the same time.

For infusion reactions of any grade/severity, immediately interrupt the daratumumab infusion and manage symptoms. Management of infusion reactions may further require reduction in the rate of infusion, or treatment discontinuation of daratumumab.

8.2.3.2.3.1. Daratumumab Infusion-Related Reactions of Grade 1 or Grade 2

If the investigator assesses a Grade 1-2 IRR adverse event to be related to administration of study drug, then the daratumumab infusion should be paused. Once IRR symptoms resolve and the subject's condition is stable, the daratumumab infusion may be restarted at the investigator's discretion. Upon restart of daratumumab infusion, the infusion rate should be half of that employed before the interruption. If the patient does not experience any further IRR symptoms, infusion rate escalation may resume at increments and intervals as clinically appropriate up to the maximum rate of 200 mL/hour (Table 8).

If the subject experiences a Grade 2 or higher event of laryngeal edema, or a Grade 2 or higher event of bronchospasm that does not respond to systemic therapy and does not resolve within 6 hours from onset, then the subject must be withdrawn from daratumumab treatment.

8.2.3.2.3.2. Daratumumab Infusion-Related Reactions of Grade 3 or Higher

For IRR adverse events that are Grade 4, the daratumumab infusion must be stopped and the subject withdrawn from daratumumab treatment.

For IRR adverse events that are Grade 3, the daratumumab infusion must be stopped and the subject must be observed carefully. Once reaction symptoms resolve, consider restarting the infusion at no more than half the rate at which the reaction occurred. If the subject does not experience additional symptoms, resume infusion rate escalation at increments and intervals as outlined in Table 8. If the intensity of the adverse event returns to Grade 3 after restart of the daratumumab infusion, then the procedure described in this section should be repeated, or the subject may be withdrawn from treatment. Should the intensity of the adverse event increase to Grade 3 for a third time, then the subject must be withdrawn from daratumumab treatment.

8.3. Reference/Control Therapy

All patients will receive open label SY-1425 single agent, or SY-1425 in combination with azacitidine or daratumumab.

8.4. Recommended Dose Modifications

8.4.1. SY-1425 Guidelines

SY-1425 dosing may be modified due to unsatisfactory response or toxicity as described below.

8.4.1.1. Dose Increases

Table 9: Dose Increases of SY-1425

Dose Level	SY-1425 Dose
Initial Dose: Level 0	6 mg/m^2/day
Dose Increase: Level +1	9 mg/m^2/day
Dose Increase: Level +2	12 mg/m^2/day

The dose of SY-1425 may be increased due to unsatisfactory response as early as C2D1 and again at C3D1 in consultation with the Sponsor.

AML and Higher-Risk MDS patients: Doses may be increased for AML and higher-risk MDS patients to Dose Increase Level +1 if a CR/CRi is not achieved at the C2D1 response assessment. The dose may be increased by one dose level (to Dose Increase Level +1, or +2 for those who already had a prior dose level increase) if a CR/CRi is not achieved at the C3D1 response assessment. If in the opinion of the Investigator, a dose increase is not recommended as outlined above, the case should be discussed with the Sponsor for approval.

Lower-Risk MDS patients: Doses may be increased for lower-risk MDS patients at C2D1 to Dose Increase Level +1 if the patient has not reduced their transfusion requirements by 50% after 4 weeks. The dose may be increased by one dose level (to Dose Increase Level +1, or +2 for those who already had a prior dose level increase) after week 8 (C3D1) for lower-risk MDS patients who have not achieved transfusion independence but have achieved a minor erythroid response.

If a patient has an SY-1425 dose increase, a dose adjustment visit must be performed within 8 to 15 days of the dose adjustment to capture safety assessments and PK data. This visit can be combined with another scheduled visit if it is scheduled to occur within that window.

8.4.1.2. Dose Reductions

Table 10: Dose Reductions of SY-1425

Dose Level	**SY-1425 Dose**
Initial Dose: Level 0	6 mg/m^2/day
Dose Reduction: Level -1	4.5 mg/m^2/day
Dose Reduction: Level -2	3.0 mg/m^2/day

Dose reductions may be recommended to optimize management of patients with adverse events as outlined in Section 8.4.1.3 and 8.4.1.4. If a patient has an SY-1425 dose reduction, a dose adjustment visit must be performed within 8 to 15 days of the dose adjustment to capture safety assessments and PK data. This visit can be combined with another scheduled visit if it is scheduled to occur within that window.

Note: For patients who previously dose escalated as outlined in Section 8.4.1.1, dose reductions should be one dose level at a time. For example, a patient at 12 mg/ m^2/day should be reduced to 9 mg/m^2/day, and a patient at 9 mg/m^2/day should be reduced to 6 mg/m^2/day for their initial dose reduction.

8.4.1.3. Non-Hematologic Adverse Events

SY-1425 doses will be withheld for patients experiencing:

- Non-hematologic AEs of ≥ Grade 3 and deemed related to SY-1425, or
- Laboratory abnormalities that are ≥ Grade 3 and deemed related to SY-1425 [ie, unrelated to the underlying hematologic malignancy, complications of the malignancy (eg, infection and bleeding), and unrelated to concurrent medications,

with the exception of asymptomatic hypertriglyceridemia, or hypercholesterolemia which should only be held if AE severity reaches Grade 4]

SY-1425 treatment may resume at the Initial Dose Level once the event has resolved to ≤ Grade 1 or baseline. The Investigator may choose to reduce the dose by 1 level based on the AE severity, time to resolution, and clinical judgment.

For recurrence of the same AE responsible for a dose interruption in patients on the Initial Dose Level, SY-1425 may be resumed, but the dose must be reduced by one Dose Reduction Level. An additional dose reduction for recurrence of the same AE may be taken if needed.

Dosing may be increased to a prior dose level if the AE remains ≤ Grade 1 or at baseline for 28 days.

8.4.1.4. Hematologic Adverse Events:

It is not anticipated that SY-1425 dose modifications would be needed for hematologic events (ie, cytopenias, complications associated with cytopenias including infection, bleeding). However, if in the opinion of the Investigator, a dose modification is clinically indicated, the dose may be reduced by one dose level, following the guidance for non-hematologic AEs.

Based upon the mechanism of action of SY-1425, which may promote myeloid cell differentiation, early signs of WBC increases are anticipated and may not represent progression of disease.

8.4.1.5. Discontinuation of Therapy Due to Treatment-Related Toxicity

Study treatment should not be resumed in the case of the following treatment-related events:

- Cardiac event (Grade 4 arrhythmia or heart failure)
- ≥ 56-day (2 cycle) dose delay due to a treatment-related adverse event

8.4.1.6. Alternative Dosing Regimens

Continuous daily dosing in 28-day (4 week) cycles will be initially evaluated. Alternative dosing regimens may be explored with Sponsor approval, should it be deemed necessary to manage chronic toxicities.

8.4.2. Azacitidine Guidelines

Azacitidine dosing may be modified if no beneficial effect is seen or due to toxicity as per the below guidelines (VIDAZA Prescribing Information 2016). Local guidelines and best practices may also be followed for azacitidine dose adjustments due to toxicity, as applicable (VIDAZA Summary of Product Characteristics 2016).

8.4.2.1. Dose Adjustments Based on Hematology Laboratory Values

For patients with baseline (start of treatment) WBC ≥ 3.0 x 10^9/L, ANC ≥ 1.5 x 10^9/L, and platelets ≥ 75.0 x 10^9/L, adjust the dose as follows, based on nadir counts for any given cycle as described in Table 11.

Table 11: Azacitidine Dose Adjustments Based on Nadir Counts

Nadir Counts		% Dose in the Next Course
Absolute Neutrophil Count ($x10^9$/L)	Platelets ($x10^9$/L)	
<0.5	<25.0	50%
0.5-1.5	25.0-50.0	67%
>1.5	>50.0	100%

For patients whose baseline counts are WBC < 3.0 x 10^9/L, ANC < 1.5 x 10^9/L, or platelets < 75.0 x 10^9/L, base dose adjustments on nadir counts and bone marrow biopsy cellularity at the time of the nadir as noted in Table 12, unless there is clear improvement in differentiation (percentage of mature granulocytes is higher and ANC is higher than at onset of that course) at the time of the next cycle, in which case continue the current dose.

Table 12: Azacitidine Dose Adjustments Based on Nadir Counts and Cellularity

White Blood Cell or Platelet Nadir % decrease in counts from baseline	Bone Marrow Biopsy Cellularity at Time of Nadir (%)		
	30-60	15-30	<15
	% Dose in the Next Course		
50-75	100	50	33
>75	75	50	33

If a nadir as defined in the table above has occurred, give the next course 28 days after the start of the preceding course, provided that both the WBC and the platelet counts are >25% above the nadir and rising. If a >25% increase above the nadir is not seen by day 28, reassess counts every 7 days. If a 25% increase is not seen by Day 42, reduce the scheduled dose by 50%.

8.4.2.2. Dose Adjustments Based on Serum Electrolytes and Renal Toxicity

If unexplained reductions in serum bicarbonate levels to <20 mEq/L occur, reduce the dosage by 50% for the next course. Similarly, if unexplained elevations of blood urea nitrogen or serum creatinine occur, delay the next cycle until values return to normal or baseline and reduce the dose by 50% for the next course. If recovery to normal or baseline has not occurred by Day 42, please consult Sponsor on how to proceed for the next course.

8.4.3. Dose Delay Guidelines for Patients Receiving SY-1425 in Combination with Azacitidine

If criteria for SY-1425 dose hold are met, azacitidine dosing may continue unless criteria for hold are also met. If discontinuation of SY-1425 is required per criteria in Section 8.4.1.5, then the patient should be discontinued from all study drug and have an end of treatment visit performed.

If criteria for azacitidine dose hold are met, SY-1425 dosing may continue unless criteria for hold are also met. Day 1 of the next treatment cycle is delayed until azacitidine dosing may resume.

8.4.4. Daratumumab Guidelines

Dose modification of daratumumab is not permitted. Dose delay is the primary method for managing daratumumab-related toxicities.

8.4.4.1. Daratumumab Cycle Delay

On the first day of each new treatment cycle and before each daratumumab dose, the subject will be evaluated by the treating physician for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to NCI CTCAE, Version 4.03. Dose modifications or delays will be made based on the toxicity experienced during the previous cycle of therapy or newly encountered on Day 1 of a cycle.

The study treatment must be held if any of the following criteria below are met, to allow for recovery from toxicity, regardless of relationship to daratumumab or SY-1425, unless attributable to underlying disease. For example, cytopenias attributable to AML may not be considered toxicities of treatment.

The criteria for a dose delay are:

- Grade 4 hematologic toxicity, except for grade 4 lymphopenia
- Grade 3 or higher thrombocytopenia
- Febrile neutropenia
- Neutropenia with infection, of any grade
- Grade 3 or higher non-hematologic toxicities with the following exceptions:
    - Grade 3 nausea that responds to antiemetic treatment within 7 days
    - Grade 3 vomiting that responds to antiemetic treatment within 7 days
    - Grade 3 diarrhea that responds to antidiarrheal treatment within 7 days
    - Grade 3 fatigue that was present at baseline or that lasts for <7 days after the last administration of daratumumab
    - Grade 3 asthenia that was present at baseline or that lasts for <7 days after the last administration of daratumumab

Administration of daratumumab may be restarted upon recovery from toxicity to Grade 2 or baseline, with the exception that Grade 2 laryngeal edema or Grade 2 bronchospasm must be fully recovered.

If daratumumab administration does not commence within the prespecified window (Table 13) of the scheduled administration date, then the dose will be considered a missed dose. Administration may resume at the next planned dosing date. A missed dose will not be made up.

Table 13: Daratumumab Administration Schedule

Cycles	Frequency	Dose Held	Dosing Re-start
1 and 2	Weekly (q1wk)	>3 days	next planned weekly dosing date
3 to 6	Biweekly (q2wks)	>7 days	next planned biweekly dosing date
7+	Every 4 weeks (q4wks)	>14 days	next planned every 4 weeks dosing date

Cycles may be delayed up to 4 weeks (Cycle 1 to Cycle 6) or up to 6 weeks (Cycle 7 and beyond). If Day 1 of a cycle is delayed, Day 1 of subsequent cycles should be adjusted accordingly to maintain the 28-day cycle duration. However, if a within-cycle dose is delayed, then the dates of the subsequent within-cycle doses should **not** be adjusted. Any adverse event deemed to be related to daratumumab that requires a dose hold of more than 4 weeks (Cycle 1 to Cycle 6) or more than 6 weeks (Cycle 7 and beyond) will result in permanent discontinuation of daratumumab.

Any dose hold of more than 56 days due to unresolved direct daratumumab toxicity will result in permanent discontinuation of daratumumab. Any dose hold of more than 28 days and less than 56 days due to unresolved direct daratumumab toxicity may lead to discontinuation or continued daratumumab and requires review by the sponsor. Dose holds of more than 28 days for other reasons should be discussed with the sponsor.

8.4.4.2. Daratumumab Interruption or Missed Doses

A daratumumab dose that is held for more than the permitted time (Table 13) from the per-protocol administration date for any reason other than toxicities suspected to be related to daratumumab should be brought to the attention of the Sponsor at the earliest possible time. Subjects whose dose was delayed for more than 4 weeks (Cycle 1 to Cycle 6) or more than 6 weeks (Cycle 7 and beyond) should have study treatment discontinued, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon.

8.4.4.3. Dose Delay Guidelines for Patients Receiving SY-1425 in Combination with Daratumumab

If criteria for SY-1425 dose hold are met, daratumumab dosing may continue unless criteria for hold are also met. If discontinuation of SY-1425 is required per criteria in Section 8.4.1.5, then the patient should be discontinued from all study drug and have an end of treatment visit performed

If criteria for daratumumab dose hold are met, SY-1425 dosing may continue unless criteria for hold are also met. Day 1 of the next treatment cycle is delayed until daratumumab dosing may resume.

8.5. Study Drug Dosing Compliance

8.5.1. SY-1425

Patients will maintain diaries to include the date and time each dose of SY-1425 is taken including hour and minute. Patients are required to return the carton or bottle(s) and unused

study medications at each study visit. If a tablet is damaged (broken, crushed, split, etc.), the patient should record the information in the diary and bring the damaged tablet to the next study visit. The diaries and study drug materials will be used to complete a compliance assessment and drug accountability. The number of tablets returned by the patient at the end of a cycle will be counted, documented, and recorded as part of drug accountability requirements. Following implementation of Amendment 7, Arm 5 patients who are still receiving study drug will no longer be required to maintain a diary to document SY-1425 compliance.

8.5.2. Azacitidine

Azacitidine will be administered via intravenous or subcutaneous injection as described in the prescribing information under the supervision of the study site staff.

8.5.3. Daratumumab

Daratumumab will be administered via intravenous infusion as described in the prescribing information under the supervision of the study site staff.

8.6. Study Drug Storage and Drug Accountability

8.6.1. SY-1425

Until dispensed to the patients, the study drug will be stored in a securely locked area, accessible to authorized personnel only. Tablets should be stored at room temperature (15°C to 30°C) and should not be removed from the blister strips or bottles until immediately before administration.

The Investigator is responsible for SY-1425 accountability throughout the study. Accurate records of all SY-1425, received, dispensed from and returned to the study site are to be maintained by the study site. SY-1425 accountability will be monitored throughout the study. SY-1425 will be disposed of according to applicable regulations and Syros instruction. Following implementation of Amendment 7, SY-1425 accountability will be communicated to the Sponsor approximately every 3 months.

Refer to the study-specific pharmacy manual for complete details for SY-1425.

8.6.2. Azacitidine

Unreconstituted vials should be stored at room temperature (15°C to 30°C). Refer the azacitidine package insert for complete details, as applicable (VIDAZA Prescribing Information 2016; VIDAZA Summary of Product Characteristics 2016).

8.6.3. Daratumumab

Daratumumab must be stored in the original carton in a refrigerator at controlled temperatures ranging from 2°C to 8°C until it is removed for dose preparation. Daratumumab must not be utilized after the expiry date printed on the label. Daratumumab must be protected from light and must not be frozen. Daratumumab does not contain preservatives; therefore, any unused portion remaining in the vial must be discarded. Refer to the study-specific pharmacy manual for complete details for daratumumab.

8.7. Concomitant Medications

Every concomitant medication and blood product required by the patient within 30 days prior to study drug administration or at any time during the course of the study are considered concomitant medications and must be documented.

8.7.1. Cytotoxic or Investigational Therapy

No concomitant cytotoxic or investigational therapy is allowed during the study.

8.7.2. Other Agents Targeting CD38 (Arm 4 Only)

The use of other agents that target CD38 is not allowed during the study.

8.7.3. Oral Hydroxyurea

If required for control of a patient's peripheral blast count, oral hydroxyurea may be administered up through the first 14 days of treatment with SY-1425. Treatment beyond 14 days will require approval from the study Sponsor.

8.7.4. Antibacterial, Antifungal, and Antiviral

The use of prophylactic antibacterial, antifungal, and antiviral agents is recommended to be used as clinically indicated according to each institution's guidelines.

For patients enrolled in Arm 4, pneumocystis carinii/jirovecii pneumonia (PCP) prophylaxis should be considered, as per institutional guidelines.

For patients enrolled in Arm 4, prophylaxis for herpes zoster reactivation is recommended during the Treatment Phase, as per institutional guidelines and continue for 3 months following treatment. Initiate antiviral prophylaxis to prevent herpes zoster reactivation within 1 week after starting study treatment and continue for 3 months following study treatment. Acceptable antiviral therapy includes acyclovir (eg, 400 mg given orally 3 times a day, or 800 mg given orally 2 times a day or per institutional standards), famcyclovir (eg, 125 mg given orally, twice a day or per institutional standards), or valacyclovir (eg, 500 mg given orally, twice a day or per institutional standards), initiated within 1 week after the start of study drug.

8.7.5. Hematopoietic Growth Factors

Hematopoietic growth factors should not be given prophylactically unless confirmation of aplasia at the first treatment assessment by bone marrow aspirate or in specific clinical conditions in accordance with American Society of Clinical Oncology (ASCO) guidelines.

8.7.6. Platelet Transfusions

Administration of platelet transfusions may be utilized throughout the study as clinically indicated.

8.7.7. Red Blood Cell Transfusions

Administration of RBC transfusions may be utilized throughout the study as clinically indicated and should be administered according to institutional guidelines.

8.7.8. Moderate and Strong Inhibitors and Strong Inducers of CYP3A4

CYP3A4 is not a major enzyme involved in the clearance of SY-1425, and therefore, CYP3A4 inhibitors and also inducers should not have a clinically significant impact on SY-1425 plasma PK exposure (see IB for more information). Administration of CYP3A4 inhibitors and inducers may be utilized throughout the study as clinically indicated.

8.7.9. Antifibrinolytic

Investigators should also be advised of the potential for thrombosis observed when drugs similar to SY-1425 (e.g., ATRA/tretinoin) have been combined with an antifibrinolytic. Antifibrinolytic medicines should be used with caution while on study drug.

8.7.10. Retinoic Acid Syndrome

Patients should be carefully monitored for the development of RAS. High-dose dexamethasone (i.e., 10 mg/m^2 IV twice daily), and supportive measures (e.g., diuretics, dialysis, mechanical ventilation) as needed, should be implemented at the earliest suspicion of RAS. Glucocorticoid therapy should continue until complete disappearance of symptoms and then tapered. SY-1425 therapy should be temporarily discontinued until RAS is considered controlled and ≤ Grade 2.

8.7.11. Multivitamin and Supplements

Vitamin A supplements (≥10,000 IU/d) are not allowed while on study treatment.

8.7.12. Antacids and Proton pump inhibitors

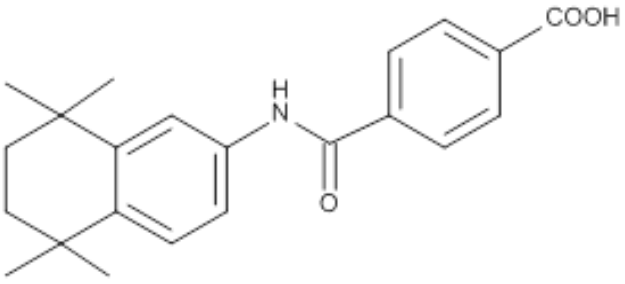
Antacids, H_2-receptor antagonists: such as cimetidine, and Proton pump inhibitors (PPIs), such as omeprazole, should be used with caution while on study treatment.

8.8. Description of SY-1425

8.8.1. Drug Substance

INN:	Tamibarotene
Company code:	SY-1425
Alternative names:	SY-1425, INNO-507; Am-80; OP-01, TOS-80T; TM-411; AMNOLAKE® Tablets (trade name in Japan); 4-[(5,5,8,8-tetramethyl-6,7-dihydronaphthalen-2-yl)carbamoyl]benzoic acid; N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)terephthalamic acid *p*-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)carbamoyl]benzoic acid; 4-[(1,1,4,4-tetramethyltetralin-6-yl)carbamoyl]benzoic acid
Chemical name:	4-[(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)carbamoyl]benzoic acid
Chem. Abst. Registry Number:	94497-51-5
Formula:	$C_{22}H_{25}NO_3$
Molecular weight:	351.4 g/mol
Physical appearance	White crystals or crystalline powder

Figure 2: Chemical Structure



8.8.2. Drug product

SY-1425 is supplied as white, uncoated tablets containing lactose, starch, hydroxypropyl cellulose and magnesium stearate and 2 mg of SY-1425. Tablets are packaged in either child-

proof aluminum blister strips or white round 30 cc HDPE bottles with 28 mm child-resistant caps. Each blister strip contains 10 tablets, with 5 blister strips contained in a sealed carton, which is labeled in accordance with applicable requirements. Each bottle contains 100 tablets, and includes a 1 gram desiccant canister and cotton coil.

8.8.3. Drug Product Precautions

It is possible that SY-1425 drug substance may contain a small amount of sodium hydrosulfite. In accordance with Federal regulations, the following warning is provided:

Contains sodium hydrosulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

SY-1425 is teratogenic; therefore, it should not be administered to women who are pregnant. Tamibarotene has been reported to cause abnormalities in spermatogenesis in animal experiments using rats and dogs. Patients who are fertile must agree to use 2 highly effective methods of birth control, one being barrier method. Intrauterine devices and birth control pills are not barrier methods, but are highly effective especially when combined with a barrier method (eg, latex condom or a diaphragm or cervical cap) while taking investigational product (SY-1425) and continuing contraception use for at least 90 days after the last dose of study drug for men and 6 months for women. Men/women should not donate sperm or ova during this timeframe.

8.9. Description of Azacitidine

For information regarding azacitidine drug substance, drug product, storage, and warnings and precautions, please refer to the azacitidine package insert, as applicable (VIDAZA Prescribing Information 2016; VIDAZA Summary of Product Characteristics 2016).

8.10. Description of Daratumumab

Daratumumab supplied for IV infusion in this study is a colorless to yellow liquid and sterile concentrate of 20 mg/mL as a liquid vial. The study agent should be essentially free of visible particulate matter at the time of dosage preparation and drug product administration.

9. ADVERSE EVENTS

9.1. Definition of an Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation patient associated with the use of a drug or with study participation, whether or not considered related to study drug. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product. An AE can arise from any use of the drug, and from any route of administration, formulation or dose, including an overdose.

Medical conditions present prior to screening, as well as ongoing changes in laboratory values/conditions that are being treated at baseline, will be captured as medical history unless the frequency, severity or character of the condition worsens during the trial (after first dose of any study drug) for which the condition would then be captured as an AE.

9.2. Definition of a Serious Adverse Event

An SAE is any AE that meets any of the following criteria:

- Death
- Life-threatening
- Inpatient hospitalization or prolongation of existing hospitalization, except for:
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF (as documented as medical history on the eCRF), or
  - Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience, or for observation only following daratumumab administration in the absence of a significant medical event
    - Any untoward occurrence during an elective or pre-planned treatment, or scheduled therapy for target disease must be reported as an AE/SAE. In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a patient who received SY-1425
- Important medical events, defined as an AE that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include intensive treatment in an emergency

room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in inpatient hospitalization, and development of drug dependency or drug abuse.

9.3. Procedures for Eliciting, Recording, and Reporting Adverse Events

9.3.1. Eliciting and Recording Adverse Events

Patients will be instructed to report all AEs and will be asked a general health status question at each study visit. All AEs occurring in treated patients will be recorded in the eCRF from the time of first dose of any study drug until 30 days after the last dose of any study drug in the eCRF. However, following implementation of Amendment 7, recording of AEs in the eCRF will no longer be required for Arm 5 patients receiving study drug. Only SAEs, AESI, and Pregnancy and Birth Events will continue to be reported via the pharmacovigilance safety database.

All SAEs occurring from the signing of ICF through 30 days post last dose of any study drug will be processed as outlined in Section 9.5. An SAE will be followed until it is either resolved, has returned to baseline, or is determined to be a stable or chronic condition.

At each required visit during the trial, all AEs that have occurred since the previous visit must be reviewed. The Investigator, or appropriate designee, must determine if the AE is serious or non-serious.

9.3.2. Adverse Event Relationship Assessment

The Investigator is required to provide an assessment of relationship of AEs and SAEs to study drug. A number of factors should be considered in making this assessment including: 1) the temporal relationship of the event to the administration of study drug; 2) whether an alternative etiology has been identified; and/or 3) biological plausibility. The following guidelines should be used by Investigators to assess the relationship of an AE to the administration of the study drug.

"Not Related" assessment

- None: The event is related to an etiology other than study drug administration (the alternative etiology must be documented in the patient's medical record).
- Remote: The event is unlikely to be related to study drug and likely to be related to factors other than study drug.

"Related" assessment

- Possible: There is an association between the event and the administration of study drug, and there is a plausible mechanism for the event to be related to study drug; but there may also be alternative etiologies, such as characteristics of the patient's clinical status or underlying disease.
- Probable: There is an association between the event and the administration of study drug, there is a plausible mechanism for the event to be related to study drug, and the event could not be reasonably explained by known characteristics of the patient's clinical status or an alternative etiology is not apparent.

- Definite: There is an association between the event and the administration of study drug, there is a plausible mechanism for the event to be related to study drug, and causes other than study drug have been ruled out and/or the event re-appeared on re-exposure to study drug.

9.3.3. Adverse Event Severity Assessment

The severity of the AE will be assessed according to the NCI CTCAE v4.03, effective date 14 June 2010 as well as changes in clinically significant clinical laboratory values, ECG parameters and vital sign measurements. Toxicities that are not specified in NCI CTCAE v4.03 will be defined as follows:

- Grade 1: The AE is noticeable to the patient, it does not require discontinuation or reduction of the dose of study drug, but may require additional therapy.
- Grade 2: The AE interferes with the patient's daily activities; it does not require discontinuation of study drug, but may require additional therapy.
- Grade 3: The AE is intolerable and necessitates discontinuing or reducing the dose of study drug or additional therapy.
- Grade 4: The patient is at immediate risk of death from the AE.
- Grade 5: The AE is fatal.

9.4. Specific Instructions for Recording Adverse Events on the eCRF

Following implementation of Amendment 7, recording of AEs (serious and nonserious) in the eCRF will no longer be required for Arm 5 patients receiving study drug; the eCRF instructions described in Section 9.4 are no longer applicable for these patients. Only SAEs (see Section 9.5), AESI (see Section 9.6), and Pregnancy and Birth Events (see Section 9.7) will continue to be reported via the pharmacovigilance safety database.

9.4.1. Diagnosis Versus Signs and Symptoms

If a diagnosis is known at the time of reporting, then the diagnosis should be recorded in the eCRF rather than the individual signs and symptoms (eg, record myocardial infarction rather than chest pain, shortness of breath); however, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome, at the time of reporting, each individual event should be recorded as an AE on the eCRF. If a diagnosis is subsequently established, it should be reported as follow-up and should replace the applicable individual signs and/or symptoms as the event term on the eCRF.

9.4.2. Adverse Events Occurring Due to Other Events

In general, AEs occurring secondary to other events should be identified by their primary cause. For example, if severe vomiting is known to result in dehydration, it is sufficient to record only vomiting as the AE on the eCRF; however, clinically significant AEs occurring secondary to an initiating event should be recorded as independent events on the eCRF. For example, if severe vomiting leads to acute renal failure, both events should be recorded on the eCRF.

9.4.3. Persistent of Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution or change in severity, between patient evaluation timepoints. Such events should only be recorded once on the AE eCRF. If a persistent AE becomes more severe or lessens in severity, it should be recorded as a new AE on the eCRF.

A recurrent AE is one that occurs and resolves between patient evaluation timepoints, and subsequently recurs. All recurrent AEs should be recorded as new events on the AE eCRF.

9.4.4. Disease Under Study

Progression of the underlying disease, including death from progression of the underlying disease, is considered an efficacy outcome parameter and should not be captured as an AE/SAE. Documentation of the progression of disease must be obtained and recorded in the eCRF.

9.4.5. New Cancers

The development of a new primary cancer should be regarded as an AE and will generally meet at least one of the serious criteria (See Section 9.2). New primary cancers are those that are not the primary reason for the administration of study drug treatment and have developed after the patient has received at least one dose of study drug upon enrollment in the study. They do not include metastases of the original cancer, or diagnosis of AML in a patient previously diagnosed with MDS.

Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

9.5. Reporting of Serious Adverse Events

All SAEs must be reported to Syros or designee (contact information provided below) within 24 hours after the Investigator's first knowledge of the event, even if the experience does not appear to be related to study drug, from the time of signing ICF through 30 days after the last dose of any study drug. This timeframe also applies to additional information that is obtained as a part of the follow-up on previously reported SAEs.

To report an SAE, the site must email, phone, or fax the information to the information listed below within 24 hours after becoming aware of the event.

SAE Reporting Contact Information	
Email	**Fax Number**
SyrosPV@primevigilance.com	1-855-234-6419

The initial SAE report must be as complete as possible, including minimally the patient number and initials or date of birth, details of the event(s), and an assessment of the causal relationship between the event and the investigational drug. Information not available at the time of the initial report (eg, an end date for the SAE, or laboratory values received after the report) must be documented on a follow-up SAE report form. All follow-up information must be reported using the same timelines as the initial report.

If, at any time, after completion of the SAE reporting period (ie, 30 days after last dose of any study drug), an Investigator becomes aware of an SAE that is suspected by the Investigator to be related to study drug, the event must be reported to the Syros, or designee, as described above.

Follow-up information may be requested by Syros or designee.

9.6. Reporting of Adverse Events of Special Interest

AESIs must be reported to Syros, or designee, within 24 hours from first knowledge of the event(s) on an SAE Report Form regardless if assessed as non-serious or serious. AESI for the study include:

- Combination of ALT or AST > 3 x ULN and total bilirubin >2 x ULN
- Triglycerides severity Grade ≥ 3
- Total cholesterol severity Grade ≥ 3
- Rash severity Grade ≥ 3
- Bleeding events with severity Grade ≥ 3
- Infectious events with severity Grade ≥ 3

AESIs are to be reported from the first dose of SY-1425 until the EoT visit. As there will be no EoT visit for Arm 5 patients still receiving study treatment at the time of implementation of Amendment 7, AESIs are to be reported from the first dose of SY-1425 until the last dose of any study drug for these patients.

9.7. Pregnancy and Birth Events Procedures

Pregnancies occurring in patients, or partners of male patients, during the study treatment period until 30 days after the patient's last dose of any study drug are considered immediately reportable events. If a pregnancy occurs in a patient, all study drug must be discontinued immediately. SY-1425 and azacitidine have both been shown to be teratogenic in animal studies, and animal studies have not been conducted to assess the risk with use of daratumumab during pregnancy. Therefore pregnant women should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

The pregnancy must be reported to Syros, or designee, within 24 hours of the Investigator's knowledge of the pregnancy using the Pregnancy Notification Form using timelines as described in Section 9.5.

The Investigator will follow the pregnant patient until completion of the pregnancy, and must notify Syros, or designee, of the outcome within 24 hours of the Investigator's knowledge of the pregnancy outcome. The Investigator will provide this information on the Pregnancy Outcome Report Form. This notification includes pregnancies resulting in live, "normal" births.

If the pregnant patient experiences an SAE, during her pregnancy, or the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be reported], stillbirth, neonatal death,

or congenital anomaly), the Investigator should follow the procedures for reporting SAEs as described in Section 9.5.

All neonatal deaths and congenital anomalies that occur within 30 days of birth (regardless of relationship to study drug) should be reported as SAEs. In addition, any infant death or congenital anomaly occurring after 30 days that the Investigator suspects is related to the *in utero* exposure to study drug should also be reported to Syros, or designee as described in Section 9.5.

The Investigator will follow the pregnancy at least until birth or pregnancy termination.

9.8. Overdose

There has been no experience with acute overdose of tamibarotene in humans. However, overdose with other retinoids has been associated with transient headache, facial flushing, cheilosis, abdominal pain, dizziness, and ataxia. These symptoms have resolved quickly without apparent residual effects. Management of overdose with tamibarotene should focus on monitoring target organ function to preserve their viability and prevent complications.

One case of overdose with azacitidine was reported during clinical trials (VIDAZA Prescribing Information 2016; VIDAZA Summary of Product Characteristics 2016). A patient experienced diarrhea, nausea, and vomiting after receiving a single intravenous dose of approximately 290 mg/m^2, almost 4 times the recommended starting dose. In the event of overdose, the patient should be monitored with appropriate blood count tests and should receive supportive treatment, as necessary. There is no known antidote for azacitidine overdose.

The dose of daratumumab at which severe toxicity occurs is not known. In the event of an overdose, monitor patients for any signs or symptoms of adverse effects and provide appropriate supportive treatment (DARZALEX Prescribing Information 2017; DARZALEX Summary of Product Characteristics 2017).

9.9. Clinical Laboratory Changes

If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as AEs. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the eCRF and SAE Report Form. Following implementation of Amendment 7, recording of AEs (serious and nonserious) in the eCRF will no longer be required for Arm 5 patients receiving study drug; the eCRF instructions described in Section 9.9 are no longer applicable for these patients. Only SAEs (see Section 9.5), AESI (see Section 9.6), and Pregnancy and Birth Events (see Section 9.7) will continue to be reported via the pharmacovigilance safety database.

Abnormal laboratory values will not be reported as AEs unless the laboratory result:

- Requires a dose adjustment or schedule change to study drug
- Leads to discontinuation of treatment
- Requires additional testing or therapeutic intervention
- Is associated with accompanying signs/symptoms
- Is considered to be an AE by the Investigator

9.10. Reporting of Serious Adverse Events to Institutional Review Boards/Ethics Committees

Syros, or designee, shall notify the Investigator of potential serious risks from clinical trials or any other sources, including the following:

- SAEs assessed by the Investigator and/or Syros as, related to study drug, and assessed by Syros as unexpected for study drug,
- Any findings from other studies that suggest a significant risk in humans exposed to the drug,
- Any findings from animal or *in vitro* testing that suggests a significant risk to humans exposed to the drug, such as mutagenicity, teratogenicity, or carcinogenicity; or report of significant organ toxicity at or near the expected human exposure

The Investigator must comply with the applicable regulatory requirements and timelines related to the reporting of SAEs to their IRB or Ethics Committee (EC). Investigators must also submit safety information provided by Syros, or designee, to the IRB or EC, according to local requirements.

The Investigator must keep copies of all SAE information, including correspondence with Syros and all IRB/EC information on file.

9.11. Reporting of Serious Adverse Events to Regulatory Authorities

Syros, or designee, shall notify Regulatory Authorities of serious, unexpected adverse reactions or other adverse events, per local requirements. Expectedness will be determined using the current tamibarotene Investigator Brochure.

10. STATISTICS

10.1. General Procedures

Frequency distributions will be used for categorical variables and appropriate summary statistics (ie, mean, median, and range) for quantitative/continuous variables. Each arm (six analysis groups) will be reported and analyzed independently, with no adjustment for multiple hypothesis testing. Two-sided 90% confidence intervals will be provided for key endpoints, ie, primary and secondary endpoints at a minimum.

Additional details of the analyses will be provided in the statistical analysis plan (SAP). Any deviations in the planned analysis as stated in the protocol will be delineated in the SAP. Any deviations from the SAP will be reported in the clinical study report.

10.2. Analysis Populations

Screened: All screened patients (consented) regardless of receipt of the investigational product comprise the screened analysis population. This population will be used only for the generation of demographics and RARA and IRF8 biomarker results.

Safety Population: All screened patients who received any amount of study drug (SY-1425 or combination treatment) comprise the safety population. This population will be further divided by arm as noted in the analysis.

PK Evaluable: All patients enrolled who receive any amount of SY-1425 and have an adequate number of SY-1425 concentration determinations for PK calculations comprise the PK evaluable analysis population.

PD Evaluable: All patients enrolled who receive any amount of SY-1425 and have an adequate number of samples for PD determination comprise the PD evaluable analysis population.

Response Evaluable: The response evaluable analysis population is comprised of all patients enrolled who:

- Complete 1 cycle of SY-1425, and have a follow-up assessment of disease status, and do not have any major protocol violations, or
- Are withdrawn from the study before completion of cycle 1 because of documented disease progression

10.3. Determination of Sample Size

Approximately 162 response-evaluable patients are required (ie, approximately 25 biomarker positive patients each in Arms 1, 2A, 3, and 5; approximately 50 patients in Arm 2B (~ 25 biomarker positive and ~ 25 biomarker negative); and approximately 12 biomarker positive patients in Arm 4) and will be analyzed separately with no adjustment for multiple hypothesis testing across arms, in part for practical reasons as arms may have very different rates of enrollment. This is a fixed design trial.

For each of Arms 1, 2A, 2B (biomarker positive subset), 3, and 5, an exact 2-sided 90% confidence interval will be calculated for ORR or TIR. Success for Arms 1, 2A and 3 (n=25

each) is achieved, if the lower bound of the confidence interval excludes 5%. Assuming a 25% response rate for SY-1425 as a single agent, the power for each of these arms of this study is 90.4%. Arm 2B has two subgroups defined by biomarker status (n=25 each). Success for the biomarker positive subgroup in Arm 2B is achieved if the lower bound of the confidence interval excludes 20%. Assuming a 45% response rate for the combination of SY-1425 and azacitidine in biomarker positive patients, the power for this subgroup of Arm 2B of the study is 86.6%. Success for Arm 5 (n=25) is achieved if the lower bound of the confidence interval excludes 10%. Assuming a 30% response rate for the combination of SY-1425 and azacitidine in relapsed/ refractory biomarker-positive AML patients, the power for this arm of the study is 80.7%.

Therefore, as an example, an ORR or TIR of 4/25 (16%) (90% CI: 5.7 to 33.0%) for Arms 1, 2A, and 3 would be considered a success for each of these arms, an ORR of 9/25 (36%) (90% CI: 20.2 to 54.4%) would be considered a success for the biomarker positive Arm 2B subgroup, and an ORR of 6/25 (24%) (90% CI: 11.0 to 42.0%) would be considered a success in Arm 5. No adjustment for multiple hypothesis testing across arms will be made.

Success for the entire Arm 2B population is achieved if the lower bound of the confidence interval excludes 20%. Assuming a 38% response rate for the combination of SY-1425 and azacitidine in the entire Arm 2B population, the power for secondary endpoint of Arm 2B is 84.6%.

The primary endpoint of Arm 4 is safety and tolerability of SY-1425 in combination with daratumumab. The sample size of 12 biomarker positive patients is not based on any hypothesis testing but is appropriate for studies of this type with a primary focus on safety.

10.4. Statistical Analysis

10.4.1. Demographic and Baseline Characteristics

The screened analysis population will be summarized by biomarker status, disease type, and prior therapy.

The safety population will be used to summarize demographic and baseline characteristics, in a descriptive fashion. Data to be evaluated will include at least age, sex, race, characteristics of disease (including baseline biomarkers), and baseline disease severity assessment as well as other potential prognostic factors and disease characteristics.

10.4.2. Analysis of Efficacy

10.4.2.1. Primary Endpoints

The ORR and TIR by group, specifically, in Arms 1, 2A, 2B (biomarker positive subgroup), 3, and 5, are the primary endpoints.

ORR is defined as:

- AML: ORR as determined by the Investigator based on the rate of CR/CRi/CRh, MLFS, and PR, per the revised IWG AML criteria (Cheson et al, 2003, Bloomfield et al, 2018).

- Higher-risk MDS: ORR as determined by the Investigator per the revised IWG AML criteria (Cheson et al, 2003) or modified IWG MDS criteria (Cheson et al, 2006). Response is based on the rate of CR/CRi, PR, and HI. CR includes marrow CR.

TIR is defined as:

- Lower-risk MDS: The transfusion independence rate (TIR) rate defined as the proportion of patients who achieve transfusion independence defined as 8 consecutive weeks of RBC transfusion independence.

The primary endpoint for Arm 4 is to characterize the safety and tolerability of SY-1425 in combination with daratumumab by assessing the type and frequency of AEs and SAEs using NCI CTCAE v4.03, as well as changes in clinically significant clinical laboratory values, ECG parameters and vital sign measurements.

10.4.3. Secondary Endpoints

Characterize the clinical activity of SY-1425 in patients positive for the *RARA* super-enhancer associated biomarker in Arms 1, 2A, 2B, 3, and 5. Summaries of ORR or TIR will be provided for all patients positive for the RARA super-enhancer associated biomarker (including IRF8 positive and IRF8 negative patients), for double positive patients (including only IRF8 positive patients), and for single positive patients (including only IRF8 negative patients), separately.

- Overall response rate (ORR) for AML or higher-risk MDS patients (Arms 1, 2A, 2B, and 5)
- Transfusion independence rate (TIR) for lower-risk MDS patients (Arm 3)

Characterize the clinical activity of SY-1425 in patients positive for the IRF8 biomarker and negative for the *RARA* super-enhancer associated biomarker in Arms 1, 2A, 2B, 3, and 5.

- Response rate (ORR + TIR) for patients treated with SY-1425 as a single agent (Arms 1, 2A, and 3)
- ORR for AML or higher-risk MDS patients (Arms 1, 2A, 2B and 5)
- TIR for lower-risk MDS patients (Arm 3)

Characterize the clinical activity of the combination of SY-1425 and azacitidine in patients in Arm 2B.

- Overall response rate (ORR) for AML patients (Arm 2B)

Characterize the clinical activity of the combination of SY-1425 and daratumumab by ORR in Arm 4.

Characterize the clinical activity of SY-1425 as measured by EFS, RFS, DOR, OS, and HI in AML and higher-risk MDS patients.

- EFS: defined as time from first treatment until date of documentation of disease relapse following CR/CRi, or death, whichever occurs first. If the patient does not achieve a CR, EFS is defined as the point of progression or death, whichever occurs first.

- RFS: defined as time from first objective documentation of CR/CRi (including CRh, MLFS for AML patients), or PR until the date of first objective documentation of disease relapse or death due to any cause, whichever occurs first.
- DOR: defined as time from first date of response (CR/CRi [including CRh, MLFS for AML patients], PR, or HI for MDS patients - if best response) until date of relapse.
- OS: defined as time from first treatment until death from any cause.
- HI Rate: defined according to the modified IWG response criteria for MDS (Cheson et al, 2006) as the proportion of patient with a response (lasting at least 8 weeks) after first treatment.

Characterize the clinical activity of SY-1425 as measured by DOR and HI in transfusion dependent lower-risk MDS patients.

- DOR is defined as the time from first date of response (HI or transfusion independence) until date of relapse.
- HI is defined according to the modified IWG response criteria for MDS (Cheson et al, 2006) as response (lasting at least 8 weeks) after first treatment.

Time to event data will be assessed using the Kaplan-Meier method. Details on censoring and the analysis will be provided in SAP.

Changes in transfusion rates, incidence and duration of use for growth factor support and antibiotics, and number of hospitalizations associated with febrile neutropenia and/or thrombocytopenic bleeding will be summarized.

Characterize the safety and tolerability of SY-1425 as a single agent and in combination with azacitidine by assessing the type and frequency of AEs, SAEs using NCI CTCAE v4.03, as well as changes in clinically significant clinical laboratory values, ECG parameters and vital sign measurements (Arms 1, 2A, 2B, 3, and 5).

Estimate the PK parameters of SY-1425, as single agent and in combination with azacitidine or daratumumab, after single and multiple doses by performing PK analysis to define t_{max}, C_{max}, C_{min}, AUC, CL/F, and $t_{1/2}$, where the data permits.

10.4.4. Exploratory Endpoints

- Sensitivity analyses to the primary endpoint to predict ORR or TIR across all patients by arm, prior treatment, and diagnosis type, *RARA* super-enhancer associated biomarker and/or IRF8 biomarker status; DHRS3 induction, peripheral blood myeloid differentiation markers, induction of CD38 expression, genotype and mutation status
- Changes from baseline in Health-Related Quality of Life (HRQOL)
  - AML/higher-risk MDS patients (Arms 1, 2A, 2B, 4, and 5): Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu) questionnaire
  - Lower-risk MDS patients (Arm 3): Functional Assessment of Cancer Therapy-Anemia (FACT-An) questionnaire

- Establish PK/PD relationships by performing analysis of PD biomarkers (DHRS3 and myeloid differentiation markers) in leukemic cells from repeat peripheral blood samples and assessing any changes over time
- PK parameters for daratumumab in combination with SY-1425, including maximum concentration (C_{max}) and minimum concentration (C_{min}; trough concentration)
- Characterize the relationship between SY-1425 activity and baseline messenger RNA (mRNA) expression of RARA and IRF8 biomarkers by correlating baseline biomarker mRNA expression levels of RARα and IRF8 with ORR, EFS, RFS, DOR, OS, and HI Rate
- Estimate of median time-to-response
- Evaluate changes in expression of myeloid differentiation markers, including CD38, over time
- Analysis of additional genes or proteins using multiplex platform

10.4.5. Analysis of Safety

Safety tabulations will include treatment-emergent adverse events (TEAEs), vital signs, ECG, laboratory tests, and concomitant medications separately by arm. Severity grade will be defined by the NCI-CTCAE v4.03.

Safety evaluations will be based on the incidence, severity, and type of AEs, and clinically significant changes in the patient's physical examination findings, vital signs and clinical laboratory results. Safety variables will be described and presented for the Safety Population. Exposure to study drug, dosing compliance, and reasons for discontinuation of study treatment will be tabulated.

10.4.5.1. Adverse Events

AEs will be coded by system organ class (SOC) and preferred term using the most current Medical Dictionary for Regulatory Activities (MedDRA) at the time of study initiation. Severity of AEs will be assigned according to NCI-CTCAE (v.4.03). AEs will be summarized by SOC, preferred term and severity accordingly.

10.4.5.2. Laboratory Determination

Actual values and change from baseline values for continuous laboratory data will be summarized descriptively. Categorical measurements will be similarly summarized for actual values. Laboratory results categorized as outside of the normal range will be summarized in worst case shift tables. Clinically significant or not clinically significant criteria may be applied for out of range values.

10.4.5.3. Other Safety Data

Temperature, vital signs, body weight, physical examination findings, ECG, and concomitant medications will be summarized.

10.5. Interim Analysis

There is no formal interim analysis in which alpha-spending is required prior to the single planned final analysis for the by Arm primary and secondary endpoints.

10.6. Pharmacokinetics

Plasma concentration versus time data will be analyzed using non-compartmental methods to determine t_{max}, C_{max}, $C_{min,}$ AUC, CL/F, and $t_{1/2}$. Parametric models will be utilized as the data permit.

10.7. Pharmacodynamics

DHRS3 gene expression is most strongly induced by SY-1425 in AML cells harboring the *RARA* super-enhancer or IRF8 biomarker. However, there is also a significant upregulation in peripheral blood mononuclear cells (PBMCs), which may act as surrogate tissue for measuring SY-1425 response. DHRS3 gene expression which may be induced by SY-1425 in PBMCs will be assessed. Relationships between RARA and IRF8 biomarker status, PK parameters, related TEAEs, and efficacy outcomes may be assessed as the data permit.

11. ETHICS AND RESPONSIBILITIES

11.1. Good Clinical Practice

This study will be conducted in accordance with ICH-GCP and all applicable requirements. Periodic monitoring visits will be conducted to ensure compliance to the protocol and all good clinical practices. Access to study documents will be provided to Syros, its designees, and the regulatory agencies to perform verification that the data being recorded in the CRFs is complete and accurate.

11.2. Ethical Conduct of the Study

The study will be conducted in accordance with all applicable regulatory requirements and adhere to the general principles set forth in the Guidelines for GCP (ICH 1996) and the Declaration of Helsinki (World Medical Association 1996 & 2008).

The Investigator is responsible for having the approval of study protocol, investigator brochure, informed consent, advertisements (if applicable), any written information to be provided to patients, safety updates, and any revisions to the documents by the IRB/IEC. The Investigator is responsible for keeping the IRB/IEC apprised of the progress of the study and of any changes made to the protocol as deemed appropriate.

Protocol modifications, except those intended to reduce immediate risk to study patients, may be made only by Syros. A protocol change intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRB/IEC is notified within 5 days.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC and the Investigator must await approval before implementing the changes. Syros will submit protocol amendments to the appropriate regulatory authorities for approval.

If in the judgment of the IRB/IEC, the Investigator, and/or Syros, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the patients and/or has an impact on the patient's involvement as a study participant, the currently approved written ICF will require similar modification. In such cases, informed consent will be renewed for patients enrolled in the study before continued participation.

11.3. Informed Consent

The Investigator must ensure that each study patient, or guardian/legal representative, is fully informed and written informed consent is obtained prior to initiation of any study specific activity. A copy of the written informed consent document must be provided to the patient. The Investigator is required to maintain the signed informed consent and documentation of the process must comply with ICH-GCP and all applicable regulatory requirements.

11.4. Records Management

The Investigator will keep all study records according to ICH-GCP and applicable regulatory requirements. The site is instructed to maintain all documentation and any other documentation that is required by law for 5 years after the termination or conclusion of the study or longer

periods as required by regulatory requirements. The Investigator must receive Syros' written permission before destroying any study documentation, even after the records retention period has expired.

If the Investigator is unable to retain the study records for the required time period, Syros must be notified to allow the transfer of study records to Syros, another institution, or to a third party as appropriate.

11.5. Source Documentation

The Investigator is required to maintain accurate source documents that record all observations for each study patient. eCRFs will be completed for each patient in the study. It is the responsibility of the Investigator to ensure the accuracy, timeliness, and completeness of the data that is reported in the eCRFs. The source records are typically the patient's chart and should be consistent with the data recorded in the eCRF. The Investigator or designee should complete the eCRF as soon as possible after the data is collected. Following implementation of Amendment 7, no further eCRFs will be required to be completed for patients enrolled in Arm 2B or Arm 5, unless the eCRF data were collected prior to implementation of the amendment.

11.6. Study Drug Accountability

The Investigator is responsible for study drug accountability throughout the study as per the study-specific pharmacy manual. Accurate records of study drug, received, dispensed from and returned to the study site are to be maintained by the study site. Study drug accountability will be monitored throughout the study. Study drug will be disposed of according to applicable regulations and Syros instruction. Following implementation of Amendment 7, SY-1425 accountability will be communicated to the Sponsor approximately every 3 months.

11.7. Auditing and Monitoring

During the study, Syros or its designee will conduct periodic monitoring visits to ensure that ICH-GCP practices are being adhered to. The monitors will review source documentation to confirm that accuracy of the data recorded in the eCRF. The investigator and institution is required to allow direct access to the source documentation, eCRFs, and any other study documentation to study monitors and any regulatory agencies to confirm the accuracy and completeness of the data recorded in the eCRFs.

11.8. Study Report and Publications

Syros is responsible for preparing and providing the appropriate regulatory authorities with CSRs according to the applicable regulatory requirements.

The publication policy of Syros is discussed in the Investigator's Clinical Trial Agreement.

11.9. Study Discontinuation

Syros reserves the right to terminate the study, or terminate the study at an investigator's site at any time. The Principal Investigator may terminate the study at his/her site at any time. Should this be necessary, Syros or a specified designee will inform the appropriate regulatory authorities

of the termination of the study and the reasons for its termination, and the PI will inform the IRB/IEC of the same. In terminating the study, Syros and the Principal Investigator will assure that adequate consideration is given to the protection of the patients' interests.

11.10. Confidentiality

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from Syros. However, authorized regulatory officials, IRB/IEC personnel, Syros and its authorized representatives are allowed full access to the records.

Identification of patients and case report forms (CRFs) shall be made by initials, screening and treatment numbers only. If required, the patient's full name may be made known to an authorized regulatory agency or other authorized official.

12. REFERENCES

Bloomfield CD, Estey E, Pleyer L, Schuh AC, Stein EM, Tallman MS, Wei A; Time to repeal and replace response criteria for acute myeloid leukemia? Blood Rev. 2018 Sep;32(5):416-425.

Chapuy CI, Nicholson RT, Aguad MD, Chapuy B, Laubach JP, Richardson, PG, et al. Resolving the daratumumab interference with blood compatibility testing. Transfusion. 2015; 55:1545-1554.

Chapuy CI, Aguad MD, Nicholson RT, AuBuchon JP, Cohn CS, Delaney M, et al. International validation of a dithiothreitol (DTT)-based method to resolve the daratumumab interference with blood compatibility. Transfusion. 2016;56(12):2964-2972.

Cheson BD, Bennett JM, Kopecky KJ, Büchner T, Willman CL, Estey EH, et al. Revised recommendations of the International Working Group in for diagnosis, standardization response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. J Clin Oncol. 2003;21(24):4642-4649.

Cheson BD, Greenberg PL, Bennett JM, Lowenberg B, Wijermans PW, Nimer SD, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood. 2006;108(2):419-425. Epub 2006 Apr 11.

Cogle CR, Iannacone MR, Yu D, Cole AL, Imanirad I, Yan L, et al. High rate of myelodysplastic syndrome cases and an improved method of case ascertainment. Leuk Res. 2014;38(1):71-75. Epub 2013 Nov 5.

Cook RJ, Moyo TK, Liesveld JL, Rizzieri DA, Stein EM, de Botton S et al; Early Results From a Biomarker-Directed Phase 2 Trial of SY-1425 in Combination with Azacitidine or Daratumumab in Non-APL Acute Myeloid Leukemia (AML) and Myelodysplastic Syndrome (MDS). Abstract 2735, American Society of Hematology, December 2018

DARZALEX (daratumumab) [Prescribing Information]. Janssen Biotech, Inc, Horsham, PA; 2017; Available from: https://www.darzalex.com/sites/www.darzalex.com/files/darzalex-prescribing-information.pdf. Accessed 01 August 2017.

DARZALEX (daratumumab) [Summary of Product Characteristics]. Janssen-Cilag International NV, Beerse, Belgium; 2017; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004077/WC500207296.pdf. Accessed 01 August 2017.

de Weers M, Tai Y-T, van der Veer MS, Bakker JM, Vink T, Jacobs DCH, et al. Daratumumab, a Novel Therapeutic Human CD38 Monoclonal Antibody, Induces Killing of Multiple Myeloma and Other Hematological Tumors. J Immunol. 2011;186:1840-1848.

Derissen E J, Beijnen J H, Schellens J H. Concise drug review: azacitidine and decitabine. Oncologist. 2013;18(5): 619–624.

DeZern AE. Nine years without a new FDA-approved therapy for MDS: how can we break through the impasse? Hematology Am Soc Hematol Educ Program. 2015;2015(1):308-316.

Döhner, H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424-447. Epub 2016 Nov 28.

FDA.gov [Internet]. Silver Spring (MD): Drug Development and Drug Interactions: Classification of Inhibitors. 2014 (updated 2014 Oct 27; cited 08 March 2016]. Available from: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#classInhibit. Accessed 08 February 2017.

Ferrara F, Schiffer CA. Acute myeloid leukemia in adults. Lancet. 2013;381(9865):484-95.

Ferrara F, Barosi G, Venditti A, Angelucci E, Gobbi M, Pane F, et al. Consensus-based definition of unfitness to intensive and non-intensive chemotherapy in acute myeloid leukemia: a project of SIE, SIES and GITMO group on a new tool for therapy decision making. Leukemia. 2013;27(5):997-999.

Gallagher RE. Retinoic acid resistance in acute promyelocytic leukemia. Leukemia. 2002;16(10):1940-1958.

Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Solé F, et al. Revised international prognostic scoring system for Myelodysplastic Syndrome, Blood. 2012;120(12):2454-65. Epub 2012 Jun 27.

Grimwade D, Ivey A, Huntly BJ. Molecular landscape of acute myeloid leukemia in younger adults and its clinical relevance. Blood. 2016;127(1):29-41. Epub 2015 Dec 10.

Hnisz D, Abraham BJ, Lee TI, Lau A, Saint-André V, Sigova AA, et al. Transcriptional super-enhancers connected to cell identity and disease. Cell. 2013;155(4):934-947. Epub 2013 Oct 10.

Kanai F, Obi S, Fujiyama S, Shiina S, Tamai H, Mochizuki H, et al. An open-label phase I/III study of tamibarotene in patients with advanced hepatocellular carcinoma. Hepatol Int. 2014;8(1):94-103. Epub 2013 Jul 25.

Kastner P, Chan S. Function of RARα during the maturation of neutrophils. Oncogene. 2001;20:7178–7185.

Keyhani A, Huh YO, Jendiroba D, Pagliaro L, Cortez J, Pierce S, et al. Increased CD38 expression is associated with favorable prognosis in adult leukemia. Leu Res. 2000;24(2):153-9.

Niederreither K, Dollé, P. Retinoic acid in development: towards an integrated view. Nat. Rev. Genet. 2008;(7):541–553. Epub 2008 Jun 10.

Oken MM, Creech RH, Tormey DC, Horton J, DavisTE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55.

Overdijk MB, Verploegen S, Bogels M, van Egmond M, van Bueren JJL, Mutis T, et al. Antibody-mediated phagocytosis contributes to the anti-tumor activity of the therapeutic antibody daratumumab in lymphoma and multiple myeloma. mAbs. 2015;7(2):311-21.

Sanford D, Lo-Coco F, Sanz MA, Di Bona E, Coutre S, Altman JK, et al. Tamibarotene in patients with acute promyelocytic leukaemia relapsing after treatment with all-*trans* retinoic acid and arsenic trioxide. Br J Haematology. 2015;171(4):471-477. Epub 2015 Jul 24.

Shinagawa K, Yanada M, Sakura T, Ueda Y, Sawa M, Miyatake M, et al. Tamibarotene as maintenance therapy for acute promyelocytic leukemia: results from a randomized controlled trial. J Clin Oncol. 2014;32(33):3729-35; Epub 2014 Sep 22.

Stresemann C, Bokelmann, I, Mahlknecht U, Lyko, F. Azacytidine causes complex DNA methylation responses in myeloid leukemia. Mol. Cancer Ther. 2008;7:2998–3005.

Tobita T, Takeshita A, Kitamura K, Ohnishi K, Yanagi M, Hiraoka A, et al. Treatment with a new synthetic retinoid, Am80, of acute promyelocytic leukemia relapsed from complete remission induced by all-trans retinoic acid. Blood. 1997;90(3): 967-73.

VIDAZA (azacitidine for injection), for subcutaneous or intravenous use [Prescribing Information]. Celgene Corporation, Summit, NJ; 2016; Available from: http://www.celgene.com/content/uploads/vidaza-pi.pdf. Accessed 08 February 2017.

VIDAZA (azacitidine for injection), for subcutaneous use [Summary of Product Characteristics]. Celgene Europe Ltd, Stockley Park, Uxbridge, UK; 2016; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000978/WC500050239.pdf. Accessed 08 February 2017.

Voso M T, Santini V, Fabiani E, Fianchi L, Criscuolo M, Falconi G, et al. Why methylation is not a marker predictive of response to hypomethylating agents. Haematologica. 2014;99(4):613-619.

Wang J, Mi Y, Jiang B, Chen X, Ji C, Li Y, et al. Tamibarotene compared to all-trans retinoic acid (ATRA) as add-on to arsenic trioxide (ATO) in subjects with relapsed acute promyelocytic leukemia (APL) ASH poster, December 2015 (220).

Wouters BJ, Delwel R. Epigenetics and approaches to targeted epigenetic therapy in acute myeloid leukemia. Blood. 2016;127(1):42-52; Epub 2015 Dec 10.

13. APPENDICES

APPENDIX 1. NAMES OF STUDY PERSONNEL

Contact information can be found in the study manual provided to the site.

APPENDIX 2. ECOG PERFORMANCE STATUS

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work)
2	In bed <50% of the time. Ambulatory and capable of all self care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of time. Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self care. Totally confined to bed or chair.
5	Dead

As published in Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55.

APPENDIX 3. CRITERIA FOR DETERMINATION OF MDS IPSS-R RISK CATEGORY

MDS Cytogenetic Scoring System (IPSS-R)

Cytogenetic prognostic subgroups	**Cytogenetic abnormalities**
Very good	-Y, del(11q)
Good	Normal, del(5q), del(12p), del(20q), double including del(5q)
Intermediate	del(7q), +8, +19, i(17q), any other single or double independent clones
Poor	-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), Complex: 3 abnormalities
Very poor	Complex: >3 abnormalities

MDS Prognostic Score Values (IPSS-R)

	Score Value						
Prognostic variable	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**
Cytogenetics	Very Good	-	Good	–	Inter-mediate	Poor	Very Poor
Marrow blasts (%)	≤2	-	>2 - < 5	-	5-10	>10	-
Hemoglobin (g/dL)	≥10	-	8 - < 10	< 8	-	-	-
Platelet Count (x 10^9/L)	≥100	50 - <100	<50	-	-	-	-
Absolute Neutrophil Count (x 10^9/L)	≥0.8	<0.8	-	-	-	-	-

MDS IPSS-R Prognostic Risk Category and Risk Score (Sum of Prognostic Score Values)

Risk Category	**Overall Risk Score**
Very Low	≤1.5
Low	>1.5-3
Intermediate	>3-4.5
High	>4.5-6
Very High	>6

Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Solé F, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood. 2012;120(12):2454-65. Epub 2012 Jun 27.

APPENDIX 4. IWG RESPONSE CRITERIA TABLE FOR AML, MDS AND HEMATOLOGIC IMPROVEMENT

Response Criteria for Acute Myeloid Leukemia

Hematologic Responses to Treatment

Response Criteria	*Neutrophils per (μL)*	*Platelets per (μL)*	*Bone Marrow Blasts (%)*
Complete Response (CR)	≥1,000	≥100,000	<5 with spicules, no Auer rods
Cytogenetic CR (CRc)	≥1,000	≥100,000	<5, cytogenetics - normal
Molecular CR (CRm)	≥1,000	≥100,000	<5, molecular - negative
CR, with incomplete blood count recovery (CRi)	<1,000 -or	<100,000	<5, either neutrophils or platelets not recovered
CR with partial hematologic recovery (CRh)	>500	>50,000	<5, with partial recovery of peripheral counts
MLFS	NA	NA	<5, with no hematologic recovery required
Partial Remission (PR)	≥1,000	≥100,000	≥50% decrease from baseline, with decrease to 5-25
Partial Remission with incomplete blood count recovery (PRi)	<1,000 -or-	<100,000	≥50% decrease from baseline, with decrease to 5-25
Minor Response	NA	NA	≥25% decrease from baseline
Stable Disease	NA	NA	Blasts stable ±25%

There is no minimum requirement for bone marrow cellularity or hemoglobin concentration for response criteria

Cheson BD, Bennett JM, Kopecky KJ, Büchner T, Willman CL, Estey EH, etc. Revised recommendations of the International Working Group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. J Clin Oncol. 2003;21(24):4642-9.

Bloomfield CD, Estey E, Pleyer L, Schuh AC, Stein EM, Tallman MS, Wei A; Time to repeal and replace response criteria for acute myeloid leukemia? Blood Rev. 2018 Sep;32(5):416-425.

Treatment Failure

Category	Definition	Comment
Progressive Disease (PD)	Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood: • >50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with <30% blasts at baseline; or persistent marrow blast percentage of >70% over at least 3 months; without at least a 100% improvement in absolute neutrophil count (ANC) to an absolute level [>0.5 x 10^9/L (500/iL), and/or platelet count to >50 x 109/L (50,000/iL) non-transfused]; or • >50% increase in peripheral blasts (WBC x % blasts) to >25 x 10^9/L (>25,000/il) (in the absence of differentiation syndrome) [a]; or • New extramedullary disease	In general, at least 2 cycles of treatment should be administered. Blast increases should be observed in 2 consecutive marrow assessments at least 4 weeks apart; the date of progression should then be defined as of the first observation date. "Progressive disease" is usually accompanied by a decline in ANC and platelets and increased transfusion requirement and decline in performance status or increase in symptoms.

[a] Differentiation syndrome, ie, a transient increase in the percentage of bone marrow blasts and an absolute increase in blood blasts, may be observed with targeted therapies; in this setting, an increase in blasts may not necessarily indicate progressive disease.

Döhner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner H, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424-447.

Response Criteria and Progression Definitions for Myelodysplasia

Response Criteria	***Peripheral Blood***				***Bone Marrow Blasts (BMB) (%)***	***Other***
	Hgb (g/dL)	**Neutrophils per (L)**	**Platelets per (L)**	**Blasts (%)**		
Complete Remission (CR)	≥11	≥1.0 x 10^9	≥100 x 10^9	0	≤5	Normal maturation of all cell lines, note if has persistent dysplasia
Partial Remission (PR)					Decreased by ≥50% from baseline, but >5%	All CR criteria if abnormal before treatment except BMB
Marrow CR (mCR)	If hematologic improvement (HI) response, note in addition to Marrow CR				decreased by ≥50% from baseline, and ≤5%	
Stable Disease						Failure to achieve PR & no evidence of progression for >8 wks
Failure						Death, or disease progression: worsening cytopenia, increase in % BM blasts, progression to a more advanced MDS FAB subtype
Relapse after CR or PR						At least one of the following: Return to pre-treatment BMB % Decrement of ≥50% from maximum remission/response levels in granulocytes or platelets Reduction in Hgb ≥1.5g/dL or transfusion dependence

Cytogenetic Response	**Evaluation**
Complete	Disappearance of chromosomal abnormality with no appearance of new ones
Partial	≥50% reduction of chromosomal abnormality

Disease Progression, patients with:	**Evaluation Criteria:**
<5% bone marrow blasts	≥50% increase to >5% bone marrow blasts
5-10% bone marrow blasts	≥50% increase to >10% bone marrow blasts
10-20% bone marrow blasts	≥50% increase to >20% bone marrow blasts
20-30% bone marrow blasts	≥50% increase to >30% bone marrow blasts
For all categories	At least 50% decrease from maximum remission/response in granulocytes or platelets or Reduction in Hgb by ≥2 g/dL or Transfusion dependence

Cheson BD, Greenberg PL, Bennett JM, Lowenberg B, Wijermans PW, Nimer SD, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood. 2006 Jul 15;108(2):419-25. Epub 2006 Apr 11.

Response Criteria for Hematologic Improvement (HI) for Myelodysplasia

Hematologic Improvement*	Response Criteria (response lasting 8 weeks)
Erythroid response (pre-treatment <11g/dL)	Hgb increase by ≥1.5 g/dL Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 weeks as compared to the pretreatment transfusion number in the previous 8 weeks (only RBC transfusions given for Hb ≤9 g/dL pretreatment will count in the RBC transfusion evaluation).
Platelet Response (pretreatment <100 $x10^9$/L)	Absolute increase of ≥30 $x10^9$/L if starting with >20 x 10^9/L platelets Increase from <20 x 10^9/L to >20 $x10^9$/L and by at least 100%
Neutrophil Response (pretreatment <1 x 10^9/L)	At least a 100% increase and an absolute increase >0.5 $x10^9$/L
Progression or relapse after HI in the absence of another explanation	At least one of the following: At least 50% decrease from maximum response levels in granulocytes or platelets; Reduction in Hgb by ≥1.5g/dL; Transfusion dependence.

Cheson BD, Greenberg PL, Bennett JM, Lowenberg B, Wijermans PW, Nimer SD, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood. 2006;108(2):419-425. Epub 2006 Apr 11.

APPENDIX 5. CYP3A INHIBITORS/INDUCERS

Strong Inhibitors (≥5-fold increase in AUC or > 80% decrease in CL)	**Moderate inhibitors (≥ 2 but < 5-fold increase in AUC or 50-80% decrease in CL)**	**Strong Inducers (≥ 80% decrease in AUC)**
boceprevir clarithromycin conivaptan grapefruit juice indinavir itraconazole ketoconazole lopinavir/ritonavir mibefradil nefazodone nelfinavir posaconazole ritonavir saquinavir telaprevir telithromycin voriconazole	amprenavir aprepitant, atazanavir ciprofloxacin darunavir/ritonavir diltiazem erythromycin fluconazole fosamprenavir grapefruit juice imatinib verapamil	avasimibe carbamazepine phenytoin rifampin St. John's wort

FDA.gov [Internet]. Silver Spring (MD): Drug Development and Drug Interactions: Classification of Inhibitors. 2014 (updated 2014 Oct 27; cited 2016 March 8]. Available from: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#classInhibit.

APPENDIX 6. FACT-AN QOL

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	<u>PHYSICAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	<u>SOCIAL/FAMILY WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	<u>EMOTIONAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	<u>FUNCTIONAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless (“washed out”)	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble <u>starting</u> things because I am tired	0	1	2	3	4
An4	I have trouble <u>finishing</u> things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An6	I have trouble walking	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An9	I feel lightheaded (dizzy)	0	1	2	3	4
An10	I get headaches	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4
An11	I have pain in my chest	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
BL4	I am interested in sex	0	1	2	3	4
An13	I am motivated to do my usual activities	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

APPENDIX 7. FACT-LEU QOL

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	<u>PHYSICAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	<u>SOCIAL/FAMILY WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
BRM2	I am bothered by the chills	0	1	2	3	4
ES3	I have night sweats	0	1	2	3	4
LEU1	I am bothered by lumps or swelling in certain parts of my body (eg, neck, armpits, or groin)	0	1	2	3	4
TH1	I bleed easily	0	1	2	3	4
TH2	I bruise easily	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
N3	I worry about getting infections	0	1	2	3	4
LEU5	I feel uncertain about my future health	0	1	2	3	4
LEU6	I worry that I might get new symptoms of my illness	0	1	2	3	4
BRM9	I have emotional ups and downs	0	1	2	3	4
LEU7	I feel isolated from others because of my illness or treatment	0	1	2	3	4

APPENDIX 8. ASTHMA GUIDELINES

Components of Severity		Classification of Asthma Severity											
		Intermittent			Persistent								
					Mild			Moderate			Severe		
		0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs
Impairment	Symptoms	≤ 2 days/week			≥ 2 days/week but not daily			Daily			Throughout the day		
	Nighttime awakenings	0	≤ 2x/month		1-2x/ month	3-4x/month		3-4x/ month	> 1x/week but not nightly		> 1x/ month	Often 7x/week	
	SABA use for symptom control (not prevention of EIB)	≤ 2 days/week			≤ 2 days/week but not daily		>2 days/ week but not daily, and not more than 1x	Daily			Several time per day		
	Interference with normal activity	None			Minor limitation			Some limitation			Extremely limited		
Normal FEV_1/FVC : 8-19 yr 85% 20-39 yr 80% 40-59 yr 75% 60-80 yr 70%	Lung function	N/A	Normal FEV_1 between exacerbations	Normal FEV_1 between exacerbations	N/A			N/A			N/A		
	FEV1		> 80%	> 80%		> 80%	> 80%		60-80%	60-80%		< 60%	< 60%
	FEV1/FVC		> 85%	Normal		> 80%	Normal		75-80%	Reduced		< 75%	Reduced
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/year			≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2/year Relative annual risk may be related to FEV_1.
		Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category.											

Recommended Step for Initiating Treatment	Step 1	Step 2	Step 3 and consider short course of oral steroids	Step 3: medium dose ICS and consider short course of	Step 3 and consider short course of oral steroids	Step 3 and consider short course of oral steroids	Step 3: medium dose ICS OR Step 4 and consider short course of oral steroids	Step 4 or 5 and consider short course of oral steroids
	In 2-6 weeks, evaluate level of asthma control that is achieved. 0-4 years: If no clear benefit is observed in 4-6 weeks, stop treatment and consider alternate diagnosis or adjusting therapy. 5-11 and 12+ years: adjust therapy accordingly.							

AMERICAN LUNG ASSOCIATION® of Minnesota

<table>
<tr><td colspan="2" rowspan="3">Components of Control</td><td colspan="9">Classification of Asthma Control</td></tr>
<tr><td colspan="3">Well Controlled</td><td colspan="3">Not Well Controlled</td><td colspan="3">Very Poorly Controlled</td></tr>
<tr><td>0-4 yrs</td><td>5-11 yrs</td><td>12 + yrs</td><td>0-4 yrs</td><td>5-11</td><td>12 + yrs</td><td>0-4 yrs</td><td>5-11</td><td>12 + yrs</td></tr>
<tr><td></td><td>Symptoms</td><td colspan="2">≤ 2 days/week but not more than once on each day</td><td>≤ 2 days/ week</td><td colspan="2">> 2 days/week or multiple times on ≤2 days/week</td><td>> 2 days/ week</td><td colspan="3">Throughout the day</td></tr>
<tr><td rowspan="5">Impairment</td><td>Nighttime awakenings</td><td colspan="2">≤ 1x/month</td><td>≤ 2x/month</td><td>> 1x/month</td><td>≥ 2x/month</td><td>1-3x/week</td><td>> 1x/week</td><td>≥ 2x/week</td><td>≥ 4x/week</td></tr>
<tr><td>Interference with normal activity</td><td colspan="3">None</td><td colspan="3">Some limitation</td><td colspan="3">Extremely limited</td></tr>
<tr><td>SABA use for symptom control (not prevention of EIB)</td><td colspan="3">≤ 2 days/week</td><td colspan="3">> 2 days/week</td><td colspan="3">Several times per day</td></tr>
<tr><td>Lung function
FEV_1 or peak flow
FEV_1/FVC</td><td>N/A</td><td>> 80%
> 80%</td><td>> 80%</td><td>N/A</td><td>60-80%
75-80%</td><td>60-80%</td><td>N/A</td><td>< 60%
< 75%</td><td>< 60%</td></tr>
<tr><td>Validated questionnaires
ATAQ
ACQ
ACT</td><td colspan="2"></td><td>0
≤ 0.75
≥ 20</td><td colspan="2"></td><td>1-2
≥ 1.5
16-19</td><td colspan="2"></td><td>3-4
N/A
≤ 15</td></tr>
<tr><td rowspan="3">Risk</td><td rowspan="2">Exacerbations requiring oral systemic corticosteroids</td><td colspan="4">0-1/year</td><td colspan="6">≥ 2/year</td></tr>
<tr><td colspan="10">Consider severity and interval since last exacerbation</td></tr>
<tr><td>Reduction in lung growth/ Progressive loss of lung function</td><td colspan="10">Evaluation requires long-term follow-up</td></tr>
<tr><td colspan="3"></td><td colspan="2">• Maintain current step
• Regular follow-up every 1-6 months</td><td>Step up 1 step</td><td>Step up at least 1 step</td><td>• Step up 1 step
• Reevaluate</td><td colspan="2">• Consider short course of oral steroids
• Step up 1-2 steps</td><td>• Consider short course of oral steroids</td></tr>
</table>

Recommended Action for Treatment	• Consider step down if well controlled for at least 3 months	• **Before step up**: Review adherence to medication, inhaler technique, and environmental control. If alternative treatment was used, discontinue it and use preferred treatment for that step. • **Reevaluate the level of asthma control in 2-6 weeks to achieve control**. 0-4 years: If no clear benefit is observed in 4-6 weeks, consider alternative diagnoses or adjusting therapy. 5-11 years: Adjust therapy accordingly. • **For side effects**, consider alternative treatment options.	in 2-6 weeks • For side effects, consider alternative treatment options	• **Before step up**: Review adherence to medication, inhaler technique, and environmental control. If alternative treatment was used, discontinue it and use preferred treatment for that step. • **Reevaluate the level of asthma control in 2-6 weeks to achieve control**. 0-4 years: If no clear benefit is observed in 4-6 weeks, consider alternative diagnoses or adjusting therapy. 5-11 years: Adjust therapy accordingly. • **For side effects**, consider alternative treatment options.	• Step up 1-2 steps • Reevaluate in 2 weeks • For side effects, consider alternative treatment options

APPENDIX 9. THE FAMILY OF ANTIHISTIMINE MEDICATIONS

The following antihistamines may be used for daratumumab preinfusion medication (including, but not limited to):

- Diphenhydramine
- Cetirizine
- Fexofenadine
- Loratadine
- Clemastine
- Dexchlorpheniramine
- Promethazine*

* The IV use of promethazine should be avoided.

APPENDIX 10. CONVERSION TABLE FOR GLUCOCORTICOID DOSE

Glucocorticoid	Approximate Equivalent Dose (mg)	Half-life (Biologic) hours
Intermediate-Acting		
Methylprednisolone	4	18-36
Prednisolone	5	18-36
Prednisone	5	18-36
Triamcinolone	4	18-36
Long-Acting		
Betamethasone	0.6 – 0.75	36-54
Dexamethasone	0.75	36-54