(54) Titre : PROCEDES D’UTILISATION DE COMPOSES IMMUNOMODULATEURS POUR LE TRAITEMENT ET LA GESTION DES SYNDROMES MEYELODYSPLASTIQUES ET COMPOSITIONS CONTENANT CES COMPOSES
(54) Title: METHODS OF USING AND COMPOSITIONS COMPRISING IMMUNOMODULATORY COMPOUNDS FOR THE TREATMENT AND MANAGEMENT OF MYELODYSPLASTIC SYNDROMES

(57) Abrégé/Abstract:
Methods of treating, preventing and/or managing myelodysplastic syndromes are disclosed. Specific methods encompass the administration of immunomodulatory compound, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, alone or in combination with a second active ingredient, and/or the transplantation of blood or cells. Specific second active ingredients are capable of affecting or blood cell production. Pharmaceutical compositions, single unit dosage forms, and kits suitable for use in methods of the invention are also disclosed.
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1. **FIELD OF THE INVENTION**

This invention relates to methods of treating, preventing and/or managing myelodysplastic and related syndromes which comprise the administration of immunomodulatory compounds alone or in combination with known therapeutics. The invention also relates to pharmaceutical compositions and dosing regimens. In particular, the invention encompasses the use of immunomodulatory compounds in conjunction with transplantation therapy and/or other standard therapies for myelodysplastic syndromes.

2. **BACKGROUND OF THE INVENTION**

2.1. **PATHOBIOLOGY OF MDS**


The initial hematopoietic stem cell injury can be from causes such as, but not limited to, cytotoxic chemotherapy, radiation, virus, chemical exposure, and genetic predisposition. A clonal mutation predominates over bone marrow, suppressing healthy stem cells. In the early stages of MDS, the main cause of cytopenias is increased programmed cell death (apoptosis). As the disease progresses and converts into leukemia, gene mutation rarely occurs and a proliferation of leukemic cells overwhelms the healthy marrow. The disease course differs, with some cases behaving as an indolent disease and others behaving aggressively with a very short clinical course that converts into an acute form of leukemia.

The actual incidence of MDS in the U.S. is unknown. MDS was first considered a distinct disease in 1976, and occurrence was estimated at 1500 new cases every year. At that time, only patients with less than five percent blasts were considered to have this disorder. Statistics from 1999 estimated 13,000 new cases per year and about 1000 cases per year in children, surpassing chronic lymphocytic leukemia as the most common form of leukemia in the western hemisphere. The perception that the incidence is increasing may be due to improvements in recognition and criteria for diagnosis. The disease is found worldwide.

There are two subgroups of refractory anemia characterized by five percent or less myeloblasts in bone marrow: (1) refractory anemia (RA) and; (2) RA with ringed sideroblasts (RARS), defined morphologically as having 15% erythroid cells with abnormal ringed sideroblasts, reflecting an abnormal iron accumulation in the mitochondria. Both have a prolonged clinical course and low incidence of progression to acute leukemia. Besa E.C., Med. Clin. North Am. 1992 May, 76(3): 599-617.

There are two subgroups of refractory anemias with greater than five percent myeloblasts: (1) RA with excess blasts (RAEB), defined as 6-20% myeloblasts, and (2) RAEB in transformation (RAEB-T), with 21-30% myeloblasts. The higher the percentage of myeloblasts, the shorter the clinical course and the closer the disease is to acute myelogenous leukemia. Patient transition from early to more advanced stages indicates that these subtypes are merely stages of disease rather than distinct entities. Elderly patients with MDS with trilineage dysplasia and greater than 30% myeloblasts who progress to acute leukemia are often considered to have a poor prognosis because their response rate to chemotherapy is lower than de novo acute myeloid leukemia patients. The World Health Organization (WHO) classification (1999) proposes to include all cases of RAEB-T, or patients with greater than 20% myeloblasts, in the category of acute leukemia because these patients have similar prognostic outcomes. However, their response to therapy is worse than the de novo or more typical acute myelogenous leukemia or acute nonlymphocytic leukemia (ANLL) patient. Id.

The fifth type of MDS, the most difficult to classify, is called chronic myelomonocytic leukemia (CMML). This subtype can have any percentage of myeloblasts but presents with a monocytosis of 1000/dL or more. It may be associated with splenomegaly. This subtype overlaps with a myeloproliferative disorder and may have an intermediate clinical course. It is differentiated from the classic chronic myelocytic leukemia (CML) that is characterized by a negative Ph chromosome. The recent WHO classification (1999) proposes that juvenile and proliferative CMML be listed separately from FAB under MDS/myeloproliferative disorder (MPD) with splenomegaly and greater than 13,000 total WBC. CMML is limited to monocytosis, less than 13,000/mm³ total
leukocytes, and requires trilineage dysplasia. Id. Harris N.L., et al., J. Clin. Oncol. 1999 Dec., 17(12): 3835-49. Finally, some other international organizations, including WHO, have suggested a sixth class of MDS patients, characterized by a del (5q) abnormality.

MDS is primarily a disease of elderly people, with the median onset in the seventh decade of life. The median age of these patients is 65 years, with ages ranging from the early third decade of life to as old as 80 years or older. The syndrome may occur in any age group, including the pediatric population. Patients who survive malignancy treatment with alkylating agents, with or without radiotherapy, have a high incidence of developing MDS or secondary acute leukemia. About 60-70% of patients do not have an obvious exposure or cause for MDS, and are classified as primary MDS patients.

The most common cases of MDS are primary, or idiopathic. However, a nonspecific history of exposure to indeterminable chemicals or radiation 10-15 years prior to onset of disease may be present in about 50% of patients. This relationship to pathogenesis remains unproved. Compounds such as, but not limited to, benzene, insecticides, weed killers, and fungicides are possible causes of MDS. Goldberg H., et al., Cancer Res. 1990 Nov 1; 50(21): 6876-81. Secondary MDS describes development of MDS or acute leukemia after known exposures to chemotherapy drugs that can cause bone marrow damage. These drugs are associated with a high incidence of chromosomal abnormalities following exposure and at the time of MDS or acute leukemia diagnosis.

Further, MDS is associated with complications associated with severe cytopenias. Other complications are development of myelofibrosis, which can accelerate decline in blood counts and increase transfusion requirements. Transformation to acute leukemia accelerates the development of complications such as anemia, bleeding, and infections.

Recently, the International MDS Risk Analysis (IMRA) Workshop proposed an International Prognosis Scoring System (IPSS) to decrease imprecision in predicting survival and AML risk in MDS patients. The IPSS is based on the number of cytopenias, percentage of BM blasts, and type of cytogenetic abnormalities (Table 1). Greenberg et al., Blood 1997, 89:2079-88. The latter are categorized into good (normal, -Y, del (5q), del (20q)), intermediate, and poor subgroups (complex or chromosome 7 abnormalities).
Table 1. International Prognostic Scoring System for MDS

<table>
<thead>
<tr>
<th>Prognostic Variable</th>
<th>Score Value</th>
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<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Bone marrow blasts (%)</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Karyotype*</td>
<td>Good</td>
</tr>
<tr>
<td>Cytopenias</td>
<td>0/1</td>
</tr>
</tbody>
</table>

*Good, normal, del (5q), del (20q), -Y; Poor, complex (>3) or chromosome 7 abnormalities; Intermediate, +8, and other single or double abnormalities.

2.2. MDS TREATMENT

The current treatment of MDS is based on the stage and the mechanism of the disease that predominates the particular phase of the disease process. Bone marrow transplantation has been used in patients with poor prognosis or late-stage MDS. Epstein and Slease, 1985, Surg. Ann. 17:125. This type of therapy, however, is both painful for donor and recipient, because of the involvement of invasive procedures and can cause severe and even fatal complications to the recipient, particularly with allogeneic transplant and related Graft Versus Host Disease (GVHD) results. Therefore, the risk of GVHD restricts the use of bone marrow transplantation to patients with otherwise fatal diseases. Further, as most patients are elderly and only a few young MDS patients will have a matched donor, the use of bone marrow transplantation is limited.

been shown to activate a number of functions of mature blood cells, including influencing
the migration of mature hematopoietic cells. Stanley et al., 1976, J. Exp. Med. 143:631;
Burgess, 1979, J. Immunol. 122:1134; Vadás et al., 1983, Blood 61:1232; Vadás et al.,

Unfortunately, hematopoietic growth factors have not proven effective in many
clinical settings. Clinical trials of MDS patients treated with recombinant human GM-CSF
and G-CSF have shown that while these cytokines can restore granulocytopoiesis in treated
patients, their efficacy is restricted to the granulocyte or monocyte lineage with little or no
improvement in hemoglobin or platelet counts. Schuster et al., 1990, Blood 76
(Suppl.1):318a. When such patients were treated with recombinant human EPO, a sustained
improvement in hemoglobin or decrease in transfusion requirement was achieved in only
less than 25% of patients. Bessa et al., 1990, 76 (Suppl.1):133a; Hellstrom et al., 1990, 76
(Suppl.1):279a; Bowen et al., 1991, Br. J. Haematol. 77:419. Therefore, there remains a
need for safe and effective methods of treating and managing MDS.

2.3. THALIDOMIDE AND OTHER COMPOUNDS
USEFUL IN THE TREATMENT OF DISEASE

Thalidomide is a racemic compound sold under the tradename Thalomid® and
chemically named α-(N-phthalimido)glutarimide or 2-(2,6-dioxo-3-piperidinyl)-1H-
isoindole-1,3(2H)-dione. Thalidomide was originally developed in the 1950’s to treat
morning sickness, but due to its teratogenic effects was withdrawn from use. Thalidomide
has been approved in the United States for the acute treatment of the cutaneous
manifestations of erythema nodosum leprosum in leprosy. Physicians’ Desk Reference,
1154-1158 (56th ed., 2002). Because its administration to pregnant women can cause birth
defects, the sale of thalidomide is strictly controlled. Id. Thalidomide has reportedly been
studied in the treatment of other diseases, such as chronic graft-vs-host disease, rheumatoid
arthritis, sarcoidosis, several inflammatory skin diseases, and inflammatory bowel disease.
has further been alleged that thalidomide can be combined with other drugs to treat
ischemia/reperfusion associated with coronary and cerebral occlusion. See U.S. Patent No.
5,643,915.
More recently, thalidomide was found to exert immunomodulatory and anti-inflammatory effects in a variety of disease states, cachexia in AIDS, and opportunistic infections in AIDS. In studies to define the physiological targets of thalidomide, the drug was found to have a wide variety of biological activities exclusive of its sedative effect including neurotoxicity, teratogenicity, suppression of TNF-α production by monocytes/macrophages and the accompanying inflammatory toxicities associated with high levels of TNF-α, and inhibition of angiogenesis and neovascularization.

Additionally, beneficial effects have been observed in a variety of dermatological conditions, ulcerative colitis, Crohn’s disease, Bechets’s syndrome, systemic lupus erythematosis, aphthous ulcers, and lupus. The anti-angiogenic properties of thalidomide in in vivo models have been reported. D’Amato et al., Thalidomide Is An Inhibitor Of Angiogenesis, 1994, PNAS, USA 91:4082-4085.


In an effort to provide compounds that have greater therapeutic safety and efficacy than thalidomide, researchers have begun investigating a large number of other compounds, some of which are derivatives of thalidomide. See, e.g., Marriott, J.B., et al., Expert Opin. Biol. Ther. 1(4):1-8 (2001); G.W. Muller, et al., Journal of Medicinal Chemistry 39(17): 3238-3240 (1996); and G.W. Muller, et al., Bioorganic & Medicinal Chemistry Letters 8:
2669-2674 (1998). Examples include, but are not limited to, the substituted 2-(2,6-dioxopiperidin-3-yl) phthalimides and substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisooindoles described in United States Patent Nos. 6,281,230 and 6,316,471, both to G.W. Muller, et al.

A group of compounds selected for their capacity to potently inhibit TNF-α production by LPS stimulated PBMC has been investigated. L.G. Corral, et al., Ann. Rheum. Dis. 58:(Suppl 1) 1107-1113 (1999). These compounds, which are referred to as IMiDs™ or Immunomodulatory Drugs, show not only potent inhibition of TNF-α but also marked inhibition of LPS induced monocyte IL1β and IL12 production. LPS induced IL6 is also inhibited by IMiDs™, albeit partially. These compounds are potent stimulators of LPS induced IL10, increasing IL10 levels by 200 to 300%. Id.

While many such compounds have shown promise as therapeutic agents, their mechanisms of action and effectiveness are still under investigation. Moreover, there remains a need for therapeutic agents to treat MDS and its related disorders.

3. SUMMARY OF THE INVENTION

This invention encompasses methods of treating or preventing myelodysplastic syndrome ("MDS") which comprise administering to a patient in need thereof a therapeutically or prophylactically effective amount of an immunomodulatory compound of the invention or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof. The invention also encompasses methods of managing MDS (e.g., lengthening the time of remission) which comprise administering to a patient in need of such management a therapeutically or prophylactically effective amount of an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

One embodiment of the invention encompasses the use of one or more immunomodulatory compounds in combination with conventional therapies presently used to treat, prevent or manage MDS such as hematopoietic growth factors, cytokines, cancer chemotherapeutics, stem cell transplantation and other transplantations.

The invention further encompasses pharmaceutical compositions, single unit dosage forms, and kits suitable for use in treating, preventing and/or managing MDS, which comprise an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.
According to one aspect of the present invention, there is provided use in the preparation of a medicament for treating a myelodysplastic syndrome in a patient of a compound of formula (I):

(I)

or a pharmaceutically acceptable salt or stereoisomer thereof, wherein one of X and Y is C=O, the other of X and Y is CH₂, and R² is hydrogen or (C₁-C₈) alkyl.

According to another aspect of the present invention, there is provided use for treating a myelodysplastic syndrome in a patient of a compound of formula (I):

(I)

or a pharmaceutically acceptable salt or stereoisomer thereof, wherein one of X and Y is C=O, the other of X and Y is CH₂, and R² is hydrogen or (C₁-C₈) alkyl.

According to still another aspect of the present invention, there is provided use in the preparation of a medicament for treating a myelodysplastic syndrome in a patient of 3-((4-amino-1-oxo-1,3-dihydro-isooindol-2-yl)-piperidine-2,6-dione having the formula:
53686-17(S)

or a pharmaceutically acceptable salt or stereoisomer thereof.

According to yet another aspect of the present invention, there is provided use for treating a myelodysplastic syndrome in a patient of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione having the formula:

or a pharmaceutically acceptable salt or stereoisomer thereof.

According to a further aspect of the present invention, there is provided a pharmaceutical composition in dosage unit form for use in the treatment of a myelodysplastic syndrome in a patient, which comprises:

(a) an active agent which is a compound of formula (I):

(I)
53686-17(S)

or a pharmaceutically acceptable salt or stereoisomer thereof, wherein one of X and Y is C=O, the other of X and Y is CH₂, and R² is hydrogen or (C₁-C₈) alkyl; and

(b) a pharmaceutically acceptable carrier,

excipient or diluent.

According to yet a further aspect of the present invention, there is provided a commercial package comprising as active agent a compound of formula (I):

![Chemical Structure](image)

(I)

or a pharmaceutically acceptable salt or stereoisomer thereof, wherein one of X and Y is C=O, the other of X and Y is CH₂, and R² is hydrogen or (C₁-C₈) alkyl, together with instructions for the use thereof for treating myelodysplastic syndrome in a patient.

According to still a further aspect of the present invention, there is provided a pharmaceutical composition in dosage unit form for use in the treatment of a myelodysplastic syndrome in a patient, which comprises:

(a) an active agent which is 3-(4-amino-1-oxo-1,3-dihydro-isooindol-2-yl)-piperidine-2,6-dione having the formula:

![Chemical Structure](image)
53686-17(S)

or a pharmaceutically acceptable salt or stereoisomer thereof; and

(b) a pharmaceutically acceptable carrier or diluent.

According to another aspect of the present invention, there is provided a commercial package comprising the pharmaceutical composition as described herein, together with instructions for use for treating myelodysplastic syndrome in a patient.

According to yet another aspect of the present invention, there is provided use in the preparation of a medicament for treating myelodysplastic syndrome in a patient of a compound of formula:

\[
\text{NH}_2
\]

or a pharmaceutically acceptable salt or stereoisomer thereof.

According to another aspect of the present invention, there is provided use in the preparation of a medicament for treating myelodysplastic syndrome in a patient of a compound of formula:

\[
\text{HN}
\]
or a pharmaceutically acceptable salt or stereoisomer thereof.

According to still another aspect of the present invention, there is provided a compound, which is 3-[(4-5 amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione having the formula:

![Chemical Structure]

or a pharmaceutically acceptable salt or stereoisomer thereof for use in treating a myelodysplastic syndrome in a patient.
4. **DETAILED DESCRIPTION OF THE INVENTION**

A first embodiment of the invention encompasses methods of treating or preventing MDS which comprise administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof. The embodiment encompasses the treatment, prevention or management of specific sub-types of MDS such as refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation and chronic myelomonocytic leukemia.

As used herein, the term “myelodysplastic syndromes” or “MDS” means hematopoietic stem cell disorders characterized by one or more of the following: ineffective blood cell production, progressive cytopenias, risk of progression to acute leukemia or cellular marrow with impaired morphology and maturation (dysmyelopoiesis). The term “myelodysplastic syndromes” or “MDS” unless otherwise noted includes: refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation and chronic myelomonocytic leukemia.

Another embodiment of the invention encompasses methods of managing MDS which comprises administering to a patient in need of such management a prophylactically effective amount of an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

Another embodiment of the invention encompasses a pharmaceutical composition comprising an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

Also encompassed by the invention are single unit dosage forms comprising an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

Another embodiment of the invention encompasses a kit comprising: a pharmaceutical composition comprising an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof and a second active or dexamethasone or instructions for use. The invention further encompasses kits comprising single unit dosage forms.

One embodiment of the invention encompasses a method of treating, preventing and/or managing MDS, which comprises administering to a patient in need of such treatment, prevention and/or management a therapeutically or prophylactically effective
amount of an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, and a therapeutically or prophylactically effective amount of a second active agent.

The second active agent is preferably a hematopoietic growth factor, a cytokine, an anti-cancer agent, an antibiotic, an anti-fungal, an anti-inflammatory, an immunosuppressive agent such as a cyclosporin, conventional therapy for MDS, or other chemotherapeutic agent found for example in the Physician’s Desk Reference 2002. Preferred anti-cancer or cancer chemotherapeutics are apoptosis inducing agents, topoisomerase inhibitors, anti-angiogenesis compounds, microtubule stabilizing agents, alkylating agents and other known conventional cancer chemotherapy. Most preferred second active agents are those capable of affecting or improving blood production. Second active agents can be large molecules (e.g., proteins) or small molecules (e.g., synthetic inorganic, organometallic, or organic molecules). The examples of specific second active agent include, but are not limited to, etanercept (Enbrel®), imatinib (Glivec®), anti-TNF-α antibodies, infliximab (Remicade®), G-CSF, GM-CSF, EPO, topotecan, irinotecan, pentoxifylline, ciprofloxacin, dexamethasone, IL2, IL8, IL18, Ara-C, vinorelbine, vinblastine, isotretinoin, and13-cis-retinoic acid. This invention also encompasses the use of native, naturally occurring, and recombinant proteins. The invention further encompasses mutants and derivatives (e.g., modified forms) of naturally occurring proteins that exhibit, in vivo, at least some of the pharmacological activity of the proteins upon which they are based. Examples of mutants include, but are not limited to, proteins that have one or more amino acid residues that differ from the corresponding residues in the naturally occurring forms of the proteins. Also encompassed by the term ‘mutants’ are proteins that lack carbohydrate moieties normally present in their naturally occurring forms (e.g., nonglycosylated forms). Examples of derivatives include, but are not limited to, pegylated derivatives and fusion proteins, such as proteins formed by fusing IgG1 or IgG3 to the protein or active portion of the protein of interest. See, e.g., Penichet, M.L. and Morrison, S.L., J. Immunol. Methods 248:91-101 (2001). Vaccines that cause the secretion of proteins disclosed herein as well as pharmacologically active mutants, derivatives, and fusion thereof are also encompassed by the invention.

Without being limited by theory, it is believed that certain immunomodulatory compounds and proteins can act in complementary or synergistic ways in the treatment or management of MDS. It is also believed that certain proteins may reduce or eliminate particular adverse effects associated with some immunomodulatory compounds, thereby allowing the administration of larger amounts of an immunomodulatory compound to
patients and/or increasing patient compliance. It is further believed that some immunomodulatory compounds may reduce or eliminate particular adverse effects associated with some protein-based MDS therapies, thereby allowing the administration of larger amounts of protein to patients and/or increasing patient compliance.

Another embodiment of the invention encompasses a method of reversing, reducing or avoiding an adverse effect associated with the administration of a chemotherapeutics or therapeutics used to treat cancer or MDS in a patient suffering from MDS, which comprises administering to a patient in need thereof a therapeutically or prophylactically effective amount of an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

As inevitable leukemic transformation develops in certain stages of MDS, transplantation of peripheral blood stem cells, hematopoietic stem cell preparation or bone marrow may be necessary. It is believed that the combined use of an immunomodulatory compound and transplantation of stem cells in a patient suffering from MDS provides a unique and unexpected synergism. In particular, without being limited by theory, it is believed that an immunomodulatory compound exhibits immunomodulatory activity that may provide additive or synergistic effects when given concurrently with transplantation therapy. Immunomodulatory compounds can work in combination with transplantation therapy reducing complications associated with the invasive procedure of transplantation and risk of related Graft Versus Host Disease (GVHD). Therefore, this invention encompasses a method of treating, preventing and/or managing MDS, which comprises administering to a patient (e.g., a human) an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, before, during, or after transplantation therapy.

The invention also encompasses pharmaceutical compositions, single unit dosage forms, and kits which comprise one or more immunomodulatory compounds, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, a second active ingredient, and/or blood or cells for transplantation therapy. For example, the kit may contain one or more compounds of the invention, stem cells for transplantation and an immunosuppressive agent, antibiotic or other drug, each of which is to be used to treat the MDS patient.

4.1. IMMUNOMODULATORY COMPOUNDS

Compounds used in the invention include immunomodulatory compounds that are racemic, stereomerically enriched or stereomerically pure, and pharmaceutically acceptable
salts, solvates, hydrates, stereoisomers, clathrates, and prodrugs thereof. Preferred
compounds used in the invention are small organic molecules having a molecular weight
less than about 1000 g/mol, and are not proteins, peptides, oligonucleotides,
oligosaccharides or other macromolecules.

As used herein and unless otherwise indicated, the term "stereomerically pure"
means a composition that comprises one stereoisomer of a compound and is substantially
free of other stereoisomers of that compound. For example, a stereomerically pure
composition of a compound having one chiral center will be substantially free of the
opposite enantiomer of the compound. A stereomerically pure composition of a compound
having two chiral centers will be substantially free of other diastereomers of the compound.
A typical stereomerically pure compound comprises greater than about 80% by weight of
one stereoisomer of the compound and less than about 20% by weight of other
stereoisomers of the compound, more preferably greater than about 90% by weight of one
stereoisomer of the compound and less than about 10% by weight of the other stereoisomers
of the compound, even more preferably greater than about 95% by weight of one
stereoisomer of the compound and less than about 5% by weight of the other stereoisomers
of the compound, and most preferably greater than about 97% by weight of one
stereoisomer of the compound and less than about 3% by weight of the other stereoisomers
of the compound. As used herein and unless otherwise indicated, the term "stereomerically
enriched" means a composition that comprises greater than about 60% by weight of one
stereoisomer of a compound, preferably greater than about 70% by weight, more preferably
greater than about 80% by weight of one stereoisomer of a compound. As used herein and
unless otherwise indicated, the term "enantiomerically pure" means a stereomerically pure
composition of a compound having one chiral center. Similarly, the term "stereomerically
enriched" means a stereomerically enriched composition of a compound having one chiral
center.

As used herein and unless otherwise indicated, the term “immunomodulatory
compounds” or “IMiDs™” (Celgene Corporation) used herein encompasses small organic
molecules that markedly inhibit TNF-α, LPS induced monocyte IL1β and IL12, and
partially inhibit IL6 production. Specific immunomodulatory compounds of the invention
are discussed below.

TNF-α is an inflammatory cytokine produced by macrophages and monocytes
during acute inflammation. TNF-α is responsible for a diverse range of signaling events
within cells. TNF-α may play a pathological role in cancer. Without being limited by
particular theory, one of the biological effects exerted by the immunomodulatory
compounds of the invention is the reduction of synthesis of TNF-α. Immunomodulatory compounds of the invention enhance the degradation of TNF-α mRNA.

Further, without being limited by particular theory, immunomodulatory compounds used in the invention may also be potent co-stimulators of T cells and increase cell proliferation dramatically in a dose dependent manner. Immunomodulatory compounds of the invention may also have a greater co-stimulatory effect on the CD8+ T cell subset than on the CD4+ T cell subset. In addition, the compounds preferably have anti-inflammatory properties, and efficiently co-stimulate T cells.

Specific examples of immunomodulatory compounds of the invention include, but are not limited to, cyano and carboxy derivatives of substituted styrenes such as those disclosed in U.S. patent no. 5,929,117; 1-oxo-2-(2,6-dioxo-3-fluoropiperidin-3-yl) isoindolines and 1,3-dioxo-2-(2,6-dioxo-3-fluoropiperidine-3-yl) isoindolines such as those described in U.S. patent no. 5,874,448; the tetra substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisooindolines described in U.S. patent no. 5,798,368; 1-oxo and 1,3-dioxo-2-(2,6-dioxopiperidin-3-yl) isoindolines (e.g., 4-methyl derivatives of thalidomide and EM-12), including, but not limited to, those disclosed in U.S. patent no. 5,635,517; and a class of non-polypeptide cyclic amides disclosed in U.S. patent nos. 5,698,579 and 5,877,200; analogs and derivatives of thalidomide, including hydrolysis products, metabolites, derivatives and precursors of thalidomide, such as those described in U.S. patent nos. 5,593,990, 5,629,327, and 6,071,948 to D’Amato; aminothalidomide, as well as analogs, hydrolysis products, metabolites, derivatives and precursors of aminothalidomide, and substituted 2-(2,6-dioxopiperidin-3-yl) phthalimides and substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisooindolines such as those described in U.S. patent nos. 6,281,230 and 6,316,471; isoindole-imide compounds such as those described in U.S. patent No. 7,091,335 filed on December 21, 2001, and International Application No. PCT/US01/50401 (International Publication No. WO 02/059106). Immunomodulatory compounds of the invention do not include thalidomide.

Other specific immunomodulatory compounds of the invention include, but are not limited to, 1-oxo-and 1,3 dioxo-2-(2,6-dioxopiperidin-3-yl) isoindolines substituted with amino in the benzo ring as described in U.S. Patent no. 5,635,517. These compounds have the structure I:
in which one of X and Y is C=O, the other of X and Y is C=O or CH₂, and R² is hydrogen or lower alkyl, in particular methyl. Specific immunomodulatory compounds include, but are not limited to:

1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisoindoline;
1-oxo-2-(2,6-dioxopiperidin-3-yl)-5-aminoisoindoline;
1-oxo-2-(2,6-dioxopiperidin-3-yl)-6-aminoisoindoline;
1-oxo-2-(2,6-dioxopiperidin-3-yl)-7-aminoisoindoline;
1,3-dioxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisoindoline;
and 1,3-dioxo-2-(2,6-dioxopiperidin-3-yl)-5-aminoisoindoline.

Other specific immunomodulatory compounds of the invention belong to a class of substituted 2-(2,6-dioxopiperidin-3-yl) phthalimides and substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindoles, such as those described in U.S. patent nos. 6,281,230; 6,316,471; 6,335,349; and 6,476,052, and International Patent Application No. PCT/US97/13375 (International Publication No. WO 98/03502).

Compounds representative of this class are of the formulas:
wherein R\(^1\) is hydrogen or methyl. In a separate embodiment, the invention encompasses the use of enantiomerically pure forms (e.g. optically pure (R) or (S) enantiomers) of these compounds.

Still other specific immunomodulatory compounds of the invention belong to a class of isoindole-imides disclosed in U.S. patent No. 7,091,353, and International Application No. PCT/US01/50401 (International Publication No. WO 02/059106). Representative compounds are of formula II:

![Chemical Structure](image)

\[ \text{II} \]

and pharmaceutically acceptable salts, hydrates, solvates, clathrates, enantiomers, diastereomers, racemates, and mixtures of stereoisomers thereof, wherein:

one of X and Y is C=O and the other is CH\(_2\) or C=O;

R\(^1\) is H, (C\(_1\)-C\(_8\))alkyl, (C\(_2\)-C\(_7\))cycloalkyl, (C\(_2\)-C\(_8\))alkenyl, (C\(_2\)-C\(_8\))alkynyl, benzyl, aryl, (C\(_0\)-C\(_4\))alkyl-(C\(_1\)-C\(_8\))heterocycloalkyl, (C\(_0\)-C\(_4\))alkyl-(C\(_2\)-C\(_8\))heteroaryl, C(O)R\(^3\), C(S)R\(^3\), C(O)OR\(^4\), (C\(_1\)-C\(_8\))alkyl–N(R\(^6\))\(_2\), (C\(_1\)-C\(_8\))alkyl–OR\(^5\), (C\(_1\)-C\(_8\))alkyl–C(O)OR\(^5\), C(O)NHR\(^5\), C(S)NHR\(^5\), C(O)NR\(^2\)R\(^3\), C(S)NR\(^2\)R\(^3\) or (C\(_1\)-C\(_8\))alkyl–O(CO)R\(^5\);

R\(^2\) is H, F, benzyl, (C\(_1\)-C\(_8\))alkyl, (C\(_2\)-C\(_8\))alkenyl, or (C\(_2\)-C\(_8\))alkynyl;

R\(^3\) and R\(^4\) are independently (C\(_1\)-C\(_8\))alkyl, (C\(_2\)-C\(_7\))cycloalkyl, (C\(_2\)-C\(_8\))alkenyl, (C\(_2\)-C\(_8\))alkynyl, benzyl, aryl, (C\(_0\)-C\(_4\))alkyl–(C\(_1\)-C\(_8\))heterocycloalkyl, (C\(_0\)-C\(_4\))alkyl–(C\(_2\)-C\(_8\))heteroaryl, (C\(_0\)-C\(_4\))alkyl–N(R\(^6\))\(_2\), (C\(_1\)-C\(_8\))alkyl–OR\(^5\), (C\(_1\)-C\(_8\))alkyl–C(O)OR\(^5\), (C\(_1\)-C\(_8\))alkyl–O(CO)R\(^5\), or C(O)OR\(^5\);

R\(^5\) is (C\(_1\)-C\(_8\))alkyl, (C\(_2\)-C\(_8\))alkenyl, (C\(_2\)-C\(_8\))alkynyl, benzyl, aryl, or (C\(_2\)-C\(_8\))heteroaryl;

each occurrence of R\(^6\) is independently H, (C\(_1\)-C\(_8\))alkyl, (C\(_2\)-C\(_8\))alkenyl, (C\(_2\)-C\(_8\))alkynyl, benzyl, aryl, (C\(_2\)-C\(_8\))heteroaryl, or (C\(_0\)-C\(_8\))alkyl–C(O)O–R\(^5\) or the R\(^6\) groups can join to form a heterocycloalkyl group;

n is 0 or 1; and

* represents a chiral-carbon center.
In specific compounds of formula II, when n is 0 then R1 is (C3-C7)cycloalkyl, (C2-
C8)alkenyl, (C2-C8)alkynyl, benzyl, aryl, (C0-C4)alkyl-(C1-C6)heterocycloalkyl, (C0-
C4)alkyl-(C2-C5)heteroaryl, C(O)R3, C(O)OR4, (C1-C8)alkyl-N(R6)2, (C1-C8)alkyl-
OR5, (C1-C8)alkyl-C(O)OR5, C(S)NHR3, or (C1-C8)alkyl-O(CO)R5;
R² is H or (C1-C₈)alkyl; and
R³ is (C1-C₈)alkyl, (C₂-C₇)cycloalkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, benzyl, aryl,
(C₀-C₄)alkyl-(C₁-C₆)heterocycloalkyl, (C₀-C₄)alkyl-(C₂-C₅)heteroaryl, (C₅-C₈)alkyl-
N(R₆)₂; (C₀-C₈)alkyl-NH-C(O)O-R²; (C₁-C₈)alkyl-OR²; (C₁-C₈)alkyl-C(O)OR²; (C₁-
C₈)alkyl-O(CO)R², or C(O)OR²; and the other variables have the same definitions.

In other specific compounds of formula II, R² is H or (C₁-C₈)alkyl.
In other specific compounds of formula II, R¹ is (C₁-C₈)alkyl or benzyl.
In other specific compounds of formula II, R¹ is H, (C₁-C₈)alkyl, benzyl, CH₂OCH₃,
CH₂CH₂OCH₃, or

\[
\begin{array}{c}
\mathrm{CH₂} \quad \mathrm{CH₂} \\
\includegraphics[width=2cm]{furan.png}
\end{array}
\]

In another embodiment of the compounds of formula II, R¹ is

\[
\begin{array}{c}
\mathrm{CH₂} \\
\includegraphics[width=2cm]{thiophene.png} \\
\includegraphics[width=2cm]{pyrrole.png}
\end{array}
\]

wherein Q is O or S, and each occurrence of R⁷ is independently H, (C₁-C₈)alkyl,
benzyl, CH₂OCH₃, or CH₂CH₂OCH₃.
In other specific compounds of formula II, R¹ is C(O)R³.
In other specific compounds of formula II, R³ is (C₀-C₄)alkyl-(C₁-C₆)heteroaryl, (C₁-
C₈)alkyl, aryl, or (C₀-C₄)alkyl-OR².
In other specific compounds of formula II, heteroaryl is pyridyl, furyl, or thienyl.
In other specific compounds of formula II, R¹ is C(O)OR⁴.
In other specific compounds of formula II, the H of C(O)NHC(O) can be replaced
with (C₁-C₄)alkyl, aryl, or benzyl.

Still other specific immunomodulatory compounds of the invention belong to a class
of isoindole-imides disclosed in U.S. patent No. 6,555,554, International
Representative compounds are of formula III:
and pharmaceutically acceptable salts, hydrates, solvates, clathrates, enantiomers, diastereomers, racemates, and mixtures of stereoisomers thereof, wherein:

one of X and Y is C=O and the other is CH₂ or C=O;

R is H or CH₂COR⁺;

(i) each of R¹, R², R³, or R⁴, independently of the others, is halo, alkyl of 1 to 4 carbon atoms, or alkoxy of 1 to 4 carbon atoms or (ii) one of R¹, R², R³, or R⁴ is nitro or -NHR⁵ and the remaining of R¹, R², R³, or R⁴ are hydrogen;

R⁵ is hydrogen or alkyl of 1 to 8 carbons

R⁶ hydrogen, alkyl of 1 to 8 carbon atoms, benzo, chloro, or fluoro;

R⁷ is R⁷-CHR¹⁰-N(R⁸R⁹);

R⁸ is m-phenylene or p-phenylene or -(CₙH₂ₙ)- in which n has a value of 0 to 4;

each of R⁸ and R⁹ taken independently of the other is hydrogen or alkyl of 1 to 8 carbon atoms, or R⁸ and R⁹ taken together are tetramethylene, pentamethylene, hexamethylene, or --CH₂CH₂[X]X₁CH₂CH₂-- in which [X]X₁ is -O-, -S-, or -NH-;

R¹⁰ is hydrogen, alkyl of to 8 carbon atoms, or phenyl; and

* represents a chiral-carbon center.

The most preferred immunomodulatory compounds of the invention are 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione and 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione. The compounds can be obtained via standard, synthetic methods (see e.g., United States Patent No. 5,635,517).

The compounds are available from Celgene Corporation, Warren, NJ. 4-(Amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione (ACTIMID™) has the following chemical structure:

3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (REVLIMID™) has the following chemical structure:
The compounds of the invention can either be commercially purchased or prepared according to the methods described in the patents or patent publications disclosed herein. Further, optically pure compounds can be asymmetrically synthesized or resolved using known resolving agents or chiral columns as well as other standard synthetic organic chemistry techniques.

As used herein and unless otherwise indicated, the term “pharmaceutically acceptable salt” encompasses non-toxic acid and base addition salts of the compound to which the term refers. Acceptable non-toxic acid addition salts include those derived from organic and inorganic acids or bases known in the art, which include, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulphonic acid, acetic acid, tartaric acid, lactic acid, succinic acid, citric acid, malic acid, maleic acid, sorbic acid, aconitic acid, salicylic acid, phthalic acid, embolic acid, enanthic acid, and the like.

Compounds that are acidic in nature are capable of forming salts with various pharmaceutically acceptable bases. The bases that can be used to prepare pharmaceutically acceptable base addition salts of such acidic compounds are those that form non-toxic base addition salts, i.e., salts containing pharmacologically acceptable cations such as, but not limited to, alkali metal or alkaline earth metal salts and the calcium, magnesium, sodium or potassium salts in particular. Suitable organic bases include, but are not limited to, N,N-dibenzylethlenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumaine (N-methylglucamine), lysine, and procaine.

As used herein and unless otherwise indicated, the term “prodrug” means a derivative of a compound that can hydrolyze, oxidize, or otherwise react under biological conditions (in vitro or in vivo) to provide the compound. Examples of prodrugs include, but are not limited to, derivatives of immunomodulatory compounds of the invention that comprise biohydrolyzable moieties such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues. Other examples of prodrugs include derivatives of immunomodulatory compounds of the invention that comprise -NO, -NO₂, -ONO, or -ONO₂ moieties. Prodrugs can typically be prepared using well-known methods, such as those described in 1 Burger's Medicinal Chemistry and Drug Discovery, 172-178, 949-982.
As used herein and unless otherwise indicated, the terms “biohydrolyzable amide,” “biohydrolyzable ester,” “biohydrolyzable carbamate,” “biohydrolyzable carbonate,” “biohydrolyzable ureide,” “biohydrolyzable phosphate” mean an amide, ester, carbamate, carbonate, ureide, or phosphate, respectively, of a compound that either: 1) does not interfere with the biological activity of the compound but can confer upon that compound advantageous properties in vivo, such as uptake, duration of action, or onset of action; or 2) is biologically inactive but is converted in vivo to the biologically active compound.

Examples of biohydrolyzable esters include, but are not limited to, lower alkyl esters, lower acyloxyalkyl esters (such as acetoxymethyl, acetoxyethyl, aminocarbohydryloxymethyl, pivaloyloxymethyl, and pivaloyloxyethyl esters), lactonyl esters (such as phthalidyl and thiophthalidyl esters), lower alkoxyacyloxyalkyl esters (such as methoxycarbonyloxymethyl, ethoxycarbonyloxoyethyl and isopropoxycarbonyloxoyethyl esters), alkoxyalkyl esters, choline esters, and acylamino alkyl esters (such as acetamidomethyl esters). Examples of biohydrolyzable amides include, but are not limited to, lower alkyl amides, α-amino acid amides, alkoxyacyl amides, and alkylaminoalkylcarbonyl amides. Examples of biohydrolyzable carbamates include, but are not limited to, lower alkylamines, substituted ethylenediamines, aminoacids, hydroxyalkylamines, heterocyclic and heteroaromatic amines, and polyether amines.

It should be noted that if there is a discrepancy between a depicted structure and a name given that structure, the depicted structure is to be accorded more weight. In addition, if the stereochemistry of a structure or a portion of a structure is not indicated with, for example, bold or dashed lines, the structure or portion of the structure is to be interpreted as encompassing all stereoisomers of it.

4.2. SECOND ACTIVE AGENTS

One or more second active ingredients can be used in the methods and compositions of the invention together with an immunomodulatory compound of the invention. In a preferred embodiment, the second active agents are capable of affecting or improving the process of blood cell production. Specific second active agents also stimulate the division and differentiation of committed erythroid progenitors in cells in vitro or in vivo.

Second active agents can be large molecules (e.g., proteins) or small molecules (e.g., synthetic inorganic, organometallic, or organic molecules). The second active agents include but are not limited to hematopoietic growth factors, cytokines, anti-cancer agents,
antibiotics, proteasome inhibitors, immunosuppressive agents and other therapeutics discussed herein. Particular agents include, but are not limited to, G-CSF, GM-CSF, EPO, dexamethasone, topotecan, pentoxifylline, irinotecan, ciprofloxacin, vinorelbine, IL2, IL8, IL18, Ara-C, isotretinoin, 13-cis-retinoic acid, 12-O-tetradecanoylphorbol-13-acetate (TPA), 5-AZA2'-deoxycytidine, 9-nitrocamptothecin, transretinoic acid, amifostine, amphotericin B and liposomal amphotericin B, anti-CD-20 monoclonal antibody, antithymocyte globulin (ATG), arsenic trioxide, azacytidine, bevacizumab, bismuth monoclonal antibody, bryostatin, busulfan, caspofungin acetate, celecoxib, cladribine, cyclophosphamide, cyclosporine, cytarabine, cytosine, daunorubicin, depsipeptide, etoposide, faresyn transferase inhibitor, flavopiridol, Flt3 ligand, fludarabine, gentuzumab ozogamicin (mylotarg), etanercept (Enbrel®), imatinib (Glivec®), anti-TNF-α antibodies, infliximab (Remicade®), humanized monoclonal anti-VEGF antibody, idarubicine, leucovorin, melphalan, mitoxantrone, monoclonal antibody ABX-CBL, monoclonal antibody CDS2, mycophenolate mofetil, oblimersen, omega-3 fatty acids, pentostatin, phenylbutyrate, PR1 leukemia peptide vaccine, montanide, proteasome inhibitor, sodium phenylbutyrate, sodium salicylate, temozolomide, thymoglobulin, troxatyl, tumor necrosis factor receptor IgG chimera, Yttrium Y 90 humanized monoclonal antibody M195. In a specific embodiment of the invention, an immunomodulatory compound of the invention is used in combination with pentoxifylline, ciprofloxacin, and/or dexamethasone.

This invention also encompasses the use of native, naturally occurring, and recombinant proteins. The invention further encompasses mutants and derivatives (e.g., modified forms) of naturally occurring proteins that exhibit, in vivo, at least some of the pharmacological activity of the proteins upon which they are based. Examples of mutants include, but are not limited to, proteins that have one or more amino acid residues that differ from the corresponding residues in the naturally occurring forms of the proteins. Also encompassed by the term “mutants” are proteins that lack carbohydrate moieties normally present in their naturally occurring forms (e.g., nonglycosylated forms). Examples of derivatives include, but are not limited to, pegylated derivatives and fusion proteins, such as proteins formed by fusing IgG1 or IgG3 to the protein or active portion of the protein of interest. See, e.g., Penichet, M.L. and Morrison, S.L., J. Immunol. Methods 248:91-101 (2001).

Recombinant and mutated forms of G-CSF can be prepared as described in U.S. patent nos. 4,810,643; 4,999,291; 5,528,823; and 5,580,755. Recombinant and mutated forms of GM-CSF can be prepared as described in U.S. patent nos. 5,391,485; 5,393,870; and 5,229,496.
In fact, recombinant forms of G-CSF and GM-CSF are currently sold in the United States for the treatment of symptoms associated with specific chemotherapies. A recombinant form of G-CSF known as filgrastim is sold in the United States under the trade name NEUPHGEN®. NEUPHGEN® is known to stimulate division and maturation of granulocytes, mostly neutrophils, in MDS patients and to enhance erythroid response in combination with EPO. *Physicians' Desk Reference*, 587-592 (56th ed., 2002). A recombinant form of GM-CSF known as sargramostim is also sold in the United States under the trade name LEUKINE®. LEUKINE® is known to stimulate division and maturation of earlier myeloid and macrophage precursor cells and has been reported to increase granulocytes. *Physicians' Desk Reference*, 1755-1760 (56th ed., 2002). A recombinant form of EPO known as epoetin alfa is sold in the United States under the trade name EPOGEN®. EPOGEN® is used to stimulate red cell production by stimulating division and maturation of committed red cell precursor cells. EPOGEN® has been reported to be effective in 20-26% of MDS patients when administered by itself and in as many as 48% of patients when combined with G-CSF or GM-CSF. *Physicians' Desk Reference*, 582-587 (56th ed., 2002).

A growth-factor or cytokine such as G-CSF, GM-CSF and EPO can also be administered in the form of a vaccine. For example, vaccines that secrete, or cause the secretion of, cytokines such as G-CSF and GM-CSF can be used in the methods, pharmaceutical compositions, and kits of the invention. See, e.g., Emens, L.A., et al., *Curr. Opinion Mol. Ther.* 3(1):77-84 (2001).

4.3. METHODS OF TREATMENT AND MANAGEMENT

Methods of this invention encompass methods of preventing, treating and/or managing various types of MDS. As used herein, unless otherwise specified, the term "preventing" includes but is not limited to, inhibition or the averting of symptoms associated with MDS. The symptoms associated with MDS include, but are not limited to, anemia, thrombocytopenia, neutropenia, cytopenia, bicytopenia (two deficient cell lines), and pancytopenia (three deficient cell lines). As used herein, unless otherwise specified, the term "treating" refers to the administration of a composition after the onset of symptoms of
MDS, whereas “preventing” refers to the administration prior to the onset of symptoms, particularly to patients at risk of MDS. As used herein and unless otherwise indicated, the term “managing” encompasses preventing the recurrence of MDS in a patient who had suffered from MDS, lengthening the time a patient who had suffered from MDS remains in remission, and/or preventing the occurrence of MDS in patients at risk of suffering from MDS.

The invention encompasses methods of treating or preventing patients with primary and secondary MDS. It further encompasses methods treating patients who have been previously treated for MDS, as well as those who have not previously been treated for MDS. Because patients with MDS have heterogeneous clinical manifestations and varying clinical outcomes, it has become apparent that staging the patients according to their prognosis and approaching therapy depending on the severity and stage is necessary. Indeed, the methods and compositions of this invention can be used in various stages of treatments for patients with one or more types of MDS including, but not limited to, refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess blasts (RAEB), RAEB in transformation (RAEB-T), or chronic myelomonocytic leukemia (CMML). The invention also contemplates treating patients diagnosed using the IPSS for MDS discussed above. Greenberg et al., Blood 1997 (89):2079-88.

Methods encompassed by this invention comprise administering an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof to a patient (e.g., a human) suffering, or likely to suffer, from MDS. Specific patient populations include the elderly, i.e., ages 60 and above as well as those over 35 years of age. Patients with familial history of MDS or leukemia are also preferred candidates for preventive regimens.

In one embodiment of the invention, an immunomodulatory compound of the invention is administered orally and in a single or divided daily doses in an amount of from about 0.10 to about 150 mg/day. In a particular embodiment, 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione (Actimid™) is administered in an amount of from about 0.1 to about 1 mg per day, or alternatively about 5 mg every other day. 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (Revlimid™) can be preferably administered in an amount of from about 5 to 25 mg per day, or alternatively from about 25 to about 50 mg every other day.
4.3.1 Combination Therapy With A Second Active Agent

Particular methods of the invention comprise administering 1) an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, and 2) a second active agent or active ingredient. Examples of immunomodulatory compounds of the invention are disclosed herein (see, e.g., section 4.1); and examples of the second active agents are also disclosed herein (see, e.g., section 4.2).

Administration of the immunomodulatory compounds and the second active agents to a patient can occur simultaneously or sequentially by the same or different routes of administration. The suitability of a particular route of administration employed for a particular active agent will depend on the active agent itself (e.g., whether it can be administered orally without decomposing prior to entering the blood stream) and the disease being treated. A preferred route of administration for an immunomodulatory compound is oral. Preferred routes of administration for the second active agents or ingredients of the invention are known to those of ordinary skill in the art. See, e.g., Physicians' Desk Reference, 1755-1760 (56th ed., 2002).

In one embodiment, the second active agent is administered intravenously or subcutaneously and once or twice daily in an amount of from about 1 to about 1000 mg, from about 5 to about 500 mg, from about 10 to about 350 mg, or from about 50 to about 200 mg. The specific amount of the second active agent will depend on the specific agent used, the type of MDS being treated or managed, the severity and stage of MDS, and the amount(s) of immunomodulatory compounds of the invention and any optional additional active agents concurrently administered to the patient. In a particular embodiment, the second active agent is GM-CSF, G-CSF, EPO, transretinoic acid, dexamethasone, topotecan, pentoxifylline, ciprofloxacin, dexamethasone, IL2, IL8, IL18, Ara-C, vinorelbine, or a combination thereof. GM-CSF is administered in an amount of from about 60 to about 500 mcg/m^2 intravenously over 2 hours, or from about 5 to about 12 mcg/m^2/day subcutaneously. G-CSF is administered subcutaneously in an amount of about 1 mcg/kg/day initially and can be adjusted depending on rise of total granulocyte counts. The maintenance dose is 300 (in smaller patients) or 480 mcg subcutaneously. EPO is administered subcutaneously in an amount of 10,000 Unit 3 times per week.

4.3.2 Use With Transplantation Therapy

In still another embodiment, this invention encompasses a method of treating, preventing and/or managing MDS, which comprises administering the immunomodulatory
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compound of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, in conjunction with transplantation therapy. As discussed elsewhere herein, the treatment of MDS is based on the stages and mechanism of the disease. As inevitable leukemic transformation develops in certain stages of MDS, transplantation of peripheral blood stem cells, hematopoietic stem cell preparation or bone marrow may be necessary. The combined use of the immunomodulatory compound of the invention and transplantation therapy provides a unique and unexpected synergism. In particular, an immunomodulatory compound of the invention exhibits immunomodulatory activity that may provide additive or synergistic effects when given concurrently with transplantation therapy in patients with MDS. An immunomodulatory compound of the invention can work in combination with transplantation therapy reducing complications associated with the invasive procedure of transplantation and risk of related Graft Versus Host Disease (GVHD). This invention encompasses a method of treating, preventing and/or managing MDS which comprises administering to a patient (e.g., a human) an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, before, during, or after the transplantation of umbilical cord blood, placental blood, peripheral blood stem cell, hematopoietic stem cell preparation or bone marrow. Examples of stem cells suitable for use in the methods of the invention are disclosed in U.S. provisional patent application no. 60/372,348, filed April 12, 2002 by R. Hariri et al., now US Patent Application No. 10/511355, having publication No. 20050118715.

4.3.3. Cycling Therapy

In certain embodiments, the prophylactic or therapeutic agents of the invention are cyclically administered to a patient. Cycling therapy involves the administration of a first agent for a period of time, followed by the administration of the agent and/or the second agent for a period of time and repeating this sequential administration. Cycling therapy can reduce the development of resistance to one or more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improves the efficacy of the treatment.

In a particular embodiment, prophylactic or therapeutic agents are administered in a cycle of about 16 weeks, about once or twice every day. One cycle can comprise the administration of a therapeutic or prophylactic agent and at least one (1) or three (3) weeks of rest. The number of cycles administered is from about 1 to about 12 cycles, more typically from about 2 to about 10 cycles, and more typically from about 2 to about 8 cycles.
4.4. **PHARMACEUTICAL COMPOSITIONS AND SINGLE UNIT DOSAGE FORMS**

Pharmaceutical compositions can be used in the preparation of individual, single unit dosage forms. Pharmaceutical compositions and dosage forms of the invention comprise an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof. Pharmaceutical compositions and dosage forms of the invention can further comprise one or more excipients.

Pharmaceutical compositions and dosage forms of the invention can also comprise one or more additional active ingredients. Consequently, pharmaceutical compositions and dosage forms of the invention comprise the active ingredients disclosed herein (e.g., an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, and a second active ingredient). Examples of optional additional active ingredients are disclosed herein (see, e.g., section 4.2).

Single unit dosage forms of the invention are suitable for oral, mucosal (e.g., nasal, sublingual, vaginal, buccal, or rectal), or parenteral (e.g., subcutaneous, intravenous, bolus injection, intramuscular, or intraarterial), transdermal or transcutaneous administration to a patient. Examples of dosage forms include, but are not limited to: tablets; caplets; capsules, such as soft elastic gelatin capsules; cachets; troches; lozenges; dispersions; suppositories; powders; aerosols (e.g., nasal sprays or inhalers); gels; liquid dosage forms suitable for oral or mucosal administration to a patient, including suspensions (e.g., aqueous or non-aqueous liquid suspensions, oil-in-water emulsions, or a water-in-oil liquid emulsions), solutions, and elixirs; liquid dosage forms suitable for parenteral administration to a patient; and sterile solids (e.g., crystalline or amorphous solids) that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a patient.

The composition, shape, and type of dosage forms of the invention will typically vary depending on their use. For example, a dosage form used in the acute treatment of a disease may contain larger amounts of one or more of the active ingredients it comprises than a dosage form used in the chronic treatment of the same disease. Similarly, a parenteral dosage form may contain smaller amounts of one or more of the active ingredients it comprises than an oral dosage form used to treat the same disease. These and other ways in which specific dosage forms encompassed by this invention will vary from one another will be readily apparent to those skilled in the art. See, e.g., Remington's *Pharmaceutical Sciences*, 18th ed., Mack Publishing, Easton PA (1990).
Typical pharmaceutical compositions and dosage forms comprise one or more excipients. Suitable excipients are well known to those skilled in the art of pharmacy, and non-limiting examples of suitable excipients are provided herein. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors well known in the art including, but not limited to, the way in which the dosage form will be administered to a patient. For example, oral dosage forms such as tablets may contain excipients not suited for use in parenteral dosage forms. The suitability of a particular excipient may also depend on the specific active ingredients in the dosage form. For example, the decomposition of some active ingredients may be accelerated by some excipients such as lactose, or when exposed to water. Active ingredients that comprise primary or secondary amines are particularly susceptible to such accelerated decomposition. Consequently, this invention encompasses pharmaceutical compositions and dosage forms that contain little, if any, lactose other mono- or disaccharides. As used herein, the term “lactose-free” means that the amount of lactose present, if any, is insufficient to substantially increase the degradation rate of an active ingredient.

Lactose-free compositions of the invention can comprise excipients that are well known in the art and are listed, for example, in the U.S. Pharmacopeia (USP) 25-NF20 (2002). In general, lactose-free compositions comprise active ingredients, a binder/filler, and a lubricant in pharmaceutically compatible and pharmaceutically acceptable amounts. Preferred lactose-free dosage forms comprise active ingredients, microcrystalline cellulose, pre-gelatinized starch, and magnesium stearate.

This invention further encompasses anhydrous pharmaceutical compositions and dosage forms comprising active ingredients, since water can facilitate the degradation of some compounds. For example, the addition of water (e.g., 5%) is widely accepted in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. See, e.g., Jens T. Carstensen, Drug Stability: Principles & Practice, 2d. Ed., Marcel Dekker, NY, NY, 1995, pp. 379-80. In effect, water and heat accelerate the decomposition of some compounds.

Thus, the effect of water on a formulation can be of great significance since moisture and/or humidity are commonly encountered during manufacture, handling, packaging, storage, shipment, and use of formulations.

Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms that comprise lactose
and at least one active ingredient that comprises a primary or secondary amine are preferably anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected.

An anhydrous pharmaceutical composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are preferably packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (e.g., vials), blister packs, and strip packs.

The invention further encompasses pharmaceutical compositions and dosage forms that comprise one or more compounds that reduce the rate by which an active ingredient will decompose. Such compounds, which are referred to herein as “stabilizers,” include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers.

Like the amounts and types of excipients, the amounts and specific types of active ingredients in a dosage form may differ depending on factors such as, but not limited to, the route by which it is to be administered to patients. However, typical dosage forms of the invention comprise an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof in an amount of from about 0.10 to about 150 mg. Typical dosage forms comprise an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof in an amount of about 0.1, 1, 2, 5, 7.5, 10, 12.5, 15, 17.5, 20, 25, 50, 100, 150 or 200 mg. In a particular embodiment, a preferred dosage form comprises 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione (Actimid™) in an amount of about 1, 2, 5, 10, 25 or 50mg. In a specific embodiment, a preferred dosage form comprises 3-(4-amino-1-oxo-1,3-dihydro-isindol-2-yl)-piperidine-2,6-dione (Revimid™) in an amount of about 5, 10, 25 or 50mg. Typical dosage forms comprise the second active ingredient in an amount of 1 to about 1000 mg, from about 5 to about 500 mg, from about 10 to about 350 mg, or from about 50 to about 200 mg. Of course, the specific amount of the second active ingredient will depend on the specific agent used, the type of MDS being treated or managed, and the amount(s) of immunomodulatory compounds of the invention, and any optional additional active agents concurrently administered to the patient.
4.4.1 ORAL DOSAGE FORMS

Pharmaceutical compositions of the invention that are suitable for oral administration can be presented as discrete dosage forms, such as, but are not limited to, tablets (e.g., chewable tablets), caplets, capsules, and liquids (e.g., flavored syrups). Such dosage forms contain predetermined amounts of active ingredients, and may be prepared by methods of pharmacy well known to those skilled in the art. See generally, Remington’s Pharmaceutical Sciences, 18th ed., Mack Publishing, Easton PA (1990).

Typical oral dosage forms of the invention are prepared by combining the active ingredients in an intimate admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form of preparation desired for administration. For example, excipients suitable for use in oral liquid or aerosol dosage forms include, but are not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents. Examples of excipients suitable for use in solid oral dosage forms (e.g., powders, tablets, capsules, and caplets) include, but are not limited to, starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid excipients are employed. If desired, tablets can be coated by standard aqueous or nonaqueous techniques. Such dosage forms can be prepared by any of the methods of pharmacy. In general, pharmaceutical compositions and dosage forms are prepared by uniformly and intimately admixing the active ingredients with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary.

For example, a tablet can be prepared by compression or molding. Compressed tablets can be prepared by compressing in a suitable machine the active ingredients in a free-flowing form such as powder or granules, optionally mixed with an excipient. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

Examples of excipients that can be used in oral dosage forms of the invention include, but are not limited to, binders, fillers, disintegrants, and lubricants. Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (e.g., ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl...
cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, (e.g., Nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof.

Suitable forms of microcrystalline cellulose include, but are not limited to, the materials sold as AVICEL-PH-101, AVICEL-PH-103 AVICEL RC-581, AVICEL-PH-105 (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, PA), and mixtures thereof. An specific binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose sold as AVICEL RC-581. Suitable anhydrous or low moisture excipients or additives include AVICEL-PH-103™ and Starch 1500 LM.

Examples of fillers suitable for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (e.g., granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The binder or filler in pharmaceutical compositions of the invention is typically present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form.

Disintegrants are used in the compositions of the invention to provide tablets that disintegrate when exposed to an aqueous environment. Tablets that contain too much disintegrant may disintegrate in storage, while those that contain too little may not disintegrate at a desired rate or under the desired conditions. Thus, a sufficient amount of disintegrant that is neither too much nor too little to detrimentally alter the release of the active ingredients should be used to form solid oral dosage forms of the invention. The amount of disintegrant used varies based upon the type of formulation, and is readily discernible to those of ordinary skill in the art. Typical pharmaceutical compositions comprise from about 0.5 to about 15 weight percent of disintegrant, preferably from about 1 to about 5 weight percent of disintegrant.

Disintegrants that can be used in pharmaceutical compositions and dosage forms of the invention include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums, and mixtures thereof.

Lubricants that can be used in pharmaceutical compositions and dosage forms of the invention include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, and mixtures thereof. Additional lubricants include, for example, a
syloid silica gel (ACROSIL200, manufactured by W.R. Grace Co. of Baltimore, MD), a
coagulated aerosol of synthetic silica (marketed by Degussa Co. of Plano, TX), CAB-O-SIL* (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, MA), and mixtures
thereof. If used at all, lubricants are typically used in an amount of less than about 1 weight
percent of the pharmaceutical compositions or dosage forms into which they are
incorporated.

A preferred solid oral dosage form of the invention comprises an
immunomodulatory compound of the invention, anhydrous lactose, microcrystalline
cellulose, polyvinylpyrrolidone, stearic acid, colloidal anhydrous silica, and gelatin.

4.4.2 DELAYED RELEASE DOSAGE FORMS

Active ingredients of the invention can be administered by controlled release means
or by delivery devices that are well known to those of ordinary skill in the art. Examples
include, but are not limited to, those described in U.S. Patent Nos.: 3,845,770; 3,916,899;
3,536,809; 3,598,123; and 4,008,719, 5,674,533, 5,059,595, 5,591,767, 5,120,548,
5,073,543, 5,639,476, 5,354,556, and 5,733,566.

Such dosage forms can be used to provide slow or controlled-release of one or
more active ingredients using, for example, hydropropylmethyl cellulose, other polymer
matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles,
liposomas, microspheres, or a combination thereof to provide the desired release profile in
varying proportions. Suitable controlled-release formulations known to those of ordinary
skill in the art, including those described herein, can be readily selected for use with the
active ingredients of the invention. The invention thus encompasses single unit dosage
forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps,
and caplets that are adapted for controlled-release.

All controlled-release pharmaceutical products have a common goal of improving
drug therapy over that achieved by their non-controlled counterparts. Ideally, the use of an
optimally designed controlled-release preparation in medical treatment is characterized by a
minimum of drug substance being employed to cure or control the condition in a minimum
amount of time. Advantages of controlled-release formulations include extended activity of
the drug, reduced dosage frequency, and increased patient compliance. In addition,
controlled-release formulations can be used to affect the time of onset of action or other
characteristics, such as blood levels of the drug, and can thus affect the occurrence of side
(e.g., adverse) effects.

*Trade-mark
Most controlled-release formulations are designed to initially release an amount of
drug (active ingredient) that promptly produces the desired therapeutic effect, and gradually
and continually release of other amounts of drug to maintain this level of therapeutic or
prophylactic effect over an extended period of time. In order to maintain this constant level
of drug in the body, the drug must be released from the dosage form at a rate that will
replace the amount of drug being metabolized and excreted from the body. Controlled-
release of an active ingredient can be stimulated by various conditions including, but not
limited to, pH, temperature, enzymes, water, or other physiological conditions or
compounds.

4.4.3 PARENTERAL DOSAGE FORMS

Parenteral dosage forms can be administered to patients by various routes including,
but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and
intraarterial. Because their administration typically bypasses patients’ natural defenses
against contaminants, parenteral dosage forms are preferably sterile or capable of being
sterilized prior to administration to a patient. Examples of parenteral dosage forms include,
but are not limited to, solutions ready for injection, dry products ready to be dissolved or
suspended in a pharmaceutically acceptable vehicle for injection, suspensions ready for
injection, and emulsions.

Suitable vehicles that can be used to provide parenteral dosage forms of the
invention are well known to those skilled in the art. Examples include, but are not limited
to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride
Injection, Ringer’s Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection,
and Lactated Ringer’s Injection; water-miscible vehicles such as, but not limited to, ethyl
alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as,
but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl
myristate, and benzyl benzoate.

Compounds that increase the solubility of one or more of the active ingredients
disclosed herein can also be incorporated into the parenteral dosage forms of the invention.
For example, cyclodextrin and its derivatives can be used to increase the solubility of an
immunomodulatory compound of the invention, and its derivatives. See, e.g., U.S. Patent
No. 5,134,127, which is incorporated herein by reference.

4.4.4 TOPICAL AND MUCOSAL DOSAGE FORMS

Topical and mucosal dosage forms of the invention include, but are not limited to,
sprays, aerosols, solutions, emulsions, suspensions, or other forms known to one of skill in
the art. See, e.g., Remington’s Pharmaceutical Sciences, 16th and 18th eds., Mack Publishing, Easton PA (1980 & 1990); and Introduction to Pharmaceutical Dosage Forms, 4th ed., Lea & Febiger, Philadelphia (1985). Dosage forms suitable for treating mucosal tissues within the oral cavity can be formulated as mouthwashes or as oral gels.

Suitable excipients (e.g., carriers and diluents) and other materials that can be used to provide topical and mucosal dosage forms encompassed by this invention are well known to those skilled in the pharmaceutical arts, and depend on the particular tissue to which a given pharmaceutical composition or dosage form will be applied. With that fact in mind, typical excipients include, but are not limited to, water, acetone, ethanol, ethylene glycol, propylene glycol, butane-1,3-diol, isopropyl myristate, isopropyl palmitate, mineral oil, and mixtures thereof to form solutions, emulsions or gels, which are non-toxic and pharmaceutically acceptable. Moisturizers or humectants can also be added to pharmaceutical compositions and dosage forms if desired. Examples of such additional ingredients are well known in the art. See, e.g., Remington’s Pharmaceutical Sciences, 16th and 18th eds., Mack Publishing, Easton PA (1980 & 1990).

The pH of a pharmaceutical composition or dosage form may also be adjusted to improve delivery of one or more active ingredients. Similarly, the polarity of a solvent carrier, its ionic strength, or tonicity can be adjusted to improve delivery. Compounds such as stearates can also be added to pharmaceutical compositions or dosage forms to advantageously alter the hydrophilicity or lipophilicity of one or more active ingredients so as to improve delivery. In this regard, stearates can serve as a lipid vehicle for the formulation, as an emulsifying agent or surfactant, and as a delivery-enhancing or penetration-enhancing agent. Different salts, hydrates or solvates of the active ingredients can be used to further adjust the properties of the resulting composition.

4.4.5 KITS

Typically, active ingredients of the invention are preferably not administered to a patient at the same time or by the same route of administration. This invention therefore encompasses kits which, when used by the medical practitioner, can simplify the administration of appropriate amounts of active ingredients to a patient.

A typical kit of the invention comprises a dosage form of an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt salt, solvate, hydrate, stereoisomer, prodrug, or clathrate thereof. Kits encompassed by this invention can further comprise additional active ingredients such as G-CSF, GM-CSF, EPO, topotecan, pentoxifylline, ciprofloxacin, dexamethasone, IL2, IL8, IL18, Ara-C, vinorelbine,
isotretinoin, 13-cis-retinoic acid, or a pharmacologically active mutant or derivative thereof, or a combination thereof. Examples of the additional active ingredients include, but are not limited to, those disclosed herein (see, e.g., section 4.2).

Kits of the invention can further comprise devices that are used to administer the active ingredients. Examples of such devices include, but are not limited to, syringes, drip bags, patches, and inhalers.

Kits of the invention can further comprise cells or blood for transplantation as well as pharmaceutically acceptable vehicles that can be used to administer one or more active ingredients. For example, if an active ingredient is provided in a solid form that must be reconstituted for parenteral administration, the kit can comprise a sealed container of a suitable vehicle in which the active ingredient can be dissolved to form a particulate-free sterile solution that is suitable for parenteral administration. Examples of pharmaceutically acceptable vehicles include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer’s Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer’s Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

5. EXAMPLES
The following studies are intended to further illustrate the invention without limiting its scope.

Excessive production of the growth inhibitory cytokine TNF-α is demonstrated in bone marrow plasma of patients with MDS, implicating TNF-α as a critical negative regulator of erythroid progenitor survival in the disorder. As a result, a study with an immunomodulatory compound of the invention was conducted.

5.1. PHARMACOLOGY AND TOXICOLOGY STUDIES
A series of non-clinical pharmacology and toxicology studies have been performed to support the clinical evaluation of an immunomodulatory compound of the invention in human subjects. These studies were performed in accordance with internationally recognized guidelines for study design and in compliance with the requirements of Good Laboratory Practice (GLP), unless otherwise noted.

The pharmacological properties of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, including activity comparisons with thalidomide, have been
characterized in *in vitro* studies. Studies examined the effects of 3-(4-amino-1-oxo-1,3-dihydro-isooindol-2-yl)piperidine-2,6-dione or thalidomide on the production of various cytokines. In all studies, 3-(4-amino-1-oxo-1,3-dihydro-isooindol-2-yl)piperidine-2,6-dione was at least 50 times more potent than thalidomide. In addition, a safety pharmacology study of 3-(4-amino-1-oxo-1,3-dihydro-isooindol-2-yl)piperidine-2,6-dione has been conducted in dogs and the effects of 3-(4-amino-1-oxo-1,3-dihydro-isooindol-2-yl)piperidine-2,6-dione on ECG parameters were examined further as part of three repeat-dose toxicity studies in primates. The results of these studies are described below.

5.2. MODULATION OF CYTOKINE PRODUCTION

Inhibition of TNF-α production following LPS-stimulation of human PBMC and human whole blood by 3-(4-amino-1-oxo-1,3-dihydro-isooindol-2-yl)piperidine-2,6-dione or thalidomide was investigated *in vitro* (Muller et al., *Bioorg. Med. Chem. Lett.* 9:1625-1630, 1999). The IC₅₀'s of 3-(4-amino-1-oxo-1,3-dihydro-isooindol-2-yl)piperidine-2,6-dione for inhibiting production of TNF-α following LPS-stimulation of PBMC and human whole blood were ~100 nM (25.9 ng/mL) and ~480 nM (103.6 ng/mL), respectively. Thalidomide, in contrast, had an IC₅₀ of ~194 μM (50.2 μg/mL) for inhibiting production of TNF-α following LPS-stimulation of PBMC.

*n vitro* studies suggest a pharmacological activity profile for 3-(4-amino-1-oxo-1,3-dihydro-isooindol-2-yl)piperidine-2,6-dione that is similar to, but 50 to 2000 times more potent than, thalidomide. The pharmacological effects of 3-(4-amino-1-oxo-1,3-dihydro-isooindol-2-yl)piperidine-2,6-dione derive from its action as an inhibitor of cellular response to receptor-initiated trophic signals (*e.g.*, IGF-1, VEGF, cyclooxygenase-2), and other activities. As a result, 3-(4-amino-1-oxo-1,3-dihydro-isooindol-2-yl)piperidine-2,6-dione suppresses the generation of inflammatory cytokines, down-regulates adhesion molecules and apoptosis inhibitory proteins (*e.g.*, cFLIP, cIAP), promotes sensitivity to death-receptor initiated programmed cell death, and suppresses angiogenic response. The studies show that 3-(4-amino-1-oxo-1,3-dihydro-isooindol-2-yl)piperidine-2,6-dione abrogates mitogenic response to VEGF in AML cells by extinguishing ligant-induced Akt-phosphorylation, and selectively suppresses MDS vs normal bone marrow progenitor formation in pre-clinical models.

5.3. CLINICAL STUDIES IN MDS PATIENTS

Protocol
An immunomodulatory compound of the invention, such as 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione and 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, is administered in an amount of from about 0.1 to about 25 mg per day to patients with MDS for 16 weeks, who are subsequently evaluated for a hematological response. Response rates are assessed in cohorts stratified by the likelihood of an MDS subtype to transform to leukemia according to the International Prognostic Scoring System (IPSS)-defined risk groups (i.e., IPSS Low and Intermediate I; versus IPSS Intermediate II and High).

For example, fifteen patients are enrolled in the first cohort and receive treatment with 25 mg per day of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione. The number of patients who subsequently experience an erythroid response (major or minor response) by week 16 is evaluated. If no responses are observed, the study is terminated due to lack of efficacy. If, however, 4 or more patients respond, the study is terminated due to promising clinical activity. In the intermediate case (e.g., 1, 2 or 3 patients respond), a second cohort of 10 patients is enrolled. If after the completion of treatment by the second cohort, 4 or more patients respond among the 25 patients treated, it is concluded that the 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione shows promising clinical activity.

**Clinical Study**

Clinical studies were performed for the remitting potential of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione in MDS patients with red blood cell transfusion-dependence (>4 units/8 weeks) or symptomatic anemia (Hgb<10 g/dl). Patients received continuous treatment with 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione at a oral dose of 25 mg daily. Responses were assessed according to IWG criteria after 16 weeks of treatments. Among 15 patients receiving the treatments, 11 patients were evaluable for toxicity, nine patients were evaluable for response (>8 wks therapy), and three patients discontinued the therapy prematurely (<2 weeks) due to cholecystitis, autoimmune hemolytic anemia, or patient refusal. Median age of the patients was 78 years ranging from 51 to 82 years. FAB types of the MDS patients include RA [4 patients], RARS [4 patients], RAEB [6 patients], and RAEB-T [1 patient] with corresponding IPSS categories of Low/Int-1 in 11 patients and Int-2/High in four patients. Myelosuppression, which was characterized by higher than grade 3 common toxicity criteria or 50% decrease in leukocyte and platelet counts [9 patients], and grade 3 fatigue [1 patient], necessitated dose reduction to 10 mg in the initial ten patients. All
subsequent patients initiated oral administrations with 10 mg daily. Grade 1,2 drug-related adverse effects were limited to the 25 mg dose and included pruritus or itchy scalp [6 patients] and myalgia [1 patient]. Six (66%) of nine evaluable patients experienced hematologic benefit (dual lineage, 1 patient), including 6/7 (86%) patients with IPSS Low/Int-1. Hematologic responses included RBC transfusion-independence [4 patients], decrease in RBC transfusions of more than 50% [1 patient], increase in Hgb of more than 1.5 g [1 patient], and one minor platelet response (increase of more than 30,000/µL).

Among five patients evaluable for cytogenetic response, three patients achieved either a complete or partial (decrease in abnormal metaphases of more than 50%) remission. Responses were associated with normalization of blast percentage [1 patient], reduced grade of BM cytologic dysplasia, and 50% to more than 40 times improvement in BM multipotent progenitor (CFU-GEMM) and erythroid burst (BFU-E) formation. Correlation with changes in apoptotic index, angiogenic features (cellular/plasma VEGF, microvessel density), cytokine generation, and proliferative fraction (Ki67) are in progress. The results of this study indicate that 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione has remarkable erythropoietic and cytogenetic remitting activity in patients with low/intermediate-1 risk MDS. Clinical benefit appears greatest in patients with low/intermediate-1 disease or the 5q-syndrome, associated with resolution of cytology dysplasia. The increase in apoptotic index, restoration of CFC, and suppression of karyotypic abnormalities suggest that the compound accelerates extinction of myelodysplastic clones. Based upon these data, the study has been expanded to treat additional subjects. Treatment with 10 mg as a continuous oral daily dose is well-tolerated with minimal myelosuppression.

**Expanded Study**

The clinical study was expanded with additional 16 MDS patients for at least eight weeks. According to the IPSS, 13 of these patients were categorized as low- or intermediate-1-risk patients and three patients were grouped as intermediate-2- or high-risk patients. According to the FAB classification, there were 11 patients with refractory anemia (RA) or RA with ringed sideroblasts (RARS), and five patients with RA with excess blasts (RAEB), RAEB in transformation (RAEB-T). The starting dose of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione was 25 mg daily for the first 13 patients and 10 mg daily for the remaining three patients. All patients receiving the starting dose of 25 mg required dose reduction by the completion of eight weeks therapy. Among these 16 patients who completed at least 8 weeks of monitoring, nine patients
achieved an erythroid response as assessed by the International MDS Working Group Criteria. The erythroid responses consisted of transfusion independence in seven previously transfusion-dependent patients, a >2 g/dL rise in blood hemoglobin concentration in one patient in with transfusion-independent anemia, and a >50 % decrease in RBC transfusion requirement in one transfusion-dependent patient. Therefore, a major erythroid response developed in eight of 16 patients and a minor erythroid response was observed in one patient. All of nine patients who showed erythroid response were low- or intermediate-1-risk patients. One patient also had a minor platelet response. In addition, complete cytogenetic responses developed in five in eight patients with abnormal karyotypes at baseline. These five patients with complete cytogenetic responses all had the Del5q31-33 abnormality, which has been discovered to be a good prognostic factor for MDS. Indeed, all five patients who enrolled in this study with 5q-syndrome achieved a complete cytogenetic response and a major erythroid response. The study also indicated an association of this therapy with an increased apoptotic index for myelodysplastic progenitors and recovery of normal hematopoietic progenitor cells.

5.4. CYCLING THERAPY IN MDS PATIENTS

As mentioned above, immunomodulatory compounds of the invention can be cyclically administered to patients with MDS. Cycling therapy involves the administration of a first agent for a period of time, followed by the administration of the agent and/or the second agent for a period of time and repeating this sequential administration. Cycling therapy can reduce the development of resistance to one or more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improves the efficacy of the treatment.

Example 1

In a specific embodiment, prophylactic or therapeutic agents are administered in a cycle of about 16 weeks, about once or twice every day. One cycle can comprise the administration of a therapeutic on prophylactic agent and at least one (1), two (2), or three (3) weeks of rest. The number of cycles administered is from about 1 to about 12 cycles, more typically from about 2 to about 10 cycles, and more typically from about 2 to about 8 cycles.

Example 2

The objectives of the study are to evaluate the efficacy and safety of oral administration of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione in
patients with MDS. Patients receive the compound in an amount of 10 mg/d or 15 mg/d for 21 days every 28 days in 4-week cycles for 16 weeks (4 cycles) or 24 weeks (6 cycles). The subject population comprises patients with low- or intermediate-1-risk MDS (International Prognostic Scoring System) with red blood cell transfusion-dependent anemia who have received at least two units of RBCs within 8 week of baseline (first day of study treatment). In addition to hematological laboratory monitoring, bone marrow aspirates/biopsies with cytogenetic analyses are obtained at baseline, after the completion of 3 cycles and after the completion of 6 cycles. The bone marrow, safety and efficacy data are reviewed to assess benefit-to-risk considerations throughout the study. The study reviews red blood cell transfusion independence and major erythroid response according to the International MDS Working Group Criteria. Further, the study observes red blood cell transfusion independence in the subgroup of patients with the 5q deletion cytogenetic abnormality; platelet, neutrophil, bone marrow and cytogenetic responses; and minor erythroid response of ≥50 % but <100 % reduction in red blood cell transfusion requirement over an 8 week period. The study further monitors adverse events, hematological tests, serum chemistries, TSH, urinalysis, urine or serum pregnancy tests, vital signs, ECG and physical examinations.

Example 3

The objectives of the study are to compare the efficacy and safety of oral administration of 3-(4-amino-1-oxo-1,3-dihydro-isoiindol-2-yl)-piperidine-2,6-dione to that of placebo plus standard care in patients with MDS. Patients receive the therapy in 4-week cycles for 16 weeks (4 cycles) or 24 weeks (6 cycles). The subject population comprise patients with low- or interemmediate-1-risk MDS (International Prognostic Scoring System) with red blood cell transfusion-dependent anemia who have received at least two units of RBCs within 8 week of baseline (first day of study treatment). The study visits to assess safety and efficacy occur every 4 weeks and hematologic laboratory monitoring is performed every 2 weeks. Bone marrow aspirates/biopsies with cytogenetic analyses are obtained at baseline after the completion of 3 cycles and after the completion of 6 cycles. Bone marrow findings, safety and efficacy data are reviewed to assess benefit-to-risk considerations throughout the study. An extension study of continued treatments with the administration of the compound is available for patients who derive clinical benefit from 6 cycles of the therapy and to provide an opportunity for subjects who were randomized to placebo to cross over to the therapy.
Embodiments of the invention described herein are only a sampling of the scope of the invention. The full scope of the invention is better understood with reference to the attached claims.
CLAiMS:

1. Use in the preparation of a medicament for treating a myelodysplastic syndrome in a patient of a compound of formula (I):

   \[ \text{(I)} \]

   or a pharmaceutically acceptable salt or stereoisomer thereof, wherein one of X and Y is C=O, the other of X and Y is CH₂, and R² is hydrogen or \((C_1-C_9)\) alkyl.

2. Use for treating a myelodysplastic syndrome in a patient of a compound of formula (I):

   \[ \text{(I)} \]

   or a pharmaceutically acceptable salt or stereoisomer thereof, wherein one of X and Y is C=O, the other of X and Y is CH₂, and R² is hydrogen or \((C_1-C_9)\) alkyl.

3. The use of claim 1 or 2, wherein R² is hydrogen.

4. The use of claim 1 or 2, wherein the compound is 3-\((4\text{-amino-1-oxo-1,3\text{-dihydro-isoindol-2-yl})-piperidine-2,6-dione, or a pharmaceutically acceptable salt or stereoisomer thereof.} \]
5. The use of any one of claims 1 to 4, which further comprises use of a therapeutically or prophylactically effective amount of a second active agent.

6. The use of claim 5, wherein the second active agent is capable of improving blood cell production.

7. The use of claim 5, wherein the second active agent is cytokine, hematopoietic growth factor, an anti-cancer agent, an antibiotic, a proteasome inhibitor, or an immunosuppressive agent.

8. The use of claim 7, wherein the second active agent is etanercept, imatinib, an anti-TNF-α antibody or a pharmacologically active mutant thereof, infliximab, G-CSF, GM-CSF, EPO, topotecan, pentoxifylline, ciprofloxacin, irinotecan, vinblastine, dexamethasone, IL2, IL8, IL18, Ara-C, vinorelbine, isotretinoin, 13-cis-retinoic acid, arsenic trioxide, or a pharmacologically active derivative of any one of the foregoing.

9. The use of any one of claims 1 to 8, wherein the myelodysplastic syndrome is refractory anemia.

10. The use of any one of claims 1 to 8, wherein the myelodysplastic syndrome is refractory anemia with ringed sideroblasts.

11. The use of any one of claims 1 to 8, wherein the myelodysplastic syndrome is refractory anemia with excess blasts.

12. The use of any one of claims 1 to 8, wherein the myelodysplastic syndrome is refractory anemia with excess blasts in transformation.
13. The use of any one of claims 1 to 8, wherein the myelodysplastic syndrome is chronic myelomonocytic leukemia.

14. The use of any one of claims 1 to 13, wherein the compound or pharmaceutically acceptable salt or stereoisomer thereof is formulated for administration to said patient before, during or after transplanting umbilical cord blood, placental blood, peripheral blood stem cell, hematopoietic stem cell preparation or bone marrow in said patient.

15. The use of any one of claims 1 to 14, wherein the compound is in the form of a free base.

16. The use of any one of claims 1 to 14, wherein the compound is in the form of a pharmaceutically acceptable salt.

17. The use of any one of claims 1 to 16, wherein the compound is a pharmaceutically acceptable stereoisomer.

18. The use of claim 17, wherein the stereoisomer is an enantiomerically pure R isomer.

19. The use of claim 17, wherein the stereoisomer is an enantiomerically pure S isomer.

20. Use in the preparation of a medicament for treating a myelodysplastic syndrome in a patient of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione having the formula:

![Chemical Structure]

or a pharmaceutically acceptable salt or stereoisomer thereof.
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21. Use for treating a myelodysplastic syndrome in a patient of 3-(4-amino-1-oxo-1,3-dihydro-isooindol-2-yl)-piperidine-2,6-dione having the formula:

![Chemical Structure]

5 or a pharmaceutically acceptable salt or stereoisomer thereof.

22. The use of claim 20 or 21, wherein the compound is formulated for administration in an amount of from about 5 mg to about 50 mg per day.

23. The use of any one of claims 20 to 22, which further comprises use of a therapeutically effective amount of a second active agent.

24. The use of claim 23, wherein the second active agent is capable of improving blood cell production.

25. The use of claim 23, wherein the second active agent is a cytokine, hematopoietic growth factor, an anti-cancer agent, an antibiotic, a proteasome inhibitor, or an immunosuppressive agent.

26. The use of claim 25, wherein the second active agent is etanercept, imatinib, anti-TNF-α antibodies, infliximab, G-CSF, GM-CSF, EPO, topotecan, pentoxifylline, ciprofloxacin, irinotecan, vinblastine, dexamethasone, IL2, IL8, IL18, Ara-C, vinorelbine, isotretinoin, 13-cis-retinoic acid, or arsenic trioxide.

27. The use of any one of claims 20 to 26, wherein the myelodysplastic syndrome is refractory anemia.
28. The use of any one of claims 20 to 26, wherein the myelodysplastic syndrome is refractory anemia with ringed sideroblasts.

29. The use of any one of claims 20 to 26, wherein the myelodysplastic syndrome is refractory anemia with excess blasts.

30. The use of any one of claims 20 to 26, wherein the myelodysplastic syndrome is refractory anemia with excess blasts in transformation.

31. The use of any one of claims 20 to 26, wherein the myelodysplastic syndrome is chronic myelomonocytic leukemia.

32. The use of any one of claims 20 to 31, wherein the compound or pharmaceutically acceptable salt or stereoisomer thereof is formulated for administration to said patient before, during or after transplanting umbilical cord blood, placental blood, peripheral blood stem cell, hematopoietic stem cell preparation or bone marrow in said patient.

33. The use of claim 26, wherein the second active agent is dexamethasone.

34. The use of any one of claims 20 to 33, wherein the patient has not been previously treated for a myelodysplastic syndrome.

35. The use of any one of claims 20 to 33, wherein the patient has been previously treated for a myelodysplastic syndrome.

36. The use of any one of claims 20 to 35, wherein the compound or pharmaceutically acceptable salt or stereoisomer thereof is formulated for oral administration.
37. The use of claim 36, wherein the compound or pharmaceutically acceptable salt or stereoisomer thereof is formulated as a capsule or tablet.

38. The use of any one of claims 20 to 37, wherein the compound or pharmaceutically acceptable salt or stereoisomer thereof is formulated for cyclical administration.

39. The use of any one of claims 20 to 37, wherein the compound or pharmaceutically acceptable salt or stereoisomer thereof is formulated for administration once or twice every day for sixteen or twenty-four weeks.

40. The use of claim 38, wherein one cycle comprises the administration of the compound or pharmaceutically acceptable salt or stereoisomer thereof for three weeks and one week of rest.

41. The use of claim 38, wherein the number of cycles is from one to twelve cycles.

42. The use of claim 38, wherein 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione is formulated for administration in an amount of from about 5 to about 25 mg per day for 21 days every 28 days for sixteen or twenty-four weeks.

43. The use of any one of claims 20 to 37 and 39, wherein the compound or pharmaceutically acceptable salt or stereoisomer thereof is formulated for administration in an amount of from about 5 mg per day to about 25 mg per day.

44. The use of claim 43, wherein the compound or pharmaceutically acceptable salt or stereoisomer thereof is formulated for administration in an amount of 10 mg per day.
45. The use of claim 43, wherein the compound or pharmaceutically acceptable salt or stereoisomer thereof is formulated for administration in an amount of 15 mg per day.

46. The use of claim 43, wherein the compound or pharmaceutically acceptable salt or stereoisomer thereof is formulated for administration in an amount of 25 mg per day.

47. The use of any one of claims 20 to 37, wherein the compound or pharmaceutically acceptable salt or stereoisomer thereof is formulated for administration in an amount of from about 25 mg every other day to about 50 mg every other day.

48. The use of any one of claims 20 to 37, wherein the compound or pharmaceutically acceptable salt or stereoisomer thereof is formulated for administration once or twice every day for about 16 weeks.

49. The use of any one of claims 20 to 37, wherein the compound or pharmaceutically acceptable salt or stereoisomer thereof is formulated for administration once or twice every day in a cycle of about 16 weeks, wherein said cycle comprises at least one, two, or three weeks of rest.

50. The use of any one of claims 20 to 37, wherein the compound or pharmaceutically acceptable salt or stereoisomer thereof is formulated for administration in an amount of 10 mg per day or 15 mg per day for 21 days out of a block of 28 days.

51. The use of any one of claims 20 to 36, wherein the compound or pharmaceutically acceptable salt or stereoisomer thereof is formulated for administration orally in an amount of 5 mg as a capsule per day.
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52. The use of any one of claims 20 to 36, wherein the compound or pharmaceutically acceptable salt or stereoisomer thereof is formulated for administration orally in an amount of 10 mg as a capsule per day.

53. The use of any one of claims 20 to 36, wherein the compound or pharmaceutically acceptable salt or stereoisomer thereof is formulated for administration orally in an amount of 15 mg as a capsule per day.

54. The use of any one of claims 20 to 36, wherein the compound or pharmaceutically acceptable salt or stereoisomer thereof is in a form suitable for administration orally in an amount of 25 mg as a capsule per day.

55. The use of any one of claims 51 to 54, wherein the capsule further comprises lactose anhydrous, microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

56. The use of any one of claims 20 to 55, wherein the compound is 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione having the formula:

![Chemical Structure](image)

wherein the compound is in the form of a free base.

57. The use of any one of claims 20 to 55, wherein the compound is in the form of a pharmaceutically acceptable salt.

58. The use of any one of claims 20 to 57, wherein the compound is a pharmaceutically acceptable stereoisomer.
59. The use of claim 58, wherein the stereoisomer is an enantiomerically pure R isomer.

60. The use of claim 58, wherein the stereoisomer is an enantiomerically pure S isomer.

61. A pharmaceutical composition in dosage unit form for use in the treatment of a myelodysplastic syndrome in a patient, which comprises:

(a) an active agent which is a compound of formula (I):

(I)

or a pharmaceutically acceptable salt or stereoisomer thereof, wherein one of X and Y is C=O, the other of X and Y is CH₂, and R² is hydrogen or (C₁₋C₈) alkyl; and

(b) a pharmaceutically acceptable carrier, excipient or diluent.

62. A commercial package comprising as active agent a compound of formula (I):

(I)

or a pharmaceutically acceptable salt or stereoisomer thereof, wherein one of X and Y is C=O, the other of X and Y
is CH₂, and R² is hydrogen or (C₁-C₈) alkyl, together with instructions for the use thereof for treating myelodysplastic syndrome in a patient.

63. A pharmaceutical composition in dosage unit form for use in the treatment of a myelodysplastic syndrome in a patient, which comprises:

(a) an active agent which is 3-(4-amino-1-oxo-1,3-dihydro-isooindol-2-yl)-piperidine-2,6-dione having the formula:

![Chemical structure image]

or a pharmaceutically acceptable salt or stereoisomer thereof; and

(b) a pharmaceutically acceptable carrier or diluent.

64. The pharmaceutical composition of claim 61 or 63, which is in the form of an orally administrable capsule.

65. The pharmaceutical composition of claim 64, wherein said capsule comprises a dose of about 5 mg of said active agent.

66. The pharmaceutical composition of claim 64, wherein said capsule comprises a dose of about 10 mg of said active agent.

67. The pharmaceutical composition of claim 64, wherein said capsule comprises a dose of about 15 mg of said active agent.
68. The pharmaceutical composition of claim 64, wherein said capsule comprises a dose of 20 mg of said active agent.

69. The pharmaceutical composition of claim 64, wherein said capsule comprises a dose of about 25 mg of said active agent.

70. The pharmaceutical composition of any one of claims 64 to 69, wherein said capsule further comprises lactose anhydrous, microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

71. A commercial package comprising the pharmaceutical composition according to any one of claims 63 to 70, together with instructions for use for treating myelodysplastic syndrome in a patient.

72. Use in the preparation of a medicament for treating myelodysplastic syndrome in a patient of a compound of formula:

![Chemical Structure](image)

or a pharmaceutically acceptable salt or stereoisomer thereof.

73. Use in the preparation of a medicament for treating myelodysplastic syndrome in a patient of a compound of formula:
or a pharmaceutically acceptable salt or stereoisomer thereof.

74. The use of claim 73, wherein said compound or a pharmaceutically acceptable salt or stereoisomer thereof is formulated to be co-administered with a therapeutically effective amount of a second active agent.

75. The use of claim 74, wherein the second active agent is capable of improving blood cell production.

76. The use of claim 74, wherein the second active agent is a cytokine, hematopoietic growth factor, an anticancer agent, an antibiotic, a proteasome inhibitor, or an immunosuppressive agent.

77. The use of claim 76, wherein the second active agent is etanercept, imatinib, anti-TNF-α antibodies, infliximab, G-CSF, GM-CSF, EPO, topotecan, pentoxifylline, ciprofloxacin, irinotecan, vinblastine, dexamethasone, IL2, IL8, IL18, Ara-C, vinorelbine, isotretinoin, 13-cis-retinoic acid, or arsenic trioxide.

78. The use of claim 73, wherein the myelodysplastic syndrome is refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts,
refractory anemia with excess blasts in transformation, or chronic myelomonocytic leukemia.

79. The use of claim 73, wherein the compound or pharmaceutically acceptable salt or stereoisomer thereof is formulated for administration before, during or after transplanting umbilical cord blood, placental blood, peripheral blood stem cell, hematopoietic stem cell preparation or bone marrow in the patient.

80. The use of claim 77, wherein the second active agent is dexamethasone.

81. The use of claim 73, wherein the patient has not been previously treated for a myelodysplastic syndrome.

82. The use of claim 73, wherein the patient has been previously treated for a myelodysplastic syndrome.

83. The use of claim 73, wherein the compound or pharmaceutically acceptable salt or stereoisomer thereof is formulated for oral administration.

84. The use of claim 73, wherein the compound or pharmaceutically acceptable salt or stereoisomer thereof is formulated for administration in the form of a capsule or tablet.

85. The use of claim 73, wherein the compound or pharmaceutically acceptable salt or stereoisomer thereof is formulated for cyclical administration.

86. The use of claim 73, wherein the compound or pharmaceutically acceptable salt or stereoisomer thereof is formulated for administration once or twice every day for sixteen or twenty-four weeks.
87. The use of claim 85, wherein one cycle comprises the administration of the compound for three weeks and one week of rest.

88. The use of claim 85, wherein the number of cycles is from one to twelve cycles.

89. The use of claim 85, wherein the compound or pharmaceutically acceptable salt or stereoisomer thereof is formulated for administration in an amount of from about 5 to about 50 mg per day for 21 days every 28 days for sixteen or twenty-four weeks.

90. The use of claim 73, wherein the compound or pharmaceutically acceptable salt or stereoisomer thereof is formulated for administration in an amount of from about 5 mg per day to about 50 mg per day.

91. The use of claim 73, wherein the compound or pharmaceutically acceptable salt or stereoisomer thereof is formulated for administration in an amount of 5 mg per day.

92. The use of claim 73, wherein the compound or pharmaceutically acceptable salt or stereoisomer thereof is formulated for administration in an amount of 10 mg per day.

93. The use of claim 73, wherein the compound or pharmaceutically acceptable salt or stereoisomer thereof is formulated for administration in an amount of 20 mg per day.

94. The use of claim 73, wherein the compound or pharmaceutically acceptable salt or stereoisomer thereof is formulated for administration in an amount of 25 mg per day.

95. The use of claim 73, wherein the compound or pharmaceutically acceptable salt or stereoisomer
thereof is formulated for administration in an amount of 50 mg per day.

96. The use of claim 73, wherein the compound or pharmaceutically acceptable salt or stereoisomer thereof is formulated for administration in an amount of from about 25 mg every other day to about 50 mg every other day.

97. The use of claim 73, wherein the compound or pharmaceutically acceptable salt or stereoisomer thereof is formulated for administration once or twice every day for about 16 weeks.

98. The use of claim 73, wherein the compound or pharmaceutically acceptable salt or stereoisomer thereof is formulated for administration once or twice every day in a cycle of about 16 weeks, wherein said cycle comprises at least one (1), two (2), or three (3) weeks of rest.

99. The use of claim 73, wherein the compound or pharmaceutically acceptable salt or stereoisomer thereof is formulated for administration in an amount of 20 mg per day or 50 mg per day for 21 days out of a block of 28 days.

100. The use of claim 73, wherein the compound or pharmaceutically acceptable salt or stereoisomer thereof is formulated for oral administration in an amount of 5 mg as a capsule per day.

101. The use of claim 73, wherein the compound or pharmaceutically acceptable salt or stereoisomer thereof is formulated for oral administration in an amount of 25 mg as a capsule per day.

102. The use of any one of claims 73 to 101, wherein the compound is N-[(2-(2,6-dioxo(3-piperidyl))-1,3-
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dioxoisooindolin-4-yl)methyl)cyclopropyl-carboxamide having the formula:

, as a free base.

103. The use of any one of claims 73 to 101, wherein the compound is a pharmaceutically acceptable salt.

104. The use of any one of claims 73 to 101, wherein the compound is a pharmaceutically acceptable stereoisomer.

105. The use of claim 104, wherein the stereoisomer is an enantiomerically pure R isomer.

106. The use of claim 104, wherein the stereoisomer is an enantiomerically pure S isomer.

107. The use of any one of claims 1 to 60 and 72, wherein the patient has low or intermediate-1-risk myelodysplastic syndrome with red blood cell transfusion-dependent anemia.

108. The use of claim 107, wherein the myelodysplastic syndrome comprises a 5q deletion cytogenetic abnormality.

109. The pharmaceutical composition of any one of claims 61 and 63 to 70, wherein the patient has low or intermediate-1-risk myelodysplastic syndrome with red blood cell transfusion-dependent anemia.

110. The pharmaceutical composition of claim 109, wherein the myelodysplastic syndrome comprises a 5q deletion cytogenetic abnormality.
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111. A compound, which is 3-(4-amino-1-oxo-1,3-dihydroisoindol-2-yl)-piperidine-2,6-dione having the formula:

![Chemical Structure](image)

or a pharmaceutically acceptable salt or stereoisomer thereof for use in treating a myelodysplastic syndrome in a patient.

112. The compound of claim 111, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein the patient has low or intermediate-1-risk myelodysplastic syndrome with red blood cell transfusion-dependent anemia.

113. The compound of claim 111 or 112, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein the myelodysplastic syndrome comprises a 5q deletion cytogenetic abnormality.

114. The compound of any one of claims 111 to 113, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein the compound is in the form of an orally administrable capsule.

115. The compound of any one of claims 111 to 114, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein the compound is formulated for oral administration in an amount of 10mg per day.

116. The compound of any one of claims 111 to 114, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein the compound is formulated for oral administration in an amount of 5mg per day.
117. The compound of any one of claims 111 to 114, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein the compound is formulated for oral administration in an amount of 5mg every other day.

118. The compound of claim 114, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein the capsule contains about 10mg of the compound.

119. The compound of claim 114, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein the capsule contains about 5mg of the compound.

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OTTAWA, CANADA

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