Phase II Study of Lenalidomide Maintenance in Patients with High Risk AML in Remission

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Study Product: *Lenalidomide*

Protocol Number: *2014-0116*

Coordinating Center: *MD Anderson Cancer Center*
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1.0 OBJECTIVES

1.1 Primary objective:
To assess relapse-free survival (RFS) of patients with acute myeloid leukemia (AML) treated with lenalidomide maintenance therapy after achieving remission.

1.2 Secondary objective
- To assess overall survival (OS) of patients with AML treated with lenalidomide maintenance.
- To assess event-free survival (EFS) of patients with AML treated with lenalidomide maintenance.
- To assess the duration of remission (CRd) of patients with AML treated with lenalidomide maintenance.
- To assess toxicity and safety of lenalidomide maintenance in patients with AML.
- To assess the effects of lenalidomide maintenance on NK cell modulation and dynamics of minimal residual disease and their relationship to outcomes.

2.0 BACKGROUND

2.1 Acute Myeloid Leukemia (AML)

AML is the cause of approximately 1.2% of all cancer deaths in the US with an annual incidence rate of 2.2 per 100,000 and approximately 10,000 new cases per year. Age-adjusted incidence ranges from 1 per 100,000 in people < 20 years to > 10 per 100,000 in the elderly. AML represents approximately 90% of all acute leukemias in adults, and accounts for about 25% of all cases of leukemia diagnosed in the Western hemisphere.[1,2] AML is a clonal myelopoietic stem cell disorder characterized by the accumulation of neoplastic cells in the bone marrow and in the peripheral circulation. Current induction chemotherapy protocols combining cytarabine and an anthracycline administered as first-line treatment induce complete remissions in a majority (55% to 75%) of patients. Standard consolidation therapy with high doses of cytarabine leads to improved survival in younger patients. Overall, up to 70% of patients can be expected to relapse, so that only about 20-30% attain long-term disease-free survival.

Two major problems in the treatment of AML remain: primary resistant/refractory disease and high risk of relapse/recurrent disease. While newer drug combinations and higher doses of therapy may begin to address upfront resistant disease, there are very few options, with the exception of allogeneic stem cell transplantation, for long term maintenance of remission after consolidation. In acute lymphoblastic leukemia (ALL), maintenance therapy has become a standard part of treatment and has contributed to long term durable remissions and cures. Results of studies of maintenance therapy in AML have been mixed. In early studies by ECOG[3,4] and CALGB[5], prolonged maintenance following a short consolidation failed to significantly prolong CR duration or overall survival. On the other hand, studies from the German AML study group randomized patients after consolidation to prolonged maintenance vs. no further

therapy. Patients who received prolonged maintenance after consolidation had improved relapse-free survival, and this effect was more pronounced in higher risk patients.[6-8]. Lowenberg, et. al.[9] randomized patients in CR after 1 cycle of consolidation to receive 8 monthly cycles of low dose araC maintenance vs. no further therapy. Patients in the maintenance arm had improved recurrence free survival, but not OS.[9] Finally, SWOG randomized patients in CR who were not eligible for an allogeneic stem cell transplant to receive one cycle of intensification followed by maintenance or intensification alone. Patients receiving maintenance had improved disease free survival, but not OS.[10] One of the shortcomings of these earlier approaches is that the therapeutic agents used in maintenance were often the same or similar agents that were used in induction and consolidation. Residual leukemia cells which would have survived the induction therapy and are the source of relapses would be presumably resistant to 'more of the same'. Newer therapies, employing different mechanisms of action are less likely to be cross-resistant to the initial cytotoxic induction regimens. For example, Brune et. al.[11] studied an immunotherapy approach investigating an IL2 + histamine maintenance therapy. A cohort of 320 patients in CR1 or greater were randomized to receive 10 cycles of IL2+histamine vs. no treatment. At 3 years, the maintenance arm had a significant improvement in leukemia-free survival.[11] Lenalidomide, a non-cytotoxic drug with activity in AML, has multiple unique mechanisms of action including immune modulation and alteration of intracellular signaling and may be an ideal candidate for long term maintenance in this disease.

As a background, we know that AML patients (young and old) with: (1)primary refractory disease, (2)adverse cytogenetics, (3)FLT3 positive disease, (4)antecedent hematologic disorder, and (in relapsed patients) (5) short CR1 duration have a high risk of relapse, despite effective induction and consolidation therapy. If these patients are not candidates for transplant, we are often beholden to "watch and wait" until their leukemia relapses. In this setting, a long term, low intensity, easy to administer, and effective antileukemia treatment needs to be developed. Lenalidomide has been shown to have single-agent activity in AML as a higher dose induction followed by a longer term, lower dose maintenance strategy.[12] Lenalidomide, in the treatment of myelodysplastic syndrome MDS and multiple myeloma (MM) has been shown to be safe during continuous, long term administration (MM, MDS) as well as in a maintenance strategy (MM).

2.2 Lenalidomide in AML

Lenalidomide, a derivative of thalidomide is currently approved for the treatment of multiple myeloma (MM) and MDS (myelodysplastic syndrome), but has been shown to have single-agent activity in AML as an induction – maintenance strategy. In a phase II trial of older patients (age ≥ 60 yrs) with untreated AML, lenalidomide was given at a high 'induction' dose, of 50 mg orally daily on a 28 day cycle (for up to 2 induction cycles), followed by a lower 'maintenance' dose of 10 mg orally daily for up to 12 months. The CR/CRi rate was 30% overall and 53% in patients who completed all of the high-dose therapy.[12] The median CR duration was 10 months (1 – 17+ months). The treatment was well tolerated in this cohort of patients, with the most common grade 3-4 toxicities being myelosuppression and infection. Based on this data of single agent activity in AML and its longer-term use in AML, MDS, and MM we propose to use this as a maintenance strategy for higher-risk patients who are in remission after induction/consolidation therapy. The exact mechanism of action of lenalidomide is not known, but may involve immunomodulatory activity and reversal of an immunosuppressive environment present in

malignancy.

2.3 NK Cells as Immunosurveillance in Leukemia

NK cells are an important component of the innate immune system and play a key role in the immune surveillance of cancer, including AML.[13-16] NK cells can exert these effects through direct cytotoxicity, secretion of cytokines, and by coordinating other immune cells (T-cells, dendritic cells) to mount anti-tumor immunity.[15,17,18] Although several studies in stem cell transplant and adoptive immunity have demonstrated the importance of NK cells in eliminating leukemia, immune evasion mechanisms or defects in autologous NK cells may thwart this anti-leukemia effect.[15,18] Among its mechanisms of action, lenalidomide has been shown to enhance NK cell mediated cytotoxicity by increasing NK cell numbers, increasing secretion of cytokines such as interferon gamma, and through enhancing ADCC by increasing IL2 secretion from T-cells.[19-23] Such reconstitution of AML immune-surveillance with lenalidomide in the maintenance setting could translate into long-term disease control and a higher cure rate. This study provides us a unique opportunity to study the efficacy of this concept as well as determine the *in vivo* effects of lenalidomide on NK cells in AML patients.

2.4 Rationale for studying lenalidomide as maintenance therapy in AML.

Therapy for maintaining longer-term remissions after consolidation therapy in AML patients with high-risk disease is a critical need. Unlike the treatment protocols for ALL, there is no current standard for maintenance therapy in AML. Previous attempts at maintenance therapy in AML, utilizing redundant chemotherapy-based protocols have been met with minimal success. We therefore propose a clinical trial evaluating low intensity, continuous dosing of lenalidomide in patients with high risk AML who have responded to induction/consolidation chemotherapy and are not immediately candidates for BMT. From our own data, the expected relapse free survival in this cohort of younger patients with higher risk disease who do not proceed for stem cell transplant is 8.5 months. Approximately 25% of these patients may become eligible for and proceed to transplant, but the majority are left without meaningful therapy until relapse.

Based on published data, NK cells are important mediators of immune surveillance, particularly in AML. In addition to affecting direct cytotoxicity of AML blasts, NK cells may also alter the cytokine and immune cell (eg. T-lymphocytes) milieu to favor anti-leukemia immunity. Lenalidomide has been shown to enhance NK cell activity and numbers – making it an important agent to study in a setting of low disease burden (ie. minimal residual disease after chemotherapy). As part of the clinical trial, we also aim to study the effects of lenalidomide on NK cell activity – both at baseline (prior to lenalidomide treatment) and at several time points during treatment. This will help us derive more insight into the actions of lenalidomide on NK cell activity and how it relates to maintenance of remission in patients with AML.

The rationale for the selected dosing of lenalidomide maintenance is drawn from previous experience in chronic dosing of lenalidomide for maintenance strategy. In the AML experience described above, Fehniger, et. al. treated patients in the maintenance phase with 10 mg orally

daily. In multiple myeloma maintenance studies,[24,25] lenalidomide was dosed at 10 – 15 mg orally daily, continuously. These doses have therefore been shown to be safe and active in a long-term dosing strategy.

2.5 Lenalidomide

Background

Lenalidomide is a proprietary IMiD® compound of Celgene Corporation. IMiD® compounds have 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.[26] 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.[27] Upregulation of T cell derived IL-2 production is achieved at least in part through increased AP-1 activity.[28]

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.[17] 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.

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. Revlimid is also for the treatment of patients with mantle cell lymphoma (MCL)whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib.

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

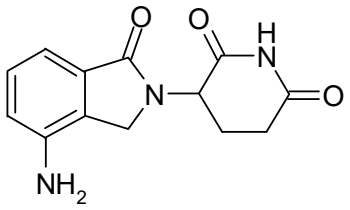
medication include: anemia, neutropenia, thrombocytopenia and pancytopenia, abdominal pain, nausea, vomiting and diarrhea, dehydration, rash, itching, infections, sepsis, pneumonia, UTI, Upper respiratory infection, atrial fibrillation, congestive heart failure, myocardial infarction, chest pain, weakness, hypotension, hypercalcemia, hyperglycemia, back pain, bone pain, generalized pain, dizziness, mental status changes, syncope, renal failure, dyspnea, pleural effusion, pulmonary embolism, deep vein thrombosis, CVA, convulsions, dizziness, spinal cord compression, syncope, disease progression, death not specified and fractures.

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

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:

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.

Clinical Pharmacology

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.

Pharmacokinetics and Drug Metabolism

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 **Error! Reference source not found.**. Exposure (AUC) in multiple myeloma patients is 57% higher than in healthy male volunteers.

Pharmacokinetic Parameters

Distribution

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

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.

Supplier(s)

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

Dosage form

Lenalidomide will be supplied as capsules for oral administration.

Packaging

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

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.

Receipt of study drug

The Investigator or designee is responsible for taking an inventory of each shipment of study drug received, and comparing it with the accompanying study drug accountability form. The Investigator will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file, and return a copy to Celgene or its representative.

Storage

Lenalidomide should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

Unused study drug supplies

Celgene will instruct the Investigator on the return or destruction of unused study drug. If any study drug is lost or damaged, its disposition should be documented in the source documents. Study drug supplies will be retained at the clinical site pending instructions for disposition by Celgene. Patients will be instructed to return empty bottles or unused capsules to the clinic site.

Special Handling Instructions

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

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1.1 Primary objective:
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1.2 Secondary objective
- To assess overall survival (OS) of patients with AML treated with lenalidomide maintenance.
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- To assess toxicity and safety of lenalidomide maintenance in patients with AML.
- To assess the effects of lenalidomide maintenance on NK cell modulation and dynamics of minimal residual disease and their relationship to outcomes.

2.0 BACKGROUND

2.1 Acute Myeloid Leukemia (AML)

AML is the cause of approximately 1.2% of all cancer deaths in the US with an annual incidence rate of 2.2 per 100,000 and approximately 10,000 new cases per year. Age-adjusted incidence ranges from 1 per 100,000 in people < 20 years to > 10 per 100,000 in the elderly. AML represents approximately 90% of all acute leukemias in adults, and accounts for about 25% of all cases of leukemia diagnosed in the Western hemisphere.[1,2] AML is a clonal myelopoietic stem cell disorder characterized by the accumulation of neoplastic cells in the bone marrow and in the peripheral circulation. Current induction chemotherapy protocols combining cytarabine and an anthracycline administered as first-line treatment induce complete remissions in a majority (55% to 75%) of patients. Standard consolidation therapy with high doses of cytarabine leads to improved survival in younger patients. Overall, up to 70% of patients can be expected to relapse, so that only about 20-30% attain long-term disease-free survival.

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therapy. Patients who received prolonged maintenance after consolidation had improved relapse-free survival, and this effect was more pronounced in higher risk patients.[6-8]. Lowenberg, et. al.[9] randomized patients in CR after 1 cycle of consolidation to receive 8 monthly cycles of low dose araC maintenance vs. no further therapy. Patients in the maintenance arm had improved recurrence free survival, but not OS.[9] Finally, SWOG randomized patients in CR who were not eligible for an allogeneic stem cell transplant to receive one cycle of intensification followed by maintenance or intensification alone. Patients receiving maintenance had improved disease free survival, but not OS.[10] One of the shortcomings of these earlier approaches is that the therapeutic agents used in maintenance were often the same or similar agents that were used in induction and consolidation. Residual leukemia cells which would have survived the induction therapy and are the source of relapses would be presumably resistant to 'more of the same'. Newer therapies, employing different mechanisms of action are less likely to be cross-resistant to the initial cytotoxic induction regimens. For example, Brune et. al.[11] studied an immunotherapy approach investigating an IL2 + histamine maintenance therapy. A cohort of 320 patients in CR1 or greater were randomized to receive 10 cycles of IL2+histamine vs. no treatment. At 3 years, the maintenance arm had a significant improvement in leukemia-free survival.[11] Lenalidomide, a non-cytotoxic drug with activity in AML, has multiple unique mechanisms of action including immune modulation and alteration of intracellular signaling and may be an ideal candidate for long term maintenance in this disease.

As a background, we know that AML patients (young and old) with: (1)primary refractory disease, (2)adverse cytogenetics, (3)FLT3 positive disease, (4)antecedent hematologic disorder, and (in relapsed patients) (5) short CR1 duration have a high risk of relapse, despite effective induction and consolidation therapy. If these patients are not candidates for transplant, we are often beholden to "watch and wait" until their leukemia relapses. In this setting, a long term, low intensity, easy to administer, and effective antileukemia treatment needs to be developed. Lenalidomide has been shown to have single-agent activity in AML as a higher dose induction followed by a longer term, lower dose maintenance strategy.[12] Lenalidomide, in the treatment of myelodysplastic syndrome MDS and multiple myeloma (MM) has been shown to be safe during continuous, long term administration (MM, MDS) as well as in a maintenance strategy (MM).

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2.4 Rationale for studying lenalidomide as maintenance therapy in AML.

Therapy for maintaining longer-term remissions after consolidation therapy in AML patients with high-risk disease is a critical need. Unlike the treatment protocols for ALL, there is no current standard for maintenance therapy in AML. Previous attempts at maintenance therapy in AML, utilizing redundant chemotherapy-based protocols have been met with minimal success. We therefore propose a clinical trial evaluating low intensity, continuous dosing of lenalidomide in patients with high risk AML who have responded to induction/consolidation chemotherapy and are not immediately candidates for BMT. From our own data, the expected relapse free survival in this cohort of younger patients with higher risk disease who do not proceed for stem cell transplant is 8.5 months. Approximately 25% of these patients may become eligible for and proceed to transplant, but the majority are left without meaningful therapy until relapse.

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daily. In multiple myeloma maintenance studies,[24,25] lenalidomide was dosed at 10 – 15 mg orally daily, continuously. These doses have therefore been shown to be safe and active in a long-term dosing strategy.

2.5 Lenalidomide

Background

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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.[17] 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.

Indications and Usage:

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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

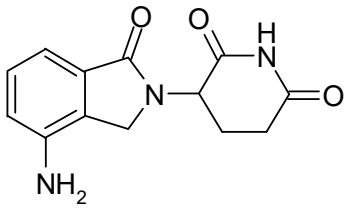
medication include: anemia, neutropenia, thrombocytopenia and pancytopenia, abdominal pain, nausea, vomiting and diarrhea, dehydration, rash, itching, infections, sepsis, pneumonia, UTI, Upper respiratory infection, atrial fibrillation, congestive heart failure, myocardial infarction, chest pain, weakness, hypotension, hypercalcemia, hyperglycemia, back pain, bone pain, generalized pain, dizziness, mental status changes, syncope, renal failure, dyspnea, pleural effusion, pulmonary embolism, deep vein thrombosis, CVA, convulsions, dizziness, spinal cord compression, syncope, disease progression, death not specified and fractures.

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

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:

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.

Clinical Pharmacology

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.

Pharmacokinetics and Drug Metabolism

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 **Error! Reference source not found.**. Exposure (AUC) in multiple myeloma patients is 57% higher than in healthy male volunteers.

Pharmacokinetic Parameters

Distribution

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

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.

Supplier(s)

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

Dosage form

Lenalidomide will be supplied as capsules for oral administration.

Packaging

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

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.

Receipt of study drug

The Investigator or designee is responsible for taking an inventory of each shipment of study drug received, and comparing it with the accompanying study drug accountability form. The Investigator will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file, and return a copy to Celgene or its representative.

Storage

Lenalidomide should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

Unused study drug supplies

Celgene will instruct the Investigator on the return or destruction of unused study drug. If any study drug is lost or damaged, its disposition should be documented in the source documents. Study drug supplies will be retained at the clinical site pending instructions for disposition by Celgene. Patients will be instructed to return empty bottles or unused capsules to the clinic site.

Special Handling Instructions

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

Phase II Study of Lenalidomide Maintenance in Patients with High Risk AML in Remission

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Study Product: *Lenalidomide*

Protocol Number: *2014-0116*

Coordinating Center: *MD Anderson Cancer Center*
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Houston, TX 77030

PHASE II Study of Lenalodimide Maintenance in Patients with High Risk AML in Remission

PHASE II Study of Lenalodimide Maintenance in Patients with High Risk AML in Remission

1.0 OBJECTIVES

1.1 Primary objective:
To assess relapse-free survival (RFS) of patients with acute myeloid leukemia (AML) treated with lenalidomide maintenance therapy after achieving remission.

1.2 Secondary objective
- To assess overall survival (OS) of patients with AML treated with lenalidomide maintenance.
- To assess event-free survival (EFS) of patients with AML treated with lenalidomide maintenance.
- To assess the duration of remission (CRd) of patients with AML treated with lenalidomide maintenance.
- To assess toxicity and safety of lenalidomide maintenance in patients with AML.
- To assess the effects of lenalidomide maintenance on NK cell modulation and dynamics of minimal residual disease and their relationship to outcomes.

2.0 BACKGROUND

2.1 Acute Myeloid Leukemia (AML)

AML is the cause of approximately 1.2% of all cancer deaths in the US with an annual incidence rate of 2.2 per 100,000 and approximately 10,000 new cases per year. Age-adjusted incidence ranges from 1 per 100,000 in people < 20 years to > 10 per 100,000 in the elderly. AML represents approximately 90% of all acute leukemias in adults, and accounts for about 25% of all cases of leukemia diagnosed in the Western hemisphere.[1,2] AML is a clonal myelopoietic stem cell disorder characterized by the accumulation of neoplastic cells in the bone marrow and in the peripheral circulation. Current induction chemotherapy protocols combining cytarabine and an anthracycline administered as first-line treatment induce complete remissions in a majority (55% to 75%) of patients. Standard consolidation therapy with high doses of cytarabine leads to improved survival in younger patients. Overall, up to 70% of patients can be expected to relapse, so that only about 20-30% attain long-term disease-free survival.

Two major problems in the treatment of AML remain: primary resistant/refractory disease and high risk of relapse/recurrent disease. While newer drug combinations and higher doses of therapy may begin to address upfront resistant disease, there are very few options, with the exception of allogeneic stem cell transplantation, for long term maintenance of remission after consolidation. In acute lymphoblastic leukemia (ALL), maintenance therapy has become a standard part of treatment and has contributed to long term durable remissions and cures. Results of studies of maintenance therapy in AML have been mixed. In early studies by ECOG[3,4] and CALGB[5], prolonged maintenance following a short consolidation failed to significantly prolong CR duration or overall survival. On the other hand, studies from the German AML study group randomized patients after consolidation to prolonged maintenance vs. no further

therapy. Patients who received prolonged maintenance after consolidation had improved relapse-free survival, and this effect was more pronounced in higher risk patients.[6-8]. Lowenberg, et. al.[9] randomized patients in CR after 1 cycle of consolidation to receive 8 monthly cycles of low dose araC maintenance vs. no further therapy. Patients in the maintenance arm had improved recurrence free survival, but not OS.[9] Finally, SWOG randomized patients in CR who were not eligible for an allogeneic stem cell transplant to receive one cycle of intensification followed by maintenance or intensification alone. Patients receiving maintenance had improved disease free survival, but not OS.[10] One of the shortcomings of these earlier approaches is that the therapeutic agents used in maintenance were often the same or similar agents that were used in induction and consolidation. Residual leukemia cells which would have survived the induction therapy and are the source of relapses would be presumably resistant to 'more of the same'. Newer therapies, employing different mechanisms of action are less likely to be cross-resistant to the initial cytotoxic induction regimens. For example, Brune et. al.[11] studied an immunotherapy approach investigating an IL2 + histamine maintenance therapy. A cohort of 320 patients in CR1 or greater were randomized to receive 10 cycles of IL2+histamine vs. no treatment. At 3 years, the maintenance arm had a significant improvement in leukemia-free survival.[11] Lenalidomide, a non-cytotoxic drug with activity in AML, has multiple unique mechanisms of action including immune modulation and alteration of intracellular signaling and may be an ideal candidate for long term maintenance in this disease.

As a background, we know that AML patients (young and old) with: (1)primary refractory disease, (2)adverse cytogenetics, (3)FLT3 positive disease, (4)antecedent hematologic disorder, and (in relapsed patients) (5) short CR1 duration have a high risk of relapse, despite effective induction and consolidation therapy. If these patients are not candidates for transplant, we are often beholden to "watch and wait" until their leukemia relapses. In this setting, a long term, low intensity, easy to administer, and effective antileukemia treatment needs to be developed. Lenalidomide has been shown to have single-agent activity in AML as a higher dose induction followed by a longer term, lower dose maintenance strategy.[12] Lenalidomide, in the treatment of myelodysplastic syndrome MDS and multiple myeloma (MM) has been shown to be safe during continuous, long term administration (MM, MDS) as well as in a maintenance strategy (MM).

2.2 Lenalidomide in AML

Lenalidomide, a derivative of thalidomide is currently approved for the treatment of multiple myeloma (MM) and MDS (myelodysplastic syndrome), but has been shown to have single-agent activity in AML as an induction – maintenance strategy. In a phase II trial of older patients (age ≥ 60 yrs) with untreated AML, lenalidomide was given at a high 'induction' dose, of 50 mg orally daily on a 28 day cycle (for up to 2 induction cycles), followed by a lower 'maintenance' dose of 10 mg orally daily for up to 12 months. The CR/CRi rate was 30% overall and 53% in patients who completed all of the high-dose therapy.[12] The median CR duration was 10 months (1 – 17+ months). The treatment was well tolerated in this cohort of patients, with the most common grade 3-4 toxicities being myelosuppression and infection. Based on this data of single agent activity in AML and its longer-term use in AML, MDS, and MM we propose to use this as a maintenance strategy for higher-risk patients who are in remission after induction/consolidation therapy. The exact mechanism of action of lenalidomide is not known, but may involve immunomodulatory activity and reversal of an immunosuppressive environment present in

malignancy.

2.3 NK Cells as Immunosurveillance in Leukemia

NK cells are an important component of the innate immune system and play a key role in the immune surveillance of cancer, including AML.[13-16] NK cells can exert these effects through direct cytotoxicity, secretion of cytokines, and by coordinating other immune cells (T-cells, dendritic cells) to mount anti-tumor immunity.[15,17,18] Although several studies in stem cell transplant and adoptive immunity have demonstrated the importance of NK cells in eliminating leukemia, immune evasion mechanisms or defects in autologous NK cells may thwart this anti-leukemia effect.[15,18] Among its mechanisms of action, lenalidomide has been shown to enhance NK cell mediated cytotoxicity by increasing NK cell numbers, increasing secretion of cytokines such as interferon gamma, and through enhancing ADCC by increasing IL2 secretion from T-cells.[19-23] Such reconstitution of AML immune-surveillance with lenalidomide in the maintenance setting could translate into long-term disease control and a higher cure rate. This study provides us a unique opportunity to study the efficacy of this concept as well as determine the *in vivo* effects of lenalidomide on NK cells in AML patients.

2.4 Rationale for studying lenalidomide as maintenance therapy in AML.

Therapy for maintaining longer-term remissions after consolidation therapy in AML patients with high-risk disease is a critical need. Unlike the treatment protocols for ALL, there is no current standard for maintenance therapy in AML. Previous attempts at maintenance therapy in AML, utilizing redundant chemotherapy-based protocols have been met with minimal success. We therefore propose a clinical trial evaluating low intensity, continuous dosing of lenalidomide in patients with high risk AML who have responded to induction/consolidation chemotherapy and are not immediately candidates for BMT. From our own data, the expected relapse free survival in this cohort of younger patients with higher risk disease who do not proceed for stem cell transplant is 8.5 months. Approximately 25% of these patients may become eligible for and proceed to transplant, but the majority are left without meaningful therapy until relapse.

Based on published data, NK cells are important mediators of immune surveillance, particularly in AML. In addition to affecting direct cytotoxicity of AML blasts, NK cells may also alter the cytokine and immune cell (eg. T-lymphocytes) milieu to favor anti-leukemia immunity. Lenalidomide has been shown to enhance NK cell activity and numbers – making it an important agent to study in a setting of low disease burden (ie. minimal residual disease after chemotherapy). As part of the clinical trial, we also aim to study the effects of lenalidomide on NK cell activity – both at baseline (prior to lenalidomide treatment) and at several time points during treatment. This will help us derive more insight into the actions of lenalidomide on NK cell activity and how it relates to maintenance of remission in patients with AML.

The rationale for the selected dosing of lenalidomide maintenance is drawn from previous experience in chronic dosing of lenalidomide for maintenance strategy. In the AML experience described above, Fehniger, et. al. treated patients in the maintenance phase with 10 mg orally

daily. In multiple myeloma maintenance studies,[24,25] lenalidomide was dosed at 10 – 15 mg orally daily, continuously. These doses have therefore been shown to be safe and active in a long-term dosing strategy.

2.5 Lenalidomide

Background

Lenalidomide is a proprietary IMiD® compound of Celgene Corporation. IMiD® compounds have 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.[26] 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.[27] Upregulation of T cell derived IL-2 production is achieved at least in part through increased AP-1 activity.[28]

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.[17] 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.

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. Revlimid is also for the treatment of patients with mantle cell lymphoma (MCL)whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib.

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

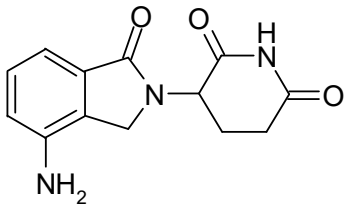
medication include: anemia, neutropenia, thrombocytopenia and pancytopenia, abdominal pain, nausea, vomiting and diarrhea, dehydration, rash, itching, infections, sepsis, pneumonia, UTI, Upper respiratory infection, atrial fibrillation, congestive heart failure, myocardial infarction, chest pain, weakness, hypotension, hypercalcemia, hyperglycemia, back pain, bone pain, generalized pain, dizziness, mental status changes, syncope, renal failure, dyspnea, pleural effusion, pulmonary embolism, deep vein thrombosis, CVA, convulsions, dizziness, spinal cord compression, syncope, disease progression, death not specified and fractures.

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

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:

Chemical Structure of Lenalidomide



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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.

Clinical Pharmacology

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.

Pharmacokinetics and Drug Metabolism

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 **Error! Reference source not found.**. Exposure (AUC) in multiple myeloma patients is 57% higher than in healthy male volunteers.

Pharmacokinetic Parameters

Distribution

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

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.

Supplier(s)

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

Dosage form

Lenalidomide will be supplied as capsules for oral administration.

Packaging

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

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.

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Storage

Lenalidomide should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

Unused study drug supplies

Celgene will instruct the Investigator on the return or destruction of unused study drug. If any study drug is lost or damaged, its disposition should be documented in the source documents. Study drug supplies will be retained at the clinical site pending instructions for disposition by Celgene. Patients will be instructed to return empty bottles or unused capsules to the clinic site.

Special Handling Instructions

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

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.

Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.

Pregnancy Testing

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

3.0 PATIENT SELECTION

3.1 Inclusion Criteria:

1. Patients aged 18 to 55 years with high risk (as defined in #2) AML who have achieved their **FIRST** CR or CRi within 12 months of enrollment and are not immediately candidates for allogeneic stem cell transplant. Patients above age 55 who are not eligible for other protocols may be considered for enrollment on a case by case basis after discussion with the PI.
2. Patients in their **FIRST** CR or CRi may be eligible for enrollment only if they have a high risk feature, including, but not limited to: adverse karyotype, FLT3 mutation, history of antecedent hematologic disorder (AHD), presence of dysplasia in the bone marrow, therapy-related AML, history of requiring more than 1 cycle of intensive induction chemotherapy to achieve first remission, or presence of persistent minimal residual disease (detected by cytogenetics, molecular markers, or flow cytometry) at any point after initial induction cycle. Patients aged > or = 18 years with AML who have achieved a **SECOND** CR or CRi within 12 months of enrollment and are not immediately candidates for allogeneic stem cell transplant are also eligible.
3. Patients should have received induction chemotherapy for AML and at least 1 consolidation.
4. Patients with history of extramedullary AML, except for CNS involvement that is currently controlled, will not be eligible for enrollment.
5. ECOG performance status of < or = 3
6. Adequate organ function as follows:
    a. Serum total bilirubin < or = to 1.5 X the Upper Limit of Normal (ULN)
    b. Serum creatinine < or = to 2.5 x ULN
7. Adequate BM reserve:
    a. Absolute neutrophil count (ANC) > 0.5 x 10^9/L
    b. Platelet count > or = 30 x 10^9/L

Prescribing Information

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7. Adequate BM reserve:
    a. Absolute neutrophil count (ANC) > 0.5 x 10^9/L
    b. Platelet count > or = 30 x 10^9/L

8. For females of childbearing age, they may participate it they:
    a. Have a negative serum or urine pregnancy test within 10 to 14 days of enrolling (A second pregnancy test will be performed within 24hrs of starting therapy and both negative pregnancy tests will be required for starting therapy.)
    b. Agree to either abstinence or 2 effective contraceptive methods throughout the treatment period and up to 28 days after discontinuing treatment.
9. For male patients with a female partner of childbearing age, they may participate if they agree to either abstinence or 2 effective contraceptive methods throughout the treatment period and up to 28 days after discontinuing treatment.
10. All study participants must be willing and able to comply with the requirements of the REMS® program.
11. Females of reproductive potential must be willing to adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program.
12. Ability to understand and sign informed consent.

3.2 Exclusion Criteria

1. Diagnosis of acute promyelocytic leukemia (APL), AML - M3 by FAB classification based on morphology, immunophenotype, molecular, or cytogenetic s studies.
2. Diagnosis of AML associated with the following karyotypes: inv(16), t(16;16), t(8;21), or t(15;17). Patients with t(9;22) are also ineligible unless they are unable or unwilling to receive therapy with a tyrosine kinase inhibitor.
3. Uncontrolled intercurrent illness including, but not limited to ongoing or active uncontrolled infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
4. Patients with active CNS disease.
5. Previous treatment with lenalidomide for AML.
6. Patients with documented hypersensitivity to any components of the study program.
7. Females who are pregnant.

4.0 TREATMENT PLAN

This is a single arm, open label phase II clinical trial evaluating low intensity, continuous dosing of lenalidomide in patients with *high risk* AML who have responded to induction/consolidation therapy and are NOT immediately candidates for stem cell transplant.

Treatment will be continued during the duration of the study, up to 24 months unless patient exhibits evidence of clinically significant treatment failure, clinically significant disease progression, unacceptable toxicity, treatment with stem cell transplantation, or if the investigator determines that discontinuation is in the best interest of the patient. Relapsing patients (that is not clinically significant) may remain on the study if participation in the study is still providing clinical benefit and is considered in the best interest of the patient after discussion with the principal investigator.

Patients will be treated with the study drug per protocol, based on fixed dosing as outlined below.

The objective is to determine the effect of lenalidomide maintenance on relapse free survival (RFS), overall survival (OS), and CR duration in patients with high risk AML in remission. We will also determine toxicity and tolerability of this regimen, as well as the effect of lenalidomide maintenance on NK cell biology and the dynamics of minimal residual disease.

All patients will be registered for the protocol via the Clinical Oncology Research (CORe) system at MDACC (single institution study).

4.1 Treatment Schema

4.1.1 Maintenance Lenalidomide Dosing:

Lenalidomide continuous dosing on days 1- 28 of a 28 day cycle.

Dose of lenalidomide is as follows:

- Starting dose (DOSE LEVEL 0): 10mg orally daily during cycle 1

- If after one cycle, the patient has persistent evidence of (1) minimal residual disease or (2) morphologically active disease AND is tolerating their starting dose of lenalidomide, their dose may be increased to the next higher dose level for the remainder of the study. A maximum of 2 dose escalations per patient are allowed if well tolerated.

Table 1. Dose escalation and de-escalation table.

Dose Level	**Lenalidomide Dosing**
-2	5 mg PO Every other Day
-1	5 mg PO Daily
0 (Starting dose level)	10 mg PO Daily
1	15 mg PO Daily
2	20 mg PO Daily

One cycle of therapy is considered 28 days. Therapy will be continuous; interruptions and dose-adjustments for toxicity will be implemented as needed.

4.2 Supportive Care Measures during treatment

Necessary supportive measures for optimal medical care can be given throughout the study as indicated by the treating physician's assessment of the patient's medical need and by the institutional guidelines. Administration of antiemetics during drug administration and throughout treatment course is permitted as clinically indicated and according to departmental guidelines. Blood products should be transfused as indicated and in accordance with institutional guidelines. The use of other anti-leukemia therapy is not allowed during the course of therapy. Concomitant

intrathecal chemotherapy and/or radiation therapy is permitted where indicated in patients with extramedullary disease.

4.2.1 Hematopoietic growth factors

Hematopoietic growth factors such as filgrastim (GCSF) or pegfligrastim is permitted as clinically indicated at the discretion of the treating physician.

4.2.2 Infection prophylaxis

Antibacterial, antifungal, and antiviral agents may be used in patients being treated on this study in accordance with the standard of care.

4.3 Duration of Therapy

In the absence of treatment delays due to adverse events, the treatment will be administered continuously for a total of 24 months. The patient will continue on the study unless one of the following criteria applies:

- Clinically significant progressive disease as defined by Modified International Working Group Criteria **(see section 9).**
- Undergoing allogeneic bone marrow transplant.
- Intercurrent illness that prevents further administration of treatment.
- Patient request.
- Unacceptable toxicity.
- Need for alternative treatment.
- General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator or treating physician.

5.0 PATIENT EVALUATION

5.1 Pretreatment Evaluation. (To be completed within 14 days of study entry unless otherwise indicated)

a. History and physical examination, including vital signs, height, weight and performance status.
b. Bone marrow aspirate and/or biopsy within 28 days of treatment start. Cytogenetics, flow cytometry and molecular studies may be performed as clinically indicated.
c. CBC with differential (within 7 days).
d. Serum chemistry: BUN, creatinine, bilirubin, AST and/or ALT, magnesium, glucose, uric acid (within 7 days).
e. Have a negative serum or urine pregnancy test within 10 to 14 days of enrolling

(A second pregnancy test will be performed within 24hrs of starting therapy and both negative pregnancy tests will be required for starting therapy.)

f. Peripheral blood for baseline correlative immune studies (if patient agrees to correlatives).
g. Signed informed consent.

5.2 During treatment Evaluation.

a. Physical examination (including vital signs, weight, performance status) every 28 days (±7 days) for the first 3 months, then every 3 months until 12 months from the start of therapy; then every 6 months (±2 months).
b. CBC with differential (differential not required if WBC ≤0.5 x10^9/L), at least once weekly for the 1st cycle, then every 2 to 4 weeks during cycles 2-6, and then every 4 weeks (±14 days) thereafter as long as they are on study.
c. Serum chemistry profile at least once weekly for the 1st cycle, then every 2 to 4 weeks during cycles 2-6, and then at least every 4 weeks (±14 days) during active treatment.
d. Bone marrow aspiration and/or biopsy after cycle 1, after 3 months of therapy (±2 weeks), then every 3 months (±1 month) until month 12, then every 6 months (±2 months). No repeat bone marrow is necessary if non-response or progressive disease can be unequivocally diagnosed from peripheral blood tests or, in patients with a WBC <0.4 x10^9/L, if the bone marrow is considered non-contributory by the investigator at any point.
e. Flow cytometry for MRD after cycle 1, after 3 months of therapy (±2 weeks), then every 3 months (±1 month) until month 12, then every 6 months (±2 months).
f. Peripheral blood for correlative immune studies once weekly for the 1st cycle, and once at the end of cycle 3, 6, and 12. (if patient agrees to correlatives)
g. Patients will be followed for survival every 6 to 12 months after completion of active treatment and while still on study or be enrolled on the leukemia department long-term follow-up umbrella protocol.
h. Women of child bearing potential must have a negative pregnancy test prior to each cycle of therapy.

6.0 DOSING DELAYS / DOSE MODIFICATIONS FOR SUBSEQUENT CYCLES

6.1 Dose levels for dose adjustments Table 1

Dose Level	Lenalidomide Dosing
-2	5 mg PO Every other Day
-1	5 mg PO Daily
0 (Starting dose level)	10 mg PO Daily
1	15 mg PO Daily
2	20 mg PO Daily

6.1.1. Dose levels different than dose described may be allowed after discussion with the PI.

Table 2. Non-Hematologic Toxicity

Drug-related Grade 2 Toxicity

Initiation/continuation of treatment will be delayed if a > Grade 1 drug-related clinically significant non-hematologic toxicity[2] has occurred or worsened and not yet returned to < Grade 2 prior to the start of the next dose.

Infection

If a patient develops a clinically significant infection[1] of any grade, treatment may be delayed or withheld until the infection is clinically controlled (e.g., the patient is afebrile and with improving signs/symptoms). Treatment may then resume at the same dose.

Description of Event: Non-Hematologic	Dose Modifications
Drug-related clinically significant non-hematologic Grade 3-4 adverse event.[3]	Hold therapy until recovery to Grade ≤ 1, then re-start and reduce dose by one dose level. If toxicity recurs, hold therapy until recovery to grade ≤1, then re-start and reduce one dose level. Dose reductions below dose level -2 will be not be considered. If dose level -2 is considered intolerable, the patient will should be taken off study.
Persistent grade 2 toxicity considered clinically significant or unacceptable.[2]	Consider holding therapy until recovery to Grade ≤ 1, then re-start and reduce one dose level. If toxicity recurs, hold therapy until recovery to grade ≤1, then re-start and reduce one dose level. Dose reductions below dose level -2 will be not be considered. If dose level -2 is considered intolerable, the patient will should be taken off study.
Any occurrence of >/= drug related Grade 2 neurologic events	The patient's study drug doses are to be re-evaluated in consultation with the Principal Investigator, and may be reduced according to the above parameters, or discontinued based on the event, and the time to resolution to </= Grade 1.

[1] Includes, but is not limited to, bacteremia, systemic fungal infections, cytomegalovirus (CMV) infection, *Pneumocystis carinii* pneumonia (PCP), disseminated *Varicella*, etc.

[2] Excludes NCI CTC >/= grade 2 drug-related neurologic toxicities, grade 2 alopecia, and grade 3 anorexia, transient elevations in hepatic transaminases or alkaline phosphatase based on institutional normals without clinical significance, and nausea/vomiting, diarrhea or mucositis that resolves (with or without supportive care) to < grade 2 within 48 hours of onset to grade 3.

[3] Excludes NCI CTC grade 4 transient elevations in hepatic transaminases or alkaline phosphatase based on institutional normals without clinical significance.

Therapy will be continuous; interruptions and dose-adjustments for toxicity will be implemented as needed, based on above table.

6.2 **Myelosuppression**: Patients with leukemias and MDS usually present with abnormal peripheral blood counts at the time therapy is started and some myelosuppression is an expected event during the course of therapy for acute leukemias and myelodysplastic syndromes. Thus, dose-adjustments or treatment interruptions for myelosuppression will be planned only for confirmed, severe neutropenia or

thrombocytopenia that is confirmed for at least 1 week according to the following guidelines:

6.2.1.1 Patients in remission who have sustained low counts (for at least 7 days) of neutrophils <0.5 x10^9/L or a platelet count <20 x x10^9/L should have therapy held until resolution. The patient may then receive subsequent treatment at 1 dose level reduction. A reduction of 2 dose levels may be considered if the myelosuppression was deemed severe and/or life threatening by the treating physician, and if it is in the patient's best interest.

7.0 AGENT FORMULATION AND PROCUREMENT

Lenalidomide will be supplied by Celgene as part of this investigational study. Commercial drug supply will be used.

7.5 CORRELATIVE STUDIES

Collection of Immune Modulation Studies will be requested from all patients on study. Heparanized blood specimens will be collected for assays to assess correlates of immune system activity prior to beginning treatment, at day 7, 14, 21, and 28 of Cycle 1 (+/- 3 days), and at the end of Cycle 3, 6 and 12 (+/- 14 days). The assays include:

1. Enumeration of immune cells (by multi-parameter flow cytometry)
2. Quantification of cytokines/chemokines (by Luminex® Multiplex assay)
3. NK cell functional assay (by Calcein-release direct cytotoxicity)
4. KIR genotyping (by SSP- or SSO-PCR analysis)
5. NK cell gene expression profile (using custom NK cell codeset on the nanoString platform)

These assays will be used to identify biological correlates of lenalidomide immune-modulatory activity, and to correlate immune function, genotype, and immunomodulation with disease response or relapse.

Sample requirements:
10 mL of blood drawn into a sodium heparin (green top) tube.

Sample preparation/handling:
Keep samples at room temperature. Notify the Lee Lab by email for same-day sample pickup. Use pager or phone as backup contact:

Dean Lee
e-mail: dalee@mdanderson.org
Phone: (713) 563-5404
Pager: (713) 404-3014

Cecele Denman
e-mail: cjdenman@mdanderson.org
Phone: (713) 792-9938

8.0 STATISTICAL CONSIDERATIONS

STATISTICAL CONSIDERATIONS

This is a phase II study of lenalidomide as a maintenance therapy in patients with high risk AML and in first or second remission. The primary objective is to assess whether the maintenance therapy can improve relapse-free survival (RFS), which is defined as the time interval from date of treatment start until the date of death or disease relapse. Patients who are alive and relapse-free at the last follow-up date will be censored at that time.

The study will be continuously monitored for the primary endpoint, RFS, using the method of Thall, Wooten, and Tannir (2005). Our goal is to improve the median RFS from 8 months (based on historical treatment) to 10.5 months using lenalidomide maintenance therapy. It is assumed that the RFS time is exponentially distributed with a median of λ_E among patients who receive lenalidomide as a maintenance therapy, and a median of λ_H is assumed for the historical treatment. Further, we assume that λ_H follows an inverse gamma distribution, i.e., $\lambda_H \sim IG(3.6, 20.8)$, which has a mean of 8 months and variance of 40. To reflect the little prior knowledge of λ_E we assume an inverse gamma prior distribution with the same mean of 8 months and a much larger variance of 500, i.e., $\lambda_E \sim IG(2.128,9.024)$. The trial will be stopped early if $Pr(\lambda_E > \lambda_H + \delta|data) < pL$, where $\delta = 2.5$ months and $pL=0.05$ and this futility monitoring rule will be first applied when 10 patients have been enrolled. A maximum of 50patients will be enrolled into this study at an expected accrual rate of 1 patient per month. From historical experience, 25% of patients in this cohort may become eligible for stem cell transplant and may come off study. For purposes of this analysis, these patients will be censored at the time of receiving transplant . Patients will be followed up for an additional 12 months after all patients have been enrolled. The trial will be conducted using the Clinical Trial Conduct (CTC) website maintained by the Department of Biostatistics at MDACC.

The operating characteristics of the design, based on an overall assumed accrual rate of 2 patients per month with 5000 simulated trials per scenario, are given in the following table. One-Arm Time-to-Event Simulator (version3.0.1) was used for the design and simulation.

Scenario	True Median (months)	Pr(Stopped Early)	Mean No. patients	Average Trial Duration (months)
1	4	0.968	18.9	21.5
2	6	0.410	37.7	30.6
3	8	0.102	46.4	34.8
4	10.5	0.030	48.9	36.0

5	12	0.017	49.3	36.2

For the primary analysis of the efficacy endpoint, we will compute the Bayesian posterior probability of $Pr(\lambda_E > \lambda_H + \delta|data)$. As a secondary analysis, we will perform a competing risk analysis treating stem cell transplant as a competing event for RFS.

In addition, we will continuously monitor treatment-related toxicities using the Bayesian approach of Thall, Simon, Estey (1995). Specifically, the trial will be stopped if Prob($\pi T>0.30$ | data)>0.92, where πT is the toxicity rate and we assume a beta (0.6, 1.4) prior for πT That is, if at any given time, there is more than 92% probability that the toxicity rate of the maintenance therapy with lenalidomide is greater than 30%, the trial will be stopped. For the purpose of toxicity monitoring, toxicities are defined as any treatment –related clinically significant grade 3 or 4 non-hematologic AEs occurred any time during the trial, which are also outlined in Table 2. We will apply this stopping rule starting from the 10th patient and in cohort size of 10. The stopping boundaries corresponding to this toxicity monitoring rule are described in the following table:

Stopping boundaries for treatment-related grade 3, 4 non-hematologic toxicities

The number of patients evaluated for toxicities	10	20	30	40	50
Stop the trial if greater than or equal to this many of patients with toxicities	6	10	13	17	20

The operating characteristics for toxicity monitoring are described in the following table. MultcLean Desktop 2.1.0 was used for the design and simulations for toxicity monitoring.

Operating characteristics for Toxicity Monitoring

True Toxicity Rate	Early Stopping Probability	Sample Size		
		25th percentile	Median	75th percentile
0.10	0.0002	50	50	50
0.20	0.010	50	50	50
0.30	0.135	50	50	50
0.40	0.542	20	40	50
0.50	0.904	10	20	30

The correlative biology studies are considered exploratory; trends and associations will be used to gain insight into the potential activity of this regimen and to help select potential biomarkers for further investigation in follow-up studies.

Correlative data will be reported by dose level with simple summary statistics: means (possibly after transformation) or medians, ranges, and standard deviations (if numbers and distribution

permit). Scatterplots will be used to explore possible associations between the dose and the immunomodulatory parameters, and between the immunomodulatory parameters and toxicity experienced (as reflected in the maximum grade of toxicity experienced or in clinical measurements). Scatterplots will also be used to explore possible associations between the immunomodulatory parameters, MRD, and relapse.

9.0 MEASUREMENT OF EFFECT

9.1 Criteria for Response

9.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment on study.

Evaluable for response. Patients who have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

9.1.2 Response Criteria

Response Criteria are based on the Revised Recommendations of the International Working Group Response Criteria in Acute Myeloid Leukemia. They are summarized below.

9.1.3 Complete remission (CR)

Disappearance of all clinical and/or radiologic evidence of disease, including extramedullary leukemia. Neutrophil count $\geq 1.0 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L, and bone marrow differential showing $\leq 5\%$ blasts.

9.1.4 Complete remission without platelet recovery (CRi)

Have met all criteria for CR, except for either residual neutropenia (ANC $< 1.0 \times 10^9$/L) or thrombocytopenia (platelet count $< 100 \times 10^9$/L).

9.1.5 Partial remission (PR)

Blood count recovery as for CR, but with a decrease in marrow blasts of at least 50% and not more than 6 to 25% abnormal cells in the bone marrow.

9.1.6 **Confirmed Relapse**

Recurrence of disease as noted by: > 30% peripheral blasts, or > 20% bone marrow blasts. If the bone marrow blasts are between 6% and 20%, 2 serial bone marrow examinations at least 2 weeks apart demonstrating successive increase in blasts by at least 2% will also be a confirmed relapse.

9.1.7 **Relapse-free survival (RFS)**

Time from CR or CRi until confirmed relapse or death.

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9.1.8 **Event-free survival (EFS)**

Time from treatment start until date of first documented event. Event will be defined as: confirmed relapse, withdrawal from study due to adverse event, or death due to any cause.

9.1.9 **CR duration (CRd)**

Time from CR or Cri until date of first objective documentation of confirmed relapse.

9.1.10 **Overall survival (OS)**

Time from date of treatment start until date of death due to any cause.

10. REGULATORY AND REPORTING REQUIREMENTS

10.1 Regulatory and Reporting Requirements

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

Refer to Section 10.2 for Leukemia-Specific Adverse Event Recording Guidelines. The Principal Investigator will sign the PDMS Case Report Form toxicity pages per each patient at the completion of each course. Following signature, the Case Report Form will be used as source documentation for the adverse events.

10.2 Leukemia-specific Adverse Event Recording and Reporting Guidelines

These guidelines serve to bring the Department of Leukemia in compliance with the institutional policy on Reporting of Serious Adverse Events-definition of expected AE-**"** All clinical protocols should include a list of the expected and anticipated events or hospitalizations relating to the study treatment" and Guideline for Good Clinical Practice 4.11.1 "All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting".

Adverse event is any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

Adverse drug reaction is a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function.

Assessing causal connections between agents and disease is fundamental to the understanding of adverse drug reactions. In general, a drug may be considered a contributory cause of an adverse event if, had the drug not been administered, 1) the event would not have happened at all, 2) the event would have occurred later than it actually did, or 3) the event would have been less severe.

Adverse Events (AEs) will be evaluated according to current CTC version in each protocol. Only unexpected AEs will be recorded in the Case Report Form (CRF). Expected events during leukemia therapy are:

1. *Myelosuppression related events (due to disease or leukemia therapy)*
    a. *febrile or infection episodes not requiring management in the intensive care unit*
    b. *epistaxis or bleeding except for catastrophic CNS or pulmonary hemorrhage*
    c. *anemia, neutropenia, lymphopenia, thrombocytopenia, leukopenia, leukocytosis*
2. *Disease related events*
    a. *symptoms associated with anemia*
        i. *fatigue*
        ii. *weakness*
        iii. *shortness of breath*
    b. *electrolyte abnormalities (sodium, potassium, bicarbonate, CO2, magnesium)*
    c. *chemistry abnormalities (LDH, phosphorus, calcium, BUN, protein, albumin, uric acid, alkaline phosphatase, glucose)*
    d. *coagulation abnormalities*
    e. *disease specific therapy (induction, maintenance, salvage, or stem cell therapy)*
    f. *alopecia*
    g. *bone, joint, or muscle pain*
    h. *liver function test abnormalities associated with infection or disease progression*
    i. *disease progression*
3. *General therapy related events*
    a. *catheter related events*

   b. *renal failure related to tumor lysis syndrome or antibiotic/antifungal therapy*
   c. *rash related to antibiotic use*

4. ***Hospitalization for the management of any of the above expected events***

Abnormal hematologic values will not be recorded on the CRF. For abnormal chemical values grade 3 or 4, the apogee will be reported per course in the CRF.

Serious Adverse Event Reporting (SAE)

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose

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

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Serious adverse events will be captured from the time the patient signs consent until 30 days after the last dose of drug. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

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.

Male Subjects

If a female partner of a male subject taking lenalidomide 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.

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

Expedited Reporting by Investigator to Celgene

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. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and lenalidomide. 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-XX-PI-###) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

Reporting to FDA

It is the responsibility of the PI and the research teams to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Reporting of external SAEs

- The MDACC institutional policy for reporting of external SAEs will be followed.

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