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(54) Title: USE OF 3- (4-AMINO-1-OXO-1,3-DIHYDRO-ISOINDOL-2-YL)-PIPERIDINE-2,6-DIONE FOR THE TREATMENT OF MANTLE CELL LYMPHOMAS

(57) Abstract: The treatment, prevention or management of mantle cell lymphomas by administration of an immunomodulatory compound of the invention known as Revlimid® or lenalidomide are disclosed. The invention further relates to the use of this compound with chemotherapy, radiation therapy, hormonal therapy, biological therapy or immunotherapy for the claimed treatment. Pharmaceutical compositions and single unit dosage forms suitable for use in the invention are also disclosed.

USE OF 3-(4-AMINO-1-OXO-1,3-DIHYDRO-ISOINDOL-2-YL)-PIPERIDINE-2,6-DIONE FOR THE TREATMENT OF MANTLE CELL LYMPHOMAS

1. FIELD OF THE INVENTION

[0001] This invention relates to methods of treating, preventing or managing certain types of lymphomas with an immunomodulatory compound having the chemical name of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, which is also known as or lenalidomide, Revlimid® or Revimid®. In particular, this invention encompasses methods of treating, preventing or managing non-Hodgkin's lymphomas, including but not limited to, mantle cell lymphoma (MCL), lymphocytic lymphoma of intermediate differentiation, intermediate lymphocytic lymphoma, ILL, diffuse poorly differentiated lymphocytic lymphoma, PDL, centrocytic lymphoma, diffuse small-cleaved cell lymphoma, DSCCL, and mentle zone lymphoma, using the compound alone as a therapeutic.

[0002] The invention also encompasses the use of specific combinations or "cocktails" of Revlimid® and other therapy, *e.g.*, radiation or other chemotherapeutics, including but not limited to, anti-cancer agents, immunosuppressive agents, and anti-inflammatories such as steroids. The invention also relates to pharmaceutical compositions and dosing regimens with said compound alone that is as a therapeutic.

2. BACKGROUND OF THE INVENTION

[0003] Cancer is characterized primarily by an increase in the number of abnormal cells derived from a given normal tissue, invasion of adjacent tissues by these abnormal cells, or lymphatic or blood-borne spread of malignant cells to regional lymph nodes and to distant sites (metastasis). Clinical data and molecular biologic studies indicate that cancer is a multistep process that begins with minor preneoplastic changes, which may under certain conditions progress to neoplasia. The neoplastic lesion may evolve clonally and develop an increasing capacity for invasion, growth, metastasis, and heterogeneity, especially under conditions in which the neoplastic cells escape the host's immune surveillance. Roitt, I., Brostoff, J. and Kale, D., *Immunology*, 17.1-17.12 (3rd ed., Mosby, St. Louis, Mo., 1993).

[0004] There is an enormous variety of cancers which are described in detail in the medical literature. Examples includes cancer of the blood, lung, colon, rectum, prostate, breast, brain, and intestine. The various forms of the cancers such as lymphomas are described in U.S. provisional application no. 60/380,842, filed May 17, 2002, the entireties of which are incorporated herein by reference (*see, e.g.*, Section 2.2. Types of Cancers).

[0005] Lymphoma is a heterogenous group of neoplasms arising in the reticuloendothelial and lymphatic systems. *The Merck Manual*, 955 (17th ed. 1999). Non-

Hodgkin's lymphoma (NHL) refers to malignant monoclonal proliferation of lymphoid cells in the immune system, including lymph nodes, bone marrow, spleen, liver and gastrointestinal (GI) tract. *The Merck Manual*, at 958.

[0006] Mantle cell lymphoma (MCL) is a distinct entity among the non-Hodgkin's lymphomas. Drach J.; *et al.*, *Expert Review of Anticancer Therapy*, 2005, 5(3), pp. 477-485. In the International Lymphoma Classification Project, MCL accounted for 8% of all non-Hodgkin lymphomas. MCL is recognized in the Revised European-American Lymphoma and World Health Organization classifications as a distinct clinicopathologic entity. MCL was not recognized by previous lymphoma classification schemes; and it was frequently categorized as diffuse small-cleaved cell lymphoma by the International Working Formulation or centrocytic lymphoma by the Kiel classification. *The Merck Manual*, at 958-959.

[0007] MCL is a lymphoproliferative disorder derived from a subset of naive pregerminal center cells localized in primary follicles or in the mantle region of secondary follicles. MCL is characterized by a specific chromosomal translocation, the t(11; 14)(q13;q32). Drach J.; *et al.*, *Expert Review of Anticancer Therapy*, 2005, 5(3), pp. 477-485. This translocation involves the immunoglobulin heavy-chain gene on chromosome 14 and the *BCL1* locus on chromosome 11. Drach J.; *et al.*, p 477. The molecular consequence of translocation is overexpression of the protein cyclin D1 (coded by the *PRAD1* gene located close to the breakpoint). *Id.* Cyclin D1 plays a key role in cell cycle regulation and progression of cells from G1 phase to S phase by activation of cyclin-dependent kinases. *Id.*

[0008] NHL has been associated with viral infection (Ebstein-Barr virus, HIV, human T-lymphotropic virus type 1, human herpesvirus 6), environmental factors (pesticides, hair dyes), and primary and secondary immunodeficiency. No causative factor has been identified for MCL or for most patients with NHL of other types.

[0009] MCL has poor clinical outcome and is an incurable lymphoma with limited therapeutic options for patients with relapsed or refractory disease. Drach J.; *et al.*, p. 477. Therefore, a tremendous demand exists for new methods and compositions that can be used to treat patients with MCL.

3. SUMMARY OF THE INVENTION

[0010] This invention encompasses methods of treating, preventing or managing certain types of lymphomas, including primary and metastatic cancer, as well as cancers that are relapsed, refractory or resistant to conventional chemotherapy. In particular, methods of

this invention encompass methods of treating, preventing or managing various forms of lymphomas such as mantle cell lymphoma, MCL, lymphocytic lymphoma of intermediate differentiation, intermediate lymphocytic lymphoma, ILL, diffuse poorly differentiated lymphocytic lymphoma, PDL, centrocytic lymphoma, diffuse small-cleaved cell lymphoma, DSCCL, follicular lymphoma, and mentle zone lymphoma, including lymphomas that are relapsed, refractory or resistant.

[0011] The methods comprise administering to a patient in need of such treatment, prevention or management a therapeutically or prophylactically effective amount of an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate (*e.g.*, hydrate), stereoisomer, clathrate, or prodrug thereof. In a preferred embodiment, the immunomodulatory compound is used alone, that is without other chemotherapeutics.

[0012] In another methods of the invention, an immunomodulatory compound of the invention is administered in combination with a therapy conventionally used to treat, prevent or manage lymphomas. Examples of such conventional therapies include, but are not limited to, surgery, chemotherapy, radiation therapy, hormonal therapy, biological therapy, immunotherapy and combinations thereof.

[0013] This invention also encompasses pharmaceutical compositions, single unit dosage forms, and dosing regimens which comprise an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate (*e.g.*, hydrate), stereoisomer, clathrate, or prodrug thereof, and a second, or additional, active agent or ingredient. Second active agents or ingredients include specific combinations, or "cocktails," of drugs or therapy, or both.

[0014] The preferred compound to be used in the methods and composition is 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (Revlimid®).

4. DETAILED DESCRIPTION OF THE INVENTION

[0015] A first embodiment of the invention encompasses methods of treating, managing, or preventing certain types of lymphomas which comprises administering to a patient in need of such treatment, management or prevention a therapeutically or prophylactically effective amount of an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate (*e.g.*, hydrate), stereoisomer, clathrate, or prodrug thereof. In particular, methods of this invention encompass methods of treating, preventing or managing various forms of lymphomas, including but not limited to, mantle cell lymphoma, MCL, lymphocytic lymphoma of intermediate differentiation, intermediate

lymphocytic lymphoma, ILL, diffuse poorly differentiated lymphocytic lymphoma, PDL, centrocytic lymphoma, diffuse small-cleaved cell lymphoma, DSCCL, follicular lymphoma, and any type of the mantle cell lymphomas that can be seen under the microscope (nodular, diffuse, blastic and mentle zone lymphoma). In one embodiment, the lymphoma is refractory, relapsed,or is resistant to chemotherapy other than an immunomodulatory compound of the invention.

[0016] In a separate and distinct embodiment of the invention, the immunomodulatory compound of the invention is administered in combination with another drug ("second active agent or ingredient") or another therapy for treating, managing, or preventing cancer. Second active agents include small molecules and large molecules (*e.g.*, proteins and antibodies), examples of which are provided herein, as well as stem cells or cord blood. Methods, or therapies, that can be used in combination with the administration of an immunomodulatory compound of the invention include, but are not limited to, surgery, blood transfusions, immunotherapy, biological therapy, radiation therapy, and other non-drug based therapies presently used to treat, prevent or manage cancer.

[0017] The invention also encompasses pharmaceutical compositions (*e.g.*, single unit dosage forms) that can be used in methods disclosed herein. Particular pharmaceutical compositions comprise an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate (*e.g.*, hydrate), stereoisomer, clathrate, or prodrug thereof, and a second active agent or ingredient.

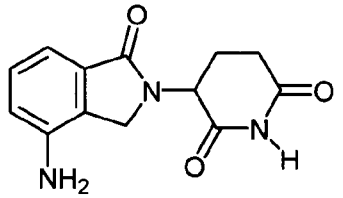
4.1 IMMUNOMODULATORY COMPOUNDS

[0018] Compounds used in the invention include compounds that are racemic, stereomerically enriched or stereomerically pure. In some embodiments, pharmaceutically acceptable salts, solvates (*e.g.*, hydrate), clathrates, and prodrugs thereof are included. Preferred compounds used in the invention are small organic molecules having a molecular weight less than about 1,000 g/mol, and are not proteins, peptides, oligonucleotides, oligosaccharides or other macromolecules.

[0019] As used herein and unless otherwise indicated, the terms "immunomodulatory compounds" and "IMiDs®" (Celgene Corporation) encompasses small organic molecules that markedly inhibit TNF-α, LPS induced monocyte IL1ß and IL12, and partially inhibit IL6 production. Specific immunomodulatory compounds of the invention are discussed below.

[0020] In the most preferred embodiment, "an immunomodulatory compound of the invention" refers to 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione

(lenalidomide, also known as Revlimid® or Revimid®). The compound 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione has the following chemical structure:



[0021] Specific examples of immunomodulatory compounds, 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-3yl) 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-dioxopiperdin-3-yl)-1-oxoisoindolines described in U.S. patent no. 5,798,368; 1-oxo and 1,3-dioxo-2-(2,6-dioxopiperidin-3-yl) isoindolines, including, but not limited to, those disclosed in U.S. patent no. 5,635,517; 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 and 6,316,471; a class of non-polypeptide cyclic amides disclosed in U.S. patent nos. 5,698,579 and 5,877,200; thalidomide analogs, including hydrolysis products, metabolites, 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; and isoindole-imide compounds such as those described in U.S. patent publication no. 2003/0096841, and International Application No. PCT/US01/50401 (International Publication No. WO 02/059106). The entireties of each of the patents and patent applications identified herein are incorporated herein by reference. Immunomodulatory compounds of the invention do not include thalidomide.

[0022] The immunomodulatory compounds of the invention can either be commercially purchased or prepared according to the methods described in the patents or patent publications disclosed herein (*see e.g.*, United States Patent No. 5,635,517, incorporated herein by reference). 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.

[0023] 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 know 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.

[0024] 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-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumaine (N-methylglucamine), lysine, and procaine.

[0025] 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, $-NO_2$, -ONO, or $-ONO_2$ 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 (Manfred E. Wolff ed., 5th ed. 1995), and *Design of Prodrugs* (H. Bundgaard ed., Elselvier, New York 1985).

[0026] 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 acetoxylmethyl, acetoxyethyl, aminocarbonyloxymethyl, pivaloyloxymethyl, and pivaloyloxyethyl esters), lactonyl esters (such as phthalidyl and thiophthalidyl esters), lower alkoxyacyloxyalkyl esters (such as methoxycarbonyl-oxymethyl, ethoxycarbonyloxyethyl and isopropoxycarbonyloxyethyl 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, amino acids, hydroxyalkylamines, heterocyclic and heteroaromatic amines, and polyether amines.

[0027] The immunomodulatory compound of the invention contains a chiral center, and thus can exist as a racemic mixture of R and S enantiomers. This invention encompasses the use of stereomerically pure forms of this compound, as well as the use of mixtures of those forms. For example, mixtures comprising equal or unequal amounts of the enantiomers may be used in methods and compositions of the invention. These isomers may be asymmetrically synthesized or resolved using standard techniques such as chiral columns or chiral resolving agents. *See, e.g.*, Jacques, J., *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley-Interscience, New York, 1981); Wilen, S. H., *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, E. L., *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, S. H., *Tables of Resolving Agents and Optical Resolutions* p. 268 (E. L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN, 1972).

[0028] 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. In other words, the invention encompasses the use of the R or S enantiomer of immunomodulatory compound in the methods.

[0029] 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

[0030] An immunomodulatory compound of the invention can be used with or combined with other pharmacologically active compounds ("second active agents or ingredients") in methods and compositions of the invention. It is believed that certain combinations work synergistically in the treatment of particular types of lymphomas. Immunomodulatory compounds of the invention can also work to alleviate adverse effects associated with certain second active agents, and some second active agents can be used to alleviate adverse effects associated with immunomodulatory compounds of the invention.

[0031] One or more second active ingredients or agents can be used in the methods and compositions of the invention together with an immunomodulatory compound of the invention. Second active agents can be large molecules (*e.g.*, proteins) or small molecules (*e.g.*, synthetic inorganic, organometallic, or organic molecules).

[0032] Examples of large molecule active agents include, but are not limited to, hematopoietic growth factors, cytokines, and monoclonal and polyclonal antibodies. Typical large molecule active agents are biological molecules, such as naturally occurring or artificially made proteins. Proteins that are particularly useful in this invention include proteins that stimulate the survival and/or proliferation of hematopoietic precursor cells and immunologically active poietic cells *in vitro* or *in vivo*. Others stimulate the division and differentiation of committed erythroid progenitors in cells *in vitro* or *in vivo*. Particular proteins include, but are not limited to: interleukins, such as IL-2 (including recombinant IL-II ("rIL2") and canarypox IL-2), IL-10, IL-12, and IL-18; interferons, such as interferon alfa-2a, interferon alfa-2b, interferon alfa-n1, interferon alfa-n3, interferon beta-I a, and interferon gamma-I b; GM-CF and GM-CSF; and EPO.

[0033] Particular proteins that can be used in the methods and compositions of the invention include, but are not limited to: filgrastim, which is sold in the United States under the trade name Neupogen® (Amgen, Thousand Oaks, CA); sargramostim, which is sold in

the United States under the trade name Leukine® (Immunex, Seattle, WA); and recombinant EPO, which is sold in the United States under the trade name Epogen® (Amgen, Thousand Oaks, CA).

[0034] 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; all of which are incorporated herein by reference. 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; all of which are incorporated herein by reference.

[0035] This invention 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).

[0036] Antibodies that can be used in combination with compounds of the invention include monoclonal and polyclonal antibodies. Examples of antibodies include, but are not limited to, trastuzumab (Herceptin®), rituximab (Rituxan®), bevacizumab (Avastin™), pertuzumab (Omnitarg™), tositumomab (Bexxar®), edrecolomab (Panorex®), and G250. Compounds of the invention can also be combined with, or used in combination with, anti-TNF-α antibodies.

[0037] Large molecule active agents may be administered in the form of anti-cancer vaccines. For example, vaccines that secrete, or cause the secretion of, cytokines such as IL-2, 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).

[0038] In one embodiment of the invention, the large molecule active agent reduces, eliminates, or prevents an adverse effect associated with the administration of an immunomodulatory compound of the invention. Depending on the particular immunomodulatory compound of the invention and the disease or disorder begin treated,

adverse effects can include, but are not limited to, drowsiness and somnolence, dizziness and orthostatic hypotension, neutropenia, infections that result from neutropenia, increased HIV-viral load, bradycardia, Stevens-Johnson Syndrome and toxic epidermal necrolysis, and seizures (*e.g.*, grand mal convulsions). A specific adverse effect is neutropenia.

[0039] Second active agents that are small molecules can also be used to alleviate adverse effects associated with the administration of an immunomodulatory compound of the invention. However, like some large molecules, many are believed to be capable of providing a synergistic effect when administered with (*e.g.*, before, after or simultaneously) an immunomodulatory compound of the invention. Examples of small molecule second active agents include, but are not limited to, anti-cancer agents, antibiotics, immunosuppressive agents, and steroids.

[0040] Examples of anti-cancer agents include, but are not limited to: acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; bortezomib (Velcade®); brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; celecoxib (COX-2 inhibitor); chlorambucil; cirolemycin; cisplatin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; dactinomycin; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; docetaxel; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; flurocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; ilmofosine; iproplatin; irinotecan; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazole; nogalamycin; ormaplatin; oxisuran;

paclitaxel; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; taxotere; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; and zorubicin hydrochloride.

[0041] Other anti-cancer drugs include, but are not limited to: 20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorlns; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone;

didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; dihydrotaxol, 9-; dioxamycin; diphenyl spiromustine; docetaxel; docosanol; dolasetron; doxifluridine; doxorubicin; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imatinib (*e.g.*, Gleevec®); imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim;Erbitux, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; oblimersen (Genasense®); O^6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; paclitaxel; paclitaxel analogues; paclitaxel derivatives; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors;

picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; and zinostatin stimalamer.

[0042] Specific second active agents include, but are not limited to, rituximab, bortezomib, oblimersen (Genasense®), remicade, docetaxel, celecoxib, melphalan, dexamethasone (Decadron®), steroids, gemcitabine, cisplatinum, temozolomide, etoposide, cyclophosphamide, temodar, carboplatin, procarbazine, gliadel, tamoxifen, topotecan, methotrexate, Arisa®, taxol, taxotere, fluorouracil, leucovorin, irinotecan, xeloda, CPT-11, interferon alpha, pegylated interferon alpha (*e.g.*, PEG INTRON-A), capecitabine, cisplatin, thiotepa, fludarabine, carboplatin, liposomal daunorubicin, cytarabine, doxetaxol, pacilitaxel, vinblastine, IL-2, GM-CSF, dacarbazine, vinorelbine, zoledronic acid, palmitronate, biaxin, busulphan, prednisone, bisphosphonate, arsenic trioxide, vincristine,

doxorubicin (Doxil®), paclitaxel, ganciclovir, adriamycin, estramustine sodium phosphate (Emcyt®), sulindac, and etoposide.

4.3 METHODS OF TREATMENTS AND PREVENTION

[0043] Methods of this invention encompass methods of treating, preventing or managing various types of lymphomas. In a preferred embodiment, methods of this invention encompass methods of treating, preventing or managing various types of lymphomas, including but not limited to, mantle cell lymphoma, MCL, lymphocytic lymphoma of intermediate differentiation, intermediate lymphocytic lymphoma, ILL, diffuse poorly differentiated lymphocytic lymphoma, PDL, centrocytic lymphoma, diffuse small-cleaved cell lymphoma, DSCCL, follicular lymphoma, and any type of the mantle cell lymphomas that can be seen under the microscope (nodular, diffuse, blastic and mentle zone lymphoma).

[0044] As used herein, unless otherwise specified, the term "treating" refers to the administration of a compound of the invention, or other additional active agent, after the onset of symptoms of the particular cancer. As used herein, unless otherwise specified, the term "preventing" refers to the administration prior to the onset of symptoms, particularly to patients at risk of cancer, and in particular lymphoma. The term "prevention" includes the inhibition of a symptom of the particular cancer. Patients with familial history of cancer or lymphoma in particular are preferred candidates for preventive regimens. As used herein and unless otherwise indicated, the term "managing" encompasses preventing the recurrence of the particular cancer in a patient who had suffered from it, lengthening the time a patient who had suffered from the cancer remains in remission, and/or reducing mortality rates of the patients.

[0045] As used herein, the term "cancer" includes, but is not limited to, solid tumors and blood born tumors. The term "cancer" refers to disease of skin tissues, organs, blood, and vessels, including, but not limited to, cancers of the bladder, bone or blood, brain, breast, cervix, chest, colon, endrometrium, esophagus, eye, head, kidney, liver, lymph nodes, lung, mouth, neck, ovaries, pancreas, prostate, rectum, stomach, testis, throat, and uterus.

[0046] The term "lymphoma" refers a heterogenous group of neoplasms arising in the reticuloendothelial and lymphatic systems. Non-Hodgkin's lymphoma (NHL) refers to malignant monoclonal proliferation of lymphoid cells in sites of the immune system, including lymph nodes, bone marrow, spleen, liver and gastrointestinal tract. The NHL includes, but is not limited to, mantle cell lymphoma, MCL, lymphocytic lymphoma of

intermediate differentiation, intermediate lymphocytic lymphoma, ILL, diffuse poorly differentiated lymphocytic lymphoma, PDL, centrocytic lymphoma, diffuse small-cleaved cell lymphoma, DSCCL, follicular lymphoma, and any type of the mantle cell lymphomas that can be seen under the microscope (nodular, diffuse, blastic and mentle zone lymphoma).

[0047] The term "relapsed" refers to a situation where patients who have had a remission of cancer after therapy have a return of lymphoid cells in the immune systems. The term "refractory or resistant" refers to a circumstance where patients, even after intensive treatment, have residual lymphoid cells in the immune systems.

[0048] This invention encompasses methods of treating patients who have been previously treated for cancer, but are non-responsive to standard therapies, as well as those who have not previously been treated. The invention also encompasses methods of treating patients regardless of patient's age, although some cancers are more common in certain age groups. The invention further encompasses methods of treating patients who have undergone surgery in an attempt to treat the cancer at issue, as well as those who have not. Because patients with cancer have heterogenous clinical manifestations and varying clinical outcomes, the treatment given to a patient may vary, depending on his/her prognosis. The skilled clinician will be able to readily determine without undue experimentation specific secondary agents, types of surgery, and types of non-drug based standard therapy that can be effectively used to treat an individual patient with cancer.

[0049] Methods encompassed by this invention comprise administering one or more immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate (*e.g.*, hydrate), stereoisomer, clathrate, or prodrug thereof, to a patient (*e.g.*, a human) suffering, or likely to suffer, from cancer, particularly mantle cell lymphoma.

[0050] In one embodiment of the invention, an immunomodulatory compound of the invention can be administered orally and in single or divided daily doses in an amount of from about 0.10 to about 150 mg/day. In a preferred embodiment, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl-piperidine-2,6-dione (Revlimid®) may be administered in an amount of from about 0.10 to 150 mg per day, from about 1 to about 50 mg per day, or from about 5 to about 25 mg per day. Specific doses per day include 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49 or 50 mg per day.

[0051] In a preferred embodiment, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl-piperidine-2,6-dione (Revlimid®) may be administered in an amount of from about 1 to 50 mg per day, or from about 5 to about 25 mg per day to patients with various types of non-

Hodgkin's lymphomas such as mantle cell lymphoma, MCL, lymphocytic lymphoma of intermediate differentiation, intermediate lymphocytic lymphoma, ILL, diffuse poorly differentiated lymphocytic lymphoma, PDL, centrocytic lymphoma, diffuse small-cleaved cell lymphoma, DSCCL, diffuse large cell lymphoma, follicular lymphoma, and mentle zone lymphoma.

[0052] In particular, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl-piperidine-2,6-dione (Revlimid®) may be administered to patients with mantle cell lymphoma in an amount of from about 1 to 50 mg per day, or from about 5 to about 25 mg per day. In a specific embodiment, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl-piperidine-2,6-dione (Revlimid®) may be administered to patients with mantle cell lymphoma in an amount of about 10, 15, 20, 25 or 50 mg per day. In a specific embodiment, Revlimid® can be administered in an amount of about 25 mg per day to patients with mantle cell lymphoma.

[0053] In one embodiment, the recommended starting dose of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (Revlimid®) is 10 mg per day. The dose can be escalated every week to 15, 20, 25, 30, 35, 40, 45 and 50 mg per day. The patients who are dosed initially at 10 mg and who experience thrombocytopenia or neutropenia that develops within or after the first four weeks of starting Revlimid® therapy may have their dosage adjusted according to a platelet count or absolute neutrophil count (ANC).

4.3.1 COMBINATION THERAPY WITH A SECOND ACTIVE AGENT

[0054] Specific methods of the invention comprise administering an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate (*e.g.*, hydrate), stereoisomer, clathrate, or prodrug thereof, in combination with one or more second active agents, and/or in combination with radiation therapy, blood transfusions, or surgery. Examples of immunomodulatory compounds of the invention are disclosed herein (*see, e.g.*, section 4.1). Examples of second active agents are also disclosed herein (*see, e.g.*, section 4.2).

[0055] Administration of an immunomodulatory compound of the invention 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 of the invention is orally. 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*, (2006).

[0056] In one embodiment of the invention, the second active agent is administered intravenously or subcutaneously and once or twice daily in an amount of from about 1 to about 1,000 mg, from about 5 to about 500 mg, from about 10 to abbut 375 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 disease being treated or managed, the severity and stage of disease, 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 rituximab, bortezomib, oblimersen (Genasense®), GM-CSF, G-CSF, EPO, taxotere, irinotecan, dacarbazine, transretinoic acid, topotecan, pentoxifylline, ciprofloxacin, dexamethasone, vincristine, doxorubicin, COX-2 inhibitor, IL2, IL8, IL18, IFN, Ara-C, vinorelbine, or a combination thereof.

[0057] In a specific embodiment, an immunomodulatory compound of the invention is administered in combination with rituximab to patients with mantle cell lymphomas. In a specific embodiment, Revlimid® is administered to patients with mantle cell lymphoma in an amount of from about 5 to about 25 mg per day in combination with rituximab in an amount of 375 mg/m^2 by intravenous infusion weekly.

[0058] In a preferred embodiment, Revlimid® is administered alone or in combination with rituximab to patients with various types of non-Hodgkin's lymphomas, including, but not limited to, mantle cell lymphoma, MCL, lymphocytic lymphoma of intermediate differentiation, intermediate lymphocytic lymphoma, ILL, diffuse poorly differentiated lymphocytic lymphoma, PDL, centrocytic lymphoma, diffuse small-cleaved cell lymphoma, DSCCL, diffuse large cell lymphoma, follicular lymphoma, and mentle zone lymphoma.

[0059] In another embodiment, an immunomodulatory compound of the invention is administered alone or in combination with a second active ingredient such as vinblastine or fludarabine to patients with various types of lymphomas, including, but not limited to, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cutaneous T-Cell lymphoma, cutaneous B-Cell lymphoma, diffuse large B-Cell lymphoma or relapsed or refractory low grade follicular lymphoma.

[0060] In another embodiment, GM-CSF, G-CSF or EPO is administered subcutaneously during about five days in a four or six week cycle in an amount of from about 1 to about 750 mg/m^2/day, preferably in an amount of from about 25 to about 500 mg/m^2/day, more preferably in an amount of from about 50 to about 250 mg/m^2/day, and

most preferably in an amount of from about 50 to about 200 mg/m^2/day. In a certain embodiment, GM-CSF may be 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. In a specific embodiment, G-CSF may be 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 of G-CSF may be administered in an amount of about 300 (in smaller patients) or 480 mcg subcutaneously. In a certain embodiment, EPO may be administered subcutaneously in an amount of 10,000 Unit 3 times per week.

[0061] This invention also encompasses a method of increasing the dosage of an anti-cancer drug or agent that can be safely and effectively administered to a patient, which comprises administering to a patient (*e.g.*, a human) an immunomodulatory compound of the invention, or a pharmaceutically acceptable derivative, salt, solvate (*e.g.*, hydrate), or prodrug thereof. Patients that can benefit by this method are those likely to suffer from an adverse effect associated with anti-cancer drugs for treating a specific cancer of the blood, skin, subcutaneous tissue, lymph nodes, brain, lung, liver, bone, intestine, colon, heart, pancreas, adrenal, kidney, prostate, breast, colorectal, or combinations thereof. The administration of an immunomodulatory compound of the invention alleviates or reduces adverse effects which are of such severity that it would otherwise limit the amount of anti-cancer drug.

[0062] In one embodiment, an immunomodulatory compound of the invention can be administered orally and daily in an amount of from about 0.10 to about 150 mg, and preferably from about 1 to about 50 mg, more preferably from about 5 to about 25 mg prior to, during, or after the occurrence of the adverse effect associated with the administration of an anti-cancer drug to a patient. In a particular embodiment, an immunomodulatory compound of the invention is administered in combination with specific agents such as heparin, aspirin, coumadin, or G-CSF to avoid adverse effects that are associated with anti-cancer drugs such as but not limited to neutropenia or thrombocytopenia.

[0063] In another embodiment, this invention encompasses a method of treating, preventing and/or managing lymphoma, which comprises administering an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate (*e.g.*, hydrate), stereoisomer, clathrate, or prodrug thereof, in conjunction with (*e.g.*, before, during, or after) conventional therapy including, but not limited to, surgery, immunotherapy, biological therapy, radiation therapy, or other non-drug based therapy presently used to treat, prevent or manage cancer. The combined use of the immunomodulatory compounds of the invention and conventional therapy may provide a

unique treatment regimen that is unexpectedly effective in certain patients. Without being limited by theory, it is believed that immunomodulatory compounds of the invention may provide additive or synergistic effects when given concurrently with conventional therapy.

[0064] As discussed elsewhere herein, the invention encompasses a method of reducing, treating and/or preventing adverse or undesired effects associated with conventional therapy including, but not limited to, surgery, chemotherapy, radiation therapy, hormonal therapy, biological therapy and immunotherapy. An immunomodulatory compound of the invention and other active ingredient can be administered to a patient prior to, during, or after the occurrence of the adverse effect associated with conventional therapy.

[0065] In one embodiment, an immunomodulatory compound of the invention can be administered in an amount of from about 0.10 to about 150 mg, and preferably from about 1 to about 50 mg, more preferably from about 5 to about 25 mg orally and daily alone, or in combination with a second active agent disclosed herein (*see, e.g.*, section 4.2), prior to, during, or after the use of conventional therapy.

4.3.2 USE WITH TRANSPLANTATION THERAPY

[0066] Compounds of the invention can be used to reduce the risk of Graft Versus Host Disease (GVHD). Therefore, the invention encompasses a method of treating, preventing and/or managing cancer, which comprises administering the immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate (*e.g.*, hydrate), stereoisomer, clathrate, or prodrug thereof, in conjunction with transplantation therapy.

[0067] As those of ordinary skill in the art are aware, the treatment of cancer is often based on the stages and mechanism of the disease. For example, as inevitable leukemic transformation develops in certain stages of cancer, 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 cancer.

[0068] 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 GVHD. This invention encompasses a method of treating, preventing and/or managing cancer which comprises administering to a patient (*e.g.*, a

human) an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate (*e.g.*, 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. patent publication nos. 2002/0123141, 2003/0235909 and 2003/0032179, by R. Hariri *et al.*, the entireties of which are incorporated herein by reference.

[0069] In one embodiment of this method, an immunomodulatory compound of the invention is administered to patients with lymphomas before, during, or after the transplantation of autologous peripheral blood progenitor cell.

[0070] In another embodiment, an immunomodulatory compound of the invention is administered to patients with relapsed lymphoma after the stem cell transplantation.

4.3.3 CYCLING THERAPY

[0071] In certain embodiments, the prophylactic or therapeutic agents of the invention are cyclically administered to a patient. Cycling therapy involves the administration of an active agent for a period of time, followed by a rest 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.

[0072] Consequently, in one specific embodiment of the invention, an immunomodulatory compound of the invention is administered daily in a single or divided doses in a four to six week cycle with a rest period of about a week or two weeks. The invention further allows the frequency, number, and length of dosing cycles to be increased. Thus, another specific embodiment of the invention encompasses the administration of an immunomodulatory compound of the invention for more cycles than are typical when it is administered alone. In yet another specific embodiment of the invention, an immunomodulatory compound of the invention is administered for a greater number of cycles that would typically cause dose-limiting toxicity in a patient to whom a second active ingredient is not also being administered.

[0073] In one embodiment, an immunomodulatory compound of the invention is administered daily and continuously for three or four weeks at a dose of from about 0.10 to about 150 mg/d followed by a break of one or two weeks. In a particular embodiment, an immunomodulatory compound of the invention is administered in an amount of from about

1 to about 50 mg/day, preferably in an amount of about 25 mg/day for three to four weeks, followed by one week or two weeks of rest in a four or six week cycle.

[0074] In a preferred embodiment, 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (Revlimid®) is administered to patients with various types of lymphomas such as mantle cell lymphoma, follicullar lymphoma and diffuse large cell lymphoma, in an amount of about 10 mg, 15 mg, 20 mg, 25 mg or 30 mg per day for 21 days followed by seven days rest in a 28 day cycle. In the most preferred embodiment, 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (Revlimid®) is administered to patients with refractory or relapsed mantle cell lymphoma in an amount of about 25 mg per day for 21 days followed by seven days rest in a 28 day cycle.

[0075] In one embodiment of the invention, an immunomodulatory compound of the invention and a second active agent or ingredient are administered orally, with administration of an immunomodulatory compound of the invention occurring 30 to 60 minutes prior to a second active ingredient, during a cycle of four to six weeks. In another embodiment of the invention, an immunomodulatory compound of the invention is administered orally and a second active ingredient is administered by intravenous infusion.

[0076] In a specific embodiment, one cycle comprises the administration of from about 10 to about 25 mg/day of Revlimid® and from about 50 to about 750 mg/m^2/day of a second active ingredient daily for three to four weeks and then one or two weeks of rest.

[0077] In one embodiment, rituximab can be administered in an amount of 375 mg/m^2 as an additional active agent to patients with various types of lymphomas such as mantle cell lymphoma, follicullar lymphoma and diffuse large cell lymphoma. In a preferred embodiment, rituximab can be administered in an amount of 375 mg/m^2 as an additional active agent to patients with refractory or relapsed mantle cell lymphoma. In a preferred embodiment, one cycle comprises the administration of Revlimid® given orally daily for 21 days followed by 7 days of rest and 375 mg/m^2 of rituximab by intravenous infusion weekly for four weeks.

[0078] Typically, the number of cycles during which the combinatorial treatment is administered to a patient will be from about one to about 24 cycles, more typically from about two to about 16 cycles, and even more typically from about four to about three cycles.

4.4 PHARMACEUTICAL COMPOSITIONS AND DOSAGE FORMS

[0079] 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 (*e.g.*, hydrate), stereoisomer, clathrate, or prodrug thereof. Pharmaceutical compositions and dosage forms of the invention can further comprise one or more excipients.

[0080] 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 and a second active agent). Examples of optional second, or additional, active ingredients are disclosed herein (*see, e.g.*, section 5.2).

[0081] Single unit dosage forms of the invention are suitable for oral, mucosal (*e.g.*, nasal, sublingual, vaginal, buccal, or rectal), parenteral (*e.g.*, subcutaneous, intravenous, bolus injection, intramuscular, or intraarterial), topical (*e.g.*, eye drops or other ophthalmic preparations), 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; eye drops or other ophthalmic preparations suitable for topical administration; 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.

[0082] 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).

[0083] 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 di-saccharides. 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.

[0084] 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.

[0085] 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.

[0086] 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.

[0087] 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.

[0088] 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.

[0089] 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 (*e.g.*, 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 (*e.g.*, hydrate), stereoisomer, clathrate, or prodrug thereof in an amount of about 0.1, 1, 2.5, 5, 7.5, 10, 12.5, 15, 17.5, 20, 25, 50, 100, 150 or 200 mg. In a specific embodiment, a preferred dosage form comprises 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (Revlimid®) in an amount of about 1, 2.5, 5, 10, 15, 20, 25 or 50 mg. 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 anti-cancer drug will depend on the specific agent used, the type of cancer being treated or managed, and the amount(s) of an immunomodulatory compound of the invention and any optional additional active agents concurrently administered to the patient.

4.4.1 ORAL DOSAGE FORMS

[0090] 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).

[0091] In one embodiment, a preferred dosage form is a capsule or tablet comprising 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (Revlimid®) in an amount of about 1, 2.5, 5, 10, 15, 20, 25 or 50 mg. In a specific embodiment, a preferred capsule or tablet dosage form comprises 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (Revlimid®) in an amount of about 5 or 10 mg.

[0092] 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.

[0100] 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.

[0101] 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.

[0102] 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.

[0103] 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.

[0104] 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.

[0105] 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.

[0106] 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.

[0107] 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 (AEROSIL200, 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.

[0108] 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

[0109] 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, each of which is incorporated herein by reference. 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, liposomes, 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.

[0110] 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.

[0111] 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

[0112] 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.

[0113] 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.

[0114] 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.

5. EXAMPLES

[0115] Certain embodiments of the invention are illustrated by the following non-limiting example.

5.1 CLINICAL STUDIES IN PATIENTS

5.1.1 TREATMENT OF MANTLE CELL LYMPHOMAS

[0116] A single-center, open label, phase I/II study was conducted to determine the maximum tolerated dose (MTD) and to evaluate the efficacy of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidin-2,6-dione (lenalidomide or Revlimid®) in combination with rituximab for relapsed or refractory mantle cell lymphoma (MCL). Patients with one to four lines of prior therapy were eligible. Patients with prior treatment using thalidomide or rituximab, regardless of resistance, were eligible. Each cycle (28 days) of treatment comprises administration of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidin-2,6-dione (Revlimid®) given orally daily for 21 days followed by 7 days of rest and 375 mg/m^2 of rituximab by intravenous infusion weekly for four weeks. A standard phase I dose escalation was used to determine MTD with dose levels at 10 mg, 15 mg, 20 mg, and 25 mg of Revlimid®. Dose-limiting toxicity (DLT) was defined as grade 3 or 4 non-hematologic or grade 4 hematologic toxicity during the first cycle.

[0117] Ten patients were enrolled with seven evaluable. Median age was 73, range 56-84; median prior lines of therapy were 3, range 1-4. Each cohort had 3 patients. No DLT was encountered and maximum dose of Revlimid® was up to 20 mg. The number of cycles given ranged from one to five cycles. There were no grade 3 or 4 toxicities during the cycle. Grade 1 non-hematologic toxic events included fatigue in 4, stomatitis in 3, pruritis in 3, and myalgias in 2. Grade 2 non-hematologic toxic events included rash in 2 and myalgias in 2. Grade 1 hematologic events included leukopenia in 3, thrombocytopenia in 2 and anemia in 1. There was one episode of grade 2 anemia. Beyond the first cycle, there was only 1 grade 3 toxicity (thrombocytopenia) during cycle 2. Therefore, the MTD has not been reached. Two patients had stable disease at cycle 3 and cycle 5, respectively. Four patients had progressive disease and were taken off the study. One patient progressed in the first cycle.

[0118] The study result shows that Revlimid® is effective in treating mantle cell lymphoma, particularly relapsed or refractory mantle cell lymphoma.

5.1.2 TREATMENT OF AGGRESSIVE NHL

[0119] A multi-center, open-label, Phase II study was conducted in patients with relapsed and refractory aggressive non-Hodgkin's lymphoma (NHL). The trial was designed to evaluate the therapeutic potential and safety of oral monotherapy with 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidin-2,6-dione (Revlimid® or lenalidomide) in 40 patients with relapsed and refractory aggressive NHL following one or more prior treatment regimen with measurable disease. Patients in the study received lenalidomide in

an amount of 25mg orally once daily for days one to 21 in a 28-day cycle and continued therapy for 52 weeks as tolerated or until disease progression.

[0120] Twenty-five patients age 45 to 80 years (median age 63), with relapsed and refractory aggressive NHL, and who had received a median of 2.5 prior treatments (range: 1-6 prior treatments), were administered with lenalidomide in an amount of 25mg orally once daily for 21 days in the treatment cycle. Sixteen patients with aggressive NHL were evaluable for tumour assessment. Of the 16 patients, eight had diffuse large cell lymphoma, three had mantle cell lymphoma, two patients had follicular lymphoma, one had transformed lymphoma, and two had aggressive lymphoma of unknown histology.

[0121] There were five (31 per cent) patients who experienced objective responses to lenalidomide monotherapy. One patient achieved complete response and four patients achieved partial responses. One patient with diffuse large cell lymphoma achieved complete response with progression free survival of more than 180 days. One patient with diffuse large cell lymphoma achieved partial response with progression free survival for 135 days. One patient with diffuse large cell lymphoma achieved partial response with progression free survival for 242 days. One patient with follicular lymphoma achieved partial response with progression free survival for more than 55 days. One patient with mantle cell lymphoma achieved partial response with progression free survival for more than 57 days. Four patients exhibited stable disease. Seven patients had disease progression after a median follow-up of two months (range one to seven months).

[0122] Grade 3 and 4 adverse events occurred in ten of 22 patients. These were predominately haematological and Grade 3 adverse reaction, with only three patients experiencing a Grade 4 adverse reaction.

[0123] The embodiments of the invention described above are intended to be merely exemplary, and those skilled in the art will recognize, or will be able to ascertain using no more than routine experimentation, numerous equivalents of specific compounds, materials, and procedures. All such equivalents are considered to be within the scope of the invention and are encompassed by the appended claims.

CLAIMS

What is claimed is:

1. A method of treating mantle cell lymphoma in a human, which comprises administering to a human in need thereof a therapeutically effective amount of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione.

2. The method of claim 1, wherein the mantle cell lymphoma is relapsed, refractory or resistant to conventional therapy.

3. The method of claim 1 or 2, wherein the amount of 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione administered is from about 1 to about 50 mg per day.

4. The method of claim 3, wherein the amount of 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione administered is about 10, 15, 20 or 25 mg per day.

5. The method of claim 4, wherein the amount of 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione administered is about 25 mg per day.

6. The method of claim 3, wherein 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione administered is enantiomerically pure.

7. The method of claim 6, wherein 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione administered is S enantiomer.

8. The method of claim 6, wherein 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione administered is R enantiomer.

9. The method of claim 3, wherein 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione is administered orally.

10. The method of claim 9, wherein 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione is administered in the form of a capsule or tablet.

11. The method of claim 3, wherein 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione is administered for 21 days followed by seven days rest in a 28 day cycle.

12. The method of claim 11, wherein 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione is administered in an amount of about 25 mg per day for 21 days followed by seven days rest in a 28 day cycle.

13. The method of claim 12, further comprising administration of rituximab in an amount of 375 mg/m^2 by intravenous infusion weekly.

14. A method of treating mantle cell lymphoma, which comprises administering to a patient in need thereof a therapeutically effective amount of 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione and a therapeutically effective amount of a second active agent.

15. The method of claim 14, wherein the second active agent is antibody, hematopoietic growth factor, cytokine, anti-cancer agent, antibiotic, cox-2 inhibitor, immunomodulatory agent, immunosuppressive agent, corticosteroid, or a pharmacologically active mutant or derivative thereof.

16. The method of claim 14, wherein the second active agent is rituximab.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/017343

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/454 A61K39/395 A61K45/06 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE, SCISEARCH, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DRACH J. ET AL: "Treatment of mantle cell lymphoma : Targeting the microenvironment." EXPERT REVIEW OF ANTICANCER THERAPY, (JUN 2005) VOL. 5, NO. 3, PP. 477-485. REFS: 60 ISSN: 1473-7140 CODEN: ERATBJ, June 2005 (2005-06), XP008085777 cited in the application abstract page 477, column 1, paragraph 1 page 478, column 2, paragraph 3 page 481, column 1, paragraph 4 - column 2, paragraph 3 page 482, column 1, paragraph 3 ----- -/--	1-10, 13-16

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 November 2007	06/12/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cielen, Elsie

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/017343

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CRANE E ET AL: "Immunomodulatory drugs" CANCER INVESTIGATION 2005 UNITED STATES, vol. 23, no. 7, 2005, pages 625-634, XP008085781 ISSN: 0735-7907 1532-4192 abstract page 625, column 2, paragraph 2 page 627, column 2, last paragraph table 1 page 628, column 2, paragraph 1 page 628, column 2, paragraph 3 - page 629, column 1, paragraph 2 page 629, column 2, paragraphs 2,3 page 632, column 1, paragraph 3 - column 2, paragraph 1	1-10, 13-16
Y	HERNANDEZ-ILIZALITURRI FRANCISCO J ET AL: "Immunomodulatory drug CC-5013 or CC-4047 and rituximab enhance antitumor activity in a severe combined immunodeficient mouse lymphoma model." CLINICAL CANCER RESEARCH : AN OFFICIAL JOURNAL OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH 15 AUG 2005, vol. 11, no. 16, 15 August 2005 (2005-08-15), pages 5984-5992, XP002459831 ISSN: 1078-0432 abstract page 5985, column 1, paragraphs 3,4,6 figure 1 table 2 page 5991, column 1, paragraph 3 - column 2, paragraph 4	1-10, 13-16
A	WO 03/097052 A (CELGENE CORP [US]) 27 November 2003 (2003-11-27) page 4, lines 18-32 page 11, line 22 - page 12, line 2 page 13, lines 27-30 page 15, lines 5-10 page 16, lines 8-13,27-32 page 21, lines 10-34 page 24, lines 21-27 page 36, lines 5-10,20,21 page 42, line 31 - page 43, line 8 page 43, line 27 - page 44, line 11 claims 1,2,5,6,8,12,13	1-16

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/017343

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	CUNNINGHAM S ET AL: "Phase II trial for lenalidomide alone in relapsed/refractory aggressive non-Hodgkin lymphoma" CLINICAL LYMPHOMA AND MYELOMA 2007 UNITED STATES, vol. 7, no. 5, 2007, page 339, XP008085792 ISSN: 1557-9190 the whole document	1-5,9, 11,12
T	GOY A.: "Mantle cell lymphoma : Evolving novel options." CURRENT ONCOLOGY REPORTS, (SEP 2007) VOL. 9, NO. 5, PP. 391-398. REFS: 67 ISSN: 1523-3790 CODEN: CORUAT, September 2007 (2007-09), XP008085785 page 391, column 1, paragraphs 1,2 page 395, column 1, paragraphs 2,3	1,2, 14-16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/017343

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2007/017343

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