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Participating Institution: CCCWFU

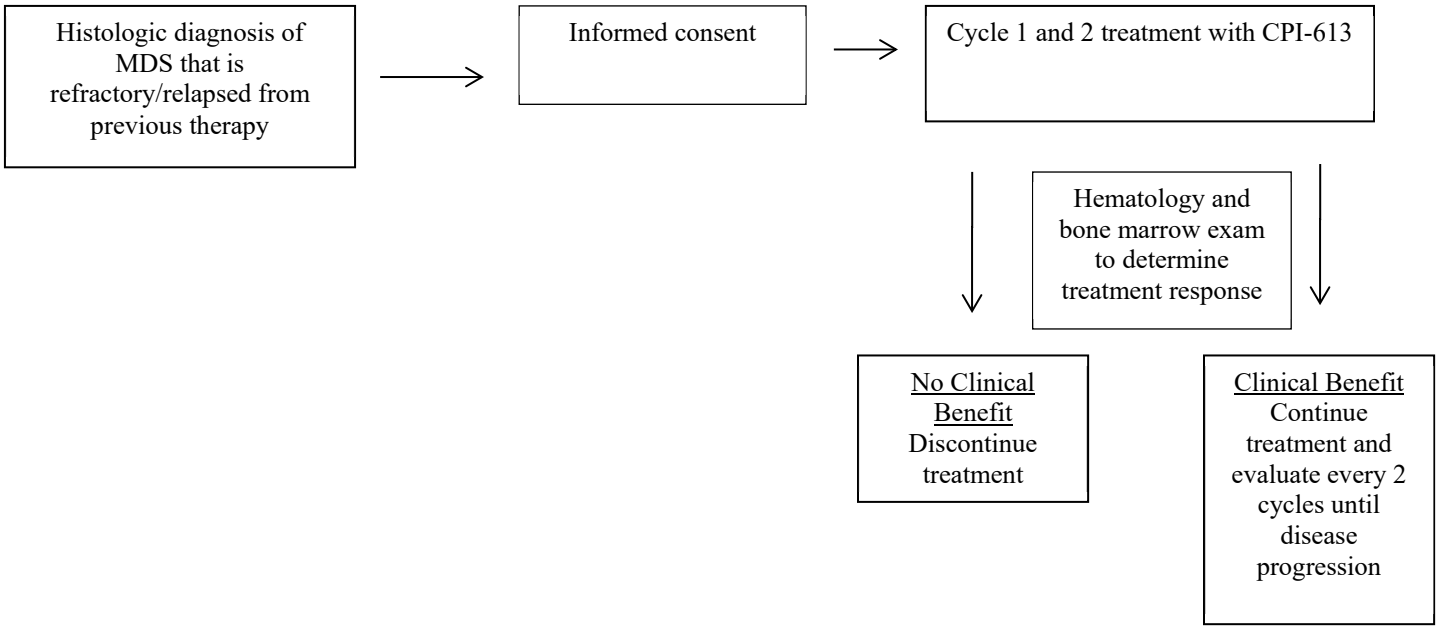
Investigational Drug:

CPI-613

IND Number: 107800

Date: 05/26/2017

SCHEMA



Primary Objective

To evaluate the response rate (RR) of CPI-613 in MDS patients who have failed previous therapy.

Secondary Objective

To evaluate the safety, progression-free-survival (PFS), overall survival (OS), and changes in the frequency of transfusion associated with treatment with CPI-613 in these patients.

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1.0 BACKGROUND AND STUDY OBJECTIVES

1.1 Myelodysplastic Syndrome

Myelodysplastic syndrome (MDS) is a diverse collection of hematological malignancies that involve dysplasia of the stem cells in the bone marrow, resulting in disorderly and ineffective hematopoiesis. The number and quality of blood-forming cells decline irreversibly, further impairing blood production. Patients with MDS often develop severe anemia resulting in susceptibility to infection, bleeding, etc., and require frequent blood transfusions. In most cases, the disease progresses over time and the patient develops cytopenia due to deteriorating bone marrow function. The outlook in MDS is poor, and some patients will progress to Acute Myeloid Leukemia (AML) within a few months. The median survival varies from years to months, depending on the risk level of the disease.

Treatment of MDS is complicated. Although allogeneic bone marrow transplant (BMT) is a potential curative treatment for MDS, a match donor is not always available. Furthermore, most patients with MDS are older and not appropriate candidates for BMT. The prognosis and treatment for MDS vary depending on the patient's International Prognostic Scoring System (IPSS) score (Greenberg et al. 1997). Regardless of risk category, a patient's age and existing comorbidities are also factored into treatment decisions. Patients with a Low/Intermediate-1-Risk score (IPSS 0-1) may live with their disease for a number of years. These patients are primarily treated with low-intensity supportive care, especially red blood cell transfusions, to treat their symptoms and maintain their quality of life. In small subsets of Low/Intermediate-1-Risk MDS patients, hematopoietic cytokines or antithymocyte globulin may reduce transfusion requirements. The drawbacks to these treatments are high failure rates even with improved predictive models, and high cost of cytokines. Patients with higher scores (intermediate-2 and high risk; IPSS $\geq$1.5) are at higher risk of transformation to AML and many will die from their disease within 1 year of diagnosis. Treatment of these patients is with intensive therapies using hypomethylating agents (decitabine and azacitidine). Unfortunately, these agents induce significant toxicities at therapeutic doses. Furthermore, after relapsing from a hypomethylating agent, there is essentially no effective treatment for this disease. Therefore, additional treatment options for MDS are greatly needed.

1.2 CPI-613

1.2.1 Background

CPI-613 is a novel anti-cancer agent (Zachar et al. 2011). It selectively targets the altered form of mitochondrial energy metabolism in tumor cells, causing changes in mitochondrial enzyme activities and redox status, which leads to apoptosis, necrosis and autophagy of tumor cells (Zachar et al. 2011). CPI-613 selectively acts on the altered catalytic and regulatory functions of pyruvate dehydrogenase complex (PDC) and the α-

ketoglutarate dehydrogenase complex (KGDHC) in tumor cells (Zachar et al. 2011). Due to its novel mechanism of action and the multi-molecular targeting approach, CPI-613 is equally effective against multi-drug resistance (MDR) cancer cell lines when compared to the parental untreated cancer cell lines, according to *in vitro* studies (Zachar et al. 2011).

Based on Phase I dose-escalated trials in patients with various advanced stages of solid and hematologic malignancies, CPI-613 has been found to be well-tolerated at doses up to 3,000 mg/m^2 when infused intravenously over 2 hours. CPI-613 also exhibits anti-tumor activities in patients with various malignancies (Pardee et al, 2011a and b, & 2012; Lee et al. 2011 & 2012; Senzer et al 2012), despite the fact that the Phase 1 patient population were those with relapsed or refractory disease.

1.2.2 Safety and Anti-Cancer Activities of CPI-613 against MDS

Preliminary results of CPI-613 against MDS were observed in the Phase I dose-escalation trial, entitled "An Open Label, Dose-Escalation Study to Evaluate Safety, Tolerability, Maximum Tolerated Dose (MTD), Efficacy & Pharmacokinetics (PKs) of CPI-613 Given 2x Weekly for 3 Weeks in Patients with Advanced Hematologic Malignancies" (Study# CCCWFU 29109). In this Phase 1 trial, study subjects had advanced histologically or cytologically documented relapsed or refractory hematologic malignancies for whom there is no available therapy known to provide clinical benefit. CPI-613 was administered IV. A treatment cycle was 3 weeks of 2x weekly dosing of CPI-613, followed by 1 week of rest. The dose of CPI-613 was escalated via a "1-3-6" dose escalation scheme, with the initial dose being 420 mg/m^2 and the highest dose being 3,780 mg/m^2. MTD was found to be 2940 mg/m^2, infused IV over 2 hrs.

Five of 26 patients in the Phase I dose-escalation trial had a diagnosis of MDS at time of enrollment. The demographics, prior therapies, and treatment information of these five patients are listed in Table 1.2.2 (below).

Table 1.2.2: Demographics, Prior Therapies and Treatment Responses in Patients with Myelodysplastic Syndrome (MDS) from the Phase 1 Dose-Escalated Trial of CPI-613, Study # CCCWFU 29109

Patient					Prior Therapies (start date: mm/dd/yr)	CPI-613 Treatment			Response Criteria[d]
#	Sex	Race	Age (yrs)	KPS (%)		Dose (mg/m^2)	# of Cycles Completed	Start Date	
004	M	Afr Am	48	80-90[c]	Ara-C/Dauno/VP-16 (3/1/04); HIDAC (cons)/ VP-16 (5/1/04); HIDAC/Mitoxantrone (12/1/08); Bulsulfan/VP-16 (5/1/10)	840-2205[a]	31 (ongoing)	12/6/10	Complete Remission
010	F	Cau	81	80-90[c]	Azacitidine (4/1/09); Decitabine (10/1/09)	2,100	8	7/18/11	Stable Disease
011	F	Cau	77	70	Decitabine (6/8/09)	1470-2940[b]	12	8/8/11	Stable Disease
013	F	Cau	57	80	7+3+3 (9/13/10); 5+2+2 (9/16/10); HIDAC cons x2 (11/3/10); unrelated ALLO Fludara/Busulfan (3/9/11)	2,940	1[e]	9/27/11	ND[e]
019	M	Cau	68	80	Azacytidine for 13 cycles (9/2/2010-	2940	1[f]	4/9/12	ND[f]

					3/28/2012)	(infused over 1 hour)			

Afr = African; Am = American; Ara-C = Cytarabine; Cau = Caucasian; Dauno = daunomycin or daunorubicin; F = female; HIDAC = high dose Cytarabine; KPS = Karnofsky Performance Status; M = male; ND = Not Determined; yr = year.

[a] The dose was 840 mg/m^2 for Cycles 1-6, 1,386 mg/m^2 for Cycles 7-10, 2,100 mg/m^2 for Cycles 11-19, and finally 2,940 mg/m^2 for Cycle 20, via intra-patient dose escalation scheme. Due to Grade 2 nausea at 2,940 mg/m^2, the dose was reduced to 2,205 mg/m^2 from Cycle 21 on.

[b] The dose was 2,100 mg/m^2 for Cycles 1-7, and was intended to escalate to 2,940 mg/m^2 via intra-patient dose escalation scheme. Due to renal adverse event associated with the first dose at 2,940 mg/m^2, the dose was reduced to 1,470 mg/m^2 from Cycle 7 on.

[c] Converted from ECOG to KFS according to the scales: 0 being 100; 1 being 80-90, 2 being 60-70, 3 being 40-50; and 4 being 20-30.

[d] Response criteria are according to Cheson et al. (2006).

[e] Off study due to uncontrolled infection, which began prior to CPI-613 treatment, after 1 cycle of treatment. Response criteria were not determined.

[f] Off study after one dose for renal adverse event.

Adverse events (AEs) were observed in Patient 011 and Patient 019. Patient 011was a 77 year old female with a KPS of 70% at the start of the trial. Patient 011 experienced taste alteration (Grade 1) and elevation of creatinine and reduction in glomerular filtration rate (both Grade 3) when treated with CPI-613 at 2,940 mg/m^2. When the dose was reduced to 2,100 mg/m^2, patients exhibited diarrhea, low serum bicarbonate and proteinuria (all Grade 1). All AEs were reversible upon termination of treatment. Patient 019 was a 68 year old male with a KPS of 70% at the start of the trial. He experienced acute renal failure after receiving one dose of CPI-613 at 2940 mg/m2 infused over 1 hour. His renal function recovered following cessation of therapy and returned to close to his baseline. While he was deciding if he wanted to resume therapy on protocol his disease progressed to AML and he was admitted for induction chemotherapy.

Anti-cancer activities were observed in all 3 evaluable MDS patients. Specifically, the first evaluable MDS patient (Patient 004) was transfusion-dependent prior to treatment with CPI-613 because of severe leukopenia and thrombopenia. Upon participation in the CPI-613 trial, he was treated with CPI-613 at 840 mg/m^2 for Cycles 1-6, 1,386 mg/m^2 for Cycle 7-10, 2,100 mg/m^2 for Cycles 11-19, and 2,940 mg/m^2 for Cycle 10, via intra-patient dose escalation scheme. Due to Grade 2 nausea at 2,940 mg/m^2, the dose was reduced to 2,205 mg/m^2 from Cycles 21 on. The patient did not receive a single transfusion starting at 1 cycle of treatment, due to improved white blood and platelet counts. He achieved complete remission (CR) after ~8 cycles of treatment in September 2011, and has maintained CR since then. The patient is currently on the 31th cycle (as of May 2013), and disease status continues to be CR. Figure 1.2.2-1a (below) shows the improvement in absolute neutrophil count (ANC) during the first ~11 cycles from pre-treatment level of ~2,000/μL to ~5,000/μL, and platelet counts from ~40,000/μL to >120,000/μL.

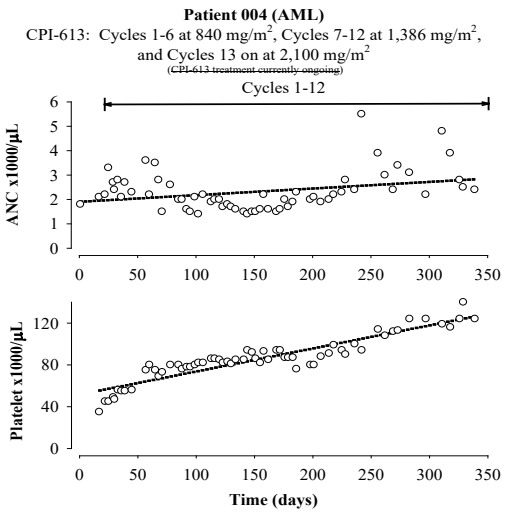


Figure 1.2.2-1a: Absolute neutrophil count (ANC, top) and platelet count (bottom) of Patient 004 pre and during treatment with CPI-613. The dotted line in each plot shows the trend of the plot.

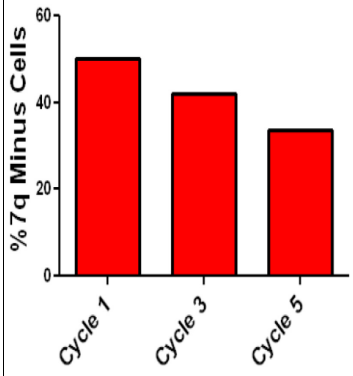


Figure 1.2.2-1b: 7q- or monosomy 7 values during the treatment with CPI-613 in Patient 004. The 7q- values are currently stabilized at ~50%.

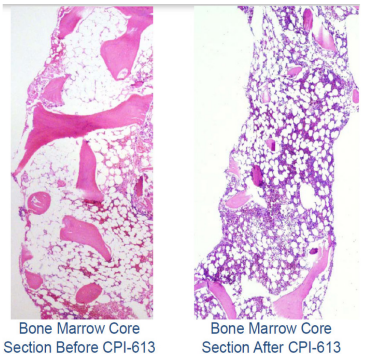
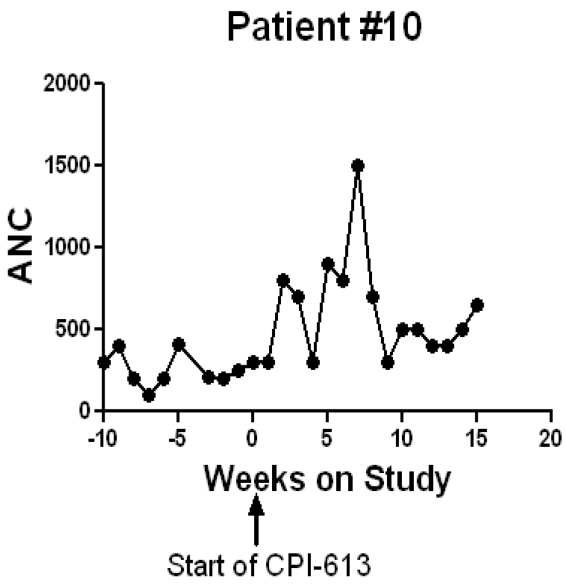


Figure 1.2.2-1c: Bone marrow before and after ~11 cycles of CPI-613 in Patient 004. The bone marrow was hypocellular prior to CPI-613 treatment (left panel), but was healthier with more bone marrow cells and less fat after CPI-613 treatment (right panel).

The efficacy of CPI-613 was further indicated by the reduction in 7q- (monosomy 7) values, an indication of cytogenetic anomaly, from ~50% after Cycle 1 to ~35 % after Cycle 5 (Figure 1.2.2-1b, above). Also, the bone marrow prior to CPI-613 treatment was hypocellular, exhibiting significant characteristic of advanced AML (Figure 1.2.2-1c, above). After ~11 cycles of CPI-613 treatment, the bone marrow was substantially healthier and with significantly more healthy bone marrow cells.

The second evaluable patient (Patient 010) is an 82 year old female with "high risk" MDS of Refractory Anemia with Excess of Blasts (RAEB)-2 (bone marrow blast cells 10-19%), who failed both decitabine and azacytidine treatments. She was admitted to hospitals 7 times for neutropenic fever during the 2 years prior to CPI-613 treatment. Upon treatment with CPI-613 at 2,100 mg/m^2, MDS improved to RAEB-1 (bone marrow blast cells 5-9%). She was not admitted for neutropenic fever since the start of CPI-613 treatment. ANC also improved with CPI-613 treatment (Figure 1.2.2-2, below). The patient achieved stable disease (SD) according to criteria described by Cheson et al. (2006) within a few cycles, and the condition of the disease continued to improve. By 8 cycles, the disease was close to partial remission (PR). Unfortunately, due to a fall, she was taken off the trial in order to received hospice care. CPI-613 treatment stopped and the patient passed away shortly after termination of CPI-613 treatment.

Figure 1.2.2-2: Absolute neutrophil count (ANC, top panel) and platelet count (bottom panel) of Patient 010 before and during the first 4 weeks of treatment with CPI-613. Patient 010 is an 82 year old female with "high risk" Myelodysplastic Syndromes (MDS) of Refractory Anemia with Excess of Blasts (RAEB)-2, who has failed both decitabine and azacytidine.



The third and last evaluable patient (Patient 011) is a 77 year old female with MDS. She was relapsed from decitabine, which had induced SD temporarily. Her bone marrow blast was 0%, and peripheral blast was barely detectable (~100/μL), before CPI-613 treatment. The patient has achieved SD with CPI-613 treatment and remained so during CPI-613 treatment. After 12 cycles of treatment with CPI-613, she was taken off the trial per protocol due to fever.

The first non-evaluable patient (Patient 013) was an eighty year old female with MDS. She was taken off the study after 1 cycle of treatment due to uncontrolled infection, which began prior to CPI-613 treatment. Accordingly, the efficacy of CPI-613 in this patient could not be evaluated. In spite of being treated with only 1 cycle (6 doses), possible anti-cancer activities were apparent, as reflected by a small upward trend in ANC values, without any changes in peripheral blasts, during treatment with CPI-613 (Figure 1.2.3-3, next page). Bone marrow blast remained to be within normal range of 2% before and during treatment with CPI-613. There was also no change in platelet counts associated with CPI-613 treatment.

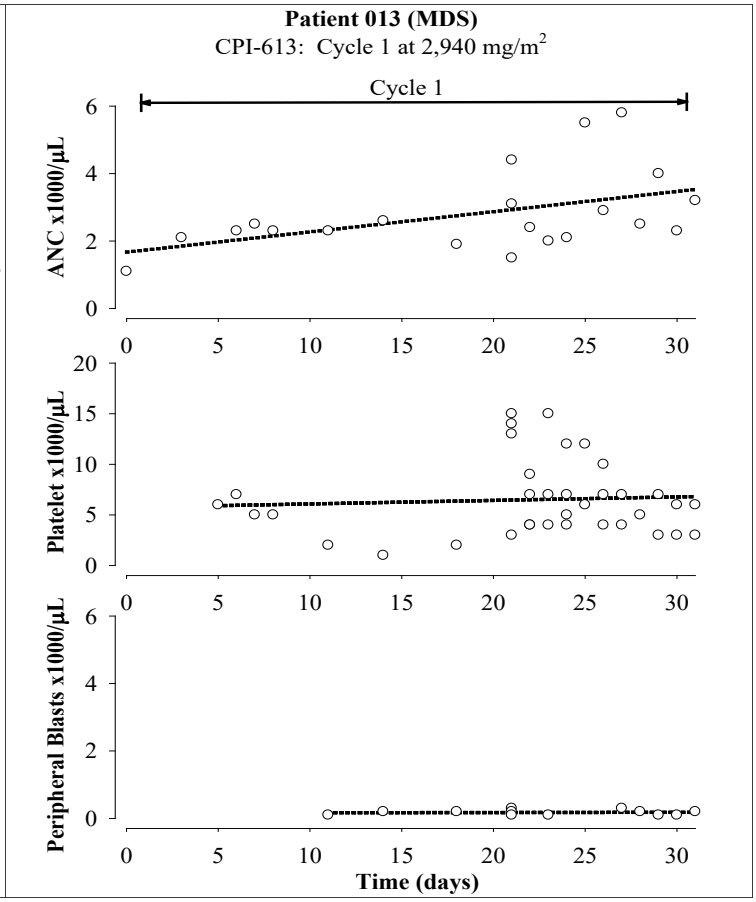


Figure 1.2.3-3: Absolute neutrophil count (ANC, top) and platelet count (bottom) of Patient 013 before and during treatment with CPI-613. The dotted line in each plot shows the trend of the plot. This patient was taken off the study after Cycle 1 due to uncontrolled infection developed prior to CPI-613 treatment.

In summary, CPI-613 has a novel mechanism of action, is well tolerated, and exhibits anti-cancer activities against various types of solid and hematologic malignancies (especially MDS), according to a Phase I dose-escalation trial. Accordingly, the safety and anti-cancer activities of CPI-613 in MDS patients who have failed hypomethylating agents are investigated in the current pilot study.

2.0 STUDY DESIGN

2.1 Study Objective

The objective of this study is to evaluate the safety and anti-cancer activities of CPI-613 in MDS patients who have failed previous agents (such as decitabine [Dacogen®], azacitidine [Vidaza®], growth factors or lenalidomide).

2.2 Outcome Measures

The primary outcome measure is to evaluate the response rate (RR) of CPI-613 in these patients. Response rate is defined as the combined rate of complete remission (CR), marrow CR, partial remission (PR), or stable disease (SD) as described by Cheson, et al. (2006).

The secondary outcome measures are:

- Safety
- Progression-free-survival (PFS)
- Overall survival (OS)
- Changes in the frequency of blood transfusion
- Hematologic improvement (HI; as defined by Cheson et al . [2006])

2.3 Open-Label, Single-Arm Study Design

This is a pilot single-arm open-label study. The investigators and study subjects are not blinded to the treatment. Also, the assignment of patients will not be randomized, since there is only a single arm in this study.

3.0 PATIENT ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

Patients must meet all of the following inclusion criteria before enrollment:

A. Histologically or cytologically documented MDS of any risk group that has failed previous therapy. (Therapy failure is defined as patients who have been sufficiently treated with previous agents without response in the opinion of the treating physician, or whose disease has progressed or relapsed while on a hypomethylating agent.)
B. ECOG Performance Status of ≤3.
C. Men and women 18 years of age or older.
D. Expected survival >2 months.

E. Women of child-bearing potential (i.e., women who are pre-menopausal or not surgically sterile) must use accepted contraceptive methods (abstinence, intrauterine device [IUD], oral contraceptive or double barrier device) during the study, and must have a negative serum or urine pregnancy test within 1 week prior to treatment initiation.
F. Fertile men must practice effective contraceptive methods during the study, unless documentation of infertility exists.
G. Patients must have fully recovered from the acute, non-hematological, non-infectious toxicities of any prior treatment with cytotoxic drugs, radiotherapy or other anti-cancer modalities. Patients with persisting, non-hematologic, non-infectious toxicities from prior treatment ≤ Grade 2 are eligible, but must be documented as such.
H. Laboratory values obtained ≤2 weeks prior to enrollment must demonstrate adequate hepatic function, renal function, and coagulation as defined below:
    - aspartate aminotransferase [AST/SGOT] ≤3x upper normal limit [UNL]
    - alanine aminotransferase [ALT/SGPT] ≤3x UNL (≤5x ULN if liver metastases present)
    - bilirubin ≤1.5x UNL
    - serum creatinine ≤1.5 mg/dL or 133 μmol/L
    - Albumin ≥2.0 g/dL or ≥20 g/L.
I. Mentally competent, ability to understand and willingness to sign an IRB-approved written informed consent form.
J. Have access via central line (e.g., portacath).

3.2 Exclusion Criteria

Patients with the following characteristics are excluded:

A. Serious medical illness, such as significant cardiac disease (e.g. symptomatic congestive heart failure, unstable angina pectoris, coronary artery disease, myocardial infarction within the past 3 months, uncontrolled cardiac arrhythmia, pericardial disease or New York Heart Association Class III or IV), or severe debilitating pulmonary disease, that would potentially increase patients' risk for toxicity.
B. Patients with active central nervous system (CNS) or epidural tumor.
C. Any active uncontrolled bleeding or bleeding diathesis (e.g., active peptic ulcer disease).
D. Any condition or abnormality which may, in the opinion of the investigator, compromise his or her safety.
E. Pregnant women, or women of child-bearing potential not using reliable means of contraception.
F. Fertile men unwilling to practice contraceptive methods during the study period.
G. Lactating females.
H. Life expectancy less than 2 months.
I. Unwilling or unable to follow protocol requirements.

J. A history of additional risk factors for torsade de pointes (e.g., heart failure, hypokalemia, family history of Long QT Syndrome, etc.)
K. Evidence of active infection or serious infection within the past month.
L. Requirement for immediate palliative treatment of any kind including surgery.
M. Prior illicit drug addiction.
N. Patients with large and recurrent pleural or peritoneal effusions requiring frequent drainage (e.g. weekly).
O. Patients with any amount of clinically significant pericardial effusion.
P. Patients with known HIV infection. (**Note:** Patients with known HIV infection are excluded because patients with an immune deficiency are at increased risk of lethal infections when treated with marrow-suppressive therapy, and because there may be unknown or dangerous drug interactions between CPI-613 and anti-retroviral agents used to treat HIV infections).
Q. Patients who have received radiotherapy, surgery, treatment with cytotoxic agents (except CPI-613), treatment with biologic agents, immunotherapy, or any other anti-cancer therapy of any kind, or any other standard or investigational treatment for their cancer, or any other investigational agent for any indication, within the past 2 weeks prior to initiation of CPI-613 treatment.
R. Patients that have received a chemotherapy regimen with stem cell support in the previous 6 months.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for participation in this trial.

4.0 REGISTRATION PROCEDURES

All patients entered on any CCCWFU trial, whether treatment, companion, or cancer control trial, **must** be registered with the CCCWFU Protocol Registrar or entered into the Oncology Research Information System (ORIS) Screening Log within 24 hours of informed consent.

Patients **must** be registered prior to the initiation of treatment. In order to ensure prompt registration of your patient, please:

1. Complete the Eligibility Checklist (Appendix A)
2. Complete the Protocol Registration Form (Appendix A)
3. Alert the WFUHS registrar by phone, *and then* send the signed Informed Consent Form, Eligibility Checklist and Protocol Registration Form to the registrar, either by fax or e-mail.

Contact Information:

Protocol Registrar PHONE (336) 713-6767
Protocol Registrar FAX (336) 713-6772
Protocol Registrar E-MAIL (registra@wakehealth.edu)

(*Protocol Registration is open from 8:30 AM - 4:00 PM, Monday-Friday.)

Please fax/e-mail ALL eligibility source documents with registration. Patients **will not** be registered without all required supporting documents.

Note: If labs were performed at an outside institution, please provide a printout of the results. Please ensure that the most recent lab values are sent.

To complete the registration process, the Registrar will:

- assign a patient study number
- register the patient on the study

5.0 STUDY PROCEDURES

Table 5-1 (below) provides an overview of assessments and procedures conducted during the pre-study screen and during each treatment cycle. Specifics are described in subsequent sections.

Table 5-1: Study Procedures

Assessments	Pre-study[8]	Each Treatment Cycle (1 cycle = 4 weeks)					Follow-Up
		Day 1	Day 2	Day 3	Day 4	Day 5	
Medical history	√						
Physical exam, height, weight, vitals	√	√[2]					
Pregnancy test	√						
Evaluation of symptoms and vital signs	√	√[2]	√[2]	√[2]	√[2]	√[2]	
ECOG performance status and survival	√	√[2]					
Clinical chemistry, hematology and coagulation[3,6]	√	√[2]					
BMP			√	√	√	√	
CPI-613[1]		√	√	√	√	√	
Assessment of response[4,6,7]		Cycles 2, 4, 6 (and every 3 cycles thereafter until disease progression)					
Bone marrow exam[6]	√	Cycles 3 and 6 (and at the discretion of the physician or if peripheral blood criteria for a complete remission are met (ie ANC>1000, Platelets >100k and freedom from blood transfusions) thereafter until disease progression)					
Survival and post-study follow-up[5]							√

CR = Complete Remission; D1 = day 1; D4 = day 4; ECOG = Eastern Cooperative Oncology Group; hr = hour; min = minute; PR = Partial Remission.

[1] CPI-613 is given as a 2-hr IV infusion via a central venous catheter.

[2] These tests are performed with results available for review within 24 hrs before administration of the anti-tumor agents.

[3] Specific chemistry, hematology and coagulation are listed in section 5.2.2. Renal function will be assessed utilizing the Cockcroft-Gault formula.

[4] Cycles 2, 4, 6 (and every 3 cycles thereafter until disease progression).

[5] Survival and post-study cancer treatment will be monitored by the treating physician during routine follow-up visits for 5 years or until death.

[6] CR, marrow CR, and PR will be assessed using hematology results from blood work and bone marrow exam results, according to the criteria described by Cheson et al. (2006).

[7] Frequency of transfusion is defined as the number of transfusions received during the previous 8 weeks. The baseline assessment should reflect the number of transfusions received in the 8 weeks prior to enrollment. On-treatment assessments should be performed at the end of cycles 2, 4, and 6, and every 3 cycles thereafter until progression)

[8] Pre-study requirements must be performed within the following time frames: **Within 4 weeks**: bone marrow exam; **Within 2 weeks**: medical history, physical exam, vital signs, height, weight, ECOG, evaluation of symptoms and medications, clinical chemistry, hematology, and coagulation; **Within 1 week**: pregnancy test for women of child-bearing potential and frequency of transfusion.

5.1 Pre-Study Screening Tests and Safety Assessment

5.1.1 Pre-Study Screening Tests

Pre-study screening tests, which are also enrollment evaluations, must be performed according the following time frames:

Within 4 weeks: bone marrow exam.
Within 2 weeks: medical history, physical exam, vital signs, height, weight, ECOG, evaluation of symptoms and medications, clinical chemistry, hematology, and coagulation.
Within 1 week: pregnancy test for women of child-bearing potential and frequency of transfusion.

5.1.2 Safety Assessment

The safety of CPI-613 will be assessed from the first dose to 1 month after last dose of CPI-613. The assessment will be based on:

- evaluation of symptoms
- vital signs
- ECOG performance status and survival
- clinical chemistry (and renal function utilizing the Cockcroft-Gault formula)
- hematology
- coagulation

The specifics of the safety tests are described in Section 5.2. All safety assessment tests are performed during screening (performed within 2 weeks prior to treatment with CPI-613). Additionally, evaluation of symptoms, vital signs, and survival will be assessed on each treatment day, with results available for review within 24 hours before administrationCPI-613. ECOG performance status will be assessed on Day 1 of each course. Clinical chemistry (renal function utilizing the Cockcroft-Gault formula) hematology, and coagulation will be performed on Day 1 of each treatment cycle, with results available for review within 24 hours before administration CPI-613.

5.1.3 Assessment of Anti-Cancer Activities

Tumor response will be assessed based on RR, PFS, and OS (as described by Cheson et al. 2006), as well as changes in the frequency of transfusion from baseline. RR and PFS, derived from hematology and bone marrow exam. Hematology will be assessed at baseline, during week 4 of every 2 treatment cycles until cycle 6, and then every 3 treatment cycles thereafter until disease progression. Bone marrow will be assessed at baseline, cycle 3 and 6 and then at the discretion of the physician or if peripheral blood criteria for a complete remission are met (ie ANC>1000, Platelets >100k and freedom from blood transfusions) thereafter until disease progression.

Baseline frequency should be recorded as the number of transfusions received during the 8 weeks prior to enrollment. Once patients have started protocol treatment, transfusion

frequency should be assessed at the end of every 2 treatment cycles.

Survival will be assessed during the study and will be monitored by treating physician contact after the patients are taken off the trial.

5.2 Specifics of Tests Performed During the Study

Described below are the specifics of the tests performed in this study.

5.2.1 ECOG Performance Status

The ECOG Performance Status scales (Oken et al 1982) will be used to assess how a patient's disease is progressing and assess how the disease affects the daily living abilities of the patient. These scales are listed in Table 5.2.1-1 (below). The higher the ECOG score, the worse the prognosis.

Table 5.2.1-1: Scales Used in ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

5.2.2 Clinical Chemistry, Hematology and Coagulation

Clinical chemistry assessed includes:

glucose	albumin
creatinine	total protein
Na^+	BUN
K^+	AST/serum glutamic-oxaloacetic transaminase (SGOT)
Cl^-	ALT/serum glutamic-pyruvic transaminase (SGPT)
Mg	alkaline phosphatase (ALP)
Ca^{+2}	lactate dehydrogenase (LDH)
PO_4	total bilirubin
CO_2	

Hematology includes:

complete blood count	hemoglobin
differential count	hematocrit
platelet count	

Coagulation includes:

Prothrombin time	Partial thromboplastin time

5.2.3 Bone Marrow Exam

The following parameters from bone marrow exam must be recorded in Appendix E (Data Collection Form for Bone Marrow Exam):

- Morphology
- Immunophenotype
- Cellularity
- Karyotype (cytogenetics and FISH as applicable)
- Molecular markers
- % of bone marrow myeloblasts
- % of dysplasia
- IPSS classification

6.0 TREATMENT WITH CPI-613

CPI-613 will be administered to patients as shown in Table 6-1 (below). Briefly, a treatment cycle is 4 weeks, with CPI-613 given on Days 1 through 5 of the first week (i.e., 1-week-on-3-weeks-off). Patients will receive pre-treatment antiemetics and supportive measures as determined by their treating physician. The default premedication will consist of odansetron 16mg IV infused 15 min prior to therapy.

Table 6-1: Administration of CPI-613 in MDS Patients Who Has Failed Previous Agents

Treatment Cycles			**Administration of CPI-613**
	Week	**Day**	
Cycle 1 (4 weeks)	1	1	2-hr IV infusion via a central venous catheter
		2	2-hr IV infusion via a central venous catheter
		3	2-hr IV infusion via a central venous catheter
		4	2-hr IV infusion via a central venous catheter
		5	2-hr IV infusion via a central venous catheter
	2		
	3		
	4		
Cycle 2 (4 weeks)	1	1	2-hr IV infusion via a central venous catheter
		2	2-hr IV infusion via a central venous catheter
		3	2-hr IV infusion via a central venous catheter
		4	2-hr IV infusion via a central venous catheter
		5	2-hr IV infusion via a central venous catheter
	2		
	3		
	4		Bone marrow biopsy (week 4 of cycles 3 and

			6, then at the discretion of the physician or if peripheral blood criteria for a complete remission are met (ie ANC>1000, Platelets >100k and freedom from blood transfusions) thereafter until disease progression)
Etc., until termination of treatment as described in Section 6.3.			

hr = hour; IV = intravenous; min = minutes

6.1 Sample Size, Dose Levels and Justification of the Dose

The sample size will be 20 for this pilot trial.

The dose will be the maximum tolerated dose (MTD) determined from CCCWFU 22112, entitled "*An Open Label, Dose-Escalation Study to Evaluate Safety, Tolerability, Maximum Tolerated Dose (MTD), Efficacy, and Pharmacokinetics (PKs) of CPI-613 given with High Dose Cytarabine and Mitoxantrone in Patients with Relapsed or Refractory Acute Myeloid Leukemia (AML)*", sponsored by Dr. Timothy Pardee. This dose was determined to be 2500mg/m^2.

6.2 Dosing Delay and Dose Modification of CPI-613 in the Event of Adverse Events

For adverse events unrelated to serum creatinine elevation or reduction in renal function but are possibly, probably or definitely related to CPI-613, the occurrence of Grade 1 toxicity does not generally require dose modification for subsequent doses for that patient. However, if Grade 2 toxicity (other than diarrhea and nausea) develop, treatment is to be withheld and can resume only after the Grade 2 toxicity has been reduced to Grade 1 or below, and the dose level for subsequent doses for that patient will be reduced by 25%. Grade 2 nausea and diarrhea do not require withholding treatment or dose reduction. If Grade 3 or 4 toxicity related to CPI-613 develops, dosing of CPI-613 of that patient will be withheld and the patient shall be monitored for recovery from, and reversibility of, such Grade 3 or 4 toxicity. To resume treatment with CPI-613 for a patient who has had CPI-613-related Grade 3 or 4 toxicity, the Grade 3 or 4 toxicity must be reduced to Grade 1 or below, and the dose level for subsequent doses for that patient will be reduced by 50%. Patients can be re-dose-escalated at the discretion of their treating physician as long as no recurrence of the toxicity is seen at the reduced dose.

For adverse events related to creatinine elevation or reduction in renal function that are possibly, probably or definitely related to CPI-613, dosing of the patient will be withheld even if the severity level is Grade 1 or above. Treatment can resume only after the toxicity has been reduced to Grade 0. The dose level for subsequent doses for that patient will be reduced by 15% if the severity level is of Grade 1, by 25% for Grade 2 toxicity, and by 50% for Grade 3 or 4 toxicity.

Furthermore, if the toxicity possibly, probably or definitely related to CPI-613 is acute renal failure and the severity level is Grade 3 or 4, further patient enrollment will be temporarily suspended in order to enable assessment of the following aspects of the trial and implementation of corrective measures or protocol amendment, and if necessary:

- compliance of the investigators to the study protocol
- evaluation of the appropriateness of the procedures for monitoring renal function

6.3 Duration of Treatment for Each Patient

Treatment with CPI-613 should be continued as long as the treating physician believes there is clinical benefit, unless or until:

- Patients exhibit disease progression
- Unacceptable toxicity from CPI-613 in spite of dose reduction
- Patient withdrawal of consent
- Investigator's discretion to withdraw patients from the study because continued participation in the study is not in the patient's best interest.
- Undercurrent illness: a condition, injury, or disease unrelated to the intended disease for which the study is investigating, that renders continuing the treatment unsafe or regular follow-up impossible
- General or specific changes in the patient's condition that renders the patient ineligible for further investigational treatment
- Non-compliance with investigational treatment, protocol-required evaluations or follow-up visits
- Termination of the clinical trial by the sponsor of CPI-613

When terminating treatment during this trial, the investigator should make every effort to contact the patient and to perform a final evaluation. Also, the reason(s) for withdrawal from the study must be recorded.

Upon being taken off the trial, patient's survival and post-study cancer treatment will be monitored by follow up physician visits once patients are removed from trial. All patients will be followed for 5 years post treatment, or until death.

7.0 STUDY DRUG - CPI-613

7.1 Description of CPI-613 Drug Product

CPI-613 is provided in 10-mL amber glass vials. Each vial contains 10 mL of CPI-613 at a concentration 50 mg/mL, equivalent to 500 mg of CPI-613. The drug product of CPI-613 is a clear and colorless solution that is free of any particulate matter.

7.2 Handling of CPI-613

CPI-613 is an investigational drug and its toxicity in humans is not fully understood. All necessary precautions in handling potentially toxic chemicals must be strictly adhered to. Gloves and protective clothing must be worn when handling CPI-613. Avoid contact by all modes of exposure. If the solution contacts the skin, it must be washed immediately and thoroughly with soap and water. If the solution comes in contact with mucous membranes, the membranes must be flushed thoroughly with water. Spills should be picked up with absorbent material and the area must be washed at least 3 times with ethyl alcohol followed by water.

CPI-613 drug product is slightly photosensitive (Study# PHO-001). Therefore, after removal of CPI-613 drug product from the amber vials, CPI-613 drug product should be protected from

excessive light before administration to patients.

7.3 Storage of CPI-613

CPI-613 should be stored under refrigeration, at 2˚-8˚C (36˚-46˚F), except when being prepared for administration.

7.4 IV Infusion Sets, Syringes and IV Bags to be used for Administration of CPI-613

CPI-613 must be administered IV by infusion, via an IV catheter with D5W running at a rate of about 125-150 mL/hr. To avoid local reactions at and around the site of administration, CPI-613 should be administered via a central venous catheter. Subsequent sections describe the appropriate types of IV catheters, IV bags, syringes and clinical solutions that can be used in mixing and administering CPI-613 to patients.

Leaching of Diethylhexyl Phthalate (DEHP): CPI-613 can cause leaching of DEHP from IV infusion sets and IV bags (Study COM-003). Therefore, DEHP-containing IV infusion sets, IV bags or syringes should not be used in mixing or administration of CPI-613. Examples of the IV sets, IV bags and syringes that do not contains DEHP and therefore can be used in the administration of CPI-613 are:

Extension Set for Syringe Pump Use: All extension sets from MED-RX do not contain DEHP.

Syringes: All Monoject syringes are DEHP free.

IV Infusion Sets: A compatibility study has been conducted showing that CPI-613 is compatible with 4 commonly used IV infusion sets (Study# COM-001). Therefore, these 4 types of IV infusion sets, and IV infusion sets that are made with the same materials, can be used to administer CPI-613. These IV infusion sets are:

- PVC material - ADDitIV® Primary IV Set with Universal Spike, Backcheck Valve, 2 Injection Sites, DEHP-Free and Latex-Free, 15 drops/mL, REF V14453, B Braun Medical Inc.
- Latex material - Interlink® System Secondary Medication Set, 10 drops/mL, 2C7451, Baxter Healthcare Corporation
- PVC material - Surshield™ Safety Winged Infusion Set, 0.19 mL Volume, Latex-Free, DEHP-Free, SV*S25BLS, Terumo Medical Products Hangzhou Co. Ltd.
- Polyethylene material - Interlink® System Paclitaxel Set by Baxter HealthCare, Non DEHP-free: Polyethylene tubing with a 0.22 microfilter Item # 2C7558 10 drops/mL

Syringes: Compatibility studies (Studies# COM-001 and COM-002) have shown that CPI-613 drug product (50 mg/mL), and drug product diluted with D5W to various concentrations (1.6-25 mg/mL) are compatible with various types of syringes, as listed below. Therefore, any of these types of syringes, and syringes that are made with the same materials, can be used to administer CPI-613. Also, glass syringes can also be used, since glass (such as glass containers) is compatible with CPI-613 drug product.

- Norm-Ject, polyethlyene barrel, polyethylene plunger, latex free (Henke Sass

Wolf GMBH) syringes
- Becton Dickinson syringes
- Terumo syringes
- Monoject syringes
- Glass syringes

7.5 Reconstitution and Administration of CPI-613

CPI-613 must be diluted from 50 mg/mL to 12.5 mg/mL with 5% Dextrose Water or D5W (i.e., 1 portion of CPI-613 diluted with 3 portions of D5W) prior to administration. The diluted drug product should be visually inspected for clarity. If haziness, precipitate or coloration (other than colorless) is observed, do not use the diluted drug product for dosing. After dilution with sterile D5W, the solution is clear and has a pH of 8.4-8.8. The diluted CPI-613 drug product has been found to be stable for 24 hrs at room temperature and refrigeration temperature (Studies STA-010).

CPI-613 must be administered IV, via an IV catheter that is free flowing and free of air in the dead space of the IV catheter, to minimize vascular irritation, inflammation and acute toxicity of CPI-613 (Study NCL-049). Accidental co-administration of extra air in the dead space of IV catheters during administration of CPI-613 has demonstrated the potential to induce acute toxicity of CPI-613 according to animal studies (Study NCL-049). Also, accidental leakage of CPI-613 into the perivascular space during IV administration, which prolongs exposure of perivascular tissue to CPI-613, can induce significant local inflammation according to animal studies (Studies NCL-027 and NCL-030). To avoid local reactions at and around the site of administration, CPI-613 must be administered via a central venous catheter.

CPI-613 must not be administered as a bolus, but by infusion, at a rate of ~0.5 mL/min, via a central venous catheter with D5W running at a rate of about 125-150 mL/hr. This is to minimize potential acute toxicity of CPI-613, according to animal studies (Study NCL-049).

The following precautions must be taken when administering CPI-613:

A. Confirmation of the placement of the IV line to ensure a lack of leakage of CPI-613 into the perivascular space.
B. Confirmation that the IV line is free flowing.
C. Confirmation that the IV line is free of dead air space.
D. Dilute CPI-613 drug product with D5W, as instructed in the study protocol.
E. Administer CPI-613 by infusion, not as a bolus.
F. After administration of CPI-613, flush the IV line with ~10 mL of D5W to remove residual CPI-613.
G. To avoid local reactions at and around the site of administration, CPI-613 should be administered via a central venous catheter.

7.6 Request for CPI-613

CPI-613 must be requested from Cornerstone by the Principal Investigator (or authorized designees). CPI-613 may not be used outside the scope of this protocol, nor can it be transferred or licensed to any party not participating in this clinical study. Cornerstone policy requires that

CPI-613 be shipped directly to the institution where the patient is to be treated. Cornerstone does not permit the transfer of CPI-613 between institutions (unless with prior written approval from Cornerstone). Requests must be submitted to Cornerstone by fax or email to the following address:

Ms. Claudia Maturo
Department of Regulatory and Clinical Affairs
Cornerstone Pharmaceuticals, Inc.
25 Health Sciences Drive
Stony Brook, NY 11790
Telephone: 631-444-6868
Telefax: 631-444-6895
Email: claudia@cornerstonepharma.com

The following information must be provided in the request of CPI-613 from Cornerstone:

- Names of the principal investigator and the requestor (if different)
- Name of the study site
- Name of the pharmacist responsible for receiving and storing CPI-613
- Name of the person and address where CPI-613 is to be shipped to
- Amount (# vials) requested
- Date of request
- Date shipment expected
- Study Protocol (title and protocol#) for which the requested CPI-613 is to be used

7.7 Procurement of Investigational Drug

Relevant regulations require investigators to establish a record of the receipt, use and disposition of all investigational products. Investigators may delegate responsibility of drug ordering, storage, accountability and preparation to their designees.

The investigator, or the designee, will be responsible for dispensing and accounting of CPI-613 provided by Cornerstone and for exercising accepted medical and pharmacy practices.

Records of inventory, dispensation and disposition (vials received, source and dates) must be maintained. In addition, all doses dispensed should be accounted for by recording the date, study number and name, patient identification, patient initials, patient medical record number and balance forward. These records must be maintained and kept at the study site, and will be reviewed by Cornerstone, or its designee, during periodic monitoring visits.

7.8 Disposal of CPI-613

The following procedures are to be taken in disposal of CPI-613:

- During the study, store the used CPI-613 vials (which must be separate from the unused CPI-613 vials) at room temperature in an access-limited area. Alternatively, destroy the used CPI-613 vials according to institutional policy after documentation of the number of used CPI-613 vials and remaining volume in each used vial.

- At the end of the study, deface the label (both used and unused vials) with a permanent marking pen.
- For used CPI-613 vials (if not already destroyed according to institutional policy), after documentation of the number of used CPI-613 units and remaining volume in each container, the used containers should be destroyed at the site according to the institutional procedures for destroying toxic chemicals. A certificate documenting the destruction of used vials must be kept on file.
- All unused CPI-613 vials must be destroyed according to the policy of the institution. The destruction of CPI-613, and the quantity destroyed, must be documented. A copy of the Certificate of Destruction should be sent to:

Ms. Claudia Maturo
Department of Regulatory and Clinical Affairs
Cornerstone Pharmaceuticals, Inc.
25 Health Sciences Drive
Stony Brook, NY 11790
Telephone: 631-444-6868
Telefax: 631-444-6895
Email: claudia@cornerstonepharma.com

7.9 Calculation of the Amount of CPI-613 for Each Patient

The amount of CPI-613 at each dose level is based on the BSA of the patient. The BSA values will be calculated based on the height and body weight taken during screening and this BSA value is used throughout the study. This is unless there is a >10% change in the body weight from baseline during the study. At that point, BSA should be revised based on the new body weight and height. The new BSA values will be used from that point on for the remainder of the study, unless there is another >10% change in body weight which will require another revision of the BSA.

7.10 Concomitant Medications and Prophylactic Treatment

Patients cannot receive any standard or investigational treatment (except CPI-613) for their cancer, or any other investigational drugs for any non-cancer indications, while on this study. All otherwise permitted concomitant medications (including trade and generic names, dosage and dosing schedule) must be recorded. Treatment of disease-related symptoms (such as nausea) is permitted. Medications administered in such instances will be considered concomitant medications and should be documented accordingly. Supportive treatment may include anti-emetic, anti-diarrhea, anti-pyretic, anti-allergic, anti-hypertensive medications, analgesics, antibiotics, allopurinol, and others such as blood products and bone marrow growth factors. Patients may use erythropoietin for chronic anemia. The treating physician may utilize erythropoietic factors, or blood or platelet transfusions at their discretion.

8.0 ADVERSE EVENTS LIST AND REPORTING REQUIREMENTS

8.1 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE 4.0) will be utilized for AE reporting. The CTEP Active Version of the CTCAE is identified and located on the CTEP website at (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE.

- **'Expectedness'**: AEs can be 'Unexpected' or 'Expected' (see Section 7.1 above) for expedited reporting purposes only.

- **Attribution** of the AE:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

List of Adverse Events to be Reported:

Abdominal pain
Alkaline phosphatase
ALT (SGPT)
Anorexia
AST (SGOT)
Bilirubin (hyperbilirubinemia)
Calcium (hypercalcemia, hypocalcemia)
Creatinine
Diarrhea
Flushing
Hemoglobin (anemia)
Injection site reaction
Leukocytes
Lymphopenia
Nausea
Neutrophils (neutropenia)
Platelets (thrombocytopenia)
Potassium
Sodium
Vomiting

All grade 3, 4, 5 adverse events should be reported on flow sheets and in ORIS regardless of whether they are on this list.

All AEs are described in the Investigator's Brochure, and all of them are considered "expected".

All Serious Adverse Events (SAEs) which are Possibly, Probably or Definitively Related to CPI-613, and Unexpected are required to be reported to Cornerstone Pharmaceuticals via the provided SAE Reporting Form within 7 days. All completed forms must be sent to Ms. Claudia Moore at Cornerstone. Cornerstone will submit any applicable SAEs to the FDA.

SAE reports must be submitted to Cornerstone by fax or email to the following address:

Department of Regulatory and Clinical Affairs
Cornerstone Pharmaceuticals, Inc.
25 Health Sciences Drive
Stony Brook, NY 11790
Telephone: 631-444-6868
Telefax: 631-444-6895
Email: claudiamoore2001@yahoo.com

8.2 STRC SAE Reporting Requirements

The Safety and Toxicity Review Committee (STRC) is responsible for reviewing SAEs for CCCWFU Institutional studies as outlined in Appendix B. STRC currently requires that all unexpected grade 4 and all grade 5 SAE's on these trials be reported to them for review. This procedure is a part of the CCCWFU Data Safety Monitoring Plan that our institution has on file at the NCI. All CRM staff members assisting a PI in investigating, documenting and reporting an SAE qualifying for STRC reporting are responsible for informing a clinical member of the STRC committee as well as the entire committee via the email notification procedure of the occurrence of an SAE.

8.3 WFUHS IRB AE Reporting Requirements

Any unanticipated problems involving risks to subjects or others and adverse events shall be promptly reported to the IRB, according to institutional policy. Reporting to the IRB is required regardless of the funding source, study sponsor, or whether the event involves an investigational or marketed drug, biologic or device. Reportable events are not limited to physical injury, but include psychological, economic and social harm. Reportable events may arise as a result of drugs, biological agents, devices, procedures or other interventions, or as a result of questionnaires, surveys, observations or other interactions with research subjects.

All members of the research team are responsible for the appropriate reporting to the IRB and other applicable parties of unanticipated problems involving risk to subjects or others. The Principal Investigator, however, is ultimately responsible for ensuring the prompt reporting of unanticipated problems involving risk to subjects or others to the IRB. The Principal Investigator is also responsible for ensuring that all reported unanticipated risks to subjects and others which they receive are reviewed to determine whether the report represents a change in the risks and/or benefits to study participants, and whether any changes in the informed consent, protocol or other study-related documents are required.

Any unanticipated problems involving risks to subjects or others occurring at a site where the

study has been approved by the WFUHS IRB (internal events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any unanticipated problems involving risks to subjects or others occurring at another site conducting the same study that has been approved by the WFUHS IRB (external events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any event, incident, experience, or outcome that alters the risk versus potential benefit of the research and as a result warrants a substantive change in the research protocol or informed consent process/document in order to insure the safety, rights or welfare of research subjects.

9.0 STATISTICAL CONSIDERATIONS

This is a pilot study with the primary goal to be able to determine initial estimates of RR, and secondary goals to determine PFS and OS. Data from this trial will also provide additional data concerning the safety profile of the CPI-613 therapy. The anticipated accrual rates, proposed analyses, and sample size considerations are described below.

Accrual Rate

We anticipate accruing five patients per year for this protocol. Thus, we anticipate that we will reach the target sample size of 20 patients treated at MTD within four years.

Proposed Analyses

The analyses for this protocol will be primarily descriptive. With a sample size of 20 treated at MTD, we do not expect to see statistically significant effects for the outcomes of interest, however this data will provide useful preliminary data on the overall safety and efficacy of CPI-613 and provide useful data to predict the variability and likely effect sizes for these outcomes.

For the primary outcome, we will present the proportion (along with a 95% confidence interval) of patients who respond. Response rate (RR) is defined as the combined rate of CR, marrow CR, PR, or SD as described by Cheson, et al. (2006). Response criteria are shown in Appendix G. In addition, we will determine the number of patients who achieve HI, and a reduction in transfusion requirements. For the time-to-event outcomes, we will estimate survival curves for OS and PFS using Kaplan-Meier techniques. In addition, we will estimate the 6 month and 1-year OS and PFS rates for these participants.
We will also examine toxicities by looking at each toxicity identified earlier in the protocol by grade.

Sample Size Considerations

Since this is a pilot study we do not anticipate having statistical power to detect specific effects. However with the sample size of 20, we will be able to estimate the response rate using a 2-sided 95% confidence interval with an interval that will extend no more than 0.22 from the observed response rate.

10.0 Data Management and Reporting Schedule

Tumor response will be assessed based on RR, PFS, and OS (as described by Cheson et al. 2006), as well

as changes in the frequency of transfusion from baseline.

RR and PFS, derived from hematology and bone marrow exam, will be assessed at the following specified time points:

- Baseline (hematology and bone marrow)
- Hematology: week 4 of every 2 treatment cycles until cycle 6 and then every 3 treatment cycles thereafter (i.e., cycle 9, cycle 12, cycle 15, etc) until evidence of disease progression.
- Bone marrow week 4 of cycles 3 and 6, and then at the discretion of the physician or if peripheral blood criteria for a complete remission are met (ie ANC>1000, Platelets >100k and freedom from blood transfusions) thereafter until disease progression

Bone marrow exam results should be documented at each specified time point using the data collection form in Appendix E, and then input into the corresponding REDCap database.

Transfusion frequency should be documented at each specified time point using the data collection form in Appendix F, and then input into the corresponding REDCap database.

Response form (Appendix I) should be completed for each specified time point.

	Data Collection Forms	**Due By**	**Database**
Pre-Study / Registration	Signed Consent	At time of registration	ORIS
	Registration Form	At time of registration	ORIS
On-Study	Adverse event log (Appendix C)	Within one week	ORIS
	Withdrawal of participation form (Appendix D)	Within one week	REDCap
	Bone marrow exam form (Appendix E)	Within one week	REDCap
	Transfusion data form (Appendix F)	Within one week	REDCap
	Response form (Appendix I)	Within one week	REDCap

10.0 REFERENCES

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Appendix A – REGISTRATION GUIDELINES AND FORMS

The following guidelines have been developed in order to ensure timely registration of your patient.

All patients entered on any CCCWFU trial, whether treatment, companion, or cancer control trial, **must** be linked to a protocol in EPIC within 24 hours of Informed Consent. Patients **must** be registered prior to the initiation of treatment.

In order to ensure prompt registration of your patient, please:

1. Complete the Eligibility Checklist (attached)
2. Complete the Protocol Registration Form (attached)
3. Alert the WFUHS registrar by phone, *and then* send the signed Informed Consent Form, Eligibility Checklist and Protocol Registration Form to the registrar, either by fax or e-mail.

   Contact Information:
   Protocol Registrar PHONE (336) 713-6767
   Protocol Registrar FAX (336) 713-6772
   Protocol Registrar E-MAIL (registra@wakehealth.edu)
   (*Protocol Registration is open from 8:30 AM - 4:00 PM, Monday-Friday.)

4. Please fax/e-mail ALL eligibility source documents with registration. Patients **will not** be registered without all required supporting documents.

Note: If labs were performed at an outside institution, please provide a printout of the results. Please ensure that the most recent lab values are sent.

CCCWFU # 29113 **Eligibility Checklist**

Yes	No	N/A	Inclusion Criteria (All responses must be **YES** in order to enter study)	Eligibility Confirmation (registrar)
☐	☐	☐	1. Does the patient have histologically proven myelodysplastic syndrome having failed at least one line of previous therapy?	
☐	☐	☐	2. Does the patient have an ECOG performance status of ≤ 3?	
☐	☐	☐	3. Is the patient 18 years of age or older?	
☐	☐	☐	4. Does the patient have an estimated survival of > 2 months?	
☐	☐	☐	5. Has the patient recovered from the acute, non-hematological, non-infectious toxicities of any prior treatment with cytotoxic drugs, radiotherapy or other anti-cancer modalities? Patients with persisting, non-hematologic, non-infectious toxicities from prior treatment ≤ Grade 2 are eligible, but must be documented as such.	
☐	☐	☐	6. If the patient is a woman of child-bearing potential (i.e., pre-menopausal or not surgically sterile), does she agree to use accepted contraceptive methods (abstinence, intrauterine device [IUD], oral contraceptive or double barrier device) during the study, and agree to have a negative serum or urine pregnancy test within 1 week prior to treatment initiation?	
☐	☐	☐	7. If the patient is a fertile man, does he agree to practice effective contraceptive methods during the study, unless documentation of infertility exists?	
☐	☐	☐	8. Does the patient have documentation of the following laboratory values? • aspartate aminotransferase [AST/SGOT] ≤3x upper normal limit [UNL] • alanine aminotransferase [ALT/SGPT] ≤3x UNL (≤5x UNL if liver metastases present) • bilirubin ≤1.5x UNL • serum creatinine ≤1.5 mg/dL or 133 μmol/L • Albumin >2.0 g/dL or >20 g/L.	
☐	☐	☐	9. Is the patient mentally competent, able to understand and willing to sign an IRB-approved written informed consent document?	
☐	☐	☐	10. Does the patient have access via a central line (e.g., portacath)?	
Yes	**No**	**N/A**	Exclusion Criteria (All responses must be **NO** in order to enter study)	**Eligibility Confirmation (registrar)**
☐	☐	☐	1. Has the patient received radiotherapy, surgery, treatment with cytotoxic agents (except CPI-613), treatment with biologic agents, immunotherapy, or any other anti-cancer therapy of any kind, or any other standard or investigational treatment for their cancer, or any other investigational agent for any indication, within the past 2 weeks prior to initiation of CPI-613 treatment?	
☐	☐	☐	2. Has the patient received a chemotherapy regimen with stem cell support in the previous 6 months?	
☐	☐	☐	3. Does the patient have a serious medical illness, such as significant cardiac disease (e.g. symptomatic congestive heart failure, unstable angina pectoris, coronary artery disease, myocardial infarction within the past 3	

CCCWFU # 29113 **Eligibility Checklist**

			months, uncontrolled cardiac arrhythmia, pericardial disease or New York Heart Association Class III or IV), or severe debilitating pulmonary disease, that would potentially increase patients' risk for toxicity.	
			4. Does the patient have any active uncontrolled bleeding or bleeding diathesis?	
☐	☐	☐	5. Is the patient a pregnant woman, or a woman of child-bearing potential who is not using reliable means of contraception?	
☐	☐	☐	6. Is the patient a lactating female?	
☐	☐	☐	7. Is the patient a fertile man who is unwilling to practice contraceptive methods during the study period?	
☐	☐	☐	8. Is the patient's life expectancy less than 2 months?	
☐	☐	☐	9. Does the patient have an unrelated central nervous system (CNS) or epidural tumor?	
☐	☐	☐	10. Does the patient have any condition or abnormality which may, in the opinion of the investigator, compromise his or her safety?	
☐	☐	☐	11. Is the patient unwilling or unable to follow protocol requirements?	
☐	☐	☐	12. Does the patient have a history of additional risk factors for torsade de pointes (e.g., heart failure, hypokalemia, family history of Long QT Syndrome)?	
☐	☐	☐	13. Does the patient have evidence of active infection, or serious infection within the past month?	
☐	☐	☐	14. Does the patient have known HIV infection?	
☐	☐	☐	15. Does the patient require immediate palliative treatment of any kind, including surgery?	
☐	☐	☐	16. Does the patient have a prior history of illicit drug addiction?	
☐	☐	☐	17. Does the patient have large and recurrent pleural or peritoneal effusions requiring frequent drainage (e.g., weekly)?	
☐	☐	☐	18. Does the patient have any amount of clinically significant pericardial effusion?	

This subject is ☐ eligible / ☐ ineligible for participation in this study.

ORIS Assigned PID: _____

Signature of research professional confirming eligibility: _____ Date: _____

Signature of Treating Physician: _____ Date: _____

Signature of Principal Investigator**: _____ Date: _____

* Examples of source documents include clinic note, pathology report, laboratory results, etc. When listing the source, specifically state which document in the medical record was used to assess eligibility. Also include the date on the document. Example: "Pathology report, 01/01/14" or "Clinic note, 01/01/14"

**Principal Investigator signature can be obtained following registration if needed

Please send source documentation with Eligibility Form.

CCCWFU # 29113 **Protocol Registration Form**

DEMOGRAPHICS

Patient: Last Name: _____ First Name: _____

MRN: ___ ___ ___ ___ ___ ___ ___ ___ DOB (mm/dd/yy): ___ ___ / ___ ___ / ___ ___

SEX: ☐ Male Ethnicity (choose one): ☐ Hispanic

☐ Female ☐Non-Hispanic

Race (choose all that apply): ☐ WHITE ☐BLACK ☐ ASIAN ☐ PAIFIC ISLANDER ☐ NATIVE AMERICAN

Height: ___ ___.___ inches Weight: ___ ___ ___.___lbs.(actual)

Surface Area: ___ ___.___m^2

Zip Code: ___ ___ ___ ___ ___

Primary Diagnosis: _____

Date of Diagnosis: ___ ___ /___ ___/___ ___

PROTOCOL INFORMATION

Date of Registration: ___ ___ / ___ ___ / ___ ___

MD Name (last) : _____

Date protocol treatment started: ___ ___ / ___ ___ / ___ ___

Informed written consent: ☐ YES ☐ NO

(consent must be signed prior to registration)

Date Consent Signed: ___ ___ / ___ ___ / ___ ___

PID # (to be assigned by ORIS): ___ ___ ___ ___ ___ ___ ___ ___

Protocol Registrar can be contact by calling 336-713-6767 between 8:30 AM and 4:00 PM, Monday – Friday.

Completed Eligibility Checklist and Protocol Registration Form must be hand delivered, faxed or e-mailed to the registrar at 336-7136772 or registra@wakehealth.edu.

Appendix B: STRC SAE REPORTING GUIDELINES

Mandatory STRC SAE Reporting Requirements – Revised 6/05/2012

Safety and Toxicity Review Committee (STRC; previously known as CROC) Serious Adverse Event (SAE) Notification SOP	**Date: 8/17/2016**

Mandatory STRC SAE Reporting Requirements

This document describes STRC reporting and use of the electronic submission form that is submitted **for unexpected grade 4 and any grade 5 (death during protocol intervention) SAEs on WFBCCC Institutional interventional trial patients**. There are multiple entities that require reporting of SAEs. Each entity has different rules for what is reported, and how it is reported.

Rules used by other entities (Institutional Review Board (IRB), AdEERS, MedWatch, etc.) should NOT be used to evaluate whether an event should be reported to STRC. Only the rules for reporting described in this document should be considered.

As defined in the NCI Data Table 4 reporting guidelines, **WFBCCC Institutional Interventional studies covered by these reporting requirements are defined as: In-house, internally reviewed trials, including those collaborative studies conducted with industry sponsorship in which the center is a primary contributor to the design, implementation, and monitoring of the trial, or participation in a multi-site trial initiated by an institutional investigator at another center.** Institutional trials are almost always authored by a researcher here at WFBCCC. Institutional protocols are labeled NCI Code="I" for Institutional on the protocol screen in ORIS. Cooperative group protocols are **not** considered Institutional, but Research Base trials **are** classified as Institutional.

The STRC is responsible for reviewing SAEs for WFBCCC Institutional Interventional studies, as defined above. STRC currently requires that unexpected grade 4 and all grade 5 SAEs on these trials be reported to the STRC for review. All Clinical Protocol and Data Management (CPDM) staff members assisting a PI in documenting and reporting an SAE that qualifies for STRC reporting are responsible for informing a clinical member of the STRC by phone (or in-person), followed by informing the entire committee via the required email notification.

THESE REPORTING REQUIREMENTS APPLY TO any faculty or staff member on the study team for a WFBCCC Institutional Interventional trial. Once an event is observed, it is the responsibility of the person who observed the event to be sure that it is reported.

What is considered an SAE under this mandatory procedure?
Any **unexpected grade 4** event and **all grade 5 events** (death during protocol intervention) should be reported. These events should be reported if they occur while a patient is on study treatment or if they occur within 30 days of last study treatment (even if patient begins a new treatment during the 30 days). This window of 30 days should be the standard window to be used in all protocols unless a specific scientific rationale is presented to suggest that a shorter

window can be used to identify events. In addition, if it is not clear whether the Grade 4 is unexpected it should be reported.

Table 1: Summary of STRC Reporting Requirements for Institutional Pilot, Phase 1, Phase 2 and Phase 3 Interventional Trials

	ADVERSE EVENT					
	Grade 1, Grade 2, Grade 3		Grade 4		Grade 5	
	Unexpected	Expected	Unexpected	Expected	Unexpected	Expected
Unrelated	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**
Unlikely	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**
Possible	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**
Probable	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**
Definite	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**

STRC reporting may not be appropriate for specific expected adverse events for protocols. In those situations the adverse events that will not require STRC reporting **must be specified in the text of the approved protocol.**

STRC notification responsibilities of the person handling the reporting/documenting of the SAE:

1. Make a phone call (or speak in person) to the appropriate clinical member of the STRC as listed below (page if necessary)—see note 2 below
2. Submit the STRC Notification Form WITHIN 24 HOURS of first knowledge of the event. This form is found at either the ORIS main menu page or by going to http://ccc.wfubmc.edu/oris/strc.aspx.
   This will ensure that all persons that need to be made aware of the event (i.e., study team members and STRC members) will be notified; remember to file a copy of your confirmation. (Form instructions will walk you through the required fields, consult the help page for further instructions.)
3. Ensure that you document that the appropriate person(s) on the STRC has been contacted. This documentation is placed on the STRC Notification form described above.
4. Follow up with/update the clinical member(s) of STRC regarding any new developments or information obtained during the course of the SAE investigation and reporting process.

Elements to complete the electronic STRC form:
Please use 'reply to All' when responding with one of these terms: Definite, Probable, Possible, Unlikely, or Unrelated

1. Patient ID (ORIS PID)
2. Patient Name
3. Patient MR#

4. WFBCCC(ORIS) Study Number
5. Title
6. PI Name
7. PI Contact Number
8. PI Comments
9. STRC Clinician notified by Phone
10. Notified Date
11. Notified Time
12. STRC Clinician Comments
13. Category [This is the Grade – Either Unexpected Grade 4 or Grade 5 should be entered]
14. Additional Information (IRB Reporting)(after discussion with PI or STRC Clinician
    i. Is This Event Related to Protocol Treatment?
    ii. Is Suspension of the Protocol Needed?
    iii. Any Changes to Consent or Protocol Needed?
    iv. Was Nature or Severity of Event Unexpected?
15. Date of the event.
16. Brief description (include brief clinical history relevant to this event, including therapies believed related to event).
17. Date of Last Dose before event
18. Relevant tests/labs.
19. Other Relevant Treatment Information
20. Other Comments/Notes (include regimen of chemo and dates the patient received them if known).
21. Cc (email) (include treating Physician; separate email list with comma”,”)
22. Your Name
23. Your Email
24. Confirm Your Email

The Clinical Members of STRC to Notify by Phone or Page:

Bayard Powell, MD – Director-at-Large, WFBCCC; Chair, PRC; Section Head, Hematology/Oncology. 6-7970 / 6-2701 / Pager 336-806-9308
Antonius Miller, MD – Hematology Oncology 6-7970 / 6-7414 / Pager 704-637-8384
Glenn Lesser, MD – Hematology Oncology 6-9527 / 6-7972 / Pager 336-806-8397
Kathryn Greven, MD – Vice Chair – Radiation Oncology. 3-3600 / 3-6505 / Pager 336-806-8314
Marissa Howard-McNatt, MD – General Surgery 6-0545 / 336-806-6438
Mercedes Porosnicu, MD- Hematology Oncology 6-7980 / 6-0230 / Pager 336-806-9150

Definition of Unavailable:

As a general guideline if the first clinician that is contacted does not respond to the phone call or page within a reasonable amount of time, then initiate contact with their backup. Give the back-up a reasonable amount of time to respond to a phone call or page before contacting another member. This is a general guideline. You must use your best judgment as a clinical research professional given the time of day, severity of the SAE, and other circumstances as to when it is appropriate to contact backup clinicians. If the event occurs near the end of day, then leave messages (voice or email) as appropriate and proceed with submitting your STRC notification form. The important criteria is that you have taken reasonable steps to notify and document that you have initiated some type of contact to one or more of the clinical members of STRC.

STRC CLINICAN RESPONSIBILITY:

It is the responsibility of the STRC clinician to review all reported events, evaluate the events as they are reported; and communicate a response to the Investigator, event reporter and the members of STRC. The review will include but not be limited to the information reported; there may be times when additional information is needed in order for an assessment to be made and further communication directly with the investigator may be warranted. STRC reserves the right to agree with the investigator's assessment if STRC does not agree with the investigator. STRC reserves the right to suspend the trial pending further investigation.
Is there any immediate danger or harm that could be present for a future patient based on the information provided in the STRC report – and if so an immediate suspension of enrollment should take place.

AMENDMENTS TO PREVIOUS REPORTS

If you are not able to supply all pertinent information with the initial submission, once the additional information is available **do not submit a new report**. Go to the original email that was received by STRC and others "reply to all" and entitle your email "**Amendment** for (list date of event and patient ID) this will avoid duplications of the same event. List the additional information which you are reporting.

Acronyms and Definitions

STRC-Safety and Toxicity Review Committee
SAE-Serious Adverse Event
IRB-Institutional Review Board
WFBCCC-Comprehensive Cancer Center Wake Forest University
ORIS-Oncology Research Information System
NCI-National Cancer Institute
CPDM-Clinical Protocol and Data Management
Interventional Trials-Therapeutic Level 1 and Level 2 trials
Therapeutic Level 1-A cancer treatment protocol aimed at directly treating/curing the patient's cancer.
Therapeutic Level 2-A therapeutic protocol not cancer treatment involves clinical activity to treat symptoms, improve the patient's quality of life, or prevent cancer.

Appendix C – CCCWFU ADVERSE EVENT LOG

WFBCCC Adverse Event (AE) Log

PI: _____ PID: _____ MRN: _____

Cycle Start Date: _____ Cycle End Date: _____ Cycle #: _____

Adverse Event CTC Term	**Value** (-5 if non-numeric)	**Grade** (0-5) per CTC	**Start Date**	**Attribution** 1=Related 2=Probably 3=Possible 4=Unlikely 5=Unrelated	**Treating MD Initials/Date**	**End Date**	**Expected** 1=Yes 0=No	***Serious Adverse Event (SAE)** 1=Yes 0=No	**Dose Limiting Toxicity (DLT)** 1=Yes 0=No	**Action Taken** 1=None 2=Tx withheld 3=Tx D/C 4=Tx adjusted 5=Other	**Reportable?** 1=IRB 2=STRC 3=FDA 4=Sponsor

*Serious Adverse Event: Hospitalization; Disability; Birth Defect; Life-threatening; Death.

CTCAE Version 4 - http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Appendix D – Withdrawal of Participation Form

ORIS PID _____ **Date Completed** ____ / ____ / ____

Name of person completing form _____
Did the subject meet eligibility criteria for study enrollment? Yes ☐ No ☐

Reasons for withdrawal: (*Check all that apply and provide additional information*)
☐ Patient exhibited progression of disease
☐ Unacceptable toxicity from CPI-613 in spite of dose reduction
☐ Patient withdrawal of consent
- ☐ For just the primary intervention (CPI-613 administration only)
- ☐ For all components of the research study (including follow up in the medical record)

☐ Investigator's discretion to withdraw patient from the study because continued participation in the study is not in the patient's best interest
☐ Undercurrent illness: a condition, injury, or disease unrelated to the intended disease for which the study is investigating, that renders continuing the treatment unsafe or regular follow-up impossible
☐ General or specific changes in the patient's condition that renders the patient ineligible for further investigational treatment
☐ Non-compliance with investigational treatment, protocol-required evaluations or follow-up visits
☐ Termination of the clinical trial by the clinical sponsor

COMMENTS: _____
_____
_____

Appendix E – Data Collection Form for Bone Marrow Exam

Study ID: _____

Date: ___ ___ / ___ ___ / ___ ___

Most recent cycle completed: Baseline ☐ Cycle 3 ☐ Cycle 6 ☐
Other ☐_____

Bone Marrow Exam:

Morphology: _____

Cellularity: _____

Karyotype (cytogenetics and FISH as applicable): _____
_____
_____

Molecular markers: _____

% of bone marrow myoblasts: _____ %

Revised IPSS Classification: ☐ Very Low ☐ Low ☐ Intermediate ☐ High ☐ Very High

Appendix F – Data Collection Form for Number of Transfusions

Study ID: _____

Date form completed: ___ ___ / ___ ___ / ___ ___

Time point of assessment: Baseline ☐ Cycle 2 ☐ Cycle 4 ☐ Cycle 6 ☐
Cycle 9 ☐ Cycle 12 ☐ Other _____ ☐

Frequency of transfusion is defined as the number of transfusions received during the previous 8 weeks. The baseline assessment should reflect the number of transfusions received in the 8 weeks prior to enrollment. On-treatment assessments should be performed at the end of every 2 treatment cycles.

Number of RBC transfusions during period (circle): 0 1 2 3 4 5 6 7 8 9 10

Date range of assessment period: ___ ___ / ___ ___ / ___ ___ to ___ ___ / ___ ___ / ___ ___

Number of platelet transfusions during period (circle): 0 1 2 3 4 5 6 7 8 9 10

Date range of assessment period: ___ ___ / ___ ___ / ___ ___ to ___ ___ / ___ ___ / ___ ___

Appendix G –Pre-Study Data Collection Form

ORIS PID: _____ DATE COMPLETED: (mm/dd/yy): ___ ___ / ___ ___ / ___ ___
The following are required prior to registration:
CURRENT DISEASE STATUS AT REGISTRATION: _____
(1^{ST} relapse, 2^{nd} relapse, 3^{rd} relapse, refractory etc., including allo or auto bone marrow transplant)

Prior Therapies/ Protocol # if applicable	Start / End Date of Prior Therapy	Best Response (CR, PR, Treatment Failure)	Date of Best Response	Date of Relapse	Duration of Best Response (in Months)
#1 _____	_____/_____	_____	_____	_____	_____
#2 _____	_____/_____	_____	_____	_____	_____
#3 _____	_____/_____	_____	_____	_____	_____
#4 _____	_____/_____	_____	_____	_____	_____
#5 _____	_____/_____	_____	_____	_____	_____
#6 _____	_____/_____	_____	_____	_____	_____

COMMENT:_____

Date of original cancer diagnosis: ___ ___ / ___ ___ / ___ ___

Date of 1st Remission: ___ ___ / ___ ___ / ___ ___

Date of 1st Relapse: ___ ___ / ___ ___ / ___ ___

Date of 2nd Relapse: ___ ___ / ___ ___ / ___ ___

ECOG Performance Status:

☐ **Score 0** – Fully active, able to carry on all pre-disease performance without restriction

☐ **Score 1** - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work

☐ **Score 2** - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours

☐ **Score 3** - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours

☐ **Score 4** - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair

CYTOGENETICS:
Cytogenetics at Diagnosis:

Date of Cytogenetics Report: ___ ___ / ___ ___ / ___ ___

Risk Category: ☐ Good ☐ Intermediate ☐ Poor

*Enter descriptive text from Cytogenetic Report (3 categories) into REDCap database on Pre-Study Data Collection Form.

Revised IPSS Classification: ☐ Very Low ☐ Low ☐ Intermediate ☐ High ☐ Very High

Appendix H – Response Criteria

Table 3. Proposed modified International Working Group response criteria for altering natural history of MDS[7]

Category	Response criteria (responses must last at least 4 wk)
Complete remission	Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines*
	Persistent dysplasia will be noted*†
	Peripheral blood‡
	Hgb ≥ 11 g/dL
	Platelets ≥ 100×10^9/L
	Neutrophils ≥ 1.0×10^9/L†
	Blasts 0%
Partial remission	All CR criteria if abnormal before treatment except:
	Bone marrow blasts decreased by ≥ 50% over pretreatment but still > 5%
	Cellularity and morphology not relevant
Marrow CR†	Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment†
	Peripheral blood: if HI responses, they will be noted in addition to marrow CR†
Stable disease	Failure to achieve at least PR, but no evidence of progression for > 8 wks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment
Relapse after CR or PR	At least 1 of the following:
	Return to pretreatment bone marrow blast percentage
	Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets
	Reduction in Hgb concentration by ≥ 1.5 g/dL or transfusion dependence
Cytogenetic response	Complete
	Disappearance of the chromosomal abnormality without appearance of new ones
	Partial
	At least 50% reduction of the chromosomal abnormality
Disease progression	For patients with:
	Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts
	5%-10% blasts: ≥ 50% increase to > 10% blasts
	10%-20% blasts: ≥ 50% increase to > 20% blasts
	20%-30% blasts: ≥ 50% increase to > 30% blasts
	Any of the following:
	At least 50% decrement from maximum remission/response in granulocytes or platelets
	Reduction in Hgb by ≥ 2 g/dL
	Transfusion dependence
Survival	Endpoints:
	Overall: death from any cause
	Event free: failure or death from any cause
	PFS: disease progression or death from MDS
	DFS: time to relapse
	Cause-specific death: death related to MDS

Deletions to IWG response criteria are not shown.

To convert hemoglobin from grams per deciliter to grams per liter, multiply grams per deciliter by 10.

MDS indicates myelodysplastic syndromes; Hgb, hemoglobin; CR, complete remission; HI, hematologic improvement; PR, partial remission; FAB, French-American-British; AML, acute myeloid leukemia; PFS, progression-free survival; DFS, disease-free survival.

*Dysplastic changes should consider the normal range of dysplastic changes (modification).[41]

†Modification to IWG response criteria.

‡In some circumstances, protocol therapy may require the initiation of further treatment (eg, consolidation, maintenance) before the 4-week period. Such patients can be included in the response category into which they fit at the time the therapy is started. Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.

Continued on next page

Table 4. Proposed modified International Working Group response criteria for hematologic improvement[7]

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

Deletions to the IWG response criteria are not shown.
To convert hemoglobin levels from grams per deciliter to grams per liter, multiply grams per deciliter by 10.
Hgb indicates hemoglobin; RBC: red blood cell; HI: hematologic improvement.
*Pretreatment counts averages of at least 2 measurements (not influenced by transfusions) ≥ 1 week apart (modification).
†Modification to IWG response criteria.
‡In the absence of another explanation, such as acute infection, repeated courses of chemotherapy (modification), gastrointestinal bleeding, hemolysis, and so forth. It is recommended that the 2 kinds of erythroid and platelet responses be reported overall as well as by the individual response pattern.

Appendix I – Response Evaluation Form

MRN: _____
Patient ID: _____
Date: ____ ___ / ___ ___ / ___ ___

Time point of assessment: Cycle 2 ☐ Cycle 4 ☐ Cycle 6 ☐
Cycle 9 ☐ Cycle 12 ☐ Other _____ ☐

Please check the response that applies to this patient. Refer to the response criteria from Cheson et al., 2006 described in Appendix G.

- ☐ Complete Remission (**CR**)
- ☐ Partial Remission (**PR**)
- ☐ Marrow Complete Response
- ☐ Stable Disease
- ☐ Failure
- ☐ Relapse after CR or PR
- ☐ Cytogenetic Response
- ☐ Disease Progression
- ☐ Survival

Hematologic Response Criteria:

- ☐ Erythroid Response (pretreatment, <11g/dL)
- ☐ Platelet Response (pretreatment, < 100 x 10^9 /L)
- ☐ Neutrophil Response (pretreatment, <1.0 x 10^9/L)
- ☐ Progression or Relapse after (HI) Hematologic Improvement

Treating Physician Signature: _____ Date: ___ ___ / ___ ___ / ___ ___

PI Signature: _____ Date: ___ ___ / ___ ___ / ___ ___