

# Stanford Cancer Institute

A National Cancer Institute  
Comprehensive Cancer Center



**Stanford** | MEDICINE

**A Phase 1b/2, Single Center, Open-Label, Safety and Efficacy Study to  
Improve Anemia in Subjects on Enasidenib with Lower-risk  
Myelodysplastic Syndrome and Non-proliferative Chronic  
Myelomonocytic Leukemia without an *IDH2* Mutation**

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**Single-Center**

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|                             |  |
|-----------------------------|--|
| <b>Study Agent:</b>         | Enasidenib mesylate (Idhifa, AG-221)   |
| <b>Manufacturer:</b>        | Celgene Corporation  |
| <b>IRB of Record:</b>       | Administrative Panels on Human Subjects in Medical Research ("Stanford IRB") |
| <b>IND Sponsor:</b>         | Tian Yi Zhang, MD  |
| <b>IND</b>                  | 158157   |
| <b>IND Cross-reference:</b> | IND-117631   |
| <b>Funding Source:</b>      | Celgene Corporation  |

## STATEMENT OF COMPLIANCE

### SPONSOR-INVESTIGATOR STATEMENT

I have read and agree to the study, as detailed by this protocol document. I am aware of my responsibilities as an Investigator pursuant to the clinical trial protocol, the guidelines of [Good Clinical Practice \(GCP\)](#)<sup>1</sup>, the Declaration of Helsinki<sup>2</sup>, and the applicable Code of Federal Regulations (CFR) at [Title 21](#)<sup>3</sup> and [Title 45§46](#)<sup>4</sup>, as well as my responsibilities as a Sponsor-Investigator and IND-holder under 21 CFR §312 or §812<sup>3</sup>, as a ClinicalTrials.gov Responsible Party under [42 CFR§11](#)<sup>5</sup> as promulgated pursuant to Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801), and other applicable requirements of the participating institutions including the Stanford Cancer Institute, the Stanford Hospitals and Clinics, and/or the Stanford University Medical Center. I agree to conduct the trial according to these regulations, guidelines, and requirements, and to appropriately direct and assist the participating staff under my authority, and ensure that all staff members are aware of, and trained in, their clinical trial responsibilities.

All key study personnel have completed Human Subjects Protection Training.

Site Principal Investigators are expected to assure that no deviation from, or changes to the protocol, will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB) of record, except where necessary to eliminate an immediate hazard(s) to the trial subjects.

**Sponsor-Investigator's Name:** Tian Yi Zhang, MD, PhD

**Name of Site:** Stanford Cancer Institute or Stanford Hospitals and Clinics  
Stanford Medicine  
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**Principal Investigator's Signature:** \_\_\_\_\_ **Date:** \_\_\_\_\_

- 1 FDA Guidance for Industry: current revision of the International Conference on Harmonization (ICH) Good Clinical Practice Guidelines E6.
- 2 World Medical Association, Declaration of Helsinki Ethical Principles for Medical Research Involving Human Patients.
- 3 United States Code of Federal Regulations (CFR), [Title 21, "Food and Drugs."](#)
- 4 CFR, [Title 45 "Public Welfare;" Part 46 "Protection of Human Subjects."](#)
- 5 CFR, [Title 42 "Public Health;" Part 11 "Clinical Trials Registration and Results Information Submission."](#)

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## PROTOCOL SYNOPSIS

|                               |   |
|-------------------------------|---|
| <b>Study Title</b>            | A Phase 1b/2, Single Center, Open-Label Study to Evaluate Safety and Efficacy of Enasidenib to Improve Anemia in Subjects with Lower-risk Myelodysplastic Syndrome and Non-Proliferative Chronic Myelomonocytic Leukemia without a Mutation in <i>IDH2</i>  |
| <b>Study Drug</b>             | Enasidenib  |
| <b>Study Description</b>      | An early phase, investigator-sponsored clinical trial to determine if enasidenib is safe and effective in improving anemia and decreasing transfusion needs in subjects diagnosed with lower-risk myelodysplastic syndrome (MDS) or nonproliferative chronic myelomonocytic leukemia (CMML) without a mutation in isocitrate dehydrogenase type 2 (IDH2 wildtype). Other objectives include assessment of improvements in platelet production and characterization of the mechanism of action of enasidenib in enhancing endogenous erythropoiesis.   |
| <b>Study Phase</b>            | Phase 1b/2  |
| <b>Study Purpose</b>          | Treatment   |
| <b>Indication</b>             | Low and intermediate risk MDS (including very low risk, low risk and intermediate risk MDS, defined by IPSS-R score $\leq 4.5$ )<br>Nonproliferative CMML   |
| <b>Primary Objective(s)</b>   | To determine the efficacy (response rate) of enasidenib in improving anemia and decreasing RBC transfusion dependence.  |
| <b>Primary Endpoint(s)</b>    | Proportion of subjects achieving modified IWG 2018-defined hematological improvement-erythroid (HI-E).  |
| <b>Secondary Objective(s)</b> | To determine the tolerability, safety and durability of the erythroid response and identify laboratory parameters as clinical markers of response.  |
| <b>Secondary Endpoint(s)</b>  | <ol style="list-style-type: none"><li>1. To determine the safety of enasidenib in subjects without IDH2 mutations using the type, incidence, severity of adverse events in accordance with the CTCAE v5.0.</li><li>2. To determine the time to HI-E, defined as time from first dose of enasidenib to the first observed hemoglobin change meeting 2018 IWG HI-E criteria.</li><li>3. To determine the duration of HI-E, defined as time from each recorded response of increase in hemoglobin meeting 2018 IWG HI-E criteria (Section 10.2.1.2) to loss of response.</li><li>4. To determine the proportion of subjects who achieve a response defined by the modified 2018 IWG criteria for improvement of platelet count (HI-P).</li></ol> |

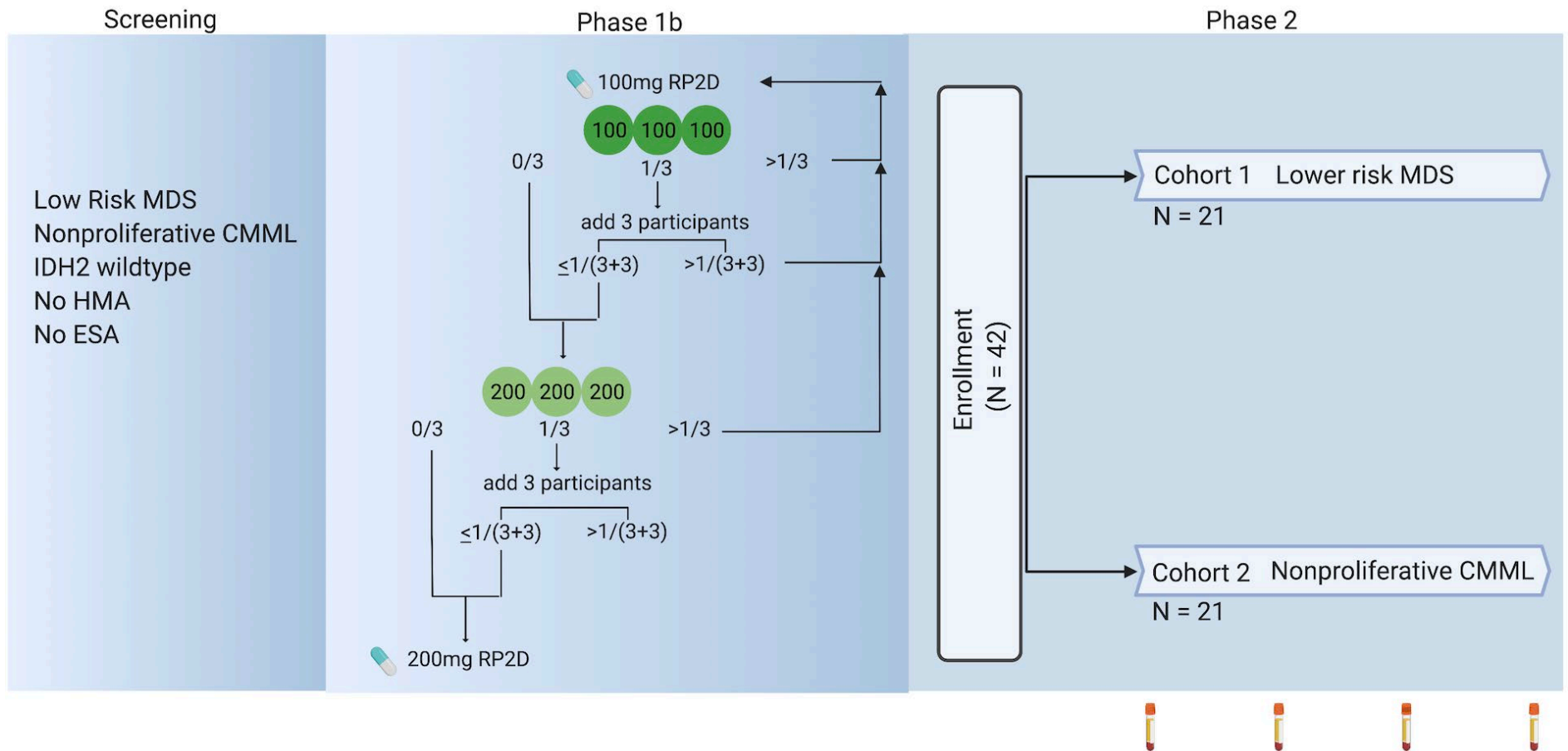
|  |  |
|--|--|
| <b>Secondary Endpoint(s) (continued)</b> | <ol style="list-style-type: none"><li>5. To determine the proportion of subjects who achieve a response defined by the modified 2018 IWG criteria in improvement of neutrophils (HI-N).</li><li>6. To determine the proportion of study subjects who are transfusion dependent achieving RBC transfusion independence (RBC-TI) for 8 weeks or longer.</li></ol>  |
| <b>Sample Size</b>                       | 42 to 48   |
| <b>Eligibility Criteria</b>              | <ol style="list-style-type: none"><li>1. 18 year or older.</li><li>2. With the pathological diagnosis of lower-risk MDS or nonproliferative CMML.</li><li>3. With diagnosis of anemia defined by the modified 2018 IWG criteria.</li><li>4. Performance status of ECOG 0 to 2.</li></ol>   |
| <b>Dose</b>                              | <p>The phase 1b portion of the trial will have a starting dose of 100 mg daily and the recommended phase 2 dose (R2PD) will be determined (100 to 200 mg daily) for the phase 2 portion of the study. "Cohort A" will be those subjects receiving 100 mg enasidenib, and "Cohort B" will be those receiving 200 mg enasidenib. Within the Phase 2 part of the study, subjects will be stratified as Cohort 1 for subjects with lower-risk MDS and Cohort 2 for subjects with non-proliferative CMML. For purposes of analysis and reporting, Phase 1b subjects with lower-risk MDS and nonproliferative CMML may be included within Cohorts 1 and 2, respectively.</p>   |
| <b>Treatment and Procedural Summary</b>  | <p>Each study subject will self-administer the enasidenib orally every day. Peripheral blood draws and bone marrow (BM) biopsies will be conducted according to timeline to assess for treatment response.</p>   |
| <b>Statistical Considerations</b>        | <p>Simon's two-stage design will be used for each of the disease cohorts of the study (MDS, CMML). The null hypothesis that the true response rate is 0.1 [<math>P_0 = 0.1</math>] will be tested against a one-sided alternative. In the first stage, 16 [<math>n_1</math>] subjects will be accrued. If there are 1 [<math>r_1</math>] or fewer responses in these 16 subjects, the study will be stopped. Otherwise, 5 additional subjects will be accrued for a total of 21 [<math>n</math>]. The null hypothesis will be rejected if 5 [<math>R_2+1</math>] or more responses are observed in 21 subjects. This design yields a type I error rate of 0.0735 and power of 0.8 when the true response rate is 0.30.</p> |
| <b>Study Duration</b>                    | <p>This study is expected to take approximately 24 months to complete enrollment, with an additional 2 to 6 months for follow up for the last subject enrolled onto the study. Anticipate data analysis to be completed in 3 months after study is completed.</p>  |

**Subject Duration**

If a study subject has not met criteria as a responder within the first 6 months of treatment, the subject will be considered a nonresponder and exit the study.

If the study subject is believed to be deriving clinical benefit on enasidenib by the end of 12 months on study protocol by the PI, the subject may continue treatment after discussion with the study sponsor.

## PROTOCOL SCHEMA



## LIST OF ABBREVIATIONS

|       |  |              |   |
|-------|--|--------------|---|
| AE    | Adverse event                                  | IRB          | Institutional Review Board                                  |
| AML   | Acute myeloid leukemia                         | LTB          | Low transfusion burden                                      |
| ALT   | Alanine aminotransferase                       | MDS          | Myelodysplastic syndrome                                    |
| AST   | Aspartate aminotransferase                     | MCV          | Mean corpuscular volume                                     |
| BM    | Bone marrow                                    | NCI          | National Cancer Institute                                   |
| BRCP  | Breast cancer resistance protein               | NGS          | Next Generation Sequencing                                  |
| CBC   | Complete blood count                           | NTD          | Nontransfused   |
| CD    | Cluster of differentiation                     | OnCore       | OnCore Enterprise Research System                           |
| CFR   | Code of Federal Regulations                    | OS           | Overall survival  |
| CMML  | Chronic Myelomonocytic Leukemia                | OAT          | Organic anion transporter                                   |
| CR    | Complete response                              | OATP         | organic anion transporter peptide                           |
| CRF   | Case report / record form                      | OCT          | organic cation transporter                                  |
| CTCAE | Common Terminology Criteria for Adverse Events | PD           | Progressive disease   |
| CYP   | Cytochrome P450                                | PCR          | Polymerase chain reaction                                   |
| DLT   | Dose-limiting toxicity                         | PLT          | Platelet  |
| DSMB  | Data Safety Monitoring Board                   | REDCap       | Research Electronic Data Capture                            |
| DSMC  | Data Safety Monitoring Committee               | RBC          | Red blood cells   |
| ECOG  | Eastern Cooperative Oncology Group             | RDW          | Red cell distribution and width                             |
| FDA   | Food and Drug Administration                   | RR           | Response rate   |
| GCP   | Good Clinical Practice                         | R/R          | Relapsed/Refractory   |
| HCT   | Hematopoietic cell transplant                  | SAE          | Serious adverse event                                       |
| Hgb   | Hemoglobin                                     | SIN          | Subject identification number                               |
| HI-E  | Hematological improvement - erythroid          | SRC          | Scientific Review Committee                                 |
| HI-N  | Hematological improvement - neutrophil         | Stanford IRB | Administrative Panels on Human Subjects in Medical Research |
| HI-P  | Hematological improvement - platelet           | TGF          | transforming growth factor                                  |
| HIV   | Human immunodeficiency virus                   | TI           | Transfusion independence                                    |
| HTB   | High transfusion burden                        | TTR          | Time to response  |
| HMA   | Hypomethylating agent                          | UDP          | uridine diphosphate   |
| HSPC  | hematopoietic stem and progenitor cell         | UGT          | glucuronosyltransferase                                     |
| ICH   | Int'l Conference on Harmonization              | ULN          | Upper Limit of Normal                                       |
| ICMJE | Int'l Committee of Medical Journal Editors     | WBC          | White blood cell  |

# 1. INTRODUCTION

## 1.1. Study Rationale

Both malignant and non-malignant causes of anemia are associated with substantial morbidity, high medical costs, and significant limitations in quality of life<sup>1</sup>. Chronic transfusion dependence is especially prevalent in patients with hematologic malignancies<sup>2</sup>. In addition to disease-directed treatments, a large percentage of patients will require supportive red blood cell (RBC) transfusions. Chronic transfusion dependence frequently results in secondary morbidities such as iron overload and transfusion-related reactions. Transfusion support may also be limited by lack of donor availability, especially in alloimmunized patients, and for patients with rare blood types<sup>1,2</sup>. Therefore, strategies that enhance endogenous erythropoiesis are urgently needed to decrease transfusion rates and improve quality of life in an already vulnerable population.

In the phase 1-2 clinical trial of enasidenib conducted in subjects with relapsed/refractory *IDH2*-mutated AML, the majority of subjects showed a decrease in their transfusion requirements or even became transfusion-independent with respect to red blood cells (RBC) and platelets<sup>3</sup>. Most strikingly, this phenomenon occurred in subjects with stable disease and appeared to be independent of *IDH2* mutation burden or serum 2-hydroxyglutarate (HG) levels. A similar result was subsequently reported for older subjects with newly-diagnosed *IDH2*-mutated AML in the subgroup analysis for the same clinical trial<sup>4</sup>. A BM biopsy from an enasidenib-treated subject has also demonstrated erythroid hyperplasia and increased erythroid differentiation<sup>5</sup>.

These important clinical observations prompted us to examine whether enasidenib can drive erythroid differentiation independent of *IDH2* mutation status.

## 1.2. Background

### 1.2.1. Overview of study intervention

This study will determine the safety, tolerability, and efficacy of enasidenib in improving anemia and decreasing transfusion needs in subjects with lower-risk MDS and non-proliferative CMML who are not on any other disease-directed therapy. After conducting baseline laboratory studies, subjects will begin self-administration of enasidenib everyday continuously through each 28-day cycle. Laboratory studies and bone marrow (BM) biopsies will be repeated at the indicated time points (see study schema) to assess response.

### 1.2.2. Mechanism(s) of Action for enasidenib

Enasidenib (*Idhfa*) is a first-in-class, selective, potent inhibitor of the neomorphic activity of *IDH2* mutant enzyme which is expressed in AML and other myeloid malignancies<sup>6</sup>. Mutant *IDH2* enzyme activity produces the oncometabolite, 2-HG. Pharmacology studies support enasidenib-mediated suppression of 2-HG, reduced abnormal histone hypermethylation, and restored myeloid differentiation<sup>6-8</sup>.

In more recent studies, enasidenib robustly increased erythropoiesis of both wildtype cord blood and BM-derived stem and progenitor cells (HSPC) in a concentration-dependent manner. This activity was independent of *IDH2* mutant activity and involved increased globin chain synthesis<sup>9</sup>.

### 1.2.3. Non-clinical Background

Enasidenib robustly increased erythropoiesis of both wildtype cord blood and BM-derived HSPCs in a concentration-dependent manner<sup>9</sup>. The erythropoietic activity was specific to enasidenib and occurred independently of mutant and wildtype *IDH2*, as well as the oncometabolite D-2-hydroxyglutarate (D-2HG). Effects of enasidenib on human HSPCs was mediated by protoporphyrin accumulation, driving heme production and erythroid differentiation in committed CD71+ HSPCs.

#### 1.2.3.1. Non-clinical and Clinical Pharmacokinetics

Preliminary analysis of pharmacokinetics (PK) data (as of 15 April 2016) from subjects with advanced hematologic malignancies in Study AG221-C-001 up to the 650 mg QD dose level demonstrated high plasma exposures, a long mean plasma half-life of enasidenib in humans (137 hours; data on file: clinical PK/pharmacodynamics study report of enasidenib-MPK-001), high drug accumulation after multiple doses, and relatively high PK variability in subjects (coefficient of variation [CV]% = ~40%). The median time to maximum plasma concentration ( $T_{max}$ ) ranged from approximately 1 to 48 hours when administered as a single dose on Day -3. Metabolite AGI-16903 mean plasma exposure is less than 10% of parent enasidenib mean plasma exposure. Preliminary analysis of pharmacodynamics data demonstrated that a daily dose of 100 mg QD suppressed 2-HG levels at Cycle 2 Day 1 in subjects with the *IDH2* R140 mutation (n = 66, median 92.8% inhibition [range 45.3% to 99.4%]) and in subjects with *IDH2* R172 mutation (n = 22, median 27.6% inhibition [range -233.7% to 93.8%]), showing on target activity in subjects.

##### 1.2.3.1.1. Major Route of Elimination

Enasidenib is metabolized by multiple cytochromes (CYPs) and uridine diphosphate (UDP)-glucuronosyltransferases (UGTs). Enasidenib is a direct inhibitor for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4, as well as UDP-glucuronosyltransferase (UGT) 1A1. The N-dealkylated metabolite, AGI-16903 is also an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6. Enasidenib is an inducer of CYP2B6 and CYP3A4. Preliminary results indicate that enasidenib increased 4 $\beta$ -hydroxycholesterol levels in subjects, indicating CYP3A induction. Enasidenib is not a substrate, but is a potent inhibitor of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). *In vitro*, enasidenib is an inhibitor of organic anion transporter (OAT) 1, organic anion transporting polypeptide (OATP) 1B1, OATP1B3, and organic cation transporter (OCT) 2, while AGI-16903 is an inhibitor of BCRP, OAT1, OAT3, OATP1B1, and OCT2. AGI-16903 is also a substrate of P-gp and BCRP. Clinical relevance of such *in vitro* interactions will be evaluated in humans as needed.

#### 1.2.3.2. Non-Clinical Pharmacology and Toxicology Studies

The toxicity profile of enasidenib has been evaluated in repeat dose oral toxicity studies of up to 90 days in Sprague-Dawley rats, and cynomolgus monkeys and for 7 days in beagle dogs; a battery of genetic toxicity assays including bacterial reverse mutation (Ames) and mammalian chromosomal aberration assays; *in vitro* and *in vivo* rat bone marrow micronucleus assay; embryo-fetal development toxicity studies in rats and rabbits; and *in vitro* phototoxicity assay using BALB/c-3T3 mouse fibroblasts in the presence of ultraviolet radiation. Dose-limiting toxicities in rats after 28 days of dosing were multifactorial and included gastrointestinal tract

atrophy and erosions, lymphoid atrophy, degeneration, and necrosis, BM hypocellularity and necrosis, skeletal muscle degeneration and necrosis, pancreas and kidney epithelial vacuolation, and adrenal cortical hemorrhage and necrosis. After 90 days of dosing, non-dosing limiting target organ toxicities in rats were limited to testes/epididymides and pancreas. In monkeys, ulcerative inflammation in the large intestine was determined as the dose-limiting toxicity. No changes in cardiovascular functions were noted in monkeys; however coronary artery lesion (periarteritis) was observed at the dose associated with dose-limiting toxicity indicated above. Findings in large intestine and coronary artery in monkeys were observed following 28 days of dosing. Additional target organ toxicities secondary to decreased body weight and food consumption in monkeys included femur/tibia (either dysplasia or decreased thickness of physis), BM (decreased cellularity), thymus (atrophy/involution), liver (cytoplasmic rarefaction) and pancreas (acinar cell degranulation). In dogs, there were enasidenib dose-related prolonged heart rate-corrected QT (QTc) intervals, hypotension and increased heart rate. These functional cardiovascular effects of enasidenib were the likely underlying causes of coronary artery lesions in dogs. Enasidenib was neither mutagenic nor clastogenic. Also, no phototoxicity potential of enasidenib was observed. Enasidenib treatment was associated with abortion in rats and rabbits. In rats, but not in rabbits, enasidenib treatment was associated with delayed fetal development (decreased fetal weight and skeletal ossification). Although no dedicated nonclinical study was conducted to assess enasidenib effects on fertility parameters, histopathologic changes in testes, epididymides, and ovaries in rats after repeated enasidenib dosing were suggestive of potential test article-related effects on male and female fertility.

#### 1.2.4. Clinical Experience

Clinical assessment of enasidenib is largely based on Study AG221-C-001, an ongoing, single-arm, phase 1-2 study that evaluates the safety and efficacy of enasidenib in subjects with advanced hematologic malignancies with an *IDH2* mutation<sup>7</sup>.

The enasidenib study AG221-C-001 was completed with 345 subjects with an *IDH2* mutation (who received at least 1 dose of the study drug), including 281 subjects with relapsed or refractory (R/R) AML, 214 of whom received enasidenib treatment with a total daily dose of 100 mg, 38 subjects with previously untreated AML, and 17 subjects with myelodysplastic syndromes (MDS). The mean duration of exposure was 7.1 months in the overall population.

As of 01 Jul 2017, a total of 344 (99.7%) subjects experienced at least 1 treatment emergent adverse event (TEAE), and for 284 (82.3%) of these subjects, at least 1 TEAE was suspected by the investigator to be related to enasidenib. Overall, 306 (88.7%) subjects had a TEAE that was Grade 3 or 4 in severity, 148 (42.9%) subjects had a treatment-related TEAE that was Grade 3 or 4 in severity, 276 (80.0%) subjects had a treatment emergent serious adverse event (TESAE), and 65 (18.8%) subjects had a TEAE leading to discontinuation. No meaningful differences in nature, incidence, or severity of the adverse events (AEs) have been observed between subjects with relapsed or refractory AML, previously-untreated AML, or MDS.

#### 1.2.5. Importance of the Clinical Trial

Determination of enasidenib to be an effective pro-erythropoietic agent could greatly improve an unmet need in multiple myeloid malignancies such as MDS and CMML. In addition, it may

open up new avenues of research in a new class of small molecules capable of increasing heme synthesis.

### **1.3. Potential Risks and Benefits**

#### **1.3.1. Known Potential Risks of Study Drug Enasidenib**

As of 1 July 2017, a total of 344 (99.7%) subjects experienced at least 1 treatment emergent adverse event (TEAE), and for 284 (82.3%) of these subjects, at least 1 TEAE was suspected by the investigator to be related to enasidenib. Overall, 306 (88.7%) subjects had a TEAE that was Grade 3 or 4 in severity, 148 (42.9%) subjects had a treatment-related TEAE that was Grade 3 or 4 in severity, 276 (80.0%) subjects had a treatment emergent serious adverse event (TESAE), and 65 (18.8%) subjects had a TEAE leading to discontinuation. No meaningful differences in nature, incidence, or severity of the adverse events (AEs) have been observed between subjects with relapsed or refractory AML, previously-untreated AML, or MDS.

The following AEs were determined to be adverse drug reactions to enasidenib: gastrointestinal (GI) events (nausea (49.8%), diarrhea (43.1%), and vomiting (34.9%) and associated decreased appetite (33.5%) and dysgeusia, increased blood bilirubin (32.7%), differentiation syndrome, leukocytosis (23.1%), and tumor lysis syndrome (3.8%).

Other commonly-reported TEAEs were disorders characteristic for subjects with hematologic malignancies: blood and lymphatic system disorders, including anemia (31.6%) and febrile neutropenia (30.7%); respiratory disorders, including dyspnea (32.2%) and cough (30.7%); infections, including pneumonia (21.7%); as well as general disorders, including fatigue (42.6%), peripheral edema (29.0%), and pyrexia (29.0%), and metabolic disorders, including hypokalemia (27.0%).

Thrombocytopenia, neutropenia, anemia, febrile neutropenia, and infections are commonly reported in subjects with AML and other hematologic malignancies, as could be expected in this population. Data available to date do not suggest a myelosuppressive effect associated with enasidenib treatment. Nonclinical data do not indicate myelosuppression with enasidenib, and laboratory data show that treatment with enasidenib did not lead to reduction in the blood cell counts.

#### **1.3.2. Known Potential Risks of Study Procedures**

Procedures associated with the study include phlebotomy and BM biopsy. Known risks related to phlebotomy and BM biopsy are the same and include: pain, redness, bleeding and infection of the procedure site.

#### **1.3.3. Known Potential Benefits of Enasidenib**

- Reduced the level of the oncometabolite serum 2-HG levels in subjects with *IDH2*-mutant AML.
- In *IDH2*-mutated AML, elicited an overall response rate of 30.8%.
- Decreased transfusion requirements of AML subjects and smaller number of MDS subjects harboring an *IDH2* mutation, including approximately 40% who became transfusion independent.

- Decreased platelet transfusion requirements of AML and MDS subjects harboring an *IDH2* mutation.

## 2. STUDY DESIGN, OBJECTIVES, AND OUTCOMES

### 2.1. Study Design

#### 2.1.1. Overall Design

This is a phase 1b/2, open-label, single arm study to evaluate enasidenib, as a safe and effective therapy to improve anemia in subjects with lower-risk MDS and nonproliferative CMML.

#### 2.1.2. Primary Purpose of the Study

**Treatment:** to determine if enasidenib is an effective therapy to improve anemia in subjects with lower-risk MDS and nonproliferative CMML.

**Basic Science:** to characterize the mechanism of action of enasidenib and evaluate biochemical or clinical biomarkers which predict response.

#### 2.1.3. Study Cohorts

- This study includes a single arm for both the phase 1b and phase 2 portion. The phase 2 portion will include 2 disease specific cohorts receiving identical treatment.
- The phase 1b portion will determine the tolerability and safety of enasidenib using an abbreviated 3 x 3 dose escalation schema at 2 dose levels (100 and 200 mg daily). Lower-risk MDS and nonproliferative CMML subjects will be screened and appropriate subjects enrolled consecutively at during phase 1b.
- **Dose Level 1 will be 100 mg daily, and may be identified as Cohort A (may include patients from Cohorts 1 and 2).**
  - If no dose-limiting toxicity (DLT) is observed in the first 3 Dose Level 1 subjects, the dose will escalate to 200 mg daily (Dose Level 2).
  - If 1 DLT is observed in the first 3 subjects at Dose Level 1, 3 more subjects will be enrolled. If no DLTs are observed in these 3 additional subjects (total of 6 Dose Level 1 subjects), the dose will escalate to Dose Level 2 (200 mg daily).
  - If  $\geq 2$  DLTs are observed in up to 6 Dose Level 1 subjects, the recommended phase 2 dose (RP2D) for the phase 2 portion of the study will be Dose Level 1 (100 mg daily, the dose described in the current FDA-approved package insert).
- **Dose Level 2 will be 200 mg daily, and may be identified as Cohort B (may include patients from Cohorts 1 and 2).**
  - For Dose Level 2, if no DLT is observed in the first 3 subjects, 200 mg daily will be the RP2D.
  - If 1 DLT is observed in the first 3 subjects, 3 more subjects will be enrolled at Dose Level 2. If no DLT is observed in these 3 additional subjects (total of 6 Dose Level 2 subjects), Dose Level 2 will be the RP2D.

- If  $\geq 2$  DLT is observed these 3 additional subjects, Dose Level 1 will be the RP2D. All evaluable subjects (Dose Levels 1 and 2) in the phase 1b portion will be included in the phase 2 analysis.
- The phase 2 portion of the study will include 2 disease cohorts receiving identical treatment. Cohort 1 will enroll subjects with lower-risk MDS and Cohort 2 will enroll subjects with nonproliferative CMML. Both cohorts will receive 100 mg QD dose during Cycle 1 which will be escalated to the established RP2D dose of enasidenib each cycle of treatment. Each cycle is 28 days in duration.
- The response criteria are specified below (Section 2.1.8). If a study subject has not met criteria as a responder within the first 6 months of treatment, the subject will be considered a nonresponder and exit the study.
- If the study subject is believed to be deriving clinical benefit on enasidenib by the end of 12 months on study protocol by the PI, the subject may continue treatment after discussion with the study sponsor.

#### 2.1.4. Scientific Justification for Study Design

- Enasidenib is a FDA-approved therapy for treatment of relapse and refractory AML with published real-world safety and tolerability data. This study aims to repurpose its use for subjects with myeloid malignancies without IDH2 mutations, and the phase 1b portion of the study is aimed to demonstrate safety and tolerability of enasidenib in IDH2 wildtype patient population.
- The 2 disease cohorts included on the study (lower-risk MDS and nonproliferative CMML) were chosen for having extreme unmet needs, with no or very limited existing options, to improve anemia.
- Thus, enasidenib's well-tolerated toxicity profile and availability as an once daily oral agent makes it an ideal candidate to repurpose as an erythropoietic agent.

#### 2.1.5. Treatment Assignment

This study is an open label study. Enrollment bias will be minimized by consecutive screening of all subjects who fit the diagnostic criteria seen at the Stanford Cancer Institute. Screen failures will have specific documentation of what constituted as screen failures by the study exclusion criteria.

#### 2.1.6. Justification for Dose(s)

Enasidenib is a FDA-approved drug to be used at 100 mg daily for the treatment of AML subjects with relapsed or refractory AML with *IDH2* mutations. Daily dosing from 50 mg to 650 mg has been demonstrated to be safe and tolerable in Study AG221-C-001 (see Section 1.2.3.1). The doses chosen in this study are based on this prior experience which determined this dosing range to be safe and well-tolerated. For the Phase 2, subjects will initially receive 100 mg dose which will be escalated to the established RP2D. Please also refer to Section 2.1.4. Scientific Justification for Study Design.

### 2.1.7. End of Study Definition

A study is considered completed when subjects are no longer being examined or the last subject's last study visit has occurred. A subject is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Events at Section 6.1 and 6.2.

## 2.2. Objectives

### 2.2.1. Primary Objectives

The primary objective for the study is to determine the efficacy (response rate) of enasidenib in improving anemia and decreasing RBC transfusion dependence. Study subjects on each arm of the study will be divided into 3 cohorts [nontransfused (NTD), low transfusion burden (LTB) and high transfusion burden (HTB)] based on transfusion needs, as partially defined by the modified 2018 IWG recommendations<sup>10</sup>:

|     | No. of RBC Units Transfused | Time Period (weeks) |
|-----|-----------------------------|---------------------|
| NTD | 0                           | 16                  |
| LTB | 3 to 7                      | 16                  |
| HTB | $\geq 8$                    | 16                  |
|     | or $\geq 4$                 | 8                   |

The proportion of study subjects in each arm of the study will be determined as the response rate. The primary efficacy endpoint is to determine the proportional of study subjects will be achieving modified IWG 2018-defined hematological improvement-erythroid (HI-E), defined as follow:

|     | 2018 IWG HI-E criteria   | Time Period (weeks) |
|-----|--|---------------------|
| NTD | $\geq 2$ consecutive Hb measurements $\geq 1.5$ g/dL for a period of minimum 8 wk in an observation period of 16 to 24 wk compared to the lowest mean of 2 Hb measurements | 8                   |
| LTD | 0 units of RBC transfusions  | 8                   |
| HTB | $\geq 4$ unit reduction of RBC transfusions; or  | 8                   |
|     | $\geq 50\%$ reduction in units of RBC transfusion  | 8                   |

### 2.2.2. Secondary Objectives

- To determine the safety and tolerability of enasidenib in subjects without IDH2 mutations.
- To determine the duration of HI-E.

- To determine the time to HI-E.
- To determine the proportion of subjects who achieve a response defined by the modified 2018 IWG criteria in improvement of platelet count (HI-P, see Section 10.2.2.4).
- To determine the proportion of subjects who achieve a response defined by the modified 2018 IWG criteria in improvement of platelet count (HI-N, see Section 10.2.2.5).
- To determine the frequency of RBC transfusions
- To determine the proportion of study subjects who are transfusion dependent (LTD and HTB) achieving RBC transfusion independence (RBC-TI) for 8 weeks or longer

## **2.3. ClinicalTrials.gov Registration, Outcomes, and Results**

### **2.3.1. Data Sharing Statement**

Pursuant to the International Committee of Medical Journal Editors (ICMJE), the following statement, regarding sharing of individual subject data (i.e., subject-level data) generated by interventional clinical trials, is provided.

It is not planned that individual subject data, including data dictionaries, will be made publicly available. Individual subject study data judged by the investigator to be pertinent to a subject's understanding of their medical condition and treatment options will be shared with that subject. Otherwise and as such, details of what, or when, or by what mechanism, data and/or documents will be shared, who would share such data, or for what purposes or analyses, are not available or not applicable.

Although not individual subject data, pursuant to the requirements of [42CFR§11.48\(a\)\(5\)](#) (if applicable), the final IRB-approved protocol document with statistical analysis will be made available in the ClinicalTrials.gov results record.

### **2.3.2. Outcome Measures for ClinicalTrials.gov Results Reporting**

#### **2.3.2.1. Primary Outcome (Outcome 1)**

- **Title:** Clinical Response: Hematological Improvement - Erythroid (HI-E)
- **Description:** Clinical response was assessed as the number of participants achieving a hematological improvement - erythroid (HI-E). Participants will be characterized and

stratified as nontransfused (NTD), low-transfusion burden (LTB) and high-transfusion burden (HTB), with response defined as follows.

- NTD =  $\geq 2$  consecutive Hb measurements  $\geq 1.5$  g/dL for a period of minimum 8 week in an observation period of 16 to 24 week compared to the lowest mean of 2 Hb measurements
- LTB = 0 units of RBC transfusions
- HTB =  $\geq 4$  unit or  $\geq 50\%$  reduction in RBC transfusions

The outcome will be reported as the number of participants by dose level (Cohort A or Cohort B) that achieve the response, a number without dispersion.

- **Time Frame:** 16 weeks
- **Completion of Primary Outcome:** The study is expected to reach Primary Completion by 31 January 2024 (6 months after enrollment of last subject).

#### 2.3.2.2. Secondary Outcomes

##### Outcome 2

- **Title:** Related Adverse Events
- **Description:** Toxicity will be assessed as the number of related non-serious adverse events and related serious adverse events (SAEs) reported by dose level (Cohort A or Cohort B) for the 12-cycle treatment period plus follow-up. The outcome will be reported as numbers without dispersion.
- **Time Frame:** 12 months.

##### Outcome 3

- **Title:** Time to Hematological Improvement - Erythroid (HI-E)
- **Description:** Time to hematological improvement - erythroid (HI-E) will be assessed as the time from first dose of enasidenib to the first observed hemoglobin response. Participants will be characterized and stratified as nontransfused (NTD), low-transfusion burden (LTB) and high-transfusion burden (HTB), with response defined as follows.
  - NTD =  $\geq 2$  consecutive Hb measurements  $\geq 1.5$  g/dL for a period of minimum 8 weeks in an observation period of 16 to 24 weeks compared to the lowest mean of 2 Hb measurements
  - LTB = 0 units of RBC transfusions
  - HTB =  $\geq 4$  unit or  $\geq 50\%$  reduction in RBC transfusionsThe outcome will be reported as the number of participants by dose level (Cohort A or Cohort B) that achieve the response, a number without dispersion.
- **Time Frame:** 16 weeks.

**Outcome 4**

- **Title:** Duration of Hematological Improvement - Erythroid (HI-E)
- **Description:** Duration of Hematological Improvement - Erythroid (HI-E) will be assessed as the time from recorded response to loss of response. Participants will be characterized and stratified as nontransfused (NTD), low-transfusion burden (LTB) and high-transfusion burden (HTB), with response defined as follows.
  - NTD =  $\geq 2$  consecutive Hb measurements  $\geq 1.5$  g/dL for a period of minimum 8 weeks in an observation period of 16 to 24 weeks compared to the lowest mean of 2 Hb measurements
  - LTB = 0 units of RBC transfusions
  - HTB =  $\geq 4$  unit or  $\geq 50\%$  reduction in RBC transfusionsThe outcome will be reported as the number of participants by dose level (Cohort A or Cohort B) that achieve the response, a number without dispersion.
- **Time Frame:** 16 weeks.

**Outcome 5**

- **Title:** Clinical Response: Hematological Improvement - Platelets (HI-P)
- **Description:** Clinical response for platelets was assessed as the number of participants achieving a hematological improvement - platelets (HI-P). Participants will be characterized and stratified as platelets  $<$  or  $\geq 20 \times 10^9/L$ , with response defined as follows.
  - $< 20 \times 10^9/L$  = increase in platelets from  $< 20 \times 10^9/L$  to  $> 20 \times 10^9/L$  AND by  $\geq 100\%$
  - $\geq 20 \times 10^9/L$  = absolute increase in platelets of  $30 \times 10^9/L$The outcome will be reported as the number of participants by dose level (Cohort A or Cohort B) that achieve the response, a number without dispersion.
- **Time Frame:** 8 weeks

**Outcome 6**

- **Title:** Clinical Response: Hematological Improvement - Neutrophils (HI-N)
- **Description:** Clinical response for neutrophils was assessed as the number of participants achieving a hematological improvement - neutrophils (HI-N). Response defined as an absolute increase in neutrophils  $> 0.5 \times 10^9/L$  that is also an increase of  $\geq 100\%$ .  
The outcome will be reported as the number of participants by dose level (Cohort A or Cohort B) that achieve the response, a number without dispersion.
- **Time Frame:** 8 weeks

**Outcome 7**

- **Title:** Red Blood Cell (RBC) transfusion independence (RBC-TI)
- **Description:** Clinical response for red blood cells was assessed as the number of participants who were transfusion-dependent that achieve red blood cell (RBC) transfusion independence (RBC-TI) for 8 weeks or longer. The outcome will be reported as the number of participants by dose level (Cohort A or Cohort B) that achieve the response, a number without dispersion.
- **Time Frame:** 12 months

**3. SUBJECT SELECTION****3.1. Eligibility Criteria and Participant Eligibility Checklist**

Inclusion and Exclusion Criteria are provided on the Eligibility Checklist which may be extracted from this document for use in screening potential subjects.

The Participant Eligibility Checklist must be completed in its entirety for each subject prior to registration (see Section 3.4 Registration / Enrollment). The completed, signed, and dated checklist is retained in the subject's record. Screening results will be collectively documented on the Study Participant Log (see references in Appendix A).

## Participant Eligibility Checklist

### I. Protocol Information

|                         |  |
|-------------------------|--|
| Protocol Title:         | A Phase 1b/2, Single Center, Open-Label, Safety and Efficacy Study to Improve Anemia and Decrease Transfusion Dependency in Subjects on Enasidenib with Low-risk Myelodysplastic Syndrome and Non-proliferative Chronic Myelomonocytic Leukemia without an IDH2 Mutation |
| OnCore number:          | HEM0056  |
| Principal Investigator: | Tian Yi Zhang, MD  |

### II. Subject Information

|                           |                               |                                 |
|---------------------------|-------------------------------|---------------------------------|
| Subject name / Unique ID: | /                             |                                 |
| Gender                    | <input type="checkbox"/> Male | <input type="checkbox"/> Female |

### III. Eligibility Criteria

#### 3.1.1. Inclusion Criteria

| Prospective Subject Must Meet ALL these Inclusion Criteria to be Eligible   | Yes                      | No                       | Supporting Documentation * |
|---|--------------------------|--------------------------|----------------------------|
| 1. Documented diagnosis of:<br>1) MDS according to WHO/FAB classification that meets IRSS-R classification of low or intermediate risk disease; and a diagnosed as de novo or secondary MDS (MDS-RS eligible if refractory to or declined luspatercept therapy).<br><b>OR</b><br>2) Dysplastic (nonproliferative) CMML with WBC < 13.0/microL | <input type="checkbox"/> | <input type="checkbox"/> |                            |
| 2. No disease-modifying therapy (HMA, hydrea) within 2 months of starting study   | <input type="checkbox"/> | <input type="checkbox"/> |                            |
| 3. Age $\geq$ 18 years of age   | <input type="checkbox"/> | <input type="checkbox"/> |                            |
| 4. ECOG $\leq$ 3  | <input type="checkbox"/> | <input type="checkbox"/> |                            |

| <b>Prospective Subject Must Meet ALL these Inclusion Criteria to be Eligible</b>  | <b>Yes</b>               | <b>No</b>                | <b>Supporting Documentation *</b> |
|---|--------------------------|--------------------------|-----------------------------------|
| 5. Negative for <i>IDH2</i> mutation by NGS   | <input type="checkbox"/> | <input type="checkbox"/> |                                   |
| 6. Meets AT LEAST ONE of the following hematologic parameters:<br>a) Has symptomatic anemia defined as hemoglobin < 10.5 g/dL with any of the following. <ul style="list-style-type: none"> <li>○ Tachypnea</li> <li>○ Shortness of breath</li> <li>○ Fatigue</li> <li>○ Malaise</li> <li>○ Worsening of cardiovascular function</li> <li>○ Asthenia</li> <li>○ Dyspnea on exertion</li> <li>○ Angina</li> <li>○ Other subject symptoms the subject reports as being associated with being anemic.</li> </ul> b) Thrombocytopenic with <100 K/uL platelets<br>c) Absolute neutrophil count <1.50 K/uL | <input type="checkbox"/> | <input type="checkbox"/> |                                   |
| 7. Stated willingness to comply with all study procedures and availability for the duration of the study  | <input type="checkbox"/> | <input type="checkbox"/> |                                   |
| 8. Ability to take oral medication and be willing to adhere to the medication regimen.  | <input type="checkbox"/> | <input type="checkbox"/> |                                   |
| 9. Females of reproductive potential need to either commit to true abstinence from heterosexual contact or agree to use, and be able to comply with highly effective contraception without interruption, 28 days prior to starting enasidenib, during the study therapy, and for 30 days after last dose of enasidenib.   | <input type="checkbox"/> | <input type="checkbox"/> |                                   |
| 10. For males of reproductive potential: agreement to use of condoms  | <input type="checkbox"/> | <input type="checkbox"/> |                                   |

| <b>Prospective Subject Must Meet ALL these Inclusion Criteria to be Eligible</b>   | <b>Yes</b>               | <b>No</b>                | <b>Supporting Documentation *</b> |
|--|--------------------------|--------------------------|-----------------------------------|
| 11. Adequate organ function defined as: <ul style="list-style-type: none"> <li>Hepatic function: total bilirubin <math>\leq 1.5 \times</math> ULN (unless attributable to Gilbert's disease), AST or ALT <math>\leq 3 \times</math> ULN</li> <li>Renal function: creatinine clearance <math>\geq 30</math> mL/minute, calculated by Cockcroft-Gault formula</li> </ul> | <input type="checkbox"/> | <input type="checkbox"/> |                                   |
| 12. Ability to understand and the willingness to sign the IRB-approved informed consent document.  | <input type="checkbox"/> | <input type="checkbox"/> |                                   |
| 13. Women of childbearing potential must have negative urine or serum pregnancy test   | <input type="checkbox"/> | <input type="checkbox"/> |                                   |

### 3.1.2. Exclusion Criteria

| <b>Prospective Subjects Must <u>NOT</u> Meet ANY of These Exclusion Criteria</b>   | <b>Yes</b>               | <b>No</b>                | <b>Supporting Documentation *</b> |
|--|--------------------------|--------------------------|-----------------------------------|
| 1. Less than 3 months of life expectancy   | <input type="checkbox"/> | <input type="checkbox"/> |                                   |
| 2. Significant cardiac disease (NYHA Class IV congestive heart failure, or unstable angina or myocardial infarction within the last 6 months   | <input type="checkbox"/> | <input type="checkbox"/> |                                   |
| 3. Harbor <i>IDH2</i> somatic mutations by NGS   | <input type="checkbox"/> | <input type="checkbox"/> |                                   |
| 4. Any uncontrolled bacterial, fungal, viral or other infection.   | <input type="checkbox"/> | <input type="checkbox"/> |                                   |
| 5. No known HIV+ or active hepatitis B or C infection, defined as positive viral load for HBV or HCV or a positive surface antigen (HBsAg) test for hepatitis B.   | <input type="checkbox"/> | <input type="checkbox"/> |                                   |
| 6. Have other causes of anemia: deficiencies in iron, B12, folate; nutritional deficiencies related to gastric surgery, anorexia nervosa, excessive zinc supplementation; gastrointestinal bleed.<br>If nutritional deficiencies can be corrected, potential subject can be rescreened and enrolled if nutritionally replete and still meets eligibility criteria. | <input type="checkbox"/> | <input type="checkbox"/> |                                   |

| Prospective Subjects Must <b><u>NOT</u></b> Meet <b><u>ANY</u></b> of These Exclusion Criteria   | Yes                      | No                       | Supporting Documentation * |
|--|--------------------------|--------------------------|----------------------------|
| 7. Any other medical history, including laboratory results, deemed by the Principal Investigator likely to interfere with their participation in the study, or to interfere with the interpretation of the results | <input type="checkbox"/> | <input type="checkbox"/> |                            |
| 8. Pregnant or breast feeding  | <input type="checkbox"/> | <input type="checkbox"/> |                            |

\* All subject files must include supporting documentation to confirm subject eligibility.

#### V. Statement of Eligibility

By signing this form of this trial I verify that this subject is:

☐ eligible for participation in the study      ☐ ineligible for participation in the study

|                                     |       |
|-------------------------------------|-------|
| Study Coordinator printed name:     | Date: |
| Signature:                          |       |
|                                     |       |
| Investigator printed name:          | Date: |
| Signature:                          |       |
|                                     |       |
| Triple-check reviewer printed name: | Date: |
| Signature:                          |       |
|                                     |       |

### **3.1.3. Lifestyle Considerations**

During this study, subjects are asked to maintain a reasonably active life style with consistency and healthy diet. It is recommended that subject take enasidenib at the same time every day but without restriction in relationship to meal times.

### **3.1.4. Screen Failures**

Subjects consent to participate in the clinical trial, but who do not meet 1 or more Eligibility Criteria during the screening procedures are considered Screen Failures. Screen Failures will not be considered enrolled subjects, although they will be tracked on the Screening Log (with reason for ineligibility) and in the OnCore study management system.

Screen failures, because of a reversible process (infections, change in ECOG, etc) may be rescreened and assigned the same sequence number and OnCore subject identifier as for the initial screening.

## **3.2. Recruitment and Retention Procedures**

### **3.2.1. Recruitment**

Potential subjects may be identified by the following methods:

- Review of the medical records of new or existing hematology subjects for potential subjects who meet eligibility criteria.
- Internal referral by Stanford physicians. Subject must consent to being contacted by study staff by referring physicians. A study investigator and/or study coordinator will discuss the study with the subject during a subject visit or with a visit scheduled for the purpose of recruitment to the study.
- Self-referral by subject after viewing study listing on ClinicalTrials.gov or the Stanford Clinical Trials website.
- Referral by external physicians
- Trial posting with ANCO (Association of Northern California Oncologists)
- All male and female subjects will be offered the same options to participate in this study. Base on the local population of the study site, we anticipate 23 female and 22 male study subjects. Based on the 2010 US Census Bureau data for the Bay Area, we anticipate 26 (58%) subjects of Caucasian ethnicity, 8 subjects of Hispanic ethnicity, 3 subjects of Black ethnicity and 8 subjects of Asian ethnicity. Community outreach to Eastbay community providers will help with recruitment of underserved and under-represented populations.

## **3.3. Informed Consent Process**

Study will provide written informed consent prior to the conduct of any study-specific procedures in accordance with institutional policies.

- Informed consent can be provided in the native language of the subject on request. An audio or video translator can be made available if requested by subject.

- Remote video consenting can be conducted if appropriate according to the local county guidelines for COVID19 directed social distancing. Electronic signatures will be accepted.

### **3.4. Registration and Enrollment**

#### **3.4.1. Subject Registration Procedures**

All subjects who provide informed consent for this study will be registered in the Stanford OnCore Enterprise Research System database within 5 days of the date of consent, regardless of the outcome of any eligibility screening. Subject identification numbers will be sequentially assigned for the entire study. The information necessary to register a subject for the study is defined below.

- A copy of the Subject Eligibility Checklist indicating that all criteria are met.  
The 3<sup>rd</sup> signature for eligibility confirmation will be provided by the Stanford study team.

To register study subjects, the study site will provide the above information to the designated Stanford representative(s) to obtain authorization. The Stanford representative(s) will process the information and register study subjects in OnCore.

Veronica de Santiago  
650-725-4047  
[desantv1@stanford.edu](mailto:desantv1@stanford.edu)

Woo In (Yustina) Cho  
650-721-2443  
[wooin@stanford.edu](mailto:wooin@stanford.edu)

The Stanford study team, at the time of subject registration in OnCore, will provide a 3<sup>rd</sup> signature on the Eligibility Checklist that confirms eligibility. Once confirmed by Stanford and consented, the subject will be promptly registered in OnCore (within no more than 5 business days).

#### **3.4.2. Subject Enrollment Procedures**

For this study, a subject is enrolled on the study when registered per Section 3.4.1; has met eligibility per the screening procedures; and has been otherwise accepted into the study.

## **4. STUDY INTERVENTION**

### **4.1. Investigational Drug**

#### **4.1.1. Name(s)**

Enasidenib (Idhifa, AG-221)

#### **4.1.2. Dose and Administration**

In phase 1b portion of the study, subjects will participate dose escalation with a starting dose of 100 mg. Enasidenib will be self-administered orally and daily.

#### 4.1.3. Regulatory Status of Enasidenib

Enasidenib is approved for marketing in the United States as Idhifa, for the indication of relapsed and refractory AML harboring an *IDH2* mutation. The indication described in this study is considered investigational relative to the approved indications. Regulatory authorization to conduct this study is pursuant to the IND submitted by Tian Yi Zhang, MD.

#### Enasidenib Preparation, Handling, Storage, and Accountability

##### 4.1.3.1. Acquisition and Accountability

Enasidenib will be delivered to and received by Stanford Investigational Drug Service (IDS) for storage. Study staff will be in charge of picking up study drug to dispense to study subjects. Expired or return of unused products will be stored by IDS and returned to the Sponsor via FedEx.

##### 4.1.3.2. Formulation, Appearance, Packaging, and Labeling

Enasidenib tablets are available in 50, 100, 150, and 200 mg free-base equivalent strength tablets for oral administration. Each tablet is formulated using excipients that are generally regarded as safe and are used in marketed drug products. Celgene Corporation will supply 50 mg and 100 mg tablets.

All tablets will be packaged in high density polyethylene (HDPE) bottles with a desiccant (silica gel) canister and child resistant closures with heat induction seal. All tablets should be swallowed whole, and should not be broken or chewed.

Bottles of Enasidenib tablets must be stored according to the package label. The storage area should be secure and have limited access. Enasidenib tablets will be monitored by the Sponsor for stability for the duration of the study.

Enasidenib tablets will be supplied in high density polyethylene (HDPE) bottles with a desiccant (silica gel) canister, a polyester coil, and child resistant closures with heat induction seal. Packaging and labeling will be prepared to meet all regulatory requirements.

##### 4.1.3.3. Storage and Stability

Bottles of Enasidenib tablets must be stored according to the FDA package label, which include storage at room temperature (from 20°C to 25°C) and in the original bottle. All study drug products must be stored in a secure, limited-access location and may be dispensed only by the Investigator or by a member of the staff specifically authorized by the Investigator.

##### 4.1.3.4. Preparation

All tablets are packaged in sealed bottles and dispensed to subject to be self-administered as a whole tablet. No special preparation is required by study staff or study subjects. Investigational Agent Supply

Enasidenib will be provided by Celgene Corporation. Responsible contact:

|         |  |
|---------|--|
| Name:   | Celgene Corporation                        |
| Address | 86 Morris Avenue, Summit, New Jersey 07901 |
| Phone:  | 718-938-1201                               |

#### 4.1.3.5. Investigational Agent Ordering

The investigational drug will be ordered by email to responsible staff at the investigator site below.

The mailing address and local contact phone number for the drug supplier contact facility is:

|         |  |
|---------|--|
| Name    | Celgene Corporation                        |
| Address | 86 Morris Avenue, Summit, New Jersey 07901 |
| Phone:  | 718-938-1201                               |

The investigational agent, enasidenib, will be delivered to and managed by the Stanford Investigative Drug Service (IDS) (the Stanford investigational pharmacy).

## 5. TREATMENT PLAN

### 5.1. Treatment Assignment

A unique study subject identifier will be assigned by the Principal Investigator for all eligible study subjects. All study subjects in this single arm study, including two disease cohorts, will be assigned to the same treatment.

### 5.2. Treatment Dose

The phase 1b portion will use an abbreviated 3 x 3 dose-escalation schema. Dose Level 1 will be 100 mg daily. If no DLT is observed in the first 3 subjects, the dose will escalate to 200 mg daily (Dose Level 2). If, in the first 3 subjects treated at Dose Level 1, 1 DLT is observed, 3 more Dose Level 1 subjects will be enrolled. If > 1 DLT is found at Dose Level 1, the recommended phase 2 dose (RP2D) will be 100 mg daily (Dose Level 1). For Dose Level 2, if no DLTs is observed in the first 3 subjects treated at Dose Level 2, 200 mg daily will be the RP2D. If 1 DLT is found, 3 more subjects will be enrolled. If no DLTs are observed in these 3 additional subjects, Dose Level 2 will be the RP2D. If > 1 DLT is observed at Dose Level 2 in the first 6 subjects, Dose Level 1 will be the RP2D.

In the phase 2 portion, Ph 2 cohorts will receive 100 mg in Cycle 1 followed by dose escalation to the established RP2D dose of enasidenib in future cycles as tolerated.

### 5.3. Treatment Schedule

All study subjects will receive daily dosing the study drug. All efforts should be made to administer enasidenib on all of the scheduled days of each 28-day treatment cycle. A dose missed earlier in a day can be made up later that day as long as it is taken as soon as possible on the same day. Any missed doses should not be taken beyond the last scheduled day of enasidenib administration, but should be returned by the subject for enasidenib accountability.

### 5.4. Treatment Duration

In subjects without disease progression or unacceptable toxicities, Enasidenib treatment is recommended for a minimum of 6 months to allow time for clinical responses. If clinical benefit is seen, treatment continuation will be permitted at the Principal Investigator's discretion and agreement from the sponsor, Celgene, to continue to provide the investigational agent.

## 5.5. Subject Medication Diary

Enasidenib is being self-administered. Each study subject will be given a medication diary to record parameters of daily administration of the investigational agent, including time taken and side effects. This medication diary will be reviewed at each clinic visit (see Section 6.1 Study Schedule) to ensure compliance by the study staff.

## 5.6. Dose Modifications and Dose-limiting Toxicities

5.6.1 Overall, Grade 3 to 4 related adverse events (toxicities) will result in a treatment pause/discontinuation until the toxicity decreases to Grade  $\leq 2$  or baseline. Dosing may be resumed with a 50% dose reduction from 200 mg QD to 100 mg QD, or 100 mg to 50 mg QD). Any subject who is unable to tolerate 50 mg QD of enasidenib should be discontinued from study treatment.

Dosing may be interrupted for toxicity or nontoxicity related reasons deemed appropriate by the PI, such as reasons involving other underlying comorbidities or due to personal reasons of the subject. Pauses or delays in enasidenib for toxicity or nontoxicity reasons deemed appropriate by PI is allowed as long as dose modifications are followed per protocol (5.6.2). If 28 days or more of study drug administration interruption have occurred and patient is to restart the study drug, the patient's schedule will reset to the CxD1 subsequent to nearest completed cycle.

The DLT assessment period for each dose level is defined by any 28 days of continuous therapy at each dose level (100mg, 200mg). An evaluable subject is any subject that completes the DLT assessment period defined as above.

Any probably or definitely related AE will be considered a DLT unless the event can be attributed to a concurrent process, the underlying disease process (MDS or CMML), or concomitant medications by the PI.

Criteria for defining DLT are outlined in table below:

| Toxicity      | DLT Criterion  |
|---------------|--|
| Hematological | <p>Neutropenia</p> <ul style="list-style-type: none"><li>• Febrile, CTCAE Grade <math>\geq 3</math>.</li><li>• CTCAE Grade <math>\geq 3</math> which does not resolve with dose modifications per protocol (5.6.2)</li></ul> <p>Thrombocytopenia</p> <ul style="list-style-type: none"><li>• CTCAE Grade <math>\geq 3</math> which does not resolve with dose modifications per protocol (5.6.2)</li></ul> <p>Anemia</p> <ul style="list-style-type: none"><li>• CTCAE Grade <math>\geq 3</math> which does not resolve with dose modifications per protocol (5.6.2)</li></ul> |
| Nausea        | <ul style="list-style-type: none"><li>• CTCAE Grade <math>\geq 3</math> which does not resolve with dose modifications per protocol (5.6.2)</li></ul>  |

|                     |  |
|---------------------|--|
| Renal/genitourinary | CTCAE Grade $\geq 3$ which does not resolve with dose modifications per protocol (5.6.2) |
|---------------------|--|

5.6.2 Each toxicity will be addressed as specified below.

If treatment is modified during the course of the study and benefit is demonstrated with a reduced level of dose, then that dose level should be maintained during the subsequent treatment cycles that are given unless toxicity develops. If no benefit is demonstrated, however, enasidenib dose may be re-escalated back to the starting dose, provided that the starting dose is now tolerated without toxicity.

a. Cytopenias

| Event            | Grade  | Action   |
|------------------|--------|--|
| Neutropenia      | 3 to 4 | <ul style="list-style-type: none"> <li>Stop enasidenib until toxicity is <math>\leq</math> Grade 1 or has returned to baseline</li> <li>Administer prophylactic anti-infectives as clinically indicated</li> <li>Resume enasidenib with a 50% dose reduction. If toxicity does not recur, can re-escalate enasidenib dose</li> <li>If toxicity recurs after resuming enasidenib at a 50% dose reduction, decrease enasidenib to 25% of starting dose, if this dose is less than 50 mg daily, stop enasidenib permanently.</li> </ul> |
| Thrombocytopenia | 3 to 4 | <ul style="list-style-type: none"> <li>Stop enasidenib until toxicity is <math>\leq</math> Grade 1 or has returned to baseline</li> <li>Transfuse as clinically indicated or per standard of care</li> <li>Resume enasidenib with a 50% dose reduction. If toxicity does not recur, can re-escalate enasidenib dose</li> <li>If toxicity recurs after resuming enasidenib at a 50% dose reduction, decrease enasidenib to 25% of starting dose, if this dose is less than 50 mg daily, stop enasidenib permanently.</li> </ul>       |

b. QT Prolongation

- Subjects who experience prolongation of the heart rate-corrected QT interval, Fridericia's correction (QTcF) to  $> 480$  msec (Grade 2) while treated with enasidenib, should be promptly evaluated for causality of the QTc prolongation and managed according to the following guidelines:
  - Levels of electrolytes (potassium, calcium and magnesium) should be checked and supplementation given to correct any values outside the normal range.

- ii. Concomitant therapies should be reviewed and adjusted as appropriate for medication with known QT prolonging effects.
  - iii. If no other cause is identified and the investigator believes it is appropriate, particularly if the QTcF remains elevated (after above measures have been implemented, or as determined by the investigator), enasidenib treatment may be interrupted, and an ECG should be rechecked in approximately 1 week after the QTcF prolongation was first observed or more frequently as clinically indicated.
  - iv. If QTcF has recovered or improved and the investigator believes it is safe to do so, a re-challenge with enasidenib should be considered if held. ECGs should be conducted at least weekly (eg, at every scheduled visit) for 2 weeks following QTcF reduction  $\leq 480$  msec.
  - v. If Grade 2 (QTcF  $> 480$  and  $\leq 500$  msec), the dose of enasidenib may be reduced without interruption of dosing. The enasidenib dose may be re-escalated to the prior dose in  $\geq 14$  days after QTcF prolongation has decreased to  $\leq$  Grade 1.
  - vi. If this is the second occurrence of QT prolongation, administration of enasidenib should continue at a reduced dose (ie, the dose may not be re-escalated).
  - vii. If Grade 3 (QTcF  $> 500$  msec), hospitalization for continuous cardiac monitoring and evaluation by a cardiologist should both be considered. Dosing with enasidenib will be interrupted. If QTcF returns to within 30 msec of baseline or  $< 450$  msec within 14 days, treatment may be resumed at a reduced dose. The enasidenib dose cannot be re-escalated following dose reduction for Grade 3 QTcF prolongation unless the prolongation was associated with an electrolyte abnormality or concomitant medication.
  - viii. If Grade 4 (QTcF  $> 500$  msec or  $> 60$  msec change from baseline with torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia), subjects should be admitted to the hospital for continuous cardiac monitoring and discharged only after review by a cardiologist. Dosing with enasidenib should be permanently discontinued.
- c. IDH Differentiation Syndrome
- Subjects treated with enasidenib have experienced symptoms of differentiation syndrome, which can be fatal if not treated. Symptoms may include fever, dyspnea, acute respiratory distress, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, lymphadenopathy, bone pain, and hepatic or renal dysfunction. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.
  - If differentiation syndrome is suspected, initiate oral or intravenous corticosteroids (eg, dexamethasone 10 mg every 12 hours) and hemodynamic monitoring until improvement. Taper corticosteroids after resolution of symptoms. If severe pulmonary symptoms requiring intubation or ventilator support, and/or renal dysfunction persist for more than 48 hours after initiation of corticosteroids, interrupt enasidenib until signs and symptoms are no longer severe. Hospitalization for close observation and monitoring of subjects with pulmonary and/or renal manifestation is

recommended. Enasidenib can be resumed when signs and symptoms improve to Grade 2 or lower. Measurements of hemoglobin changes during steroid treatment will not be used until prednisone dose reaches 10mg daily or less.

- Further information on diagnosis and treatment of IDH differentiation syndrome can be found in the current version of IDH differentiation syndrome guidance documents.

d. Noninfectious Leukocytosis

- Subjects with hematologic malignancies treated with enasidenib may experience rapid myeloid cell proliferation, presenting as an increase in WBC count without evidence of infection or signs of IDH differentiation syndrome.
- If leukocytosis is identified during the screening period, standard of care work up (blood cultures, chest X-ray, urine analysis) will be conducted to rule out infectious etiologies.
- Blood counts should be assessed for noninfectious leukocytosis (defined as WBC greater than  $30 \times 10^9/L$ ) prior to the initiation of enasidenib and monitored at a minimum of every 2 weeks for at least the first 3 months during treatment.

e. Tumor Lysis Syndrome

- Subjects with hematologic malignancies treated with enasidenib may experience tumor lysis syndrome. Manage any abnormalities promptly. If enasidenib-related toxicity is Grade 3 or more, enasidenib dosing will be stopped until toxicity returns to  $\leq$  Grade 1 or below. Allopurinol will be prescribed as standard of care for any subject experiencing tumor lysis syndrome.

f. Gastrointestinal Disorders

- Appropriate monitoring and management of GI toxicities, including nausea, and vomiting will be done at every study visit.
- For Grade 2 or 1 nausea, subjects will be given with antiemetics to be taken prior to enasidenib (30 to 60 minutes), as per standard of care.
- For Grade 3 or 4 nausea, enasidenib will be dose reduced by 50% (from 200 mg to 100 mg, or from 100 mg to 50 mg) until nausea is  $\leq$  Grade 2. Antiemetics will also be given, as per standard of care.

g. Elevated Serum Bilirubin

- Hyperbilirubinemia is induced by enasidenib inhibition of UGT1A1, the enzyme responsible for the metabolism of bilirubin (a condition similar to Gilbert's syndrome).
- Subjects with Gilbert's syndrome genotype treated with enasidenib experienced earlier onset of bilirubin elevation following treatment initiation, as compared to subjects with normal UGT1A1 genotype. With continuing treatment, maximum severity of bilirubin elevation was similar in subjects with Gilbert's syndrome and subjects with normal UGT1A1 genotype.

- Subjects with increasing hyperbilirubinemia will undergo standard of care work up including but not limited to: fractionated evaluation of bilirubin, LDH, haptoglobin, abdominal ultrasound.
- Other causes of hyperbilirubinemia (such as hemolysis, choledocholithiasis) will be treated accordingly as per standard of care.
- Enasidenib dosing will not be stopped or modified for hyperbilirubinemia related to enasidenib as it does not cause pathophysiology.

### **5.7. Concomitant Medications, Procedures, and Supportive Care Guidelines**

All prior and concomitant medications (prescription and non-prescription) taken and treatment procedures received from the 4-week period (i.e., 28 days) prior to starting study treatment up to 28 days after the last study treatment must be recorded on the appropriate eCRF page(s). Particularly, all prior anti-cancer treatments should be recorded regardless of discontinuation date of treatment.

#### **Prohibited Concomitant Medications or Procedures**

Systemic anti-cancer therapy (excluding hydroxyurea) is not permitted during the course of study treatment, unless ECG monitoring can be done during the time of concurrent use. Use of the medications below with ECG monitoring will be documented in subject progress notes. Use of these medications will also be document as concomitant medications.

- Corticosteroids, with the exception of topical cutaneous, ophthalmic, nasal, and inhalational steroids. Note that short course steroid therapy will be permitted to treat co-morbidities such as IDH Differentiation Syndrome. Steroids may temporarily increase hemoglobin levels, however, sustained steroid use has never been necessary to treatment enasidnib associated differentiation syndrome. Hemoglobin increases after steroid use will not be used satisfy response criteria unless it has been sustained for at least 8 weeks from last day of steroid dose (the minimal duration of sustain responses according to the 2018 IWG HI-E).
- The following medications that are known to prolong QT interval: amiodarone, arsenic trioxide, astemizole, azithromycin, bepridil, chloroquine, chlorpromazine, cisapride, citalopram, clarithromycin, disopyramide, dofetilide, domperidone, droperidol, erythromycin, escitalopram, flecainide, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, moxifloxacin, pentamidine, pimozide, probucol, procainamide, quinidine, sevoflurane, sotalol, sparfloxacin, terfenadine, thioridazine, or vandetanib
- Sensitive CYP substrate medications that have a narrow therapeutic range: paclitaxel and docetaxel (CYP2C8), phenytoin (CYP2C9), S-mephenytoin (CYP2C19), thioridazine (CYP2D6), theophylline and tizanidine (CYP1A2)
- The BCRP transporter-sensitive substrate rosuvastatin
- Coadministration of CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2B6, CYP3A4, and CYP1A2 substrates other than those listed in Section 2.1.3 should be used only if medically necessary

- Coadministration of P-gp or BCRP substrates, OAT, OATP1B and OCT2 substrates other than those listed in Section 2.1.3 should be used only if medically necessary (refer to Appendix C for a list of transporter substrates)
- Given the solubility profile of enasidenib, the exposure can be much lower for subjects with elevated gastric pH. Thus antacids, H2 blockers, or proton pump inhibitors should be used only if medically necessary and with at least 4 hours of elapsed time after enasidenib administration.
- As an inhibitor of UGT1A1, enasidenib may slow down the metabolism of drugs that are substrates for UGT1A1, such as irinotecan, ezetimibe, raloxifene, and raltegravir. If this applies, especially in subjects who develop hyperbilirubinemia, it might be necessary to lower the doses for UGT1A1 substrates or switch to alternate therapies, or otherwise monitor for AEs associated with the respective products.

### **5.8. Criteria for Removing Subjects from Study Intervention and/or Study**

Subjects are free to withdraw consent and discontinue participation in a study at any time without prejudice to further treatment. The investigator may discontinue a subject from treatment intervention or the entire study for medical or administrative reasons. The following reasons may lead to discontinuation from the study intervention or the entire study.

- There is need for any treatment not allowed by the protocol
- Disease progression
- Toxicity precluding further study treatment
- Withdrawal of consent
- Study non-compliance
- Becomes pregnant
- Investigator discretion

If the subject elects to withdraw consent from further treatment with the study intervention, or is withdrawn by the investigator, it will be confirmed and documented if the subject will consent to continue to be followed per protocol, if applicable. The rationale for the investigator's decision to discontinue treatment will be clearly documented.

### **5.9. Duration of Follow-Up**

After completion of treatment (i.e., date of last treatment, subjects will be followed for 3 months after completion or removal from study or until death or until the start of a subsequent therapy, whichever occurs first. If a subject is removed from study due to unacceptable adverse event(s) or toxicity, that subject will be followed and safety data collected for 90 days after their last dose or resolution or stabilization of the adverse event, whichever is longest, to the extent possible. Subjects that personally withdraw will be requested to attend an end of treatment visit, or otherwise receive a follow-up contact, unless specifically countermanded by the subject.

### **5.10. Study Completion or Discontinuation**

The study will be complete when the last study data, including all follow-up data, has been collected, and analysis is complete. This is expected to occur when the last enrolled study subject has completed 6 months of follow-up and all studies have been completed (estimated to be 31 January 2024). Studies to be completed include biobanking of PB and BM biopsy samples. All follow-up must occur within the on-study follow-up period. Subjects will no longer be followed or subject data collected once the study is complete per this section.

Conditions may be discovered during the conduct of the study by the investigator, regulatory authorities, or other oversight bodies that indicate that the study should be terminated prematurely. The reasons that may warrant termination include, but are not limited to:

- The study is determined to be non-feasible, including inadequate accrual
- Determination of unexpected, significant, and/or unacceptable risk to subjects
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Demonstration of efficacy that would warrant termination by the sponsor and investigator
- Determination of futility
- Business decision by the Principal Investigator, institution, or funding source

Written notification will be provided by the investigator to Celgene Corporation and regulatory authorities as appropriate, including the IRB of record.

## 6. STUDY PROCEDURES AND ASSESSMENTS

### 6.1. Study Procedures Table

|  | Screening <sup>1</sup> | C1D1    | C1D15   | C2D1    | C2D15   | C3D1    | C3D15   | C4D1    | C4D15   | C5D1    | C5D15   | C6D1    | C6D15   | C7-C12                    | End of Study |
|--|------------------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------------------------|--------------|
| Study Window                               |                        | ±3 days | ±3 days | ±3 days | ±3 days | ±3 days | ±3 days | ±3 days | ±3 days | ±3 days | ±3 days | ±3 days | ±3 days | ±3 days                   | ±28 days     |
| Drug dispensing                            |                        | X       |         | X       |         | X       |         | X       |         | X       |         | X       |         | X                         |              |
| Drug diary                                 |                        | X       |         | X       |         | X       |         | X       |         | X       |         | X       |         | X                         | X            |
| Adverse events <sup>2</sup>                |                        | ← X →   |         |         |         |         |         |         |         |         |         |         |         |                           |              |
| Informed consent                           | X                      |         |         |         |         |         |         |         |         |         |         |         |         |                           |              |
| Demographics <sup>3</sup>                  | X                      |         |         |         |         |         |         |         |         |         |         |         |         |                           |              |
| Medical history                            | X                      |         |         |         |         |         |         |         |         |         |         |         |         |                           |              |
| Medications                                | X                      |         |         | X       |         | X       |         | X       |         | X       |         | X       |         | X                         | X            |
| Physical Exam                              | X                      |         |         | X       |         | X       |         | X       |         | X       |         | X       |         | X                         | X            |
| Vital signs                                | X                      |         |         | X       |         | X       |         | X       |         | X       |         | X       |         | X                         | X            |
| Height <sup>4</sup>                        | X                      |         |         |         |         |         |         |         |         |         |         |         |         |                           |              |
| Weight                                     | X                      |         |         | X       |         | X       |         | X       |         | X       |         | X       |         | X                         | X            |
| ECOG                                       | X                      |         |         | X       |         | X       |         | X       |         | X       |         | X       |         | X                         | X            |
| CBC w/diff <sup>5</sup>                    | X                      | X       | X       | X       | X       | X       | X       | X       | X       | X       | X       | X       | X       | X                         | X            |
| Reticulocyte                               | X                      | X       |         | X       |         | X       |         | X       |         | X       |         | X       |         | X                         | X            |
| CMP <sup>6</sup> , Magnesium <sup>16</sup> | X                      |         | X       | X       | X       | X       | X       | X       | X       | X       | X       | X       | X       | X                         | X            |
| Conjugated/Direct bilirubin                | X                      |         | X       | X       | X       | X       | X       | X       | X       | X       | X       | X       | X       | X                         | X            |
| Haptoglobin, LDH                           | X                      |         |         |         |         |         |         |         |         |         |         |         |         |                           |              |
| B-HCG <sup>15</sup>                        | X                      |         |         |         |         |         |         |         |         |         |         |         |         |                           |              |
| Iron studies <sup>8</sup>                  | X                      |         |         | X       |         | X       |         | X       |         | X       |         | X       |         | X                         | X            |
| Nutritional Panel <sup>9</sup>             | X                      |         |         |         |         |         |         |         |         |         |         |         |         |                           |              |
| Erythropoietin level                       | X                      |         |         | X       |         | X       |         | X       |         | X       |         | X       |         | X                         | X            |
| ECG <sup>14</sup>                          | X                      |         |         | X       |         | X       |         | X       |         |         |         |         |         |                           |              |
| Biobanking <sup>10</sup>                   | X                      |         |         | X       |         | X       |         | X       |         | X       |         | X       |         | X                         | X*           |
| BM Biopsy <sup>11,12,13</sup>              | X                      |         |         | X       |         |         |         | X       |         |         |         | X       |         | addition<br>biopsies will |              |

**Footnotes for Study Schedule**

- <sup>1</sup> Screening is done within 45 days of C1D1.
- <sup>2</sup> All adverse events and SAEs will be recorded by the Investigator from the time the subject signs informed consent until 90 days after the last dose of IP or start of new treatment, and those SAEs made known to the investigator at any time thereafter that are suspected of being related to IP.
- <sup>3</sup> Demographics will include age, sex/gender, self-reported ethnicity
- <sup>4</sup> Height measurement is only required during screening.
- <sup>5</sup> CBC with differential includes total white blood cell count with differential count of neutrophils, lymphocytes, monocytes, eosinophils, basophils, blast count, and immature granulocytes, hemoglobin, hematocrit, and platelet count. If a CBC was obtained during screening and is more than 14 days prior to C1D1, a repeat CBC and reticulocyte will be done on C1D1.
- <sup>6</sup> CMP or complete metabolic panel includes: sodium, potassium, chloride, carbon dioxide, glucose, creatinine, blood urea nitrogen, calcium, total protein, albumin, total bilirubin, alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase.
- <sup>7</sup> Conjugated bilirubin is synonymous with direct bilirubin.
- <sup>8</sup> Iron studies include serum iron, ferritin, transferrin saturation. For patients who are approved to continue after 12 cycles of treatment, iron studies will no longer be collected after Cycle 12.
- <sup>9</sup> Nutritional panel includes B12, methylmalonic acid, folate, TSH and free T3. If TSH is abnormal, also obtain free T4.
- <sup>10</sup> Biobanking samples include 25 mL of peripheral blood in EDTA tube and 15mL of bone marrow aspirate in EDTA tubes. \*EOT biobanking is collected at the PI's discretion.
- <sup>11</sup> Bone marrow biopsy performed at screening includes: aspirate, biopsy, flow, iron stain, cytogenetics, hemeSTAMP for verification of diagnosis and risk stratification. If a bone marrow biopsy was previously done and samples are available for biobanking, a biopsy is not required at time of screening.
- <sup>12</sup> Subsequent bone marrow biopsies while on study protocol will only include: aspirate, biopsy, iron stain and biobanking.
- <sup>13</sup> Bone marrow biopsy will be performed at the PI's discretion taking the following into consideration: at time of loss of response, a change in the response (sudden increase or decrease), for subjects who respond late on the protocol such as Cycle 5 or Cycle 6
- <sup>14</sup> Single ECG.
- <sup>15</sup> B-HCG is only collected for females of child bearing potential
- <sup>16</sup> Magnesium is only collected through Cycle 4 Day 15 (+/-3 day) .

## 6.2. Description of Procedures and Assessments

### 6.2.1. Efficacy Assessments

#### Informed Consent and Screening Period

- All subjects who are seen at Stanford Cancer Center with the diagnosis of MDS, CMML will be considered by the PI and offered participation in the study.
- PI or co-PI will explain the study to the potential study candidate verbally and in written format providing all the pertinent information (purpose of the study, procedures, risks, benefits and alternatives to study participation, etc.). All study candidates will be given ample opportunity to ask questions and the PI will ensure all questions are answered satisfactorily.
- The potential candidates will be given the IRB approved consent form and given ample time to consider participation. All questions pertaining to the consent will be answered satisfactorily. If the candidates decided to become a subject, both the study subject, the PI (or co-PI) or study coordinator will sign the consent form. A signed copy of the consent will be 1) given to the study subject; 2) scanned and retained in medical records; 3) distributed to the pharmacy and CTRU as per Stanford Cancer Clinical Trial Office (CCTO) Standard Operating Procedures; and 4) consent will be documented in the form of a progress note in the subject's chart.
- The screening period will take place up to 45 days prior to or on first treatment day (Cycle 1 Day 1). Each potential study candidate will undergo the following:
  - Informed consent form
  - Medical history and complete physical exam
  - Obtain vital signs/ECOG performance status
  - Monitoring of concurrent medications
  - Baseline safety labs: CBC with differential, Complete Metabolic Panel, magnesium level, reticulocyte count, erythropoietin level, B12, methylmalonic acid and folate level, serum iron, ferritin, transferrin saturation, TSH, T3, T4
  - Unless a prior bone marrow biopsy (conducted at Stanford or outside) is available for biobanking, diagnostic confirmation and next generation sequencing testing by Stanford Pathology, a baseline BM biopsy will be conducted, including: aspirate, core biopsy, cytogenetics, hemeSTAMP, iron stain to verify diagnosis and provide risk stratification.
  - HemeSTAMP (multigene panel to detect somatic mutations by next generation sequencing).
- Virtual visits maybe conducted for evaluation.

**Treatment Period**

- Baseline labs and studies will be collected during the screening period.
- On Cycle 1 Day 1, each study subject will:
  - Receive 28-day supply of enasidenib, a study diary
  - Begin to self-administer enasidenib orally.
  - Each subject will be counseled to take enasidenib at the same time daily, approximately 24 hours apart.
  - Each subject will also begin recording each dose and any additional side effects or concerns in the study diary.
- On Day 15 of the first 6 cycles ( $\pm 3$  days), subjects will have laboratory evaluation for CBC with differential, CMP, conjugated/direct bilirubin and magnesium. \*Magnesium is only required up until Cycle 4 Day 15 ( $\pm 3$  days).
- On the first days of each 28-day treatment cycle (Day 1,  $\pm 3$  days), each study subject will be evaluated by the PI or designate. The following will be obtained/performed at each visit:
  - Study diary monitoring, medication review, adverse events reporting
  - Symptom-directed physical exam with ECOG performance status
  - Vital signs, including weight
  - Laboratory evaluation: CBC with differential, CMP, magnesium\*, conjugated/direct bilirubin, iron studies, erythropoietin level, and biobanking. \*Magnesium is only required up until Cycle 4 Day 15 ( $\pm 3$  days).
  - Drug dispensing for the next cycle
- Virtual visits maybe conducted for evaluation.
- For patients who are approved to continue treatment after 12 cycles, patients will have labs drawn as clinically indicated. Iron studies and erythropoietin are not required to be collected after Cycle 12.
- 

**Final Study Visit**

- Study subjects who withdraw from treatment due to progressive disease will be seen within 4 weeks of determination of progressive disease for a final visit (End of Study Visit).
- Study subjects who withdraw due to intolerance of treatment should be followed until all toxicities have resolved.
- All study subjects who withdraw for any reason other than progressive disease or treatment intolerance will be seen within 4 weeks of withdrawal for a final visit. Subjects without progression of disease and intolerance of treatment will have their final study visit within 4 weeks of the Cycle 12 Day 28.

- At the End of Study Visit, the following procedures will be performed:
  - Study diary and all remaining Enasidenib returned to study staff
  - Symptom-directed physical exam with ECOG performance status
  - Vital signs including weight
  - Laboratory evaluation: CBC with differential, CMP, reticulocyte count, conjugated/direct bilirubin, erythropoietin, iron studies
  - Biobanking per investigator discretion
- Virtual visits maybe conducted for evaluation.

### **Follow-Up Period**

- Study subjects with unresolved AEs or SAEs will continue to be followed for 90 days or until resolutions of AEs/SAEs, or until the start of a new therapy, whichever occurs first.

#### **6.2.2. Safety and Other Assessments**

- Study subjects will be screened according the inclusion and exclusion criteria to ensure their baseline health and performance status is fit for study participation within 45 days of starting the study medication.
- All study subjects who have received at least one dose of the Enasidenib will be included for safety evaluation.
- A study diary will be used for each study subject to keep track of self-administered doses and prevent overdose.
- All concurrent medications will be evaluated continuously to prevent drug-drug interactions and potentiation of known side effects.
- All study subjects will have laboratory evaluation and BM biopsies conducted at baseline to verify diagnosis/eligibility based on diagnostic criteria. Additionally, laboratory evaluation will be done according to schedule of events in Section 6.1.
- All study subjects of child bearing age will have a pregnancy test done at baseline (for female study subjects) and be counseled in depth regarding the use of birth control to minimize risk of in utero exposure (see Scheduled Events in Section 6.1).

## **7. ADVERSE EVENTS AND REPORTING PROCEDURES**

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section. References for Stanford Cancer Institute adverse event (AE) policies and practices are provided in Appendix A.

### **7.1. Adverse Event Definitions**

An adverse event is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. An adverse event can be any unfavorable and unintended sign or symptom, including abnormal laboratory findings, or disease, that is temporally associated with the use of a drug, and does not imply any judgment about causality.

An adverse event may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values, regardless of etiology. An adverse reaction is any event that is caused by a drug or device, ie, possibly-, probably-, or definitely-related to the use of the drug or device.

Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. However, anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen over time are not considered adverse events. However, except as otherwise explicitly defined within this section, **this also includes all events of clinical deterioration such as tumor relapse, recurrence, or upstaging, or new cancers.**

Abuse, withdrawal, sensitivity or toxicity to enasidenib should be reported as an AE. An overdose, accidental or intentional, whether or not it is associated with an AE, should be reported. Any sequela of an accidental or intentional overdose of enasidenib should be reported as an AE. If the sequela of an overdose is a serious adverse event (SAE), both the AE page/screen of the CRF and the SAE Report Form must be completed. For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to IP, action taken regarding IP, and outcome.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

Serious adverse events (SAEs) are defined per the FDA definition at [21CFR§312.32\(a\)](#) and [ICH GCP E6](#). An adverse event is considered "serious" if, in the opinion of the PD, investigator, or sponsor, it results in ANY of the following.

- Death
- Life-threatening adverse event with an **actual and immediate risk of death** [21CFR§312.32(a)]
- Insubject hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Event jeopardizes the subject and may require medical or surgical intervention to prevent one of the outcomes listed here

## 7.2. Classification of Adverse Events

### 7.2.1. Severity of Event

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

**Events not considered SAEs are hospitalizations for:**

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied Indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (ie, planned prior to starting of treatment on study) must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of or an elective procedure for a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

For both AEs and SAEs, the Investigator must assess the severity / intensity of the event.

The severity/intensity of AEs will be graded based upon the subject's symptoms according to the NCI Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0);

[http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm#ctc\\_40](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40)

AEs that are not defined in the CTCAE should be evaluated for severity/intensity according to the following scale:

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
- Grade 4 = Life-threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death - the event results in death

The term “severe” is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor

medical significance (such as severe headache). This criterion is not the same as “serious” which is based on subject/event outcome or action criteria associated with events that pose a threat to a subject’s life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

NCI CTCAE version 5.0 is used to assess the severity of adverse events in this study.

#### **7.2.2. Adverse Event Attribution to Intervention or Study**

For this study, all recorded AEs will be assessed on the basis of whether or not the AE was caused by / due to (ie, related) to the study intervention(s). AEs, serious or otherwise, will be attributed by the PI or qualified designate to study treatment in accordance with the definitions below.

The Investigator must determine the relationship between the administration of IP and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected: A causal relationship of the adverse event to IP administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

Suspected: There is a **reasonable possibility** that the administration of IP caused the adverse event. ‘Reasonable possibility’ means there is evidence to suggest a causal relationship between the IP and the adverse event.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary or additional IP that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

|  |  |
|--|--|
| <ul style="list-style-type: none"> <li>• <b>Definitely Related.</b> There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.</li> <li>• <b>Probably Related.</b> There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.</li> <li>• <b>Potentially / Possibly Related.</b> There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events). Although an adverse event may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.</li> </ul> | <p>These are treated as <b>"Related"</b></p>     |
| <ul style="list-style-type: none"> <li>• <b>Unlikely to be related.</b> A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the subject's clinical condition, other concomitant treatments).</li> <li>• <b>Not Related.</b> The adverse event is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.</li> </ul>  | <p>These are treated as <b>"Not Related"</b></p> |

In addition, for adverse events determined "Not Related" to the study intervention(s), the Principal Investigator or qualified designate will attribute the event to the study or procedures according to the definitions above. Note that adverse events can be determined related to both the intervention(s) and/or the study / procedures.

### 7.2.3. Expectedness of Event

The PI or co-PI will also assess all recorded AEs on basis of event severity, frequency (if applicable/assessable), and the established product risk information described within the product Investigator Brochure; the FDA-approved product labeling (if an approved agent); and/or this protocol document, as to whether the events are "expected" or "not expected" relative to the study interventions and/or the study / procedures.

Note that unexpected adverse events may have reporting requirements as described elsewhere in this section.

#### **7.2.4. Time Period of Event Assessment and Follow-up**

All adverse events and SAEs will be recorded by the Investigator from the time the subject signs informed consent until 90 days after the last dose of IP and those SAEs made known to the investigator at any time thereafter that are suspected of being related to IP. AEs and SAEs will be recorded in the subject's source documents.

The Investigator will report the action taken with IP as a result of an AE or SAE, as applicable (eg, discontinuation, interruption of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

The Investigator will report the outcome of the event for both AEs and SAEs. All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered (returned to baseline), recovered with sequelae, or death (due to the SAE). For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

### **7.3. Potential Adverse Events and Risks**

Potential adverse events and risks were described at Section 1.3.1 Known Potential Risks.

In addition, adverse events described by the enasidenib Investigator Brochure and the FDA-approved product labeling (package insert) of enasidenib considered anticipated, ie, not unexpected. Events occurring at demonstrably higher frequency than described in the Investigator Brochure of the package insert should be considered adverse events, and handled, documented, and reported accordingly. Procedural risks described in Section 1.3.1 are considered anticipated.

### **7.4. Adverse Event Monitoring and Collection**

Untoward medical events experienced by a subject within 30 days of receiving enasidenib, will be considered an AE, regardless of whether or not considered drug-related. All events of disease progression or second cancer will be recorded as a SAE using the Preferred Term appropriate for the clinical finding.

All adverse events Grade 1 and higher will be collected and recorded as AEs. In addition, laboratory values without a requirement for intervention, clinical consequence, or outcome will not be considered AEs.

#### **7.4.1. Case Report Forms for Adverse Event Reporting**

Both SAEs and non-serious adverse events will be described in source documentation and listed on study-specific Case Report Forms (CRFs or eCRFs). SAEs will be reported to the SCI DSMC, via submission to CCTO-Safety. The event must be described on either the Stanford Cancer Institute SAE form (see references in Appendix A), or a study-specific form. The Form FDA 3500A (see Section 7.6) for mandatory IND Safety Reports may be substituted.

AEs will be recorded on a log (see references in Appendix A) providing the unique subject identifier, event preferred term, CTCAE body system, date of occurrence, date of resolution; and

type of resolution. All signs, symptoms, significant laboratory findings, AND diagnoses should be recorded, regardless of relationship, except as described in this document. A single “overarching” diagnosis should not be solely entered as the adverse event term in lieu of the full list of observed signs, symptoms, and significant laboratory findings, which may include the diagnostic preferred term. Any pre-existing condition that worsens in severity/Grade or frequency should be recorded as a new adverse event, except as described in this document.

Types of resolution are:

- “Resolved,” i.e., to Grade 0 (or baseline if a pre-existing condition)
- “Continuing” and stable (includes downgrades from a higher grade to a lower grade)
- “Deceased” (due to any cause will on-study)
- Lost-to-follow-up.

#### **7.4.2. Progressive Disease**

Progressive disease will be reported by the clinical signs or symptoms of disease progression. If the event is Grade 5 fatal and signs/symptoms of disease progression are not available / informative for the event, the CTCAE v5.0 preferred term “Disease Progress” may be used.

### **7.5. Adverse Events of Special Consideration**

#### **7.5.1. Second vs Secondary Malignancy**

##### **7.5.1.1. Second Malignancy**

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). A second malignancy is by definition a serious adverse event (SAE), and will be recorded and reported accordingly.

##### **7.5.1.2. Secondary Malignancy**

In the context of a clinical study, a secondary malignancy is a cancer caused by chemotherapy, radiation, or the investigational agent/intervention. A secondary malignancy is not considered a metastasis of the initial neoplasm, but nonetheless, a secondary malignancy is by definition a serious adverse event (SAE), and will be recorded and reported accordingly. Secondary malignancies are usually described as one of the following:

- Leukemia secondary to oncology chemotherapy [e.g., acute myelocytic leukemia (AML)]
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

By definition, secondary malignancies are adverse events that are both serious and related to the research, and should be anticipated to be an Unanticipated Problem (UP) and reported accordingly. If also determined to be related to the study treatment, and not described by the Investigator Brochure or package insert as known to be associated with the study agent, the secondary malignancies may also necessitate Expedited Reporting to FDA, e.g., an IND Safety Report to the IND.

### 7.5.2. Progressive Disease

Progressive disease will be reported by the clinical signs or symptoms of disease progression. If the event is Grade 5 fatal and signs/symptoms of disease progression are not available / informative for the event, the CTCAE v5.0 preferred term "Disease Progress" may be used.

## 7.6. Adverse Event Reporting

All adverse clinical experiences, whether observed by the investigator or reported by the subject, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the event's outcome, including lab abnormalities. The investigator will evaluate each adverse experience for its relationship to the test drug and for its seriousness.

The investigator will appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the event's outcome or lab abnormality.

### Reportable adverse events

Based on relatedness (attribution) to the study agent; expectedness, severity (Grade 1 to 5), seriousness (Yes/No), or any other aspect of the investigation, will be reported as described below.

- Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat; and head congestion should be reported as "upper respiratory infection").
- Serious adverse events (SAEs) per the definition at [21CFR§312.32](#) will be reported to the sponsor-investigator **within 24 hours of the knowledge of the event**. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form (such as via secure email with CRF/eCRF attached).
- SAEs will be reported to the SCI Data and Safety Monitoring Committee (DSMC) by submitting the study-specific CRF or the Stanford Cancer Institute CRF for SAE reporting through **secure** email to [CCTO-safety@stanford.edu](mailto:CCTO-safety@stanford.edu) at the time of the **first** notification to any of drug manufacturer Celgene Corporation; the IRB of record; or the IND (ie, FDA). The SAE form must be signed by the investigator.
- SAEs per [21CFR§312.32](#) will be reported by the IND-holder to the IND under which this study is being conducted within 7 days (for a life-threatening or fatal event) or 15 days (for other SAEs) of the IND-holder's determination that the SAE meets the criteria for an IND safety report, ie, the event was serious, unexpected, and at least possibly-related to the study drug [a serious, unexpected, suspected adverse reaction (SUSAR)]. IND Safety Reports will be submitted to the IND using the MedWatch Form FDA 3500A for mandatory reporting. IND Safety Reports will also be distributed to all participating Principal Investigators within 60 days.

IND Safety Reports will be submitted to either the address specified in the IND Study May Proceed letter, any other address specified by the IND reviewers, or via the

Electronic Submissions Gateway (contact [CCTO-Regulatory@Stanford.edu](mailto:CCTO-Regulatory@Stanford.edu) for electronic submission assistance), or via the CDER NextGen portal.

- All SAEs per protocol will be reported will be reported by each clinical site to the IRB of record in the Continuing Review, and/or the Final Report. IRB reporting format can be as an event line listing (such as the Adverse Event log), or as an aggregate listing or summary (such as an IND Annual Report or SAE listing for ClinicalTrials.gov).
- All **Unanticipated Problem (UPs)** associated with the use of a drug, biologic, or device will be reported as follows.
  - Note that for the purposes of Stanford IRB Unanticipated Problem reporting, subjects are considered to be study subjects when consented, ie, events during screening and/or pre-treatment through that subject's official end of study participation may qualify as reportable.
  - To the Stanford IRB, by the Stanford Protocol Director, if an adverse event meets the Stanford IRB's current definition of an Unanticipated Problem (UP) as specified by the IRB document "Events and Information that Require Prompt Reporting to the IRB" (GUI-P13), per the timeframes defined therein. Once the DSMC has received the SAE report via OnCore, the DSMC may also issue a report on the event, which may be also provided to the IRB. See also Section 9.4 Data and Safety Monitoring Plan. In addition to event triggered expedited UP reports, all UPs should be summarized in the Continuing Review, with, as applicable, a discussion of any change in assessment of risk (ie, different than previously described).

Subsequent follow-up reports, whether to SAEs or UPs, will be reported as required by the receiving entities.

Adverse events that are serious and unexpected suspected adverse reactions (i.e., serious, unexpected events are possibly, probably, or definitely-related to the study drug enasidenib), will be reported by the IND-holder on a MedWatch 3500A form as an IND Safety Report [21CFR§312.32] to the IND within 15 calendar days, or within 7 calendar days if the event is an unexpected fatal or life-threatening suspected adverse reaction. The IND annual report as submitted by the IND-holder will include summaries of the collected AEs, as specified by [21CFR§312.33](#).

Serious adverse events (SAEs) will be reported to the IRB of record and to the DSMC in accordance with the applicable guidelines and regulations.

All serious adverse events (SAEs) will be followed for 90 days after the last dose of the enasidenib, or until the SAE(s) is(are) resolved or stable, or until patient initiates a new/alternative therapy (including but not limited to growth factors, chemotherapy or bone marrow transplant), whichever occurs first.

#### Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;

- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance, e.g., one that indicates a new disease process and/or organ toxicity, or is an exacerbation or worsening of an existing condition.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (e.g., record thrombocytopenia rather than decreased platelets).

### Overdose

Overdose, as defined for this protocol, refers to enasidenib dosing only (as applicable).

On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of > 240 mg (+20%) assigned to a given subject, regardless of any associated adverse events or sequelae.

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

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported.

To date, doses of enasidenib up to 650 mg QD were well-tolerated in clinical trials. No information is currently available regarding overdose with enasidenib. In the event of overdose with toxicity, supportive clinical care should be provided.

### Pregnancy

All female study subjects of reproductive potential will be advised to avoid becoming pregnant while receiving enasidenib (Idhifa) and to use effective contraception during treatment with enasidenib and for at least 2 months after the last dose. Coadministration of enasidenib may increase or decrease the concentrations of combined hormonal contraceptives. The clinical significance of this potential drug interaction is unknown at this time.

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on IP, or within (2 months), are considered immediately reportable events. IP is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form. The female subject may be referred to an obstetrician-gynecologist (not necessarily one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

### Male Subjects

All male study subjects with female partners of reproductive potential will be advised to use effective contraception during treatment with enasidenib (Idhifa) and for at least 2 months after the last dose of enasidenib.

If a female partner of a male subject taking investigational product becomes pregnant while the male subject is on study treatment or within 2 months of the male subject's last study treatment, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

### Expedited Reporting by Investigator to Celgene

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events of being related to enasidenib based on the Investigator Brochure. In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number (XX-XX-XX- PI-#####) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the subject records.

### **Drug Safety Contact Information:**

Celgene Corporation  
Global Drug Safety and Risk Management  
86 Morris Avenue  
Summit, New Jersey 07901

BMS Patient Safety fax number: 1-609-818-3804

E-mail: [WorldWide.Safety@bms.com](mailto:WorldWide.Safety@bms.com)

### **7.7. Adverse Event Records**

The investigator will retain adverse event source data, supporting documentation of attribution and seriousness, and copies of official adverse event reports or SAE CRFs, as well as documentation of informal communications (such as telephone calls or emails) in accordance with the current version of Stanford School of Medicine standard operating procedure SOP-005 "Identifying and Reporting Adverse Events" (see Appendix 1).

## **8. CORRELATIVE / SPECIAL STUDIES**

### **8.1. Correlative Studies Background**

#### **8.1.1. Explore the identity of the target cell population of enasidenib**

Primary samples will be interrogated to determine which erythroid progenitor population enasidenib is acting upon to increase endogenous erythropoiesis.

#### **8.1.2. Explore the mechanism of enasidenib**

Samples from responders and nonresponders will be used for transcriptional studies to discern regulatory pathways influenced by enasidenib.

#### **8.1.3. Explore immune differentiation effects of enasidenib**

The immune repertoire of each subject at baseline and while receiving enasidenib will be interrogated.

### **8.2. Laboratory Correlative Studies Collection of Specimen(s)**

#### **8.2.1. Collection of Specimens**

The following samples will be collected for each study subject concomitant to standard of care studies according to protocol.

- 1) peripheral blood mononuclear cells;
- 2) peripheral blood plasma;
- 3) bone marrow aspirate mononuclear cells;
- 4) bone marrow plasma.

#### **8.2.2. Handling and Storage of Specimens**

All samples collected will be processed in the laboratory of Dr Tian Yi Zhang, Principal Investigator at Stanford University and cryopreserved for future studies. All samples biobanked for correlative studies will remain in the purview of Tian Yi Zhang and her team members and will be used for future studies, provided the subject has furnished their consent. A detailed log of all biobanked samples will be kept and provided for DSMC review upon request.

### **8.2.3. Coding of Specimens for Privacy Protection**

All biobanked samples will be given a unique identifier and only the identifier used for the purposes of correlative studies. This allows complete de-identification of the primary samples. All sample acquisition, handling and processing will follow HIPAA guidelines.

## **9. REGULATORY CONSIDERATIONS AND DATA REPORTING**

### **9.1. Institutional Review Board Approval of Protocol**

This protocol, the proposed informed consent, and all forms of information related to the study that will be provided to the subjects (e.g., handouts, written instructions, diaries, advertisements used to recruit subjects) will be submitted, reviewed, and approved by the Stanford Administrative Panels on Human Subjects in Medical Research of the Research Compliance Office (ie, the Stanford IRB) and the Stanford Cancer Institute Scientific Review Committee (SRC) prior to initiation of the research. Any changes made to the protocol will be submitted as a modification and will be approved by the IRB of record prior to implementation. This study will be conducted in accordance with the iteration of the protocol that is currently IRB-approved Stanford.

### **9.2. Protocol Compliance and Deviations**

#### **9.2.1. Compliance with the Protocol**

No deviation or changes from the procedures and process described by the IRB-approved protocol, except those necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial [e.g., change in study monitor(s), change of telephone number(s)], will be knowingly permitted without review and approval by the IRB of record.

#### **9.2.2. Protocol Deviations**

Any deviation from the IRB-approved protocol, including those that eliminate an immediate hazard or are administrative in nature, will be documented and explained in the study site file. In addition, any deviation from the approved protocol that meets the reporting requirements defined in the Stanford University HRPP Policy Guidance “Events and Information that Require Prompt Reporting to the IRB” GUI-P13 will be reported to the IRB within the defined timeframes.

For all studies monitored by the Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) as defined in Section 9.4 Data and Safety Monitoring Plan, all deviations, exceptions, and/or violations of the protocol, as well as deviations, exceptions, and/or violations to applicable IRB policies and overarching regulations, will be reported to the Stanford Cancer Institute data Safety and Monitoring Committee (DSMC). Accordingly, as the DSMC only reviews reports recorded in OnCore, such events will be promptly submitted in the OnCore record for the study, per the current SCI DSMC SOP.

### **9.3. Data and Safety Monitoring Plan**

The Principal Investigator is responsible for monitoring the conduct of the study including oversight of safety and protocol compliance. On an ongoing basis, the Principal Investigator will review safety data and identify any changes to the research necessary to ensure the appropriate measures and monitoring necessary for subject safety. In addition to the Principal Investigator's safety monitoring role, the SCI DSMC will conduct data and safety monitoring activities for this study.

#### **9.3.1. Monitoring**

In addition to investigator self-monitoring (Section 9.3.1.1), the SCI DSMC will monitor study-related activities to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, [GCP, and SOPs](#). In addition, the DSMC will regularly review serious adverse events and protocol deviations associated with the research to ensure the protection of human subjects. Results of DSMC monitoring activities will be communicated to the investigator, who has the responsibility to provide such reports to the IRB of record and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

##### **9.3.1.1. Investigator Monitoring**

Pursuant to the Guideline for [GCP](#), monitoring is defined as the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), GCP, and the applicable regulatory requirement(s).

The Principal Investigator is responsible for self-monitoring the progress of the trial on a continuous basis. Monitoring may be delegated to an appropriately-trained individual. Self-monitoring includes, but is not limited to, those items that will be reviewed during an audit (see also Section 9.5). Routine monitoring by the Principal Investigator or designated clinical research coordinator will be conducted at an estimated frequency of not less than monthly.

### **9.4. Data Management**

Source documents for all research data will be retained in accordance with all applicable regulations and institutional requirements for data retention. These materials will be made available for monitoring and/or auditing by SCI DSMC, other monitoring body and/or regulatory agencies.

#### **9.4.1. Data Management Plan**

The data manager will manually enter data from Epic into a study-specific eCRF created in REDCap by the PI in conjunction with Stanford CCTO. The PI will certify that the data are complete and accurate by applying an electronic signature to the eCRF. The study specific REDCap database will be maintained by the CCTO with password-protected access limited to the study team of each clinical site. Original source documents, including consent, clinical charts and hospital, laboratory, and pharmacy records will be kept in a designated area on a secure floor, only accessible to the research team.

Study monitoring will be done by the PI and/or designated person(s) (i.e., data manager) in a timely manner to ensure that valid consent is obtained and documented; the per-protocol data is collected; records and databases are maintained with adequate and accurate subject case histories; adverse events are reported; clinical protocol is maintained; and the study is conducted according to the established procedures of the IRB of record.

Queries will be issued for any discrepant or missing data. Query reports and study status will be reviewed by the PI monthly. Any ongoing data management, documentation, or protocol related issues will be discussed during scheduled clinical research team conferences (or teleconferences). Additional conferences/teleconferences will be arranged on an as needed basis.

At study completion, data will be locked after the last study visit has been completed which will be approximately 6 months after the enrollment of the last subject.

### **9.5. Site Documentation and Management**

The following information will be maintained by the PI at Stanford Cancer Center.

- Delegation of Authority Log, indicating study role, training date, on-study date, and off-study date
- Financial Disclosure Forms and updates
- Copies of all correspondence with the IRB of record, including all approval letters and approved template informed consent documents, in chronological order by date.
- Copies of all correspondence with the local Scientific Review Committee, including approval letters, renewals, and other types of communication.
- Study agent accountability log
- Serious adverse event (SAE) log, documenting the subject, date, event, relatedness, follow-up, and outcome, with dates of communication to the IRB of record and OnCore/CCTO-Safety (Stanford site)
- Log of Exceptions (ie, authorized by Stanford Investigator) and Log of Deviations (not authorized)
- Log of Deviations (ie, excursions from the protocol not authorized by the Stanford investigator and approved by the IRB). The Log of Deviations must be maintained in OnCore.
- Laboratory documentation, including copies of local site CAP and CLIA certificates, State licenses, laboratory director CV and medical license, with laboratory normal values/reference ranges for all labs used in the study.
- Printed, dated copy of roster for IRB of record, for each year of the study

### **9.6. FDA Oversight**

#### **9.6.1. Investigational New Drug (IND) Application Considerations**

##### **IND required**

This study will be conducted under IND TBD, held by Tian Yi Zhang, MD.

#### 9.6.1.1. Protocol Amendments

The protocol will be conducted at all times according to the current version of the protocol as approved by the IRB of record. IRB-approved protocol versions will be submitted to the IND as a Protocol Amendment: Change in Protocol.

#### 9.6.1.2. IND Reports

Information regarding the progress and status of this study will be submitted to IND TBD, in accordance to the content and format defined at [21CFR§312.32 \(Safety Reports\)](#) and [312.33 \(Annual Reports\)](#).

## 10. STATISTICAL CONSIDERATIONS

### 10.1. Statistical Plan

Cohort A will be considered to be those subjects receiving 100 mg enasidenib, and as Cohort B will be those receiving 200 mg. enasidenib. Within the Phase 2 part of the study, subjects will be stratified as Cohort 1 for subjects with lower-risk MDS and Cohort 2 for subjects with non-proliferative CMML, and will receive the dose level for Cohort A or Cohort B, depending on the results of the Paks 1B portion of the study. Although the outcome for Cohorts 1 and 2 after determination of the recommended phase 2 dose( RP2D) is the nominal intent of the study, results may be analyzed and/or reported to include subjects from Cohort A or Cohort B who receive the eventual the RP2D.

Simon's two-stage design will be used for each of the 2 disease cohorts of the study (ie, study phase 2). The null hypothesis that the true response rate is 0.1 [ $P_0$ ] will be tested against a one-sided alternative. In the first stage, 16 [ $n_1$ ] subjects will be accrued. If there are 1 [ $r_1$ ] or fewer responses in these 16 [ $n_1$ ] subjects, the study will be stopped for futility. Otherwise, 5 additional subjects will be accrued for a total of 21 [ $n$ ]. The null hypothesis will be rejected if 5 [ $r_{2+1}$ ] or more responses are observed in 21 subjects. This design yields a type I error rate of 0.075 and power of 0.80 when the true response rate is 0.30.

#### 10.1.1. Method of Treatment Assignment

This single arm study will use open label enrollment for two disease cohorts, lower-risk MDS and nonproliferative CMML. Subjects from both disease cohorts will be screened and enrolled consecutively.

#### 10.1.2. Sample Size Determination

Sample size is determined based on Simon's two-stage design. See statistical plan in above.

#### 10.1.3. Minimization of Bias

- Subjects are screened and enrolled in a consecutive manner which reduces selection bias by the investigators.
- Both male and female study subjects of 18 years of age are included in study.
- Independent adjudication for enrollment by a subinvestigator will be used as needed to reduce selection bias

- Independent adjudication for DLT assessment by a subinvestigator will be used as needed to reduce bias.

## 10.2. Study Endpoints

### 10.2.1. Primary Endpoint

#### 10.2.1.1. Primary Objective / Outcome

The primary objective for the study is to determine the efficacy (response rate) of enasidenib in improving anemia and decreasing RBC transfusion dependence. Study subjects on each arm of the study will be based on their transfusion status at study entry according to the modified 2018 IWG recommendations:

|     | # of RBC Units Transfused | Time Period (weeks) |
|-----|---------------------------|---------------------|
| NTD | 0                         | 16                  |
| LTD | 3-7                       | 16                  |
| HTB | $\geq 8$                  | 16                  |
|     | or $\geq 4$               | 8                   |

The proportion of study subjects in each disease specific cohort of the study will be determined as the response rate.

#### 10.2.1.2. Endpoint Definition for Primary Objective / Outcome

The subject response to treatment is determined by modified IWG 2018-defined hematological improvement-erythroid (HI-E) as below. For example, subjects with entry as NTD will require an improvement of hemoglobin by 1.5 g/dL in a 8-week period.

|     | 2018 IWG HI-E criteria   | Time Period (weeks) |
|-----|--|---------------------|
| NTD | Hemoglobin increase $\leq 1.5$ g/dL  | 8                   |
| LTD | 0 units of RBC transfusions  | 8                   |
| HTB | $\geq 4$ unit reduction of RBC transfusions; or<br>$\geq 50\%$ reduction in units of RBC transfusion | 8                   |

The primary efficacy endpoint is the response rate defined as the proportion of study subjects achieving treatment response.

#### 10.2.1.3. Assessment Methods for Primary Objective / Outcome

The hemoglobin and the number of transfusions for each study subject will be recorded from each laboratory evaluation during the course of the study. The changes in these parameters will be used to assess the primary objective. These parameters will be captured by the data manager and recorded in the EDC (REDCap).

#### 10.2.1.4. Measurement Time Points for Primary Objective / Outcome

The changes in hemoglobin and number of transfusions for each study subject will be calculated and evaluated every 4 weeks according to the modified 2018 IWG HI-E criteria by the principal investigator and/or a designated research team member.

#### 10.2.1.5. Response Review

The responses for each study subject will be reviewed by the principal investigator monthly. If a study subject has not met criteria as a responder within the first 6 months of treatment, the subject will be considered a nonresponder and exit the study. If the study subject is believed to be deriving clinical benefit on enasidenib by the end of 12 months on study protocol by the PI, the subject may continue treatment after discussion with the study sponsor, until unacceptable toxicity, loss of response or closure of the protocol. Patients who are approved to continue treatment after 12 cycles will have routine lab draws as clinically indicated.

#### 10.2.2. Secondary Endpoints

The secondary endpoints are as follows:

- 1) To determine the safety of enasidenib in subjects without *IDH2* mutations using the type, incidence, severity, and relatedness of adverse events in accordance with the CTCAE v5.0.
- 2) To determine the time to HI-E, defined as time from first dose of enasidenib to the first observed hemoglobin change meeting 2018 IWG HI-E criteria (Section 10.2.1.2).
- 3) To determine the duration of HI-E, defined as time from each recorded response of increase in hemoglobin meeting 2018 IWG-HI-E criteria (Section 10.2.1.2) to loss of that specific response.
- 4) To determine the proportion of subjects who achieve a response defined by the modified 2018 IWG criteria in improvement of platelet count (HI-P).

| <b>Pre-treatment platelets<br/>(average value during the 16-week<br/>baseline monitoring period)</b> | <b>2018 IWG HI-P</b>   | <b>Time Period<br/>(weeks)</b> |
|--|--|--------------------------------|
| $< 20 \times 10^9/\text{L}$  | increase from $< 20 \times 10^9/\text{L}$ to $> 20 \times 10^9/\text{L}$<br>and by at least 100% | 8 weeks                        |
| $\geq 20 \times 10^9/\text{L}$   | absolute increase of $30 \times 10^9/\text{L}$   | 8 weeks                        |

- 5) To determine the proportion of subjects who achieve a response defined by the modified 2018 IWG criteria in improvement of neutrophils (HI-N).

| Pre-treatment neutrophils<br>(average value during the 16-week<br>baseline monitoring period) | 2018 IWG HI-P  | Time Period<br>(weeks) |
|---|--|------------------------|
| Any   | At least 100% increase and an absolute<br>increase $> 0.5 \times 10^9/L$ | 8 weeks                |

- 6) To determine the proportion of study subjects who are transfusion dependent (LTD and HTB) achieving RBC transfusion independence (RBC-TI) for 8 weeks or longer.

### 10.2.3. Exploratory Endpoints

The following exploratory endpoints will be analyzed:

- Erythropoiesis indices and potential predictive biomarkers in the responders and nonresponders will be analyzed using logistic regression or Cox proportional hazard ratio.
- The frequency of hematopoietic and erythroid progenitors in responders and nonresponders will be compared using unpaired t-test.
- Correlation of mutation status of each study subject and their response to therapy will be performed using multivariable Cox regression analysis.
- Transcriptomic analysis and gene expression profiling will be performed to identify potential pathways targeted by enasidenib. Differentially expression genes will be determined using a negative binomial model. Gene ontology analysis will be performed using the PANTHER Gene ontology Consortium tool.

## 10.3. Interim Analyses

### 10.3.1. Stopping Rules

An interim efficacy analysis will be provided after enrolling 16 evaluable subjects for each disease cohort which is the end of the first stage of the study. In the first stage, 16 [ $n_1$ ] subjects will be enrolled. If there are 1 [ $r_1$ ] or less responses in stage 1, the study will be stopped for futility.

## 10.4. Primary Analysis

### 10.4.1. Primary Analysis Population

The primary efficacy population will include all subjects who have received at least one dose of enasidenib at the RP2D and with at least one post-baseline laboratory evaluation.

### 10.4.2. Primary Analysis Plan

The response rate of subjects to enasidenib in improving hemoglobin and reducing RBC transfusion dependence will be analyzed using primary endpoint defined in Section 10.2.1.2. Response assessments will be summarized tables to best display and reflect the variation, timing and duration of responses of individual subjects.

## 10.5. Secondary Analysis

### 10.5.1. Secondary Analysis Population

**Safety** - The safety population will consist of all enrolled subjects who received at least 1 dose of any study treatment. The safety population will be used for the analysis of safety data.

**All other secondary endpoints** – The secondary analysis population will include all subjects who have received at least 1 dose of enasidenib at the RP2D and with at least 1 post-baseline laboratory evaluation.

### 10.5.2. Secondary Analysis Plan

#### **Safety**

All adverse events will be recorded and tabulated. Dose limiting toxicity will be noted. Adverse events will be graded according to the CTCAE v5.0 and divided into those that are Grade 1 to 2 and those that are Grade 3 or higher. Serious adverse events will also be analyzed separately, as will adverse events leading to discontinuation of study drug or exit from study.

#### **Time to HI-E**

Time to HI-E for each study subject will be determined as the interval between day of first dose of enasidenib to meeting response criteria as defined in Section 12.2.1.2 (2018 modified IWG HI-E). Results will be summarized descriptively using the Kaplan-Meier method.

#### **Duration of HI-E**

The duration of response for HI-E for each study subject will be determined as the interval between the time of first response to loss of the response according to criteria as defined in Section 12.2.1.2 (2018 modified IWG HI-E). Results will be summarized descriptively using the Kaplan-Meier method.

#### **Response rate of HI-P**

The response rate of subjects to enasidenib in improving platelet count and reducing platelet transfusion dependency will be analyzed using a repeated measures model using secondary endpoint defined in Section 10.2.2 (2018 IWG HI-P). Response assessments will be summarized in spider plots to best display and reflect the variation, timing and duration of responses of individual subjects.

#### **Response rate of HI-N**

The response rate of subjects to enasidenib in improving neutrophil count will be analyzed using a repeated measures model using secondary endpoint defined in Section 10.2.2

(2018 IWG HI-P). Response assessments will be summarized in spider plots to best display and reflect the variation, timing and duration of responses of individual subjects.

### **Transfusion rate**

The transfusion rate is defined as the number of transfusions (red blood cells and platelets) received by each study subject during an 8-week period.

### **Transfusion independence**

Transfusion independence will be defined as the proportion of study subjects (defined by their transfusion needs in Section 10.2.1.1) which become transfusion independent after receiving at least one dose of enasidenib.

## **10.5.3. Sample Size**

Each disease cohort will be evaluated independently. This study has an accrual goal of 21 subjects for each disease cohort. The sample size is determined using Simon's two-stage design to achieve a power of 0.80 with a type I error rate of 0.075 to detect a true response rate of 0.30. See statistical plan in Section 10.1 for details.

## **10.5.4. Accrual estimates**

We expect the study to take 24 months to accrue for each arm of the study and the core study will be completed by the end of 24 months. Accrual estimates are made to the best of the Principal Investigator's knowledge prior to study opening. The PI will review study accrual with Celgene every 6 to 12 months and revise the accrual estimates in the protocol accordingly.

### **10.5.4.1. Sample size justification**

Sample size is justified by the power calculations above in Section 10.5.3.

### **10.5.4.2. Effect size justification**

Based on historical data and our experience in taking care of subjects with lower-risk MDS and nonproliferative CMML, the expected true response rate on best supportive therapy as standard of care would be 0, since there are no spontaneous remissions. Therefore, a conservative true response rate of 0.1 [ $P_0$ ] was chosen to achieve a power of 0.80 with a type I error rate of 0.075 to detect a response rate of 0.3 [ $P_1$ ]. The response rate of 0.3 would be considered a robust response given constraints of resources.

### **10.5.4.3. Criteria for future studies**

If the trial is not stopped early for futility, and if 5 or more responses are observed in 21 subjects in each disease cohort, then the null hypothesis will be rejected which supports further development of enasidenib in improving erythropoiesis.

## **10.6. Descriptive Statistics and Exploratory Data Analysis**

All statistical analysis will be performed using Graph Pad Prism 8 or R studio.

Qualitative background variables (sex, age, race/ethnicity) will be summarized using contingency tables. Descriptive statistics, including frequency and confidence intervals, will be used to describe the study population. Comparison will be made using institutional and published historical data.

**Exploratory endpoint analysis** will including the following:

- Erythropoiesis indices and potential predicative biomarkers in the responders and nonresponders will be analyzed using logistic regression or cox proportional hazard ratio. Erythropoiesis indices will include the following:

|                                      |
|--------------------------------------|
| Reticulocyte count                   |
| Red cell distribution                |
| MCV                                  |
| Plasma erythropoietin level          |
| Plasma TGF beta family member levels |
| Serum iron                           |
| Transferrin saturation               |
| Ferritin                             |

- The frequency of hematopoietic and erythroid progenitors in responders and nonresponders will be compared using unpaired t test.
- Correlation of mutation status of each study subject and their response to therapy will be performed using multivariable Cox regression analysis.
- Transcriptomic analysis and gene expression profiling will be performed to identify potential pathways targeted by enasidenib. Differentially expression genes will be determined using a negative binomial model. Gene ontology analysis will be performed using the PANTHER Gene ontology Consortium tool (ref).

## 11. REFERENCES

1. Goodnough LT, Schrier SL. Evaluation and management of anemia in the elderly: Evaluation and management of anemia in the elderly. *Am J Hematol*. 2014;89:88-96.
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6. Yen K, *et al*. AG-221, a First-in-Class Therapy Targeting Acute Myeloid Leukemia Harboring Oncogenic IDH2 Mutations. *Cancer Discovery*. 2017;7:478-493.
7. Stein EM, *et al*. Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. *Blood*. 2017;130:722-731.
8. Amatangelo MD, *et al*. Enasidenib induces acute myeloid leukemia cell differentiation to promote clinical response. *Blood*. 2017;130:732-741.
9. Dutta R, *et al*. Enasidenib drives human erythroid differentiation independently of isocitrate dehydrogenase 2. *Journal of Clinical Investigation*. 2020;130:1843-1849.
10. Platzbecker U, *et al*. Proposals for revised IWG 2018 hematological response criteria in patients with MDS included in clinical trials. *Blood*. 2019;133:1020-1030.

## 12. PROTOCOL HISTORY

| <b>Version Date *</b> | <b>Change Summary</b>  |
|-----------------------|--|
| 19 Aug 2021           | Submission to SCI Scientific Review Committee (SRC)  |
| 24 Aug 2021           | Initial IND submission (courtesy rush)   |
| 8 Sep 2021            | SRC-approved version   |
| 21 Sep 2021           | Response to FDA comments. IRB submission   |
| 2 Sep 2022            | <ul style="list-style-type: none"> <li>• Clarifies the previously stated study population vs the inclusion criteria (Synopsis and Section 3.1.1.1).</li> <li>• Adjusts upper limit of hemoglobin level from &lt; 10.0 g/dL to &lt; 10.5 g/dL, as part of the corresponding Inclusion Criteria (Section 3.1.1.6).</li> <li>• Removes prior treatment with iron chelation therapy as an Exclusion Criteria (Section 3.1.2.2).</li> <li>• Revises the Concomitant Medications list to allow the medications if the subject will also receive ECG monitoring during the period of concurrent use.</li> <li>• Updates study procedures and table from specifying unconjugated bilirubin to specifying conjugated or direct bilirubin (Sections 6.1 and 6.2).</li> <li>• Clarifies study procedures and table regarding TSH; free T3; and free T4 testing (Sections 6.1 and 6.2).</li> <li>• Omits redundant text in Section 7.6.</li> <li>• Corrects the Stanford eProtocol number throughout.</li> <li>• Populates protocol history table (Protocol History).</li> <li>• Other typographical and administrative corrections and updates</li> </ul> |
| 9 Sep 2022            | Corrects typographical error in Inclusion Criteria for creatinine clearance.   |
| 9 November 2022       | <ul style="list-style-type: none"> <li>• Updates to the cohort descriptions</li> <li>• Protocol statement that the determination of the recommended phase 2 dose will be reported to the SCI DSMC and SRC is omitted.</li> </ul>   |
| 7 December 2022       | <ul style="list-style-type: none"> <li>• Clarifies that virtual visits maybe conducted for evaluation. (Section 6.2.1)</li> <li>• Typographical correction on page 38</li> </ul>   |

| Version<br>Date *  | Change Summary   |
|--------------------|--|
| 2 February<br>2023 | <ul style="list-style-type: none"> <li>• Updates language regarding dose interruptions. (Section 5.6.1)</li> <li>• Clarifies dose limiting criterion (Section 5.6.1)</li> <li>• Updates Study Procedure table to include +/- 3 window for Day 15 to be consistent with Treatment Period visit description in Section 6.2.1 (Table 6.1)</li> <li>• Corrects End of Study window in Study Procedure table to be consistent with +28-day in Final Study Visit description in Section 6.2.1 (Table 6.1)</li> <li>• Removes ECG procedure from Final Study Visit description in 6.2.1 to be consistent with Table 6.1 (Section 6.2.1)</li> <li>• Other typographical and administrative corrections and updates.</li> </ul>   |
| 6 April 2023       | <ul style="list-style-type: none"> <li>• Omits IDH2 PCR testing requirement from eligibility criteria (Sections 3.1.1 and 3.1.2).</li> <li>• Updates study team contact information (Section 3.4.1).</li> <li>• Modifies visit nomenclature “Day 28+ 7 days” to “Day 1+/-3” and updates exams listed under Final Visit to be consistent with Study Procedures Table (6.2.1).</li> <li>• Clarifies duration of follow-up for participants and those that discontinue treatment for unacceptable adverse events or toxicity (Sections 6.2.1 and 5.9).</li> <li>• Expands screening window to 45 days (Sections 6.1: Footnote1, 6.2.1, and 6.2.2).</li> <li>• Clarifies that EOT biobanking collection is collected per investigator discretion (Sections 6.1:Footnote 10 and 6.2.1).</li> <li>• Clarifies that a single ECG is captured at designated timepoints (Sections 6.1: Footnote 14 and 6.2.1).</li> <li>• Clarifies that B-HCG is only collected for participants who are female of child bearing potential (Sections 6.1: Footnote15 and 6.2.1).</li> <li>• Updates magnesium collection requirement through Cycle 4 Day 15 (Sections 6.1: Footnote 16 and 6.2.1).</li> <li>• Removes IDH2 PCR testing requirement (Sections 6.1 and 6.2.1) .</li> <li>• Omits adverse events of special interest language not applicable to protocol (Section 7.2)</li> <li>• Addition of language to note that all SAEs will be followed for up to 90 days after the last dose of the enasidenib, or until SAE(s) is (are) resolved or stable, or until patient initiates a new/alternative therapy (including but not limited to growth factors, chemotherapy or bone marrow transplant), whichever is occurs first (Section 7.6).</li> <li>• Updates drug manufacturer patient safety reporting email and fax (Section 7.6).</li> <li>• Other typographical and administrative corrections and updates.</li> </ul> |

| Version Date * | Change Summary   |
|----------------|--|
| 13 Jun2023     | <ul style="list-style-type: none"><li>• Changes the amount of blood and aspirate being collected for biobanking</li><li>• Other typographical and administrative corrections and updates.</li></ul>  |
| 15 Aug 2023    | <ul style="list-style-type: none"><li>• Eligibility inclusion criteria 6 has been updated to include patients presenting with thrombocytopenia and/or neutropenia. (Section 3.1.1)</li><li>• Clarification to bone marrow biopsy requirements at screening (Section 6.2.1)</li><li>• Clarification to laboratory requirements for those patients who continue therapy with enasidenib beyond twelve cycles. (6.1 Study procedure table and 10.2.1.5)</li><li>• Other typographical and administrative corrections and updates.</li></ul>   |
| 20 Mar 2024    | <ul style="list-style-type: none"><li>• Update that Ph 2 cohorts will receive 100 mg in Cycle 1 followed by dose escalation to 200 mg (RP2D) dose of enasidenib in future cycles as tolerated. (Section 2.1.3; Section 2.1.6; and Section 5.2)</li><li>• Removed Exclusion criteria that limits the use of erythropoietic agents and G-CSF within 20 days of study enrollment (Section 3.1.2)</li><li>• Clarification to the patient's study schedule in the setting of a dose interruption of 28 days or more (Section 5.6)</li><li>• Other typographical and administrative corrections and updates.</li></ul> |
| 23 Jul 2024    | <ul style="list-style-type: none"><li>• Revised language to clarify duration of AE follow-up period so it is consistent with language in Section 7.2.4 (Section 6, footnote 2)</li><li>• Other typographical and administrative corrections and updates.</li></ul>   |

\* Latest date should match footer date of the current document

## 13. APPENDICES

### 13.1. Appendix A. References for Stanford Cancer Institute Policies & Practices

#### Standard Operating Procedures (SOPs):

- Stanford School of Medicine standard operating procedure SOP-005 “Identifying and Reporting Adverse Events.” This document is available on the Spectrum website.

[http://med.stanford.edu/spectrum/b4\\_research\\_quality/b4\\_3\\_standard\\_operating\\_procedures.html](http://med.stanford.edu/spectrum/b4_research_quality/b4_3_standard_operating_procedures.html).

- SCI Scientific Review Committee (SRC) Policies and Procedures

[http://med.stanford.edu/content/dam/sm/cancer/documents/PRMSDocuments/SRC\\_SOP.pdf](http://med.stanford.edu/content/dam/sm/cancer/documents/PRMSDocuments/SRC_SOP.pdf).

- Confirmation of Participant Eligibility in Clinical Trials

[http://med.stanford.edu/content/dam/sm/ccto/sunet\\_id\\_resources/regulatory\\_documents/sop/SOP\\_Participant\\_Eligibility\\_Confirmation.pdf](http://med.stanford.edu/content/dam/sm/ccto/sunet_id_resources/regulatory_documents/sop/SOP_Participant_Eligibility_Confirmation.pdf).

- SCI Institutional Data and Safety Monitoring Plan.

<http://med.stanford.edu/cancer/research/trial-support/dsmc.html>.

- SCI Data Management in Clinical Investigations

[http://med.stanford.edu/content/dam/sm/ccto/sunet\\_id\\_resources/regulatory\\_documents/sop/SOP-Data%20Management.pdf](http://med.stanford.edu/content/dam/sm/ccto/sunet_id_resources/regulatory_documents/sop/SOP-Data%20Management.pdf).

#### Logs and Forms:

- The SCI Adverse Event Log (editable):

[http://med.stanford.edu/content/dam/sm/ccto/sunet\\_id\\_resources/coordinator\\_documents/Adverse%20Event%20Log.pdf](http://med.stanford.edu/content/dam/sm/ccto/sunet_id_resources/coordinator_documents/Adverse%20Event%20Log.pdf).

- SCI Serious Adverse Event Report Form (editable):

[http://med.stanford.edu/content/dam/sm/ccto/sunet\\_id\\_resources/coordinator\\_documents/SAE\\_CRF.pdf](http://med.stanford.edu/content/dam/sm/ccto/sunet_id_resources/coordinator_documents/SAE_CRF.pdf).

- Sample Study Participant Log (editable):

[http://med.stanford.edu/content/dam/sm/ccto/sunet\\_id\\_resources/coordinator\\_documents/Subject\\_Log\\_07.29.11.doc](http://med.stanford.edu/content/dam/sm/ccto/sunet_id_resources/coordinator_documents/Subject_Log_07.29.11.doc).

#### Guidelines:

- SCI Guideline for Studies Relying on External Central or Single IRBs.

[http://med.stanford.edu/content/dam/sm/ccto/sunet\\_id\\_resources/regulatory\\_documents/NCTN%20Guideline\\_Studies\\_Relying\\_on\\_External\\_Central\\_or\\_Single\\_IRBs.pdf](http://med.stanford.edu/content/dam/sm/ccto/sunet_id_resources/regulatory_documents/NCTN%20Guideline_Studies_Relying_on_External_Central_or_Single_IRBs.pdf).

#### Current Stanford University IRB policies and procedures:

- Stanford University Human Research Protection Program (HRPP) Policy Manual at:

[http://researchcompliance.stanford.edu/hs/hrpp/Documents/hrpp\\_entire.pdf](http://researchcompliance.stanford.edu/hs/hrpp/Documents/hrpp_entire.pdf).

- Stanford University HRPP Policy Guidance Events and Information that Require Prompt Reporting to the IRB GUI-P13 at:

[http://humansubjects.stanford.edu/research/documents/Events-Info-Report-to-IRB\\_GUI03P13.pdf](http://humansubjects.stanford.edu/research/documents/Events-Info-Report-to-IRB_GUI03P13.pdf).

- Stanford University HRPP Unanticipated Problem reporting process is defined at Section 3.10, in the Human Research Protection Program (HRPP) Policy Manual

[http://researchcompliance.stanford.edu/hs/hrpp/Documents/hrpp\\_entire.pdf](http://researchcompliance.stanford.edu/hs/hrpp/Documents/hrpp_entire.pdf).

### Other regulatory documentation and resources

- Contact a Department of Biomedical Data Science (DBDS) biostatistician:

<https://redcap.stanford.edu/surveys/?s=7TTM3AELCT>.

- The US FDA requirements for adverse event reporting for investigational drugs are defined at 21CFR§312.32(a)

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.32>.

- The Common Terminology Criteria for Adverse Events (CTCAE) **version 5** are available at:

[https://ctep.cancer.gov/protocoldevelopment/electronic\\_applications/ctc.htm#ctc\\_50](https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50), see

[https://ctep.cancer.gov/protocoldevelopment/electronic\\_applications/docs/CTCAE\\_v5.0.xlsx](https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5.0.xlsx) OR

[https://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/CTCAE\\_v5\\_Quick\\_Reference\\_8.5x11.pdf](https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf).

- The International Conference on Harmonization (ICH) Guideline on Good Clinical Practice (ICH GCP E6r1), including adverse event reporting, is available at:

[http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Efficacy/E6/E6\\_R1\\_Guideline.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf).

These links may change from time to time, and will be updated in this template as needed. Consult issuing authority as needed.

**13.2. Appendix B. Reference reports submitted for DSMC audit**

- Delegation of Authority (DOR/DOA) log
- Statement of Investigator (FDA Form 1572)
- Electronic copies of source documents and CRFs, including signed informed consent forms, eligibility checklists with reviewer signatures
- Documents that are available in EPIC do not need to be and are not provided
- Direct access to electronic data capture EDC system is required for monitoring purposes, effective 9/21/2020
- Investigational Drug services (IDS) drug dispense log and report
- IDS Drug accountability records, temperature logs, drug orders, and shipment records
- Electronic copies of drug diary from each subject
- Protocol Deviation (PD) aggregate review deviations reported in EDC
- Documentation justifying the RP2D at the end of phase 1b portion of the study.
- Sample log documenting all samples collected for research purposes.