Clinical Study Protocol

A phase I clinical trial to evaluate the maximally tolerated dose (MTD), dose limiting toxicities (DLTs) and safety profiles of increasing doses of lenalidomide after allo-HCT in AML and MDS subjects with minimal residual disease (MRD) detected by the CD34+ mixed chimerism analysis.

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ABBREVIATIONS

AE	Adverse Event
aGVHD	Acute Graft-Versus-Host-Disease
ALT	Alanine Transaminase (also SGPT)
AML	Acute Myelogenous Leukemia
ANC	Absolute Neutrophil Count
AST	Aspartate Transaminase (also SGOT)
AUC	Area Under Curve
$AUC_{(0-t)}$	Area Under the Plasma Concentration-time curve from time zero to time t
$AUC_{(0-\infty)}$	Area Under the Plasma Concentration-time curve from time zero to infinity
$AUC_{(0-Tlast)}$	Area Under the Plasma Concentration-time curve from time zero to the last measurable time point
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CIBMTR	Center for International Blood and Marrow Transplant Research
C_{max}	Maximum Plasma Concentration
CR	Complete Remission
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease-free Survival
DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic Acid
DISC	Data Integrity and Safety Committee

eCRF	Electronic Case Report Form
FCBP	Female of Child-Bearing Potential
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GVHD	Graft-Versus-Host-Disease
GVL	Graft-Versus-Leukemia
HCT	Hematopoietic Cell Transplant
HI	Hematologic Improvement (see Appendix D)
ICH	International Conference on Harmonization
IND	Investigational New Drug
IP	Investigational Product
IPSS	International Prognostic Scoring System
IRB	Institutional Review Board
IWG	International Working Group
MDS	Myelodysplastic syndromes
MG	Milligram
MRD	Minimal Residual Disease
MTD	Maximum Tolerated Dose
NIH	National Institutes of Health
NK	Natural Killer
OS	Overall Survival
PD	Pharmacodynamics

PI	Principal investigator
PML	Promyelocytic Leukemia
PO	By Mouth
PR	Partial Remission
QD	Every Day
QOD	Every Other Day
RBC	Red Blood Cells
REMS	Risk Evaluation and Mitigation Strategy
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase (also AST)
SGPT	Serum Glutamic Pyruvate Transaminase (also ALT)
SPM	Second Primary Malignancy
STR	Short Tandem Repeat
UFHCC	University of Florida Health Cancer Center
US	United States
WBC	White Blood Cell
WHO	World Health Organization

PROTOCOL SYNOPSIS

Title:	A phase I clinical trial to evaluate the maximally tolerated dose (MTD), dose limiting toxicities (DLTs) and safety profiles of escalating doses of lenalidomide after allo-HCT in AML and MDS subjects with minimal residual disease (MRD) detected by the CD34+ mixed chimerism analysis
Rationale:	Prognosis of high risk AML and MDS remains poor and less than 30% of these patients achieve long term survival. Allogeneic transplant (allo-HCT) is an effective therapy for high risk AML and MDS, however, post-transplant disease relapse continues to be a major obstacle to treatment success and cure. Therefore, there is an urgent need to develop novel therapeutic strategies to effectively prevent disease relapse in AML and MDS patients after allo-HCT. This phase I clinical trial is designed to evaluate the maximally tolerated dose (MTD), dose limiting toxicities (DLTs) and safety profiles of increasing doses of lenalidomide after allo-HCT in AML and MDS subjects with minimal residual disease (MRD) detected by the CD34+ mixed chimerism analysis. Lenalidomide has a potent immunomodulatory activity and is capable of activating T- and natural killer (NK)-cells. T- and NK-cells mediated immunity plays a critical role in host defense against progression of myeloid malignances, therefore restoration of impaired cytotoxic activity of T- and NK cells with lenalidomide could have significant clinical implications in patients with relapsing MDS and AML after allo-HCT because alloreactive T- and NK-cells play a crucial role in the GVL effect, which is considered to be a key mechanism preventing disease relapse after allo-HCT. Treatment of relapsed disease is more successful if initiated early when tumor burden is minimal. Previous studies evaluating the role of lenalidomide in patients with relapsed myeloid malignances showed its efficacy only in patients with low blast count. For this purpose, monitoring of MRD allows timely therapeutic interventions before the hematologic relapse becomes clinically apparent and while tumor burden is minimal. However, in AML and MDS patients monitoring of MRD is technically difficult and is not routinely implemented in clinical practice. For these purposes, new approaches for MRD detection are currently being explored. Lineage-specific chimerism analysis of CD34+ cells is a novel approach, which has better sensitivity and specificity for early MRD detection after allo-HCT. It was demonstrated that monitoring of CD34+ chimerism in patients with AML and MDS after allo-HCT is a very sensitive technique, which is capable to early identify patients at a very high risk for a hematologic relapse. Our preliminary data showed that of 10 enrolled patients 4 patients had hematologic relapse confirmed by a bone marrow

	evaluation. In each patient with relapsed disease there was a significant decline in CD34+ specific chimerism, which was detected for at least a month prior to confirmed hematologic relapse. The CD34+ specific STR analysis is superior to conventional chimerism analysis for MRD monitoring and identification of early relapse after allo-HCT. More importantly, drop of CD34+ specific chimerism occurred significantly earlier that decrease in chimerism assessed by conventional STR-based techniques. Therefore, the use of highly sensitive and specific MRD monitoring by the CD34+ chimerism analysis substantially increases the reliability of early MRD detection after allo-HCT allowing early therapeutic interventions and is potentially practice changing. Therefore, the proposed research project is highly significant because it seeks to develop a novel therapeutic strategy to effectively delay or prevent AML and MDS relapse in allo-HCT recipients. Successful completion of this phase I study will build the foundation for a subsequent phase II trial of pre-emptive lenalidomide administration to prevent or delay an imminent hematological relapse after allo- HCT in subjects with MDS and AML with minimal residual disease (MRD) detected by the CD34+ mixed chimerism analysis, which would likely impact the clinical care of allo-HCT recipients with high risk AML and MDS and will give valuable insights into mechanisms of action of lenalidomide after allo-HCT.
Primary Objective:	To determine safety and the maximum tolerated dose of lenalidomide after allo-HCT in AML and MDS subjects with MRD detected by the CD34+ mixed chimerism analysis.
Secondary Objective:	To monitor changes in the CD34+ mixed chimerism after allo-HCT in AML and MDS subjects with detectable MRD in response to escalating doses of lenalidomide.
Study Design:	This is an open-label, phase I dose escalation study of lenalidomide after allo-HCT in AML and MDS subjects with MRD detected by the CD34+ mixed chimerism analysis. The study is designed to evaluate the safety profile, MTD and biologic activity of lenalidomide after allo-HCT in patients with AML and MDS The dose levels of lenalidomide will be as follows: Dose Level 1: 2.5 mg PO QOD Day 1-21 for 28 day cycle X 2 cycles Dose Level 2: 2.5 mg PO QD Day 1-21 for 28 day cycle X 2 cycles Dose Level 3: 5 mg PO QD Day 1-21 for 28 day cycle X 2 cycles Dose Level 4: 7.5 mg PO QD Day 1-21 for 28 day cycle X 2 cycles Subjects will be enrolled in cohorts of three (3). Lenalidomide will be administered for 21 consecutive days in a 28 day cycle X 2 cycles. The starting dose will be 2.5 mg given orally every other day for 21 days.

Subjects will be individually assessed for safety and dose limiting toxicity (DLT) for the purpose of determining the MTD .Three eligible subjects will be enrolled in sequential cohorts at increasing dose levels until at least one DLT is seen between the first dose and 14 days after the last dose of lenalidomide. For this study, MTD will be defined as the highest dose which no more than 34% of the subjects observed at a given dose level experience a DLT. The following dose escalation rules will be used and applied:

1. Three subjects are initially studied at each dose level.
2. If none of these 3 subjects experience DLT, then the dose is escalated to the next dose level in 3 subsequent subjects.
3. If 1 of these 3 subjects experiences DLT at current dose, then up to 3 more subjects are accrued at the same level.
    a) If none of these 3 additional subjects experience DLT, then the dose is escalated to the next dose level in 3 subsequent subjects.
    b) If 1 or more of these 3 additional subjects experiences DLT, then the MTD is considered to have been exceeded and the previous dose level will be the MTD.
4. If 2 or more of the initial 3 subjects at a dose level experience DLT, then the MTD is considered to have been exceeded and dose escalation will be stopped. Up to 3 more subjects are treated at the next lower dose.

A subject must meet one of the following 3 criteria to be evaluable for subsequent dose-escalation decisions:

1. Complete at least 21 days of lenalidomide without a DLT by 14 days after the last dose of lenalidomide;
2. Experienced a DLT between the first dose and 14 days after the last dose of lenalidomide; or
3. Withdrawn from the study after at least 14 days of lenalidomide administration.

If a subject does not meet any of these criteria, the subject is not evaluable for dose escalation decisions and will be replaced in that cohort. No more than 3 subjects will be added simultaneously to a dose cohort during dose escalation.

The study ends when there is a maximum dose where 2 or more subjects out of 6 have a DLT, or when the maximum sample size of twenty four (24) subjects has been reached.

<u>Dose Limiting Toxicity</u>

DLT will be defined as any of the following adverse events that are not clearly unrelated to drug administration or treatment-emergent from lenalidomide and constitute a change from baseline irrespective of outcome. For the purpose of dose-escalation decisions and MTD

	determination, only DLTs that occur within 14 days after the last dose of lenalidomide administration will be taken into account. 1. Grade 3 or greater nausea, diarrhea, or vomiting despite the use of maximal medical intervention; 2. Grade 3 or greater acute GVHD despite the use of maximal medical intervention; 3. Any other clinically significant non-hematologic toxicity of grade 3 or greater considered not related to the underlying disease or intercurrent illness; 4. Grade 3 or greater neutropenia; 5. Grade 4 thrombocytopenia or platelet count $\leq$ 50 thou/mm^3 by day 28 of lenalidomide administration; or 6. Any treatment-related effect leading to a subject missing 3 or more doses of lenalidomide. Correlative Studies: Peripheral blood will be collected to examine the CD34+ specific chimerism.
Inclusion/ Exclusion Criteria:	Inclusion Criteria: 1. Subjects must be at least 18 years of age; 2. Subjects must be 60 (+/- 7) days post-allogeneic transplant from any donor source; 3. Subjects must have either: a) High risk CD34+ AML (*de novo* or secondary, and any WHO 2008 classification excluding acute promyelocytic leukemia, see Appendix A). High risk AML is defined as (a) disease status beyond complete remission (CR) #1 at transplant or (b) treatment related AML or (c) presence of adverse cytogenetics including inv(3); t(3;3); t(6;9); t(v;11); -5 or del(5q); -7; abnl(17p) or complex karyotype; or b) High risk CD34+ MDS (WHO 2008 classification, see Appendix B). High risk is defined as (a) blast count $\geq$5% at the time of transplant or (b) treatment related MD or (c) presence of adverse cytogenetics including -7/del7q or complex karyotype; 4. For AML subjects, they must have a documented CR within 45 days prior to allo-HCT; 5. For MDS subjects, they must have < 20% myeloblasts in the bone marrow within 45 days prior to allo-HCT; 6. Subject Karnofsky performance status must be $\geq$ 70; 7. Subjects must be platelet transfusion independent (Platelet transfusion independence is defined as 7 days or greater without a platelet transfusion); 8. Neutrophil count $\geq$ 1.0 thou/mm^3 and platelet count $\geq$ 30 thou/mm^3;

	9. Subjects must have total bilirubin ≤ 2 mg/dL; 10. Subjects must have serum AST and ALT levels ≤ 2.5 times upper limit of normal; 11. Subjects must have serum creatinine < 2.5 times upper limit of normal and a calculated creatinine clearance ≥ 30 ml/min by Cockcroft-Gault formula (see Appendix I: Cockcroft-Gault Creatinine Clearance Calculation); 12. All study participants who will receive lenalidomide based on the CD34+ chimerism testing must be registered into the mandatory Revlimid REMS® program, and be willing and able to comply with the requirements of the REMS® program; 13. Females of child-bearing potential (*i.e.*, women who are pre-menopausal or not surgically sterile) may participate, provided they meet the following conditions: a) Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program; and 14. Written, voluntary informed consent, willingness, and ability to comply with all study procedures. <u>Exclusion Criteria:</u> 1. CD34- AML or MDS; 2. Subjects with peripheral blasts or progressive cytopenias will be excluded unless a CR or CRi confirmed by a bone marrow biopsy within two weeks post of the allo-HCT; 3. Inability to give informed consent; 4. Uncontrolled active infection(s) requiring intravenous antibiotics; 5. Known or suspected hypersensitivity to lenalidomide; 6. Grade II-IV acute GVHD or extensive GVHD; 7. Not able to swallow the lenalidomide capsule as a whole; or 8. Female subjects who are pregnant or nursing;
Accrual:	The sample size for the study is based on incidence of DLT; however, it is not to exceed 24 subjects. The accrual period will be three years.
Study Duration and Dates:	The subject recruitment period is approximately 36 months, starting last quarter 2015. The study duration encompasses the following: • Screening period of up to 14 days (+/-7 days from Day +60); and • The CD34+ donor chimerism will be performed on days +60 and +90 (± 7 days) post-transplant until the CD34+ donor chimerism drops to ≤ 90%. If the CD34+ donor chimerism continues to be > 90% by day +90 (± 7 days) post-transplant the patient will be removed from the study; • Treatment with lenalidomide will start within 10 days after detection of the CD34+ donor chimerism ≤ 90% and be continued

	for 21 days in a 28 day cycle X 2 cycles or until terminating event occurs; • In subjects receiving lenalidomide, the CD34+ donor chimerism will be performed at Days +60 and +120 (± 7 days) of lenalidomide therapy.
Safety Assessments:	Subjects will be examined weekly per institutional standard of care. Examinations will consist of vital sign measurements, physical examinations, laboratory assessments (hematology, serum chemistries) and assessment of acute GVHD. NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 will be used to grade toxicity and adverse events. GVHD assessment: Acute GVHD will be evaluated as per institutional practice guidelines using established staging criteria (see Appendix F). GVHD severity will be determined clinically; however, biopsies of affected organs are encouraged whenever possible. GVHD assessments will be performed at screening and Days +60 & +90. If lenalidomide is initiated, GVHD assessments will be performed weekly during scheduled visits and continuing until 30 days after the last dose of lenalidomide. GVHD assessments will also be documented at Days +60 and Day +120 after the initiation of lenalidomide. Overall grading and response to GVHD therapy will be measured through the use of the consensus and IBMTR GVHD severity indices based on physical exam and laboratory serum values (see Appendix F). Individual organ stages will be scored by the attending physician or other trained provider.
Immunosuppression:	All patients should receive standard GVHD prophylaxis per institutional guidelines per the treating physician.
Efficacy Assessments:	The efficacy outcome of interest will be reversal of the decreased CD34+ specific donor chimerism by day 60 of lenalidomide administration.
Statistical Procedures:	This study is descriptive in nature and not designed to provide analytical inferential results regarding primary or secondary endpoints. The sample size is based primarily on clinical considerations and not on statistical power calculations. Statistical characteristics of the “3 + 3” design are described in Appendix G. Descriptive statistics will be used to summarize baseline subject characteristics, treatment administration, and safety variables. All subjects who receive at least 5 doses of lenalidomide and have one post-dose safety assessment will comprise the safety population. The efficacy evaluable population will comprise all subjects who complete

	at least 15 days of lenalidomide and have at least one post-therapy CD34+ specific chimerism assessment.

Schedule of Events

Assessment	Screening (+/-7 days from Day +60)	Post-Transplant Monitoring Days +60 & 90 (± 7 days)	Revlimid C1D1, C2D1	End of Treatment 30 Days post-last Revlimid Dose (± 2 days)	Post-Revlimid Monitoring Days +60 & +120 (± 7 days)	Survival Every 3-months for 1 year
Signed Informed Consent	X					
Demographics, Medical /Treatment History	X					
MDS and AML WHO Classification	X					
Weight, Height	X					
Physical Examination	X	X	X	X	X	
GVHD Assessment [A]	X	X	X	X	X	
Vital Signs	X	X	X	X	X	
Karnofsky Performance Score	X	X	X	X	X	
CBC + Differential	X	X	X	X	X	
Serum Chemistry	X	X	X	X	X	
Serum Pregnancy Test (females) [B]	X		X			
Bone Marrow Aspiration and Biopsy [C]	X					
Peripheral Blood Chimerism		X				
Peripheral blood CD34+ donor chimerism [D]		X			X	
Dispense Revlimid (21-day supply)			X			
Concomitant Medications	X	X	X	X		
Adverse Events Assessments	X	X	X	X		
Concomitant Blood Products	X	X	X	X		
Disease Response Assessment [C]	X	X				X
Survival Assessment				X		X

A. Overall grading and response to GVHD therapy will be measured through the use of the consensus and IBMTR GVHD severity indices. GVHD assessments will be performed at screening and Days +60 &+ 90. If lenalidomide is initiated, GVHD assessments will be performed weekly during scheduled visits and continuing until 30 days after the last dose of lenalidomide. GVHD assessments will also be documented at Days +60, and Day +120 after the initiation of lenalidomide.

B. Females of reproductive potential must have 2 negative pregnancy tests prior to initiating therapy. The first test should be performed within 10-14 days, and the second test within 24 hours prior to prescribing REVLIMID therapy and then weekly during the first month, then monthly thereafter in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles.

C. All disease assessments which occur during routine care of the subject will be recorded in the CRF. Bone marrow procedures or other disease assessments will be performed according to institutional guidelines or physician discretion.

D. The peripheral blood CD34+ donor chimerism will be performed on days +60 and +90 (± 7 days) post-transplant until the CD34+ donor chimerism drops to ≤ 90%. In subjects receiving lenalidomide, the CD34+ donor chimerism will be performed at Days +60 and +120 (± 7 days) of lenalidomide therapy. Additional CD34+ donor chimerism testing will be performed at the discretion of the clinical investigator (*e.g.*, when a subject develops peripheral blasts, worsening pancytopenia, or extramedullary relapse).

1. BACKGROUND

This clinical trial provides an investigational therapeutic option to prevent disease relapse in patients with high risk AML and MDS after allo-HCT.

1.1 Acute Myelogenous Leukemia

Acute myelogenous leukemia (AML) is a hematologic malignancy arising from a clonal hematopoietic stem cell and characterized by accumulation of malignant myeloblasts in the bone marrow and resulting in ineffective hematopoiesis. AML is the most common type of acute leukemia in adults in the United States, with over 11,000 new cases reported each year. [1] It is widely known that AML remits initially to conventional cytotoxic chemotherapy, but often relapses due to (1) genetic and epigenetic abnormalities conferring insensitivity to conventional cytotoxic agents, and (2) protective microenvironments that support leukemia cell survival and proliferation. [2,3] Whereas initial remission rates are 50-80%, long-term disease-free survival is 20% in patients achieving a complete remission and less than 10% overall.[1] Relapsed and refractory disease are major challenges.

The prognosis for patients with AML relapsing after allo-HCT is very poor. The duration of first remission in relapsed patients is the most important prognostic factor correlating with the probability of second CR and survival.[4] Patients with primary refractory and early relapsed disease with a CR duration < 6 months have a significantly poorer response to therapy and OS than do patients who relapsed after a first CR lasting ≥ 6 months (CR rate 10%–30% vs. 40%–60%, respectively).[5-8] The optimum strategy at the time of relapse for patients with resistant disease remains uncertain.

1.2 Myelodysplastic Syndromes

The myelodysplastic syndromes (MDS) are a heterogeneous group of clonal neoplastic hematopoietic stem cell disorders. They are characterized by a hypercellular bone marrow, with dysplastic ineffective hematopoiesis resulting in peripheral blood cytopenias. MDS most often affects elderly people. The incidence of MDS is 50 per 100,000 in the population over age of 60, and it is the most common hematological malignancy in this age group.[9] Thirty to fifty percent of cases of MDS eventually evolve into AML, therefore this syndrome historically has been called oligoblastic leukemia, smoldering acute leukemia, or preleukemia.[10]

The decision to treat MDS is generally based on age of the patient, performance status, and International Prognostic Scoring System (IPSS) score.[11-13] While some patients with low risk disease and stable blood counts do not need immediate treatment and can be followed without therapy, others with Low and Intermediate-1 risk IPSS scores may require treatment to alleviate cytopenias and improve quality of life. Such patients are usually treated with low intensity approaches such as supportive care, including antibiotics, blood product transfusion, hematopoietic growth factors, immunosuppressants, immunomodulators, and inhibitors of angiogenesis. Epigenetic modulators, farnesyltransferase and tyrosine kinase inhibitors target molecular aberrations seen in later stages of MDS. Higher intensity therapies which aim at changing the natural history of disease are usually reserved for patients with excess myeloblasts (RAEB-1 and RAEB-2 disease) and Intermediate-2 and High risk IPSS scores.

Despite significant progress in treatment of advanced disease MDS (RAEB-1, RAEB-2, Intermediate-2 IPSS, High IPSS), the only curative therapy is allogeneic hematopoietic cell transplant, which is risky.[14-19] In addition, few MDS patients are eligible for transplant due to co-morbidities and lack of suitable donors. Standard induction therapy for patients with advanced MDS include azanucleosides such as azacitidine (Vidaza®) and decitabine (Dacogen®), which exhibit dual properties as pyrimidine analogues and hypomethylating agents.[20,21] These agents change the natural history of MDS, reduce transfusion requirements, extend survival, and delay progression to acute leukemia.[20,22-25] However, only 20% of patients achieve complete and partial bone marrow remissions (CR+PR) and only 50% of patients achieve hematologic improvements. Moreover, in spite of any improvement nearly all MDS patients suffer from disease relapse and progression.

Treatment for relapsed MDS after allo-HCT is poor. There is no standard therapy. Most patients are referred to clinical trials for investigational therapy. [13] If no clinical trial is available, best supportive care and hospice services are recommended.

1.3 Experience with Revlimid after allo-HCT in patients with Multiple Myeloma

There is a limited amount of published data available about the feasibility of lenalidomide administration after allo-HCT in patients with multiple myeloma.

Coman et al. showed that administration of lenalidomide at 25 mg/day (alone or in combination with dexamethasone) after allo-HSCT in patients with multiple myeloma was associated with high response rate, however led to the development or worsening of aGVHD in 31% patients. Importantly development of aGVHD was significantly associated with a stronger anti-myeloma response1[26]. Alsina et al. reported similar findings demonstrating that maintenance therapy with lenalidomide in myeloma patients after allo-HSC is feasible. In this study lenalidomide was started at 10 mg/day and the doses were further escalated. The median time from allo-HSCT to lenalidomide initiation was 96 days and aGVHD developed in 37% patients with a cumulative incidence of grades III to IV aGVHD of 17% 2 [27]. However, Kneppers et al reported that even low doses of lenalidomide at 10 mg given for 21 days of a 28-day schedule led to relatively high rates of its discontinuation, mainly because of aGVHD, which developed in 43%3 [28].

1.4 CD34+ mixed chimerism analysis

The CD34+ chimerism analysis allows early identification of patients at a very high risk for relapse. Our preliminary data showed the ability of the CD34+ specific chimerism analysis to monitor MRD and identify of AML and MDS patients at a very high risk for hematologic relapse after allo-HCT. To obtain the CD34+ specific chimerism analysis, CD34+ cells from 12 subjects were positively selected by immunomagnetic isolation from peripheral blood and processed by fluorescence-activated cell sorting. Purified CD34+ cells were subsequently evaluated for percentage of donor DNA contribution by short tandem repeat (STR) analysis. We were able to isolate CD34+ cells from peripheral blood with a very high purity (Figure 1) and in sufficient amount for a reliable STR testing analysis in all 12 study patients. The CD34+ specific donor chimerism analysis was repeated monthly until hematologic relapse or death occurred. Simultaneously, conventional donor chimerism analysis was measured in the subpopulations of peripheral blood cells. Out of 12 enrolled subjects 6 subjects had hematologic relapse confirmed by a bone marrow evaluation. In 5

out of 6 patients with relapsed disease CD34+ specific chimerism dropped to <10% prior to confirmed hematologic relapse, whereas routine STR analysis in subpopulations of peripheral blood cells failed to convincingly demonstrate a significant decrease in donor/recipient chimerism (Figure 2). One patient (pt#7) with hematologic relapse steadily dropped the CD34+ specific donor chimerism down to 52%, however was lost to follow up with no further chimerism testing for the period of 3 months preceding hematologic relapse.

Figure 1. CD34+ Chimerism cells

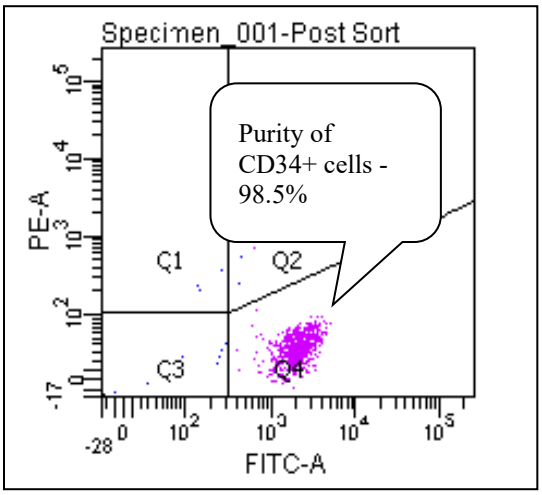
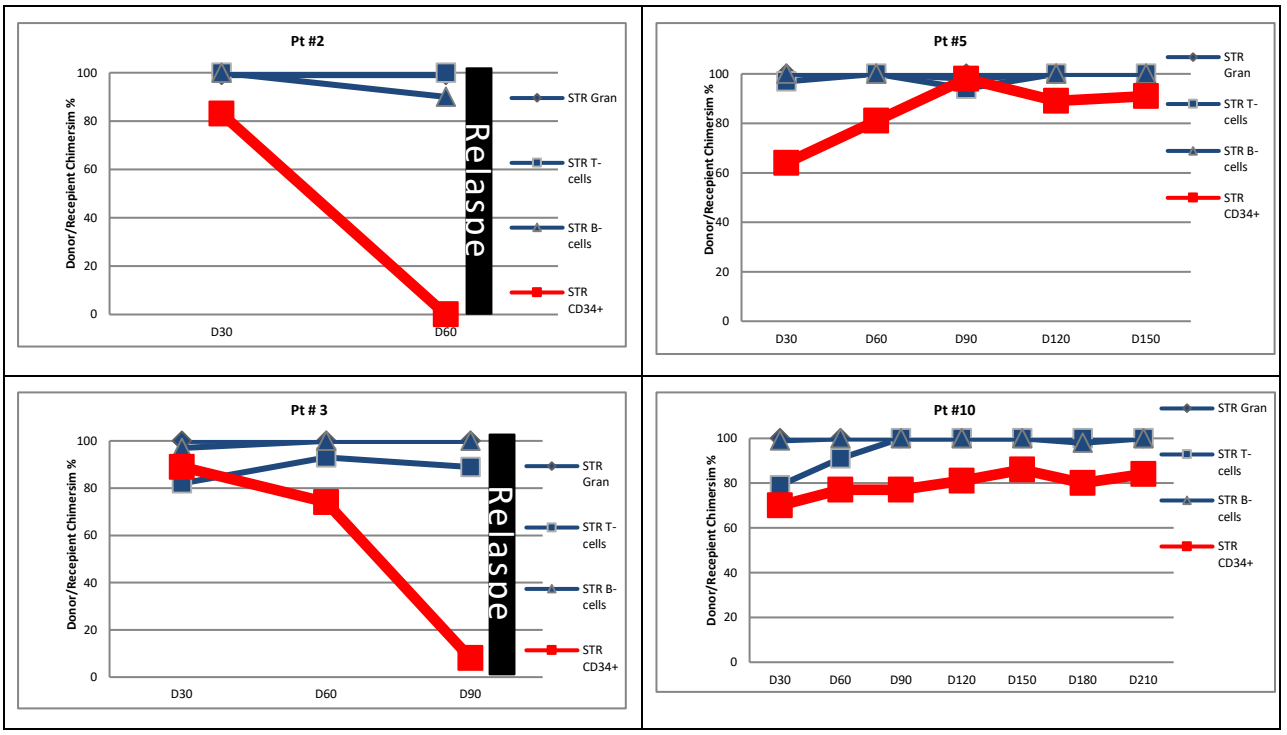
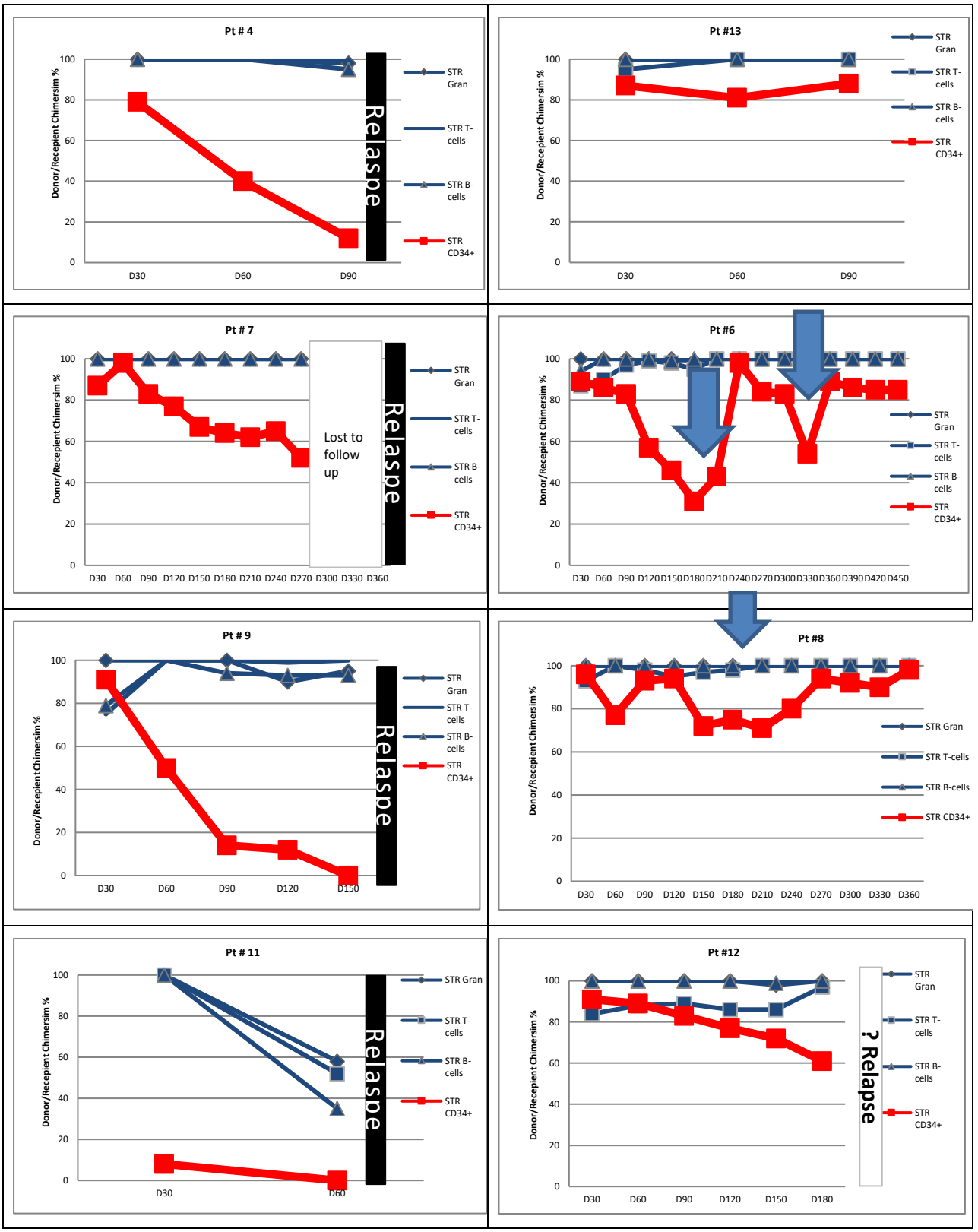


Figure 2. Conventional and CD34+ donor chimerism monitoring in patients with (left column) and without (right column) hematologic relapse




Pt # 4
Donor/Recepient Chimersim %
100
80
60
40
20
0
D30
D60
D90
Relaspe
STR Gran
STR T-cells
STR B-cells
STR CD34+
Pt #13
Donor/Recepient Chimersim %
100
80
60
40
20
0
D30
D60
D90
STR Gran
STR T-cells
STR B-cells
STR CD34+
Pt # 7
Donor/Recepient Chimersim %
100
80
60
40
20
0
D30 D60 D90 D120 D150 D180 D210 D240 D270 D300 D330 D360
Lost to follow up
Relaspe
STR Gran
STR T-cells
STR B-cells
STR CD34+
Pt #6
Donor/Recepient Chimersim %
100
80
60
40
20
0
D30 D60 D90 D120 D150 D180 D210 D240 D270 D300 D330 D360 D390 D420 D450
STR Gran
STR T-cells
STR B-cells
STR CD34+
Pt # 9
Donor/Recepient Chimersim %
100
80
60
40
20
0
D30
D60
D90
D120
D150
Relaspe
STR Gran
STR T-cells
STR B-cells
STR CD34+
Pt #8
Donor/Recepient Chimersim %
100
80
60
40
20
0
D30 D60 D90 D120 D150 D180 D210 D240 D270 D300 D330 D360
STR Gran
STR T-cells
STR B-cells
STR CD34+
Pt # 11
Donor/Recepient Chimersim %
100
80
60
40
20
0
D30
D60
Relaspe
STR Gran
STR T-cells
STR B-cells
STR CD34+
Pt #12
Donor/Recepient Chimersim %
100
80
60
40
20
0
D30
D60
D90
D120
D150
D180
? Relapse
STR Gran
STR T-cells
STR B-cells
STR CD34+

These results demonstrated the feasibility of using the CD34+ specific chimerism analysis to monitor MRD and timely detect an imminent hematologic relapse. The CD34+ specific STR analysis is superior to conventional chimerism analysis for MRD monitoring and identification of early relapse after allo-HCT. More importantly, drop of CD34+ specific chimerism occurred significantly earlier that decrease in chimerism assessed by conventional STR-based techniques. Therefore, the use of highly sensitive and specific MRD monitoring by the CD34+ chimerism analysis **substantially increases the reliability of early MRD detection** after allo-HCT **allowing early therapeutic interventions** and is **potentially practice changing**.

2. STUDY AGENT

2.1 Lenalidomide

2.1.1 Background

Lenalidomide has both immunomodulatory and anti-angiogenic properties which could confer antitumor and antimetastatic effects. Lenalidomide has been demonstrated to possess anti-angiogenic activity through inhibition of bFGF, VEGF and TNF-alpha induced endothelial cell migration, due at least in part to inhibition of Akt phosphorylation response to bFGF.[29] In addition, lenalidomide has a variety of immunomodulatory effects. Lenalidomide stimulates T cell proliferation, and the production of IL-2, IL-10 and IFN-gamma, inhibits IL-1 beta and IL-6 and modulates IL-12 production.[30] Upregulation of T cell derived IL-2 production is achieved at least in part through increased AP-1 activity.[31]

Although the exact antitumor mechanism of action of lenalidomide is unknown, a number of mechanisms are postulated to be responsible for lenalidomide's activity against multiple myeloma. Lenalidomide has been shown to increase T cell proliferation, which leads to an increase in IL-2 and IFN-gamma secretion. The increased level of these circulating cytokines augment natural killer cell number and function, and enhance natural killer cell activity to yield an increase in multiple myeloma cell lysis.[32] In addition, lenalidomide has direct activity against multiple myeloma and induces apoptosis or G1growth arrest in multiple myeloma cell lines and in multiple myeloma cells of patients resistant to melphalan, doxorubicin and dexamethasone.[33]

2.1.1.1 Indications and Usage:

Revlimid® (lenalidomide) is indicated for the treatment of patients with transfusion-dependent anemia due to Low- or Intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. Revlimid® is also approved in combination with dexamethasone for the treatment of patients with multiple myeloma that have received at least one prior therapy.

2.1.2 Adverse Events

Most frequently reported adverse events reported during clinical studies with lenalidomide in oncologic and non-oncologic indications, regardless of presumed relationship to study medication include: anemia, neutropenia, thrombocytopenia and pancytopenia, abdominal pain, nausea, vomiting and diarrhea, dehydration, rash, itching, infections, sepsis, pneumonia, urinary tract infection, upper respiratory infection, atrial fibrillation, congestive

heart failure, myocardial infarction, chest pain, weakness, hypotension, hypercalcemia, hyperglycemia, back pain, bone pain, generalized pain, dizziness, mental status changes, syncope, renal failure, dyspnea, pleural effusion, pulmonary embolism, deep vein thrombosis, cerebrovascular accident, convulsions, dizziness, spinal cord compression, syncope, disease progression, death not specified and fractures.

2.1.3 Second New Cancers

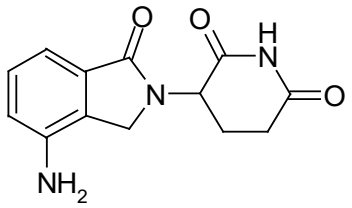
According to researchers, patients with cancer have a higher risk of developing a second new cancer when compared to people without cancer. In clinical studies of patients with newly diagnosed multiple myeloma, a higher number of second cancers were reported in patients treated with lenalidomide as induction therapy (treatment for several cycles to reduce number of cancer cells) and/or bone marrow transplant followed by lenalidomide for a long period of time compared to patients treated with induction therapy and/or bone marrow transplant then placebo (a capsule containing no lenalidomide). Patients should make their doctors aware of their medical history and any concerns they may have regarding their own increased risk of other cancers.

Complete and updated adverse events are available in the Investigational Drug Brochure and the IND Safety Letters.

2.1.4 Lenalidomide Description

REVLIMID® (lenalidomide), a thalidomide analogue, is an immunomodulatory agent with anti-angiogenic properties. The chemical name is 3-(4-amino-1-oxo 1,3-dihydro -2*H*-isoindol-2-yl) piperidine-2,6-dione and it has the following chemical structure:

Figure 3. Chemical Structure of Lenalidomide



3-(4-amino-1-oxo 1,3-dihydro-2*H*-isoindol-2-yl) piperidine-2,6-dione

The empirical formula for lenalidomide is $C_{13}H_{13}N_3O_3$, and the gram molecular weight is 259.3.

Lenalidomide is an off-white to pale-yellow solid powder. It is soluble in organic solvent/water mixtures, and buffered aqueous solvents. Lenalidomide is more soluble in organic solvents and low pH solutions. Solubility was significantly lower in less acidic buffers, ranging from about 0.4 to 0.5 mg/ml. Lenalidomide has an asymmetric carbon atom and can exist as the optically active forms S(-) and R(+), and is produced as a racemic mixture with a net optical rotation of zero.

2.1.5 Clinical Pharmacology

2.1.5.1 Mechanism of Action:

The mechanism of action of lenalidomide remains to be fully characterized. Lenalidomide possesses immunomodulatory and antiangiogenic properties. Lenalidomide inhibited the secretion of pro-inflammatory cytokines and increased the secretion of anti-inflammatory cytokines from peripheral blood mononuclear cells. Lenalidomide inhibited cell proliferation with varying effectiveness (IC50s) in some but not all cell lines. Of cell lines tested, lenalidomide was effective in inhibiting growth of Namalwa cells (a human B cell lymphoma cell line with a deletion of one chromosome 5) but was much less effective in inhibiting growth of KG-1 cells (human myeloblastic cell line, also with a deletion of one chromosome 5) and other cell lines without chromosome 5 deletions. Lenalidomide inhibited the expression of cyclooxygenase-2 (COX-2) but not COX-1 in vitro.

2.1.6 Pharmacokinetics and Drug Metabolism

2.1.6.1 Absorption:

Lenalidomide, in healthy volunteers, is rapidly absorbed following oral administration with maximum plasma concentrations occurring between 0.625 and 1.5 hours post-dose. Co-administration with food does not alter the extent of absorption (AUC) but does reduce the maximal plasma concentration (Cmax) by 36%. The pharmacokinetic disposition of lenalidomide is linear. Cmax and AUC increase proportionately with increases in dose. Multiple dosing at the recommended dose-regimen does not result in drug accumulation.

Pharmacokinetic analyses were performed on 15 multiple myeloma patients treated in the phase I studies. Absorption was found to be rapid on both Day 1 and Day 28 with time to maximum blood levels ranging from 0.7 to 2.0 hours at all dose levels (5mg, 10mg, 25mg, and 50mg). No plasma accumulation was observed with multiple daily dosing. Plasma lenalidomide declined in a monophasic manner with elimination half-life ranging from 2.8 to 6.1 hours on both Day 1 and 28 at all 4 doses. Peak and overall plasma concentrations were dose proportional over the dosing range of 5mg to 50mg.[33] Exposure (AUC) in multiple myeloma patients is 57% higher than in healthy male volunteers.

2.1.7 Pharmacokinetic Parameters

2.1.7.1 Distribution

In vitro (^{14}C)-lenalidomide binding to plasma proteins is approximately 30%.

2.1.8 Metabolism and Excretion

The metabolic profile of lenalidomide in humans has not been studied. In healthy volunteers, approximately two-thirds of lenalidomide is eliminated unchanged through urinary excretion. The process exceeds the glomerular filtration rate and therefore is partially or entirely active. Half-life of elimination is approximately 3 hours.

2.1.9 Supplier(s)

Celgene Corporation will supply lenalidomide (Revlimid®) to study participants at no charge through Celgene's Revlimid Risk Evaluation and Mitigation Strategy™ (REMS) (formerly known as RevAssist® Program).

2.1.10 Dosage form

Lenalidomide will be supplied as capsules for oral administration.

2.1.11 Packaging

Lenalidomide will be shipped directly to the clinical site. Bottles will contain a sufficient number of capsules for one cycle of dosing**.**

2.1.12 Labeling

Lenalidomide supplies are dispensed in individual bottles of capsules. Each bottle will identify the contents as study medication. In addition, the label will bear Celgene's name, quantity contained and the standard caution statement as follows: "Caution: New drug - Limited by Federal law to investigational use." Lenalidomide should not be handled by FCBP unless wearing gloves.

The study drug label must be clearly visible. Additional labels must not cover the Celgene label.

2.1.13 Special Handling Instructions

Females of childbearing potential should not handle or administer lenalidomide unless they are wearing gloves.

2.1.14 Prescribing Information

Lenalidomide (Revlimid®) will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers. Lenalidomide will be provided in accordance with the Celgene Corporation's Revlimid REMS® program. Per standard Revlimid REMS® program requirements, all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in, and must comply with, all requirements of the Revlimid REMS® program.

Drug will be shipped on a per patient basis by the contract pharmacy to the clinic site for IND studies. Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.

2.1.15 Pregnancy Testing

Females must follow pregnancy testing requirements as outlined in the Revlimid REMS® program material.

3. OBJECTIVES

3.1 Primary

To determine safety and the maximum tolerated dose of lenalidomide after allo-HCT in AML and MDS subjects with MRD detected by the CD34+ mixed chimerism analysis.

3.2 Secondary

To monitor changes in the CD34+ mixed chimerism after allo-HCT in AML and MDS subjects with detectable MRD in response to escalating doses of lenalidomide.

4. STUDY DESIGN

4.1 Overall Study Design

This is an open-label, phase I study of lenalidomide in after allo-HCT in AML and MDS subjects with MRD detected by the CD34+ mixed chimerism analysis. The study is designed to evaluate the safety profile, maximum tolerated dose and biologic activity of lenalidomide in patients with AML and MDS after allo-HCT. Subjects will be recruited in cohorts of 3. Each subject will receive lenalidomide daily for 21 days per cycle for 2 cycles (42 days). Duration of each cycle is 28 days. The starting dose will be 2.5 mg given orally every other day. Subjects will be evaluated for DLTs from the first dose and until 14 days after the last dose of lenalidomide.

4.2 Dose Escalation

The dose levels of lenalidomide will be as follows:

- Dose Level 1: 2.5 mg PO QOD Day 1-21 for 28-day cycle X 2 cycles
- Dose Level 2: 2.5 mg PO QD Day 1-21 for 28-day cycle X 2 cycles
- Dose Level 3: 5 mg PO QD Day 1-21 for 28-day cycle X 2 cycles
- Dose Level 4: 7.5 mg PO QD Day 1-21 for 28-day cycle X 2 cycles

The dose escalation phase of the study will utilize a standard "3 + 3" design to estimate the MTD for lenalidomide. A description of the statistical characteristics (probabilities of halting or continuing dose escalation) of this design is provided in Appendix G: Statistical Characteristics of the "3+3" Design. For this study, MTD will be defined as the highest dose at which no more than 34% of the subjects observed at a given dose level experience a DLT. Subjects will be individually assessed for safety and DLTs for the purpose of determining the MTD. Three eligible subjects will be enrolled in sequential cohorts at increasing dose levels until at least one (1) DLT is seen between the first dose and 14 days after the last dose of lenalidomide. The following dose escalation rules will be used and applied:

1. Three subjects are initially studied at each dose level.
2. If none of these 3 subjects experience DLT, then the dose is escalated to the next dose level in 3 subsequent subjects.
3. If 1 of these 3 subjects experiences DLT at the current dose, then up to 3 more subjects are recruited at the same dose level.
    a) If none of these 3 additional subjects experience DLT, then the dose is escalated to the next dose level in 3 subsequent subjects.
    b) If 1 or more of these 3 additional subjects experiences DLT, then the MTD is considered to have been exceeded and the previous dose level will be the MTD.
4. If 2 or more of the initial 3 subjects at a dose level experience DLT, then the MTD is considered to have been exceeded and dose escalation will be stopped. Up to 3 more subjects are treated at the next lower dose.

A subject must meet one of the following 3 criteria to be evaluable for dose-escalation decisions:

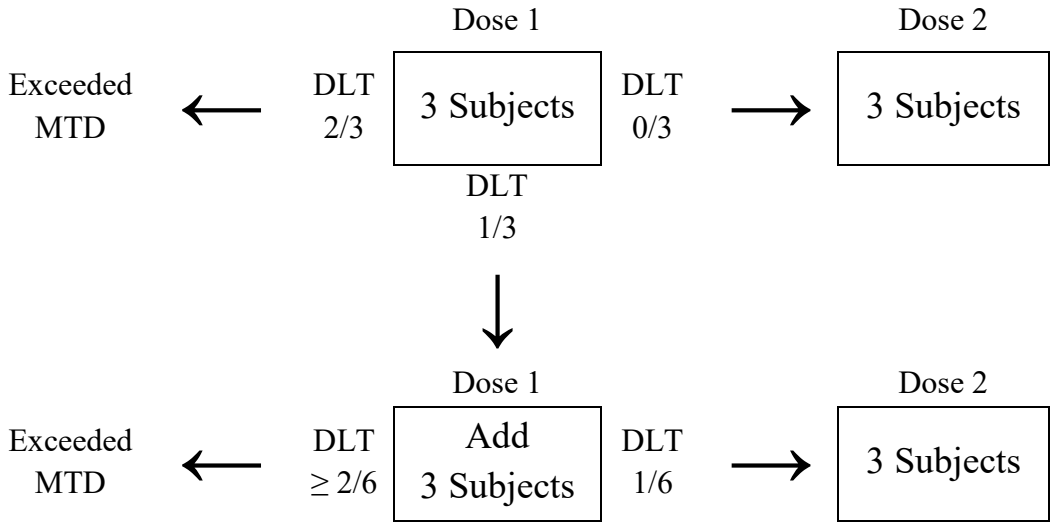
1. Completed at least 21 days of lenalidomide without a DLT by 14 days after the last dose of lenalidomide;

2. Experienced a DLT between the first dose and 14 days after the last dose of lenalidomide; or
3. Withdrawn from the study after at least 14 days of lenalidomide administration.

The study ends when there is a maximum dose where 2 or more subjects out of 6 have a DLT, or when the maximum sample size of twenty-four (24) subjects has been reached.

Figure 4 provides an example of how the MTD will be determined in Cycle 1.

Figure 4. Dose Limiting Toxicity Flow Diagram



4.3 Dose Limiting Toxicity

DLT will be defined as any of the following adverse events that are not clearly unrelated to drug administration or treatment-emergent from lenalidomide and constitute a change from baseline irrespective of outcome. For the purpose of dose-escalation decisions and MTD determination, only DLTs that occur before 14 days after the last dose of lenalidomide administration will be taken into account.

1. Grade 3 or greater nausea, diarrhea, or vomiting despite the use of maximal medical intervention;
2. Grade 3 or greater acute GVHD despite the use of maximal medical intervention;
3. Any other clinically significant nonhematologic toxicity of grade 3 or greater considered not related to the underlying disease or intercurrent illness;
4. Grade 3 or greater neutropenia
5. Grade 4 thrombocytopenia or platelet count $\leq$50 thou/mm^3 by day 28 of lenalidomide administration; or
6. Any treatment-related effect leading to a subject missing 3 or more doses of lenalidomide.

4.4 Study Duration and Dates

The subject recruitment period is approximately 36 months, starting last quarter 2015. The study duration encompasses the following:

- Screening period of up to 14 days (+/- 7) days from Day +60; and

- The CD34+ donor chimerism will be performed on days +60 and +90 (± 7 days) post-transplant until the CD34+ donor chimerism drops to ≤ 90%. If the CD34+ donor chimerism continues to be > 90% by day +90 (± 7 days) post-transplant the patient will be removed from the study;
- Treatment with lenalidomide will start within 10 days after detection of the CD34+ donor chimerism ≤ 90% and be continued for 21 days in a 28-day cycle X 2 cycles or until terminating event occurs, whichever occurs first;
- In subjects receiving lenalidomide, the CD34+ donor chimerism will be performed at Days +60 and +120 (± 7 days) of lenalidomide therapy.

4.5 Correlative Studies

Peripheral blood will be collected to examine the CD34+ specific chimerism at the time-points as described in the Schedule of Events.

5. SELECTION OF SUBJECTS

5.1 Number of Subjects

It is anticipated that up to 24 allo-HCT recipients with AML and MDS will receive lenalidomide in this study. Justification for sample size is provided in Section 13.1. Subjects in this study can be of any race, gender and ethnic group.

5.2 Inclusion Criteria

1) Subjects must be at least 18 years of age;
2) Subjects must be 60 (+/- 7) days post-allogeneic transplant from any donor source;
3) Subjects must have either:
    a) High risk CD34+ AML (*de novo* or secondary, and any WHO 2008 classification excluding acute promyelocytic leukemia, see Appendix A: AML WHO 2008 Classification System[3]). High risk AML is defined as (a) disease status beyond complete remission (CR) #1 at transplant or (b) treatment related AML or (c) presence of adverse cytogenetics including inv(3); t(3;3); t(6;9); t(v;11); -5 or del(5q); -7; abnl(17p) or complex karyotype; or
    b) High risk CD34+ MDS (WHO 2008 classification, see Appendix B: MDS WHO 2008 Classification System[34]). High risk is defined as (a) blast count ≥5% at the time of transplant or (b) treatment related MD or (c) presence of adverse cytogenetics including -7/del7q or complex karyotype;
4) For AML subjects, they must have a documented CR within 45 days prior to allo-HCT;
5) For MDS subjects, they must have < 20% myeloblasts in the bone marrow within 45 days prior to allo-HCT;
6) Subject Karnofsky performance status must be ≥ 70 (see Appendix E: Karnofsky Performance Status);
7) Subjects must be platelet transfusion independent (Platelet transfusion independence is defined as 7 days or greater without a platelet transfusion);
8) Neutrophil count ≥ 1.0 thou/mm^3 and platelet count ≥ 30 thou/mm^3;
9) Subjects must have total bilirubin ≤ 2 mg/dL;

10) Subjects must have serum AST and ALT levels ≤ 2.5 times upper limit of normal;
11) Subjects must have serum creatinine < 2.5 times upper limit of normal and a calculated creatinine clearance ≥ 30 ml/min by Cockcroft-Gault formula (see Appendix I: Cockcroft-Gault Creatinine Clearance Calculation);
12) All study participants who will receive lenalidomide based on the CD34+ chimerism testing must be registered into the mandatory Revlimid REMS® program, and be willing and able to comply with the requirements of the REMS® program;
13) Females of child-bearing potential (*i.e.*, women who are pre-menopausal or not surgically sterile) may participate, provided they meet the following conditions:
    a) Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program; and
14) Written, voluntary informed consent, willingness, and ability to comply with all study procedures.

5.3 Exclusion criteria

1) CD34- AML or MDS;
2) Subjects with peripheral blasts or progressive cytopenias will be excluded unless a CR or CRi confirmed by a bone marrow biopsy within two weeks post of the allo-HCT;
3) Inability to give informed consent;
4) Uncontrolled active infection(s) requiring intravenous antibiotics;
5) Known or suspected hypersensitivity to lenalidomide;
6) Grade II-IV acute GVHD or extensive GVHD;
7) Not able to swallow the lenalidomide capsule as a whole; or
8) Female subjects who are pregnant or nursing.

6. STUDY TREATMENT

All subjects entering the screening phase will receive a unique subject number. This number will be used to identify the subject throughout the study. Subjects withdrawn from the study retain their subject number. New subjects will be assigned a new subject number.

6.1 Treatments to be Administered

Lenalidomide will be administered for a total of 42 days. The starting dose will be 2.5 mg given orally every other day on days 1-21 of a 28-day cycle for 2 cycles. Dose escalations and de-escalations will be made until the MTD is reached.

To ensure subject safety in the dose-escalation portion of the study, an early stopping rule will be implemented in the event that a DLT rate of greater than 34% is observed at a dose level of 2.5 mg, the lowest dose level to be evaluated in this study. In the event a DLT rate of greater than 34% observed at the starting dose of 2.5 mg orally every other day, the study will be terminated.

The dose levels of lenalidomide will be as follows:

- Dose Level 1: 2.5 mg PO QOD Day 1-21 for 28-day cycle X 2 cycles
- Dose Level 2: 2.5 mg PO QD Day 1-21 for 28-day cycle X 2 cycles

- Dose Level 3: 5 mg PO QD Day 1-21 for 28-day cycle X 2 cycles
- Dose Level 4: 7.5 mg PO QD Day 1-21 for 28-day cycle X 2 cycles

Doses should be taken at approximately the same time each day.

Subjects must be instructed to swallow lenalidomide capsules whole with water at the same time each day. Do not break, chew or open the capsules.

If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up.

Subjects who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

6.2 Instructions for initiation of lenalidomide

Lenalidomide may begin if each of the following criteria are met:

- The ANC is $\geq$ 1.0 thou/mm^3;
- The platelet count is $\geq$ 50 thou/mm^3;
- The CD34+ donor chimerism is $\leq$ 90% at day +60 or +120 ($\pm$ 7 days) post-transplant.

Lenalidomide dosing will continue as scheduled unless a DLT occurs.

6.3 Management of Toxicity

Lenalidomide at higher doses can cause hematopoietic toxicities. Management of neutropenia, neutropenic fever, thrombocytopenia, anemia, bleeding, infection, nausea, vomiting, mucositis, enteritis, and/or diarrhea will follow standard guidelines within the institution.

6.3.1 Hematopoietic Supportive Care

Platelet transfusions should be given to maintain counts > 10,000/µL. Platelets should not be transfused electively on study if the patient has a platelet count $\geq$ 20,000/µL and has no other medical indication for platelet transfusion (for example, bleeding, surgical procedure). For patients with platelet count of < 20,000/µL, elective platelet transfusions will be given as necessary according to institutional guidelines (depending on the threshold level for transfusion at the institutions and individualized based on concurrent medical problems).

All blood and platelet transfusions will be recorded on the CRF.

6.4 Method of Treatment Assignment

The dose of lenalidomide will be assigned according to the dose escalation schedule in section 4.2 and the dose level description in section 6.1.

6.5 Record of Administration

Each subject will keep an accurate record of lenalidomide dosing on the Subject Dosing Diary. This diary will be kept in the research record as source documentation of lenalidomide dosing. Study personnel will review the dosing instructions with each subject at each study visit. Subjects will be asked to bring any unused drug and empty drug containers to the study site at the next visit for reconciliation with the Subject Dosing Diary.

Any unused Revlimid® (lenalidomide) will be returned to the site for disposition in accordance with Celgene's Revlimid Risk Evaluation and Mitigation Strategy™ (REMS) (formerly known as RevAssist® Program).

7. CONCOMITANT MEDICATIONS

7.1 Concomitant Medications and Therapy

Any therapy or medication (except study drug), administered from screening until 28 days after the last dose of study drug, is considered a concomitant therapy or medication. If the use of any concomitant treatments (medications or procedures) becomes necessary, the treatment must be recorded, including the name of the drug or treatment, dose, route, date, indication for use, and frequency of treatment.

No other investigational drugs may be administered.

Concomitant medications should be kept to a minimum during the study. However, if these are considered necessary for the study subject's welfare and are unlikely to interfere with the study drug, they may be given at the discretion of the treating physician. Subjects may receive blood transfusions and ongoing supportive and palliative care (*e.g.*, pain control) as clinically indicated throughout the study. Anti-emetics and other supportive medications such as antibiotics should be recorded on the CRF. The administration of prophylactic antimicrobials is left to the discretion of the treating physician.

7.2 Excluded Medications

The following drugs are excluded:

- azacitidine (Vidaza);
- decitabine (Dacogen);
- Other investigational drugs.

7.3 Immunosuppression

All patients should receive standard GVHD prophylaxis per institutional guidelines per the treating physician.

8. STUDY PROCEDURES

8.1 Protocol Procedures

All subjects will have study-related procedures as described in the Schedule of Events table.

9. DATA MEASUREMENTS AND METHODS OF COLLECTION

9.1 Data Measurements

9.1.1 Safety Data

Safety variable for this study include the following:

- DLTs;
- Physical examinations including assessment of skin GVHD;
- Vital signs;
- Clinical laboratory measurements, including hematology and serum chemistry; and
- Adverse events.

9.1.2 Correlative Studies

The CD34+ specific chimerism analysis from peripheral blood will be performed on days +60 and +90 (± 7 days) post-HCT until the CD34+ donor chimerism drops to ≤ 90% and/or on days +60 and +120 (± 7 days) days after the initiation of lenalidomide. Additional CD34+ donor chimerism testing will be performed at the discretion of the clinical investigator (*e.g.*, when a subject develops peripheral blasts, worsening pancytopenia, or extramedullary relapse).

9.2 Methods of Collection

9.2.1 Sample Collection for Correlative Studies

9.2.1.1 Blood Samples

Peripheral blood samples will be obtained by venipuncture or from venous catheter (if in place) and will be collected at the same time as other laboratory assessments are drawn for necessary clinical care, if possible. The risks of drawing blood from a vein include discomfort at the site of injection, bruising and/or swelling around the injection site, infection, or syncope from the procedure.

Approximately 50 mL of blood will be collected at each time point for the CD34+ specific chimerism testing.

9.2.2 Safety Measurements

Safety measurements for this study include AEs, clinical laboratory measurements (hematology and blood chemistry), physical examination findings, GVHD assessments, and vital signs.

9.2.2.1 Adverse Events

Prior to initiation of lenalidomide therapy, only serious and non-serious adverse events deemed to be related or possibly related to study interventions will be recorded as adverse events for the study. Adverse events will be collected at each clinic visit based on observation and spontaneous reporting.

9.2.2.2 Clinical Laboratory Measurements

All clinical laboratory assessments are outlined in the Schedule of Events.

Hematology assessments will be performed at Screening and then weekly during lenalidomide administration and for 3 weeks after therapy is completed. The hematology assessments will include:

- Complete blood count including hemoglobin, hematocrit, WBC absolute differential and platelet count.

Blood chemistry assessments will be performed at screening and then weekly during lenalidomide administration. The chemistry assessments will include:

- Electrolytes: (sodium, potassium, calcium, magnesium, phosphorous, bicarbonate, and chloride);
- Renal function: (BUN, creatinine, and uric acid);
- Liver function: SGOT (also known as AST), SGPT (also known as ALT), total bilirubin; and
- Alkaline phosphatase.

Serum pregnancy test for females of childbearing potential will be performed at Screening and must follow the pregnancy testing requirements as outlined in the Revlimid REMS® program material.

Abnormal values and/or noteworthy changes will be graded according to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE).

Abnormalities of laboratory values:

The Investigator shall classify laboratory values occurring outside of the normal range obtained for the safety assessment as:

- "Abnormal, but not clinically significant" or
- "Abnormal and clinically significant"

Laboratory abnormalities should be judged as "clinically significant" if they lead to treatment modifications, therapeutic actions, or if additional diagnostic measures are required for their resolution and in the Investigator's opinion is relevant for the clinical study.

Each clinically relevant laboratory abnormality must be recorded as a separate AE if it fits within the AE criteria outlined in Section 10.1 of the protocol and is not already described by another documented AE.

Hematology and serum chemistry assessments will be performed according to the standard operating procedures by the validated local laboratory.

9.2.2.3 Physical Examination

Targeted post-transplant physical examinations will also include vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature) and aGVHD assessments. The aGVHD assessment will be assessed using established staging criteria (see Appendix F: Graft-versus-host-disease scales). Overall grading and response to GVHD therapy will be measured through the use of the consensus and IBMTR GVHD severity indices. GVHD assessments will be performed at screening and Days +60 & +90. If lenalidomide is initiated, GVHD assessments will be performed weekly during scheduled

visits and continuing until 30 days after the last dose of lenalidomide. GVHD assessments will also be documented at Day +60 and Day +120 after the initiation of lenalidomide

10. ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Event (AE)

The term "adverse event" covers any sign, symptom, syndrome, or illness that appears or worsens in a subject during the period of observation in the clinical study and that may impair the wellbeing of the subject. The term also covers laboratory findings or results of other diagnostic procedures that are considered to be clinically significant (*e.g.*, that requires unscheduled diagnostic procedures or treatment measures, or result in withdrawal from the study).

The adverse event may be:

- A new illness/condition;
- Worsening of a sign or symptom of the condition under treatment, or of a concomitant illness/condition;
- An effect of the study drug; or
- A combination of 2 or more of these factors.

No causal relationship with the study drug or with the clinical study itself is implied by the use of the term "adverse event."

Surgical procedures themselves are not adverse events; they are therapeutic measures for conditions that require surgery. The condition(s) for which the surgery is required may be an adverse event. Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures are not adverse events.

When a clear diagnosis is available that explains the abnormal objective findings, this diagnosis will be recorded as an adverse event and not the abnormal objective findings (*e.g.*, viral hepatitis will be recorded as the adverse event and not the transaminase elevation). If a definitive diagnosis is not available, then the sign(s) (*e.g.*, clinically significant elevation of transaminase levels) or symptom(s) (*e.g.*, abdominal pain) will be recorded as the adverse event.

Adverse events fall into the categories "serious" and "nonserious."

10.1.2 Serious Adverse Event (SAE)

A serious adverse event is one that at any dose of the study drug or at any time during the period of observation:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect; or
- Is medically important.

Life-threatening means the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

Persistent or significant disability or incapacity means there is a substantial disruption of a person's ability to carry out normal life functions.

Medical and scientific judgment should be exercised in deciding whether other adverse events may be considered serious because they jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are: intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. "Medically important" should be marked only if no other serious criteria are met.

An "unexpected SAE" is any SAE for which the nature, specificity or severity is not consistent with the current Revlimid Investigator Brochure or in other risk information that has been given to the Investigator.

Clarification of the difference in meaning between "severe" and "serious"

The term "severe" is often used to describe the intensity (severity) 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 is not the same as "serious," which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

10.1.3 Events not considered to be 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 (*i.e.*, 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.

If an AE is considered serious, both the AE 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 investigational product (IP), action taken regarding IP, and outcome.

10.1.4 Non-Serious Adverse Event

A non-serious adverse event is any adverse event not meeting any of the serious adverse event criteria.

10.1.5 Abnormal Laboratory Values

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

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.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a SAE. If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE 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).

10.2 Period of Observation

For the purpose of this study, the period of observation for adverse events starts on the day the subject signs informed consent. For subjects who fail screening, the period of observation ends on the date of screening failure. Treated subjects, including those who were prematurely discontinued from the study, will be followed for any adverse events that occur during the study from the time the subject signs the informed consent form until 28 days (± 2 days) following the last dose of study treatment (*i.e.*, the Follow-up Visit). However, if another course of anti-cancer therapy is initiated prior to the 28-day follow-up period visit, collection of adverse events will no longer be performed, with the exception of events that may be possibly, probably, or definitely related to the investigational agent or are clinically significant.

10.3 Documenting and Reporting of Adverse Events by the Investigator

Prior to initiation of the investigational agent, lenalidomide, only serious and non-serious adverse events deemed to be related or possibly related to study interventions will be

recorded and reported as adverse events for the study. Adverse events will be collected at each clinic visit based on observation and spontaneous reporting.

Once lenalidomide is initiated, all adverse events that occur must be documented in the case report form.

Toxicity will be scored using CTCAE Version 4.0 for toxicity and adverse event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP homepage (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.03. All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

The following approach will be taken for documentation and reporting:

- All adverse events (whether serious or nonserious) must be documented on the "Adverse Event" page of the case report form.
- For adverse events classified as serious (see Section 10.1.2) the Investigator must complete the "Serious Adverse Event" form at the time the SAE is detected. This form must be faxed to Celgene Drug Safety within 24 hours of discovery. All SAE's must also be reported to the IRB and DISC in accordance with the institution's policy. Serious and unexpected AE's must be reported to the appropriate regulatory agencies (*e.g.*, FDA) by the sponsor to comply with regulatory requirements in accordance with 21 CFR parts 56 and 312.

Every attempt should be made to describe the adverse event in terms of a diagnosis that encompasses the component signs and symptoms. If only nonspecific signs or symptoms are present, then these should be recorded as separate diagnoses on the pages of the case report form.

All subjects who have adverse events, whether considered associated with the use of study drug or not, must be monitored to determine the outcome. The clinical course of the adverse event will be followed according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the Principal Investigator considers it medically justifiable to terminate follow-up. Should the adverse event result in death, a full pathologist's report should be supplied, if possible.

10.3.1 Assessment of Causal Relationship of Study Drug

The Investigator will provide an assessment of the potential causal relationship between adverse events and study medication by determining whether or not there is a reasonable possibility that the event was caused by the study medication. The relationship or association of the adverse event to the study medication will be characterized as not related, probably not related, possibly related, probably related, or related:

Not Related: There is not a temporal relationship to the study drug administration or the adverse event is clearly due only to the progression of the underlying disease state, intercurrent illness, concomitant medication, concurrent therapy or other known cause.

Unlikely Related: There is little or no chance that the study drug administration caused the adverse event; the event is most likely due to another competing cause, including intercurrent illness, progression or expression of the disease state, or a reaction to a concomitant medication or concurrent therapy appearing to explain the reported adverse event.

Possibly Related: The association of the adverse event with the study drug administration is unknown; however, the adverse event is not reasonably attributed to any other condition.

Probably Related: When a reasonable temporal relationship exists between the adverse event and the study drug administration; significant symptoms abate upon discontinuation of the study drug and there is a reasonable explanation based on known characteristics of the study drug and there is no clear association with preexisting disease or therapy, intercurrent illness, concurrent therapy or other factor(s).

Related: When the adverse event is a known side effect of the study drug or there is a temporal relationship to the administration of the study drug; or the adverse event reappears upon re-administration of the study drug (rechallenge); or the significant symptoms of the adverse event abate upon discontinuation of the study drug (dechallenge).

10.3.2 Intensity of Adverse Events

The intensity of adverse changes in physical signs or symptoms will be graded according to the CTCAE version 4. For all other adverse events not described in the CTCAE, the intensity will be assessed by the Investigator using the following categories:

Mild (Grade 1) – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.

Moderate (Grade 2) – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required.

Severe (Grade 3) – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible.

Life-threatening (Grade 4) – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.

Death (Grade 5) – the event resulted in death.

10.3.3 Action Taken with Study Drug

The action the Investigator took with study drug as a result of the event should be recorded as one of the following:

None – No action was taken with regard to the study drug as a result of the adverse event.

Interrupted – Study drug was stopped due to the adverse event, but was later resumed at the same dose.

Dose decreased – The dose of study drug was decreased as a result of the adverse event.

Permanently discontinued – The subject was withdrawn from the study due to the adverse event.

Only one item should be chosen. If multiple actions apply, the following "worst case" scenario hierarchy should be used to determine the preferred entry:

Discontinued > dose decreased > therapy interrupted.

10.3.4 Definition of Outcome

The outcome of the AE should be recorded as 1 of the following:

Resolved without sequelae – The subject fully recovered from the adverse event with no observable residual effects.

Resolved with sequelae – The subject recovered from the adverse event with observable residual effects.

Not resolved – The adverse event was present at the time of last observation.

Death – The subject died as a result of the adverse event.

10.4 Immediately Reportable Events

10.4.1 Serious Adverse Events

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/1 business day. All SAE's must also be reported to the IRB and DISC in accordance with the institution's policy per 21 CFR 56.

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 RV-CL-AML-PI-002987 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 patient records.

Serious and unexpected AEs that are at least possibly related to the study drug must be reported to the FDA in accordance with 21CFR 312.32 IND Safety Reports.

Celgene Drug Safety Contact Information:
Celgene Corporation
Global Drug Safety and Risk Management
Connell Corporate Park
300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922
Fax: (908) 673-9115
E-mail: drugsafety@celgene.com

10.4.2 Other Events Requiring Immediate Reporting

Any overdose of lenalidomide should be reported via an SAE form within 24 hours of being made aware of the event, regardless of association with an adverse event. In case the overdose did not result in any adverse event, the Investigator should report this as "overdose, no adverse event" on the SAE form and provide the intended amount, as well as the actual amount, of drug administered. In the event of overdose or exaggerated response, appropriate supportive measures should be employed. At this time, no specific additional measures or unique treatments are known or indicated for management of lenalidomide overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

10.5 Second Primary Malignancies

Second Primary Malignancies (SPMs) are considered events of interest and should be included as part of the assessment of adverse events throughout the course of the study. Investigators are to report any second primary malignancies as serious adverse events regardless of causal relationship to lenalidomide, occurring at any time for the duration of the study For all subjects who develop second primary malignancies, sites will be required to submit all diagnostic reports (*e.g.*, pathology, cytogenetics, flow cytometry results) from the indication diagnostic confirmation samples submitted at screening and all reports for the tumor samples from the SPM diagnosis. For SPMs diagnosed at another institution (outside the investigational site), sites are to make every effort to obtain these reports for the SPM confirmation.

10.6 Pregnancies

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 lenalidomide, or within 28 days of the subject's last dose of lenalidomide, are considered immediately reportable events. Lenalidomide is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile or email using the Pregnancy Initial Report Form. The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

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. 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.

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.

10.6.1 Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking lenalidomide should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

10.7 Investigator Reporting Responsibilities

The conduct of the study will comply with all FDA safety reporting requirements.

10.7.1 IND Annual Reports

If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report. The Annual Report should be filed in the study's Regulatory Binder, and a copy provided to Celgene Corporation as a supporter of this study as follows.

Celgene Corporation
Attn: Medical Affairs Operations
Connell Corporate Park
400 Connell Drive Suite 700
Berkeley Heights, NJ 07922

All adverse experience reports must include the patient number, age, sex, weight, severity of reaction (*e.g.*, mild, moderate, severe), relationship to drug (*e.g.*, probably related, unknown relationship, definitely not related), date and time of administration of test medications and all concomitant medications, and medical treatment provided. The investigator is responsible for evaluating all adverse events to determine whether criteria for "serious" and as defined above are present. The investigator is responsible for reporting adverse events to Celgene as described below.

10.7.2 Investigator Reporting to the FDA

Serious adverse events (SAEs) that are **unlisted/unexpected, and at least possibly associated to the drug,** and that have not previously been reported in the Investigators brochure, or reference safety information document should be reported promptly to the Food and Drug Administration (FDA) by telephone or by fax. Fatal or life threatening SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 7 calendar days after awareness of the event. All other SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 15 calendar days after awareness of the event. A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related.

10.7.3 Adverse event updates/IND safety reports

Celgene shall notify the Investigator via an IND Safety Report of the following information:

- Any AE associated with the use of drug in this study or in other studies that is both serious and unexpected.
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

The Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all AE information, including correspondence with Celgene and the IRB/EC, on file (see Section 15.6 for records retention information).

11. DISCONTINUATIONS

11.1 Discontinuation of Subjects

A subject must be discontinued from protocol-prescribed therapy under the following circumstances:

- Consent withdrawal at the subject's own request or at the request of their legally authorized representative;
- Unacceptable toxicity or adverse event as determined by the Principal Investigator and/or subject;
- Significant deviation from inclusion/exclusion criteria, in the opinion of the Principal Investigator;
- If, in the Principal Investigator's opinion, continuation in the study could be detrimental to the subject's well-being;
- Relapsed or progressive disease;
- Initiation of chemotherapy for relapsed or progressive disease.

If a female subject or the female partner of a male subject who is required to use defined contraceptive methods becomes pregnant after the study, the female subject or pregnant partner must be followed until the outcome of the pregnancy is known.

As far as possible, all end-of-study examinations must be performed on all subjects who receive the study drug but do not complete the study according to protocol. All subjects who discontinue from protocol-prescribed therapy for any of the reasons above will be followed for a period of 30 days following the last day of study drug administration.

11.2 Replacement of Subjects

Subjects who are withdrawn prior to completion of 21 days of lenalidomide for any reason will be replaced.

11.3 Study Stopping Rules

To reduce the risk of exposing subjects to an excessively toxic dose level, a stopping rule will be implemented if more than 34% of subjects in a given lenalidomide dose cohort experience a DLT. The study ends when there is a dose where 2 or more subjects out of 6 have a DLT, or when the maximum sample size of twenty-four (24) subjects has been reached.

12. DATA AND SAFETY MONITORING

12.1 Summary

This protocol will be reviewed and monitored by the University of Florida Health Cancer Center (UFHCC) Data Integrity and Safety Committee (DISC). This study will have at minimum semi-annual monitoring by the UFHCC DISC. Any adverse event fulfilling

expedited reporting requirements must be reported to the DISC coordinator within 5 working days. The DISC coordinator will forward the report to the DISC Chairperson. If there are any safety concerns, the chairperson will take appropriate action. This may involve a request for additional information, or a request for an early, unscheduled meeting of the DISC.

As part of the responsibilities assumed by conducting this study, the Principal Investigator (PI) agrees to maintain and have available for monitoring adequate case records (accurate source documents and CRFs) for the subjects treated under this protocol.

The PI will be primarily responsible for monitoring of adverse events, protocol violations, and other immediate protocol issues. The study coordinator will collect information on subjects enrolled through the use of electronic or paper adverse event (AE) forms, CRFs, and Informed Consent forms.

Identification of oversight responsibility:

The PI has primary responsibility.

The UFHCC DISC will meet at least semi-annually to review accrual, patterns and frequencies of all adverse events, protocol violations, and when applicable, internal audit results.

Description of internal (PI) safety review and monitoring process:

The PI and study team will meet biweekly to identify and review subject accrual, adverse events, and protocol violations.

Adverse events will be reported along with all of the other collected data in the OnCore database. The PI or PI designee will report all adverse events to the UFHCC DISC and IRB per reporting guidelines.

13. STATISTICAL METHODS

The sections below provide an overview of the proposed statistical considerations and analyses.

13.1 Determinations of Sample Size

No formal sample size calculations were performed. It is estimated that up to 24 subjects will be enrolled in this study. Precise sample size cannot be defined, as it is dependent on the observed toxicity rate. A description of the statistical characteristics (probabilities of halting or continuing dose escalation) of the “3 + 3” design is provided in section 16.7 (Appendix G: Statistical Characteristics of the “3+3” Design). Cohorts of 3 to 6 subjects will be treated at each lenalidomide dose level until the MTD is reached or a total of 24 subjects have been evaluated.

13.2 Analysis Populations

13.2.1 Safety Population

The safety population will consist of all subjects who received at least one dose of study drug and had at least one post-dose safety assessment. Safety summaries will include all subjects in the safety population.

13.2.2 Dose Limiting Toxicity Evaluable Population

A subject is evaluable in dose-escalation decisions provided the subject has received at least five doses without a DLT, has experienced a DLT, or has been withdrawn from the study prior to completing of 21 days of lenalidomide due to a DLT. If a subject withdraws from the study without meeting these criteria, the subject will be replaced in that cohort. Tabulations of DLTs will only include the DLT-evaluable population.

13.2.3 Efficacy Evaluable Population

The efficacy population will include all subjects who receive at least 21 days of study drug and had at least one post-cycle efficacy assessment.

13.3 Analysis Methods

13.3.1 Safety

Safety evaluation will include monitoring for adverse events, scheduled laboratory assessments, vital sign measurements, and physical examinations. The intensity of adverse changes in physical signs or symptoms will be graded according to the CTCAE version 4. For all other adverse events not listed in the CTCAE, the intensity of these events will be assessed by the Investigator using a 5-point scale as described in Section 10.3.2.

The number of adverse events and the incidence of adverse events will be summarized. Adverse events will be summarized by maximum intensity (as described in Section 10.3.2) and relationship to study drug for each treatment group. Separate summaries will be provided for all adverse events, serious adverse events, treatment-related adverse events, and other significant adverse events (*e.g.*, adverse events leading to study discontinuation).

Clinical laboratory results will be listed by subject or, as appropriate, summarized descriptively by treatment group, which will include a display of change from baseline. Laboratory values outside of the normal ranges will be identified. Clinically significant hematologic laboratory abnormalities (*i.e.*, meet Grade 3, 4, or 5 criteria according to CTCAE v.4) will be listed and summarized.

Physical examination, vital sign, and GVHD data will be listed for each subject at each study visit. If appropriate, descriptive statistics for vital signs, both observed values and changes from baseline, will be summarized by treatment group.

13.3.2 Efficacy

All efficacy endpoints will be summarized descriptively using frequency distributions. In addition, 95% confidence intervals will be provided for the proportion of each response/improvement.

14. EMERGENCY PROCEDURES

14.1 Emergency Contact

In emergency situations, the treating physician should contact the Principal Investigator by telephone at the number listed on the title page of the protocol.

14.2 Emergency Identification of Investigational Products

This is an open-label study; therefore, study drug will be identified on the package labeling.

14.3 Emergency Treatment

During and following a subject's participation in the study, the treating physician and/or institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the study.

15. ADMINISTRATIVE CONSIDERATIONS

15.1 Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Principal Investigator and Co-Investigators abide by Good Clinical Practice (GCP), as described in International Conference on Harmonization (ICH) Guideline E6, the US Code of Federal Regulations (CFR), and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an Institutional Review Board (IRB) prior to commencement. The Principal Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

15.2 Delegation of Investigator Responsibilities

The Principal Investigator will ensure that all persons assisting with the study are adequately informed about the protocol, any amendments to the protocol, the study treatments, and their study-related duties and functions. The Principal Investigator will maintain a list of Sub-Investigators and other appropriately qualified persons to whom he has delegated significant study-related duties.

15.3 Subject Information and Informed Consent

The Principal Investigator or designee must obtain valid informed consent of a subject prior to any study related procedures occur as per GCP set forth in the CFR and ICH guidelines.

Documentation that informed consent occurred prior to the subject's entry into the study and the informed consent process will be recorded in the subject's source documents. The original informed consent form will be signed and dated by the subject and by the person conducting the consent discussion prior to entry into the study. An informed consent document that includes information about the study and investigational drug will be prepared and given to each potential subject. This document will contain all ICH, GCP, and locally required regulatory elements. The document must be in a language understandable to the subject and must specify who informed the subject. The original informed consent form must be maintained in the Investigator's study files. A copy of the informed consent document must be given to the subject.

15.4 Confidentiality

Each subject will be assigned a unique acrostic that will contain no protected health information. The Principal Investigator will retain a copy of the acrostic key in a locked office. Study files stored on a computer will be stored in accordance with local data

protection laws. Subjects will be told that the IRB, Data Integrity and Safety Committee, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection law.

15.5 Protocol Amendments

Once the study has started, amendments should be made only in exceptional cases. The changes then become part of the study protocol.

15.6 Record Retention

Essential documents will be retained by the Principal Investigator for a minimum of 5 years have elapsed since study closure. Essential documents include the following:

- Signed informed consent documents for all subjects;
- Subject identification code list, screening log, and enrollment log;
- Record of all communications between the Principal Investigator and the IRB;
- Composition of the IRB;
- Record of all communications between the Principal Investigator and the DISC;
- Composition of the DISC;
- List of Sub-Investigators and other appropriately qualified persons to whom the Principal Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, start/stop date(s) of participation, and their signatures;
- Copies of CRFs and of documentation of corrections for all subjects (for electronic case report forms [eCRF], electronic files of the eCRF and audit trails will be utilized and provided to the site, as necessary);
- Drug accountability records;
- Record of any blood samples retained; and
- Other source documents (subject records, hospital records, laboratory records, etc.).

16. APPENDICES

16.1 Appendix A: AML WHO 2008 Classification System[3]

- Acute myeloid leukemia with recurrent genetic abnormalities
  - AML with t(8;21)(q22;q22); *RUNX1-RUNX1T1*
  - AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
  - APL with t(15;17)(q22;q12); *PML-RARA*
  - AML with t(9;11)(p22;q23); *MLLT3-MLL*
  - AML with t(6;9)(p23;q34); *DEK-NUP214*
  - AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
  - AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1*
- Acute myeloid leukemia with myelodysplasia-related changes
- Therapy-related myeloid neoplasms
- Acute myeloid leukemia, not otherwise specified
  - AML with minimal differentiation
  - AML without maturation
  - AML with maturation
  - Acute myelomonocytic leukemia
  - Acute monoblastic/monocytic leukemia
  - Acute erythroid leukemia
    - Pure erythroid leukemia
    - Erythroleukemia, erythroid/myeloid
  - Acute megakaryoblastic leukemia
  - Acute basophilic leukemia
  - Acute panmyelosis with myelofibrosis
- Myeloid sarcoma
- Myeloid leukemia associated with Down syndrome

16.2 Appendix B: MDS WHO 2008 Classification System[34]

Disease	Blood	Bone Marrow
Refractory Cytopenia with Unilineage Dysplasia (RCUD): • Refractory Anemia (**RA**) • Refractory Neutropenia (**RN**) • Refractory Thrombocytopenia (**RT**)	Unicytopenia or Bicytopenia No or rare blasts (< 1%)	Unilineage dysplasia ≥ 10% < 5% blasts < 15% of erythroid are RS
Refractory Anemia with Ringed Sideroblasts (**RARS**)	Anemia No blasts	≥ 15% of erythroid are RS Erythroid dysplasia only < 5% blasts
Refractory Cytopenia with Multilineage Dysplasia (**RCMD**)	Cytopenia(s) No or rare blasts (< 1%) No Auer rods Absolute monocyte count < 1000	Dysplasia in ≥ 10% of cells in ≥ 2 lineages < 5% blasts No Auer rods ± 15% of erythroid are RS
Refractory Anemia with Excess Blasts 1 (**RAEB-1**)	Cytopenia(s) < 5% blasts No Auer rods Absolute monocytes count < 1000	Unilineage or multilineage dysplasia 5% - 9% blasts No Auer rods
Refractory Anemia with Excess Blasts 2 (**RAEB-2**)	Cytopenia(s) 5% - 9% blasts Auer rods ± Absolute monocytes count < 1000	Unilineage or multilineage dysplasia 10% - 19% blasts Auer rods ±
Myelodysplastic Syndromes Unclassifiable (**MDS-U**)	Cytopenias < 1% blasts	Dysplasia < 10% Cytogenetic abnl c/w MDS < 5% blasts
MDS associated with **del(5q)**	Anemia Platelets: normal or increased No or rare blasts (< 1%)	Megas: normal to increased < 5% blasts Isolated del(5q) No Auer rods

16.3 Appendix C: AML Response Criteria According to IWG[35]

Hematologic Response According to IWG Criteria for AML

Response Criterion	Time of Assessment	Neutrophils (µL)	Platelets (µL)	Bone Marrow Blasts (%)	Other
Early treatment assessment	7-10 days after therapy	NA	NA	<5	
Morphologic leukemia-free state	Varies by protocol	NA	NA	<5	Flow cytometry EMD
Morphologic CR	Varies by protocol	>1,000	>100,000	<5	Transfusion EMD
Cytogenetic CR	Varies by protocol	>1,000	>100,000	<5	Cytogenics—normal, EMD
Molecular CR	Varies by protocol	>1,000	>100,000	<5	Molecular—negative, EMD
Partial remission	Varies by protocol	>1,000	>100,000	>50 or decrease to 5-25	Blasts <5% if Auer rod positive

Key: AML=acute myelogenous leukemia; CR=complete remission; EMD=extramedullary disease; IWG=International Working Group; NA=not applicable

16.4 Appendix D: MDS Response Criteria According to IWG[36]

Disease Remission			Hematologic Improvements (HI)	
Category	**Response (at least 4 weeks)**		**Category**	**Response (at least 8 weeks)**
CR	BM ≤ 5% blasts, may have persistent dysplastic changes in marrow, normal CBC		Erythroid Response (pre-rx Hgb < 11)	Hgb increase by ≥ 1.5, RBC tx reduction by 4 units/8 wks
PR	Blasts decreased by ≥ 50%, but BM still has > 5% blasts		Platelet Response (pre-rx PLT < 100K)	If starting with > 20K, then increase by ≥ 30K; If starting with < 20K, then > 100% increase (and over 20K)
Marrow CR	BM blasts ≤ 5% and decreased by ≥ 50%, if HI then noted individually			
SD	No PR, but progression in > 8 wk			
Failure	Progression to a more advanced class, worsened counts, death due to MDS		Neutrophil Response (pre-rx ANC < 100)	At least 100% increase and absolute increase of 500
Relapse	Return to pre-rx blasts, grans or plts decrease by ≥ 50%, Hgb decrease by ≥ 1.5 or tx dependent		Progression or Relapse after HI	At least 1 of the following: • At least 50% decrease from max response (ANC and PLTS) • Reduction of Hgb by 1.5 • Transfusion dependence
Cytogenetic Response	Complete: Disappearance of abnormality Partial: at least 50% reduction in abnormality			
Disease Progression	≥ 50% increase in blasts, decreased counts by ≥ 50%, tx dependent		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

16.5 Appendix E: Karnofsky Performance Status

Karnofsky Score	Activity
100	Normal; no complaints; no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self; unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his personal needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled; requires special care and assistance.
30	Severely disabled; hospital admission is indicated although death not imminent.
20	Very sick; hospital admission necessary; active supportive treatment necessary.
10	Moribund; fatal processes progressing rapidly.
0	Dead

16.6 Appendix F: Graft-versus-host-disease scales

GVHD Staging

Stage	Skin	GI	Liver
1	< 25% rash	Diarrhea > 500 mL/day or persistent nausea	Bilirubin 2-3 mg/dL
2	25-50%	> 1000 mL/day	Bilirubin 3-6 mg/dL
3	> 50%	> 1500 mL/day	Bilirubin 6-15 mg/dL
4	Generalized erythroderma with bullae	Large volume diarrhea and severe abdominal pain ± ileus	Bilirubin > 15 mg/dL

Consensus GVHD Grading

Grade	Skin	GI	Liver
I	Stage 1-2	0	0
II	Stage 3 or	Stage 1 or	Stage 1
III	-----	Stage 2-4	Stage 2-3
IV	Stage 4	-----	Stage 4

(Przepiorka, et. al., 1995)[37]

CIBMTR GVHD Index

Stage	Skin	GI	Liver
A	Stage 1	0	0
B	Stage 0-2 or	Stage 0-2 or	Stage 0-2
C	Stage 3 or	Stage 3 or	Stage 3
D	Stage 4 or	Stage 4 or	Stage 4

(Rowlings, et. al., 1997)[38]

16.7 Appendix G: Statistical Characteristics of the "3+3" Design

Probabilities of Stopping or Continuing Dose Escalation for Given Probabilities of DLT Associated with the Dose Level

True Probability of DLT at a Dose Level	0.05	0.1	0.2	0.33	0.4	0.5	0.6	0.67	0.7	0.8
Probability of Dose Escalation Based on 3 or 6 Subjects (2 or more DLTs)	0.97	0.91	0.71	0.43	0.31	0.17	0.08	0.04	0.03	0.01
Probability of Ceasing Dose Escalation Based on 3 or 6 Subjects (2 or more DLTs)	0.03	0.09	0.29	0.57	0.69	0.83	0.92	0.96	0.97	0.99
Probability Based on only 3 Subjects (0 DLT)	0.86	0.73	0.51	0.30	0.22	0.13	0.06	0.04	0.03	0.01

Key: DLT = dose limiting toxicity

The probability that dose escalation will cease is at least 92% when the DLT probability is > 60%. If the true probability of DLT for a dose level is at least 34%, the probability of stopping dose escalation is at least 57%. If the true probability of DLT for a dose level is less than 10%, the probability of stopping dose escalation is less than 10%. The probability of dose escalation continuing is at least 91% when the DLT probability is < 10%.

16.8 Appendix H: RBC Transfusion Independence

RBC transfusion independence and RBC transfusion dependence are defined according to modified IWG criteria,[36] as described below:

Definitions of RBC transfusion status at screening:

- **RBC transfusion independence:**
  - Subjects with hemoglobin > 90 g/L (9.0 g/dL);
  - Subjects who received ≤ 1 RBC transfusion during the previous 8 weeks (56 days).
- **RBC transfusion dependence:**
  - Subjects with hemoglobin ≤ 90 g/L (9.0 g/dL);
  - Subjects who received ≥ 2 RBC transfusions during the previous 8 weeks (56 days).

16.9 Appendix I: Cockcroft-Gault Creatinine Clearance Calculation

For purposes of determining eligibility, creatinine clearance will be estimated using the Cockcroft-Gault formula as follows:

$$\text{Creatinine Clearance} = \frac{(140 - \text{Age}) \times \text{Weight (kg)} \times [0.85 \text{ if Female}]}{72 \times \text{Serum Creatinine (mg/dL)}}$$

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