Title: DOSAGE REGIMEN OF MDM2 INHIBITOR FOR TREATING CANCERS

Abstract: The present invention provides a method for treating a cancer in a subject in need thereof, comprising administering a specific MDM2 inhibitor to the subject according to a specific dosage regimen and a pharmaceutical composition for use in treating a cancer according to the dosage regimen. The present invention also provides a method for treating hpsarcoma in a subject in need thereof, comprising administering a specific MDM2 inhibitor to the subject and a pharmaceutical composition for use in treating hpsarcoma, comprising the MDM2 inhibitor.
DESCRIPTION

Title of Invention

DOSAGE REGIMEN OF MDM2 INHIBITOR FOR TREATING CANCERS

Field of the Invention

[0001] The present invention relates to a method for treating a cancer in a subject in need thereof, comprising administering a specific MDM2 inhibitor to the subject according to a specific dosage regimen and a pharmaceutical composition for use in treating a cancer according to the dosage regimen. The present invention also relates to a method for treating liposarcoma in a subject in need thereof, comprising administering a specific MDM2 inhibitor to the subject and a pharmaceutical composition for use in treating liposarcoma, comprising the MDM2 inhibitor.

Background of the Invention

[0002] MDM2, located on Chromosome 12 q13-15, is a negative regulator of the p53 tumor suppressor protein. The 90 kDa MDM2 protein contains a p53 binding domain at its N-terminus and a RING (really interesting new gene) domain at its C-terminus, which functions as an E3 ligase that ubiquitinates p53. The activation of wild-type p53 by cell stimuli and stresses results in the binding of MDM2 to p53 at the N-terminus to inhibit the transcriptional activation of p53 and promote the degradation of p53 via the ubiquitin-proteasome pathway. Thus, MDM2 can interfere with p53-mediated apoptosis and arrest of cancer cell proliferation, attributing a significant oncogenic activity to MDM2 in cancer cells. In some cases, MDM2 can cause carcinogenesis independent of the p53 pathway, for example, in cells which possess an alternative splice form of MDM2 (H.A. Steinman et al., 2004, J. Biol. Chem.,
Therefore, several MDM2 inhibitors have been developed to treat cancers, including (3'R,4'S,5'R)-N-[3(R,6S)-6-carbamoyltetrahydro-2H-pyran-3-yl]-6''-chloro-4'-(2-chloro-3-fluoropyridin-4-yl)-4,4-dimethyl-2''-oxo-1',2''-dihydrodispiro[cyclohexane-1,2'-pyrrole-3',3''-indole]-5''-carboxamide (WO2012/121361 and US Patent Application Publication No. 2012/0264738A).

Liposarcoma (LPS) is one of the most common soft tissue sarcoma (STS) subtype, comprising about 18 to 26% of STS cases in humans. LPS can be categorized into four subtypes: well-differentiated type (WD, 46 to 54%), de-differentiated type (DD, 18 to 26%), myxoid/round-cell type (13 to 28%) and pleomorphic type (7 to 8%). Chromosome 12 q13-15 amplification is frequently found in WD/DD LPS (i.e. up to -90% of patients) (Coindre et al., 2010, Virchows. Arch., 456:167-179, Momand et al., 1998, Nucleic Acid Research, 26 (15):3453-3459, and Rayburn et al., 2005, Current Cancer Drug Targets, 5:27-41). Thus, some of the MDM2 antagonists were developed as a therapeutic drug for liposarcoma (Ray-Coquard et al., 2012, Lancet Oncol., 13:1133-1140).

Summary of the Invention

The present invention provides a method for treating a cancer in a subject in need thereof, comprising administering a specific MDM2 inhibitor to the subject according to a specific dosage regimen and a pharmaceutical composition for use in treating a cancer according to the dosage regimen. The present invention also provides a method for treating liposarcoma in a subject in need thereof, comprising administering a specific MDM2 inhibitor to the subject and a pharmaceutical composition for use in treating liposarcoma, comprising the MDM2 inhibitor.

The inventors have discovered that solid cancers and lymphoma can be treated by orally administering to the subjects (3'R,4'S,5'R)-N-[3(R,6S)-6-carbamoyltetrahydro-2H-pyran-3-yl]-6''-chloro-4'-(2-chloro-3-fluoropyridin-4-yl)-4,4-dimethyl-2''-oxo-1',2''-dihydrodispiro[cyclohexane-1,2'-pyrrole-3',3''-indole]-5''-carboxamide (WO2012/121361 and US Patent Application Publication No. 2012/0264738A).
lidine-3',3''-indole]-5'-carboxamide (hereinafter also referred to as "Compound 1") or pharmaceutically acceptable salt thereof according to a dosage schedule, wherein the dosage schedule comprises administering a daily dose of 80 to 250 mg of the compound or salt thereof to the subject in a cyclical dosing (QD21/28 or QD28/28). The inventors have also discovered that liposarcoma can be treated with Compound 1.

[0006] The present invention provides:

(1) A pharmaceutical composition for use in treating a cancer in a subject in need thereof, comprising a therapeutically effective amount of the compound of formula (I) or pharmaceutically acceptable salt thereof, wherein the pharmaceutical composition is orally administered according to a dosage schedule comprising administering a daily dose of about 80 mg to about 250 mg of the compound or salt thereof to the subject.

(2) A pharmaceutical composition according to above (1), wherein the dosage schedule comprises administering a daily dose of about 80 mg to about 140 mg of the compound or salt thereof to the subject.

(3) A pharmaceutical composition according to above (1), wherein the dosage schedule comprises administering a daily dose of about 80 mg to about 100 mg of the compound or salt thereof to the subject.
(4) A pharmaceutical composition according to above (1), wherein the dosage schedule comprises administering a daily dose of about 90 mg of the compound or salt thereof to the subject.

(5) A pharmaceutical composition according to above (1), wherein the dosage schedule comprises administering a daily dose of about 100 mg to about 140 mg of the compound or salt thereof to the subject.

(6) A pharmaceutical composition according to above (1), wherein the dosage schedule comprises administering a daily dose of about 120 mg of the compound or salt thereof to the subject.

(7) A pharmaceutical composition for use in treating a cancer in a subject in need thereof according to any one of above (1) to (6), wherein the cancer is liposarcoma.

(8) A pharmaceutical composition for use in treating a cancer in a subject in need thereof according to above (7), wherein the cancer is a liposarcoma having amplified MDM2 genes in the genome of the liposarcoma.

(9) A pharmaceutical composition for use in treating a cancer in a subject in need thereof, comprising a therapeutically effective amount of the compound of formula (I) or pharmaceutically acceptable salt thereof, wherein the pharmaceutical composition is orally administered for at least one cycle of a cyclical dosing schedule, wherein each cycle has a dosing period of at least 10 days, in which the compound or salt thereof is administered daily at a daily dosage of about 80 mg to about 250 mg.

(10) A pharmaceutical composition according to above (9), wherein the compound or salt thereof is administered daily at a daily dosage of about 80 mg to about 140 mg.

(11) A pharmaceutical composition according to above (9), wherein the compound or salt thereof is administered daily at a daily dosage of about 80 mg to about 100 mg.

(12) A pharmaceutical composition according to above (9), wherein the compound or salt thereof is administered daily at a daily dosage of about 90 mg.

(13) A pharmaceutical composition according to above (9), wherein the compound
or salt thereof is administered daily at a daily dosage of about 100 mg to about 140 mg.

(14) A pharmaceutical composition according to above (9), wherein the compound or salt thereof is administered daily at a daily dosage of about 120 mg.

(15) A pharmaceutical composition according to above (9), wherein the compound or salt thereof is administered daily at a daily dosage of about 140 mg to about 180 mg.

(16) A pharmaceutical composition according to above (9), wherein the compound or salt thereof is administered daily at a daily dosage of about 160 mg.

(17) A pharmaceutical composition according to above (9), wherein the compound or salt thereof is administered daily at a daily dosage of about 180 mg to about 250 mg.

(18) A pharmaceutical composition according to above (9), wherein the compound or salt thereof is administered daily at a daily dosage of about 210 mg.

(19) A pharmaceutical composition for use in treating a cancer in a subject in need thereof, comprising a therapeutically effective amount of the compound of formula (I) or pharmaceutically acceptable salt thereof, wherein the pharmaceutical composition is orally administered for at least one cycle of a cyclical dosing schedule, wherein each cycle has a dosing period of about 15 days to about 25 days, in which the compound or salt thereof is administered daily at a daily dosage of about 80 mg to about 250 mg of the compound or salt thereof, followed by a rest period of about 5 days to about 10 days in which any of the compound and salt thereof is not administered.

[Chem. 1]
3-fluoropyridin-4-yl)-4,4-dimethyl-2"-oxo-1"",2"'-dihydrodispirocyclohexane-1,2'-pyrrolidine-3',3"'-indole]-5'-carboxamide

(20) A pharmaceutical composition according to any one of above (9) to (19), wherein each cycle has a dosing period of about 15 days to about 25 days, in which the compound or salt thereof is administered daily at a daily dosage of about 100 mg to about 140 mg, followed by a rest period of about 5 days to about 10 days, in which any of the compound and salt thereof is not administered.

(21) A pharmaceutical composition according to any one of above (9) to (19), wherein each cycle has a dosing period of about 15 days to about 25 days, in which the compound or salt thereof is administered daily at a daily dosage of about 120 mg, followed by a rest period of about 5 days to about 10 days, in which any of the compound and salt thereof is not administered.

(22) A pharmaceutical composition according to any one of above (9) to (19), wherein each cycle has a dosing period of about 15 days to about 25 days, in which the compound or salt thereof is administered daily at a daily dosage of about 140 mg to about 180 mg, followed by a rest period of about 5 days to about 10 days, in which any of the compound and salt thereof is not administered.

(23) A pharmaceutical composition according to any one of above (9) to (19), wherein each cycle has a dosing period of about 15 days to about 25 days, in which the compound or salt thereof is administered daily at a daily dosage of about 160 mg, followed by a rest period of about 5 days to about 10 days, in which any of the compound and salt thereof is not administered.

(24) A pharmaceutical composition according to any one of above (9) to (19), wherein each cycle has a dosing period of about 15 days to about 25 days, in which the compound or salt thereof is administered daily at a daily dosage of about 180 mg to about 250 mg, followed by a rest period of about 5 days to about 10 days, in which any of the compound and salt thereof is not administered.

(25) A pharmaceutical composition according to any one of above (9) to (19), wherein each cycle has a dosing period of about 15 days to about 25 days, in which the
compound or salt thereof is administered daily at a daily dosage of about 210 mg, followed by a rest period of about 5 days to about 10 days, in which any of the compound and salt thereof is not administered.

(26) A pharmaceutical composition according to any one of above (9) to (19), wherein each cycle has a dosing period of about 21 days, in which the compound or salt thereof is administered daily at a daily dosage of about 100 mg to about 140 mg, followed by a rest period of about 7 days, in which any of the compound and salt thereof is not administered.

(27) A pharmaceutical composition according to any one of above (9) to (19), wherein each cycle has a dosing period of about 21 days, in which the compound or salt thereof is administered daily at a daily dosage of about 140 mg to about 180 mg, followed by a rest period of about 7 days, in which any of the compound and salt thereof is not administered.

(28) A pharmaceutical composition according to any one of above (9) to (19), wherein each cycle has a dosing period of about 21 days, in which the compound or salt thereof is administered daily at a daily dosage of about 180 mg to about 250 mg, followed by a rest period of about 7 days, in which any of the compound and salt thereof is not administered.

(29) A pharmaceutical composition according to any one of above (9) to (19), wherein each cycle has a dosing period of about 15 days to about 25 days, in which the compound or salt thereof is administered daily at a daily dosage of about 80 mg to about 100 mg, followed by a rest period of about 5 days to about 10 days, in which any of the compound and salt thereof is not administered.

(30) A pharmaceutical composition according to any one of above (9) to (19), wherein each cycle has a dosing period of about 15 days to about 25 days, in which the compound or salt thereof is administered daily at a daily dosage of about 90 mg, followed by a rest period of about 5 days to about 10 days, in which any of the compound and salt thereof is not administered.

(31) A pharmaceutical composition according to any one of above (9) to (19),
wherein each cycle has a dosing period of about 21 days, in which the compound or salt thereof is administered daily at a daily dosage of about 80 mg to about 100 mg, followed by a rest period of about 7 days, in which any of the compound and salt thereof is not administered.

(32) A pharmaceutical composition according to any one of above (9) to (19), wherein each cycle has a dosing period of about 21 days, in which the compound or salt thereof is administered daily at a daily dosage of about 120 mg of the compound or salt thereof, followed by a rest period of about 7 days, in which any of the compound and salt thereof is not administered.

(33) A pharmaceutical composition according to any one of above (9) to (19), wherein each cycle has a dosing period of about 21 days, in which the compound or salt thereof is administered daily at a daily dosage of about 160 mg of the compound or salt thereof, followed by a rest period of about 7 days, in which any of the compound and salt thereof is not administered.

(34) A pharmaceutical composition according to any one of above (9) to (19), wherein each cycle has a dosing period of about 21 days, in which the compound or salt thereof is administered daily at a daily dosage of about 210 mg of the compound or salt thereof, followed by a rest period of about 7 days, in which any of the compound and salt thereof is not administered.

(35) A pharmaceutical composition according to any one of above (9) to (19), wherein each cycle has a dosing period of about 21 days, in which the compound or salt thereof is administered daily at a daily dosage of about 90 mg of the compound or salt thereof, followed by a rest period of about 7 days, in which any of the compound and salt thereof is not administered.

(36) A pharmaceutical composition for use in treating a cancer in a subject in need thereof according to any one of above (9) to (35), wherein the cancer is liposarcoma.

(37) A pharmaceutical composition for use in treating a cancer in a subject in need thereof according to above (36), wherein the cancer is a liposarcoma having amplified MDM2 genes in the genome of the liposarcoma.
(38) A pharmaceutical composition for use in treating a cancer in a subject in need thereof according to any one of above (1) to (37), wherein the compound or salt thereof is in a form of p-toluenesulfonic acid salt monohydrate (hereinafter also referred to as "Compound 2") as shown in formula (II).

(39) A pharmaceutical composition for use in treating liposarcoma, comprising (3'R,4S,5'R)-N-[(3i?,65)-6-Carbamoyltetrahydro-2 H-pyrano-3-yl]-6'″-chloro-4'-(-2-chloro-3-fluoropyridin-4-yl)-4.4-dimethyl-2"-oxo- 1",2"-dihydropyrido[cyclohexane]-1,2'-pyrrolidine-3',3"'-indole]-5'-carboxamide or pharmaceutically acceptable salt thereof.

(40) A pharmaceutical composition according to above (39), wherein liposarcoma has amplified MDM2 genes in the genome of the liposarcoma.

**Brief Description of Drawings**

[0007] Fig. 1 is a waterfall plot showing the best tumor response in all the evaluable subjects in the clinical study (n=23). Subjects with liposarcoma are indicated by the letter "L" above the bars. Baseline is defined as the last non-missing value taken before the first dose of Compound 2. For each subject, the best (minimum) percent change from baseline in the sum of diameters for all target lesions is represented by a vertical bar. The term "PD" and "SD" mean Progressive Disease and Stable Disease, respectively, as are defined in RECIST guidelines v1.1.

[0008] Fig. 2 is a waterfall plot showing the best tumor response in all the subjects suffering from liposarcoma in the clinical study (n=13). Subjects with WD and DD liposarcoma are indicated by the letter 'WD' and 'DD' above the bars, respectively.
Baseline is defined as the last non-missing value taken before the first dose of Compound 2. For each subject, the best (minimum) percent change from baseline in the sum of diameters for all target lesions is represented by a vertical bar. The term "PD" and "SD" mean Progressive Disease and Stable Disease, respectively, as are defined in RECIST guidelines v1.1.

**Detailed Description of the Invention**

[0009] The term "comprise" as used herein is intended to be an open-ended, inclusive and does not exclude additional, unrecited features, and then encompasses the closed term "consist of" or "essentially consist of.

[0010] The term "subject" refers to a mammal, especially a human, suffering or suspected of suffering from a cancer. The subject can be a subject which has been or was previously treated by other therapy. The subject can be an adult human.

[0011] The term "treat" refers to reducing the severity of the disease or slowing progression of the disease, which can be determined by physicians according to Response Evaluation in Solid Tumors guidelines (RECIST) version 1.1.

[0012] The term "MDM2" refers to an E3 ubiquitin ligase which can interact with p53 and cause p53 degradation. "MDM2" as used herein includes, but not limited to, mouse MDM2 and the human ortholog of MDM2 (also called "Human Double Minute 2" or "HDM2"). The term "MDM2 inhibitor" refers to an inhibitor inhibiting MDM2 functions or activities on p53 degradation.

[0013] The term "binding" refers generally to an interaction or association between two substances or molecules, such as the hybridization of one nucleic acid molecule to another (or to itself); the association of an antibody with a polypeptide, protein, or peptide; or the association of a protein with another protein or nucleic acid molecule. An oligonucleotide molecule binds or stably binds to a target nucleic acid molecule if a sufficient amount of the oligonucleotide molecule forms base pairs or is hybridized to its target nucleic acid molecule, to permit detection of that binding. Preferentially, binding refers to an association in which one molecule binds to another with high affinity, and binds to heterologous molecules at a low affinity. Binding can be detected by any
procedure known to one skilled in the art, such as by physical or functional properties of the target/oligonucleotide complex. For example, binding can be detected functionally by determining whether there is an observable effect upon a biosynthetic process, e.g., expression of a gene, DNA replication, transcription, translation, etc.

[0014] The term "gene" as used herein refers to a DNA sequence which is expressed in a subject as an RNA transcript; a gene can be a full-length gene (protein encoding or non-encoding).

[0015] As used in accordance with the present invention, "gene expression" means the process of converting genetic information encoded in a gene into RNA (e.g., mRNA, rRNA, tRNA, or snRNA) through transcription of the gene (e.g., as mediated by the enzymatic action of an RNA polymerase), and for protein-encoding genes, into protein through "translation" of mRNA.

[0016] The term "cancer" as used herein is understood to encompass neoplasms and tumors, which refer to abnormal growths or abnormally growing cells that can invade surrounding tissues and spread to other organs, i.e., become malignant, if left untreated. Neoplasms are abnormal growths (or masses) of tissues comprised of cells that form as a result of neoplasia, which is the abnormal growth and proliferation of cells, either malignant or benign. Neoplasms and tumors can include the abnormal growths of precancerous and cancerous cells and tissues, which grow more rapidly than normal cells and that will continue to grow and compete with normal cells for nutrients if not treated. Neoplasms may include, without limitation, solid and non-solid tumors, such as hollow or liquid-filled tumors, and also hematological cell neoplasias or neoplasms, e.g., lymphomas, leukemias and myelomas.

[0017] The term "cancer" is also intended to embrace neoplasms and tumors of various origins within and on the body, various types and subtypes, as well as organ, tissue and cell samples and specimens, e.g., biological samples or specimens, thereof. Illustratively, appropriate cancer samples or specimens include any conventional biological samples or specimens, including clinical samples obtained from a human, e.g., a patient undergoing treatment for cancer, or a veterinary subject. A sample may refer to a part of a tissue that is a diseased or healthy portion of the tissue, or to the entire
tissue. Tissue samples can be obtained from a subject by employing any method or procedure as known and practiced in the art.

[0018] The term "liposarcoma" is one of the most commons soft tissue sarcomas in adults that resemble fat cells in a histological section under a microscope. Liposarcoma represents about 18 to 26% of soft tissue sarcomas. According to its pathological study, liposarcomas can be classified into four subtypes: well-differentiated (WD, 46 to 54%), de-differentiated (DD, 18 to 26%), myxoid/round-cell (13 to 28%), and pleomorphic (7 to 8%) liposarcomas. Chromosome 12 qL3-15 amplification is frequently found in a subject suffering from liposarcoma, such as WD or DD liposarcomas. It is known that MDM2 gene is located on Chromosome 12 qL3-15 and therefore it is presumed that MDM2 genes are frequently amplified in a subject suffering from liposarcoma.

[0019] The term "pharmaceutically acceptable salt" refers to salts of the active compounds which are relatively nontoxic acid or base addition salts. Non-limited examples of the acid addition salts include hydrochloric, hydrobromic, nitric, carbonic, phosphoric, acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, fumaric, lactic, benzenesulfonic, p-toluenesulfonic, citric, tartaric, oxalic, and methanesulfonic acids. The term "pharmaceutically acceptable salt" includes pharmaceutically acceptable solvate or salt thereof. The solvate is a stoichiometric complex of a molecule and one or more solvent molecules. Non-limited examples of pharmaceutically acceptable solvates include water, methanol, ethanol, dimethylsulfoxide, and acetate as solvent. A solvate which contains water as solvent is hydrate. In a preferable embodiment of the invention, the pharmaceutically acceptable salt of the compound can be hydrate and more preferably monohydrate.

[0020] The term "about" used herein refers to the specific value subsequent to the term and a range of values ± 10% of the specific value. For example, the phrase "about 100" refers to 100, which is the specific value in this case, and a range of 90 to 110.

[0021] The compound of formula (I):

\[(3'R,4'S,5'R)-(\text{3'R,6S})-6\text{-carbamoyltetrahydro-2H-pyran-3-yl})-6'-\text{chloro-4'}-(2\text{-chloro-}
\]
3-fluoropyridin-4-yl)-4,4-dimethyl^ "-oxo-1",2"-dihydrodispiro[cyclohexane-1,2'-pyrro
didine-3',3''-indole]-5'-carboxamide and pharmaceutically acceptable salts thereof,
including the p-toluenesulfonate thereof, are disclosed as one of MDM2 inhibitors (see,
No. 2012/0264738A, which are incorporated by reference herein in its entirety).

Unless otherwise indicated, the compound of formula (I) means the compound and
pharmaceutically acceptable salt and pharmaceutically acceptable solvate, and prodrug
thereof.

[0022] In one of the most preferable embodiments of the invention, this compound can
be the compound of formula (II):

(3'R,4'S,5'R)-N-[(3R,6S)-6-carbamoyltetrahydro-2H-pyran-3-yl]-6''-chloro-4'-((2-chloro-
3-fluoropyridin-4-yl)-4,4-dimethyl-2"-oxo-1",2"-dihydrodispiro[cyclohexane-1,2'-pyrro
lidine-3',3''-indole]-5'-carboxamide mono(4-methylbenzenesulfonate) monohydrate
(also referred to as mono p-toluenesulfonate monohydrate of the compound).

[Chem. 2]
[0023] The compound of formula (I) can be administered once daily to a subject suffering from a cancer according to a dosage schedule of the present invention in order to treat the cancer in the subject.

[0024] In a preferable embodiment of the invention, the compound of formula (I) can be orally administered to the subject at a daily dose of about 80 mg to about 250 mg of the compound. In a particular embodiment of the invention, the compound of formula (I) can be orally administered to the subject at a daily dose of about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, or about 250 mg.

[0025] In a preferable embodiment of the invention, the compound of formula (I) can be orally administered to the subject at a daily dose of about 80 mg to about 140 mg, more preferably about 80 mg to about 100 mg, still more preferably about 90 mg of the compound for at least one week, two weeks, three weeks, four weeks or more.

[0026] In a preferable embodiment of the invention, the compound of formula (I) can be orally administered to the subject at a daily dose of about 100 mg to about 140 mg, more preferably about 120 mg of the compound for at least one week, two weeks, three weeks, four weeks or more. In another preferable embodiment of the invention, the compound of formula (I) can be orally administered to the subject at a daily dose of about 140 mg to about 180 mg, more preferably about 160 mg of the compound for at least one week, two weeks, three weeks, four weeks or more. In another preferable embodiment of the invention, the compound of formula (I) can be orally administered to the subject at a daily dose of about 180 mg to about 250 mg, more preferably about 210 mg of the compound for at least one week, two weeks, three weeks, four weeks or more.

[0027] In a preferable embodiment of the invention, the compound of formula (I) or pharmaceutically acceptable salt thereof is orally administered for at least one cycle of a cyclical dosing schedule, wherein each cycle has a dosing period of at least 10 days, in which the compound or salt thereof is administered daily at a daily dosage of about 80 mg to about 250 mg is provided. In this embodiment, the dosing period is preferably at least 15 days, more preferably between about 15 days to about 25 days, still more
preferably about 21 days, and the daily dosage is preferably about 80 mg to about 100 mg or about 100 mg to 140 mg, more preferably about 90 mg or about 120 mg. In another embodiment, the dosing period is preferably at least 15 days, more preferably between about 15 days to about 25 days, still more preferably about 21 days, and the daily dosage is preferably about 140 mg to about 180 mg or about 180 mg to 250 mg, more preferably about 160 mg or about 210 mg. In a specific embodiment, the dosing period is at least 15 days and the daily dosage is about 80 mg to about 100 mg, more preferably about 90 mg. In another specific embodiment, the dosing period is at least 15 days and the daily dosage is about 100 mg to about 140 mg, more preferably about 120 mg. In a specific embodiment, the dosing period is at least 15 days and the daily dosage is about 140 mg to about 180 mg, more preferably about 160 mg. In another specific embodiment, the dosing period is at least 15 days and the daily dosage is about 180 mg to about 250 mg, more preferably about 210 mg.

[0028] In another preferable embodiment of the invention, the compound of formula (I) can be orally administered to the subject at a daily dose of about 100 mg to about 140 mg, more preferably about 120 mg of the compound for at least one cycle of a cyclical dosing schedule, wherein each cycle has a dosing period of about 15 days to about 25 days, in which the compound is administered daily at the above-mentioned dose, followed by a rest period of about 5 days to about 10 days in which any of the compounds is not administered. In a specific embodiment of the invention, the compound of formula (I) can be orally administered to the subject at a daily dose of about 120 mg of the compound for at least one cycle of a cyclical dosing schedule, wherein each cycle has a dosing period of about 15 days to about 25 days, more preferably about 21 days, in which the compound is administered daily at the above-mentioned dose, followed by a rest period of about 5 days to about 10 days, more preferably about 7 days in which any of the compounds is not administered. In a specific embodiment of the invention, the compound of formula (I) can be orally administered to the subject at a daily dose of about 120 mg of the compound for at least one cycle of a cyclical dosing schedule, wherein each cycle has a dosing period of about 21 days, in which the compound is administered daily at the above-mentioned dose, followed by a rest period of about 7 days in which any of the compounds is not administered.
In another preferable embodiment of the invention, the compound of formula (I) can be orally administered to the subject at a daily dose of about 80 mg to about 100 mg, more preferably about 90 mg of the compound for at least one cycle of a cyclical dosing schedule, wherein each cycle has a dosing period of about 15 days to about 25 days, in which the compound is administered daily at the above-mentioned dose, followed by a rest period of about 5 days to about 10 days in which any of the compounds is not administered. In more specific embodiment of the invention, the compound of formula (I) can be orally administered to the subject at a daily dose of about 90 mg of the compound for at least one cycle of a cyclical dosing schedule, wherein each cycle has a dosing period of about 15 days to about 25 days, more preferably about 21 days, in which the compound is administered daily at the above-mentioned dose, followed by a rest period of about 5 days to about 10 days, more preferably about 7 days in which any of the compounds is not administered. In a specific embodiment, the compound of formula (I) can be orally administered to the subject at a daily dose of about 90 mg of the compound for at least one cycle of a cyclical dosing schedule, wherein each cycle has a dosing period of about 21 days, in which the compound is administered daily at the above-mentioned dose, followed by a rest period of about 7 days in which any of the compounds is not administered.

In another preferable embodiment of the invention, the compound of formula (I) can be orally administered to the subject at a daily dose of about 140 mg to about 180 mg, more preferably about 160 mg of the compound for at least one cycle of a cyclical dosing schedule, wherein each cycle has a dosing period of about 15 days to about 25 days, in which the compound is administered daily at the above-mentioned dose, followed by a rest period of about 5 days to about 10 days in which any of the compounds is not administered. In a specific embodiment of the invention, the compound of formula (I) can be orally administered to the subject at a daily dose of about 160 mg of the compound for at least one cycle of a cyclical dosing schedule, wherein each cycle has a dosing period of about 15 days to about 25 days, more preferably about 21 days, in which the compound is administered daily at the above-mentioned dose, followed by a rest period of about 5 days to about 10 days, more preferably about 7 days in which any of the compounds is not administered. In a specific embodiment of the invention, the compound of formula (I) can be orally
administered to the subject at a daily dose of about 160 mg of the compound for at least one cycle of a cyclical dosing schedule, wherein each cycle has a dosing period of about 21 days, in which the compound is administered daily at the above-mentioned dose, followed by a rest period of about 7 days in which any of the compounds is not administered.

[0031] In another preferable embodiment of the invention, the compound of formula (I) can be orally administered to the subject at a daily dose of about 180 mg to about 250 mg, more preferably about 210 mg of the compound for at least one cycle of a cyclical dosing schedule, wherein each cycle has a dosing period of about 15 days to about 25 days, in which the compound is administered daily at the above-mentioned dose, followed by a rest period of about 5 days to about 10 days in which any of the compounds is not administered. In a specific embodiment of the invention, the compound of formula (I) can be orally administered to the subject at a daily dose of about 210 mg of the compound for at least one cycle of a cyclical dosing schedule, wherein each cycle has a dosing period of about 15 days to about 25 days, more preferably about 21 days, in which the compound is administered daily at the above-mentioned dose, followed by a rest period of about 5 days to about 10 days, more preferably about 7 days in which any of the compounds is not administered. In a specific embodiment of the invention, the compound of formula (I) can be orally administered to the subject at a daily dose of about 210 mg of the compound for at least one cycle of a cyclical dosing schedule, wherein each cycle has a dosing period of about 21 days, in which the compound is administered daily at the above-mentioned dose, followed by a rest period of about 7 days in which any of the compounds is not administered.

[0032] In the invention, cancers to be treated includes, but not limited to, solid cancers and hematological cancers. Solid cancers to be treated in the invention include, but not limited to, soft tissue sarcoma, such as liposarcoma, melanoma, neuroendocrine cancer, adenoid cystic cancer, leiomyosarcoma, colorectal cancer, renal cancer, lung cancer, chordoma, salivary adenocarcinoma, adrenocortical carcinoma, and maxillary sinus adenocarcinoma. Hematological cancers to be treated in the invention include, but not limited to, lymphoma. In a preferable embodiment of the invention, solid
cancers to be treated can be liposarcoma such as DD or WD liposarcoma.

[0033] The compound of formula (I) can act as an MDM2 inhibitor. MDM2 is a negative regulator of the p53 tumor suppressor protein. The 90 kDa MDM2 protein contains a p53 binding domain at its N-terminus and a RING (really interesting new gene) domain at its C-terminus, which functions as an E3 ligase that ubiquinates p53. The activation of wild-type p53 by cell stimuli and stresses results in the binding of MDM2 to p53 at the N-terminus to inhibit the transcriptional activation of p53 and promote the degradation of p53 via the ubiquitin-proteosome pathway. Thus, MDM2 can interfere with p53-mediated apoptosis and arrest of cancer cell proliferation, attributing a significant oncogenic activity to MDM2 in cancer cells. In some cases, MDM2 can cause carcinogenesis independent of the p53 pathway, for example, in cells which possess an alternative splice form of MDM2. (H.A. Steinman et al., 2004, J. Biol. Chem., 279(6):4877-4886). In addition, about 50% of human cancers are observed to have a mutation in or deletion of the TP53 gene. MDM2 is overexpressed in a number of human cancers, including, for example, melanoma, non-small cell lung cancer (NSCLC), breast cancer, esophageal cancer, leukemia, non-Hodgkin's lymphoma and sarcoma. Overexpression of MDM2 has been reported to correlate positively with poor prognosis in individuals having sarcoma, glioma and acute lymphoblastic leukemia (ALL).

[0034] Therefore, it is preferable that cancers to be treated in the invention have amplified MDM2 genes or have MDM2 overexpressed in the cancer. In a specific embodiment of the invention, cancers to be treated in the invention can be liposarcoma which have amplified MDM2 genes on the genome of the cancer.

[0035] It is also preferable that cancers to be treated in the invention have wild-type TP53 gene on the genome of the cancer. In a specific embodiment of the invention, cancers to be treated in the invention can be liposarcoma (for example, DD or WD liposarcoma) which has wild-type TP53 gene on the genome of the cancer.

[0036] In a more specific embodiment of the invention, cancers to be treated in the invention can be liposarcoma which has wild-type TP53 gene and amplified MDM2 genes on the genome of the cancer.
[0037] In these specific embodiments, the cancers which have wild-type TP53 gene and/or amplified MDM2 genes on the genome of the cancer can effectively be treated by the administration of the compound of formula (I), which can act as a MDM2 inhibitor.

5 [0038] In an embodiment of the invention, the pharmaceutical composition for use in treating a cancer in a subject in need thereof, comprising the compound of formula (I) or pharmaceutically acceptable salt thereof, wherein the pharmaceutical composition is orally administered to the subject according to a dosage schedule comprising administering to the subject a daily dose of about 80 mg to about 250 mg, more preferably about 100 mg to about 140 mg, about 140 mg to about 180 mg, or about 180 mg to about 250 mg of the compound or salt thereof is provided.

10 [0039] In an embodiment of the invention, the pharmaceutical composition for use in treating a cancer in a subject in need thereof, comprising the compound of formula (II), wherein the pharmaceutical composition is orally administered to the subject according to a dosage schedule comprising administering to the subject a daily dose of about 80 mg to about 250 mg, more preferably about 100 mg to about 140 mg, about 140 mg to about 180 mg, or about 180 mg to about 250 mg of the compound is provided.

15 [0040] In an embodiment of the invention, the present pharmaceutical composition for use in treating a cancer in a subject in need thereof, comprising the compound of formula (II), wherein the pharmaceutical composition is orally administered to the subject according to a dosage schedule comprising administering to the subject a daily dose of about 80 mg to about 250 mg, more preferably about 100 mg to about 140 mg, about 140 mg to about 180 mg, or about 180 mg to about 250 mg of the compound, wherein the cancer is liposarcoma such as DD or WD liposarcoma. In a specific embodiment, the daily dose is between about 100 mg to about 140 mg, and the cancer is liposarcoma such as DD or WD liposarcoma.

20 [0041] In an embodiment of the invention, the pharmaceutical composition for use in treating a cancer in a subject in need thereof, comprising a therapeutically effective amount of the compound of formula (I) or pharmaceutically acceptable salt thereof, wherein the pharmaceutical composition is orally administered to the subject for at least
one cycle of a cyclical dosing schedule, wherein each cycle has a dosing period of at least 10 days, at least 11 days, at least 12 days, at least 13 days, at least 14 days or at least 15 days, in which the compound or salt thereof is administered to the subject daily at a daily dosage of about 80 mg to about 140 mg. In a specific embodiment, the daily dosage is between about 100 mg to about 140 mg. In a specific embodiment of the invention, the dosing period is between about 15 days to about 25 days, more preferably about 21 days. In a specific embodiment of the invention, the dosing period is between about 15 days to about 25 days and the daily dosage is about 100 mg to about 140 mg. In a specific embodiment of the invention, the dosing period is about 21 days and the daily dosage is about 100 mg to about 140 mg, the dosing period is between about 15 days to about 25 days and the daily dosage is about 120 mg, or the dosing period is about 21 days and the daily dosage is about 120 mg.

[0042] In an embodiment of the invention, the pharmaceutical composition for use in treating a cancer in a subject in need thereof, comprising a therapeutically effective amount of the compound of formula (I) or pharmaceutically acceptable salt thereof, wherein the pharmaceutical composition is orally administered to the subject for at least one cycle of a cyclical dosing schedule, wherein each cycle has a dosing period of at least 10 days, at least 11 days, at least 12 days, at least 13 days, at least 14 days or at least 15 days, in which the compound or salt thereof is administered to the subject daily at a daily dosage of about 140 mg to about 180 mg. In a specific embodiment of the invention, the dosing period is between about 15 days to about 25 days, more preferably about 21 days. In a specific embodiment of the invention, the dosing period is between about 15 days to about 25 days and the daily dosage is about 140 mg to about 180 mg. In a specific embodiment of the invention, the dosing period is about 21 days and the daily dosage is about 140 mg to about 180 mg, the dosing period is between about 15 days to about 25 days and the daily dosage is about 160 mg, or the dosing period is about 21 days and the daily dosage is about 160 mg.

[0043] In an embodiment of the invention, the pharmaceutical composition for use in treating a cancer in a subject in need thereof, comprising a therapeutically effective amount of the compound of formula (I) or pharmaceutically acceptable salt thereof, wherein the pharmaceutical composition is orally administered to the subject for at least
one cycle of a cyclical dosing schedule, wherein each cycle has a dosing period of at least 10 days, at least 11 days, at least 12 days, at least 13 days, at least 14 days or at least 15 days, in which the compound or salt thereof is administered to the subject daily at a daily dosage of about 180 mg to about 250 mg. In a specific embodiment of the invention, the dosing period is between about 15 days to about 25 days, more preferably about 21 days. In a specific embodiment of the invention, the dosing period is between about 15 days to about 25 days and the daily dosage is about 180 mg to about 250 mg. In a specific embodiment of the invention, the dosing period is about 21 days and the daily dosage is about 180 mg to about 250 mg, the dosing period is between about 15 days to about 25 days and the daily dosage is about 210 mg, or the dosing period is about 21 days and the daily dosage is about 210 mg.

[0044] In an embodiment of the invention, the pharmaceutical composition for use in treating a cancer in a subject in need thereof, comprising a therapeutically effective amount of the compound of formula (I) or pharmaceutically acceptable salt thereof, wherein the pharmaceutical composition is orally administered to the subject for at least one cycle of a cyclical dosing schedule, wherein each cycle has a dosing period of at least 10 days, at least 11 days, at least 12 days, at least 13 days, at least 14 days or at least 15 days, in which the compound or salt thereof is administered to the subject daily at a daily dosage of about 80 mg to about 100 mg. In a specific embodiment of the invention, the dosing period is between about 15 days to about 25 days, more preferably about 21 days. In a specific embodiment of the invention, the dosing period is about 21 days and the daily dosage is about 80 mg to about 100 mg.

[0045] In an embodiment of the invention, the pharmaceutical composition for use in treating a cancer in a subject in need thereof, comprising a therapeutically effective amount of the compound of formula (I) or pharmaceutically acceptable salt thereof, wherein the pharmaceutical composition is orally administered to the subject for at least one cycle of a cyclical dosing schedule, wherein each cycle has a dosing period of about 15 days to about 25 days, preferably about 21 days, in which the compound or salt thereof is administered to the subject daily at a daily dosage of about 100 mg to about 140 mg, more preferably about 120 mg, followed by a rest period of about 5 days to about 10 days, preferably about 7 days, in which any of the compound and salt thereof is
not administered, is provided.

[0046] In an embodiment of the invention, the present pharmaceutical composition for use in treating a cancer in a subject in need thereof, comprising a therapeutically effective amount of the compound of formula (I) or pharmaceutically acceptable salt thereof, wherein the pharmaceutical composition is orally administered for at least one cycle of a cyclical dosing schedule, wherein each cycle has a dosing period of about 21 days, in which the compound or salt thereof is administered to the subject daily at a daily dosage of about 100 mg to about 140 mg, more preferably about 120 mg, followed by a rest period of about 7 days in which any of the compound and salt thereof is not administered, is provided.

[0047] In an embodiment of the invention, the pharmaceutical composition for use in treating a cancer in a subject in need thereof, comprising a therapeutically effective amount of the compound of formula (I) or pharmaceutically acceptable salt thereof, wherein the pharmaceutical composition is orally administered to the subject for at least one cycle of a cyclical dosing schedule, wherein each cycle has a dosing period of about 15 days to about 25 days, preferably about 21 days, in which the compound or salt thereof is administered to the subject daily at a daily dosage of about 140 mg to about 180 mg, more preferably about 160 mg, followed by a rest period of about 5 days to about 10 days, preferably about 7 days, in which any of the compound and salt thereof is not administered, is provided.

[0048] In an embodiment of the invention, the present pharmaceutical composition for use in treating a cancer in a subject in need thereof, comprising a therapeutically effective amount of the compound of formula (I) or pharmaceutically acceptable salt thereof, wherein the pharmaceutical composition is orally administered for at least one cycle of a cyclical dosing schedule, wherein each cycle has a dosing period of about 21 days, in which the compound or salt thereof is administered to the subject daily at a daily dosage of about 140 mg to about 180 mg, more preferably about 160 mg, followed by a rest period of about 7 days in which any of the compound and salt thereof is not administered, is provided.

[0049] In an embodiment of the invention, the pharmaceutical composition for use in
treating a cancer in a subject in need thereof, comprising a therapeutically effective amount of the compound of formula (I) or pharmaceutically acceptable salt thereof, wherein the pharmaceutical composition is orally administered to the subject for at least one cycle of a cyclical dosing schedule, wherein each cycle has a dosing period of about 15 days to about 25 days, preferably about 21 days, in which the compound or salt thereof is administered to the subject daily at a daily dosage of about 180 mg to about 250 mg, more preferably about 210 mg, followed by a rest period of about 5 days to about 10 days, preferably about 7 days, in which any of the compound and salt thereof is not administered, is provided.

[0050] In an embodiment of the invention, the present pharmaceutical composition for use in treating a cancer in a subject in need thereof, comprising a therapeutically effective amount of the compound of formula (I) or pharmaceutically acceptable salt thereof, wherein the pharmaceutical composition is orally administered for at least one cycle of a cyclical dosing schedule, wherein each cycle has a dosing period of about 21 days, in which the compound or salt thereof is administered to the subject daily at a daily dosage of about 180 mg to about 250 mg, more preferably about 210 mg, followed by a rest period of about 7 days in which any of the compound and salt thereof is not administered, is provided.

[0051] In an embodiment of the invention, the pharmaceutical composition for use in treating a cancer in a subject in need thereof, comprising a therapeutically effective amount of the compound of formula (I) or pharmaceutically acceptable salt thereof, wherein the pharmaceutical composition is orally administered to the subject for at least one cycle of a cyclical dosing schedule, wherein each cycle has a dosing period of about 15 days to about 25 days, preferably about 21 days, in which the compound or salt thereof is administered to the subject daily at a daily dosage of about 80 mg to about 100 mg, more preferably about 90 mg, followed by a rest period of about 5 days to about 10 days, preferably about 7 days, in which any of the compound and salt thereof is not administered, is provided.

[0052] In an embodiment of the invention, the present pharmaceutical composition for use in treating a cancer in a subject in need thereof, comprising a therapeutically
effective amount of the compound of formula (I) or pharmaceutically acceptable salt thereof, wherein the pharmaceutical composition is orally administered for at least one cycle of a cyclical dosing schedule, wherein each cycle has a dosing period of about 21 days, in which the compound or salt thereof is administered to the subject daily at a daily dosage of about 80 mg to about 100 mg, more preferably about 90 mg, followed by a rest period of about 7 days in which any of the compound and salt thereof is not administered, is provided.

[0053] In an embodiment of the invention, the present pharmaceutical composition for use in treating a cancer in a subject in need thereof, comprising a therapeutically effective amount of the compound of formula (II), wherein the pharmaceutical composition is orally administered to the subject for at least one cycle of a cyclical dosing schedule, wherein each cycle has a dosing period of about 15 days to about 25 days, preferably about 21 days, in which the compound is administered daily at a daily dosage of about 80 mg to about 140 mg, preferably about 100 mg to about 140 mg, more preferably about 120 mg, followed by a rest period of about 5 days to about 10 days, preferably about 7 days, in which the compound is not administered, is provided. In a specific embodiment of the invention, the daily dosage is between about 100 mg to about 140 mg, the dosing period is between about 15 days to about 25 days, and the rest period is between about 5 days to about 10 days. In another specific embodiment of the invention, the daily dosage is about 120 mg, the dosing period is between about 15 days to about 25 days, and the rest period is between about 5 days to about 10 days. In another specific embodiment of the invention, the daily dosage is between about 100 mg to about 140 mg, the dosing period is about 21 days, and the rest period is about 7 days. In another specific embodiment of the invention, the daily dosage is about 120 mg, the dosing period is about 21 days, and the rest period is about 7 days.

[0054] In an embodiment of the invention, the present pharmaceutical composition for use in treating a cancer in a subject in need thereof, comprising a therapeutically effective amount of the compound of formula (II), wherein the pharmaceutical composition is orally administered to the subject for at least one cycle of a cyclical dosing schedule, wherein each cycle has a dosing period of about 15 days to about 25 days, preferably about 21 days, in which the compound is administered daily at a daily
dosage of about 140 mg to about 180 mg, more preferably about 160 mg, followed by a
rest period of about 5 days to about 10 days, preferably about 7 days, in which the
compound is not administered, is provided. In a specific embodiment of the invention,
the daily dosage is between about 140 mg to about 180 mg, the dosing period is
between about 15 days to about 25 days, and the rest period is between about 5 days to
about 10 days. In another specific embodiment of the invention, the daily dosage is
about 160 mg, the dosing period is between about 15 days to about 25 days, and the rest
period is between about 5 days to about 10 days. In another specific embodiment of
the invention, the daily dosage is between about 140 mg to about 180 mg, the dosing
period is about 21 days, and the rest period is about 7 days. In another specific
embodiment of the invention, the daily dosage is about 160 mg, the dosing period is
about 21 days, and the rest period is about 7 days.

[0055] In an embodiment of the invention, the present pharmaceutical composition for
use in treating a cancer in a subject in need thereof, comprising a therapeutically
effective amount of the compound of formula (II), wherein the pharmaceutical
composition is orally administered to the subject for at least one cycle of a cyclical
dosing schedule, wherein each cycle has a dosing period of about 15 days to about 25
days, preferably about 21 days, in which the compound is administered daily at a daily
dosage of about 180 mg to about 250 mg, more preferably about 210 mg, followed by a
rest period of about 5 days to about 10 days, preferably about 7 days, in which the
compound is not administered, is provided. In a specific embodiment of the invention,
the daily dosage is between about 180 mg to about 250 mg, the dosing period is
between about 15 days to about 25 days, and the rest period is between about 5 days to
about 10 days. In another specific embodiment of the invention, the daily dosage is
about 210 mg, the dosing period is between about 15 days to about 25 days, and the rest
period is between about 5 days to about 10 days. In another specific embodiment of
the invention, the daily dosage is between about 180 mg to about 250 mg, the dosing
period is about 21 days, and the rest period is about 7 days. In another specific
embodiment of the invention, the daily dosage is about 180 mg, the dosing period is
about 21 days, and the rest period is about 7 days.

[0056] In an embodiment of the invention, the present pharmaceutical composition for
use in treating a cancer in a subject in need thereof, comprising a therapeutically effective amount of the compound of formula (II), wherein the pharmaceutical composition is orally administered for at least one cycle of a cyclical dosing schedule, wherein each cycle has a dosing period of about 15 days to about 25 days, preferably about 21 days, in which the compound or salt thereof is administered daily at a daily dosage of about 80 mg to about 140 mg, preferably about 100 mg to about 140 mg, more preferably about 120 mg, followed by a rest period of about 5 days to about 10 days, preferably about 7 days, in which the compound is not administered, wherein the cancer is liposarcoma such as DD or WD liposarcoma is provided. In a specific embodiment of the invention, the daily dosage is between about 100 mg to about 140 mg, the dosing period is between about 15 days to about 25 days, and the rest period is between about 5 days to about 10 days. In another specific embodiment of the invention, the daily dosage is about 120 mg, the dosing period is between about 15 days to about 25 days, and the rest period is between about 5 days to about 10 days. In another specific embodiment of the invention, the daily dosage is between about 100 mg to about 140 mg, the dosing period is about 21 days, and the rest period is about 7 days. In another specific embodiment of the invention, the daily dosage is about 120 mg, the dosing period is about 21 days, and the rest period is about 7 days.

[0057] In an embodiment of the invention, the present pharmaceutical composition for use in treating a cancer in a subject in need thereof, comprising a therapeutically effective amount of the compound of formula (II), wherein the pharmaceutical composition is orally administered for at least one cycle of a cyclical dosing schedule, wherein each cycle has a dosing period of about 15 days to about 25 days, preferably about 21 days, in which the compound or salt thereof is administered daily at a daily dosage of about 140 mg to about 180 mg, more preferably about 160 mg, followed by a rest period of about 5 days to about 10 days, preferably about 7 days, in which the compound is not administered, wherein the cancer is liposarcoma, for example, DD or WD liposarcoma is provided. In a specific embodiment of the invention, the daily dosage is between about 140 mg to about 180 mg, the dosing period is between about 15 days to about 25 days, and the rest period is between about 5 days to about 10 days. In another specific embodiment of the invention, the daily dosage is about 160 mg, the dosing period is between about 15 days to about 25 days, and the rest period is between about
about 5 days to about 10 days. In another specific embodiment of the invention, the daily dosage is between about 140 mg to about 180 mg, the dosing period is about 21 days, and the rest period is about 7 days. In another specific embodiment of the invention, the daily dosage is about 160 mg, the dosing period is about 21 days, and the rest period is about 7 days.

[0058] In an embodiment of the invention, the present pharmaceutical composition for use in treating a cancer in a subject in need thereof, comprising a therapeutically effective amount of the compound of formula (II), wherein the pharmaceutical composition is orally administered for at least one cycle of a cyclical dosing schedule, wherein each cycle has a dosing period of about 15 days to about 25 days, preferably about 21 days, in which the compound or salt thereof is administered daily at a daily dosage of about 180 mg to about 250 mg, more preferably about 210 mg, followed by a rest period of about 5 days to about 10 days, preferably about 7 days, in which the compound is not administered, wherein the cancer is liposarcoma such as DD or WD liposarcoma is provided. In a specific embodiment of the invention, the daily dosage is between about 180 mg to about 250 mg, the dosing period is between about 15 days to about 25 days, and the rest period is between about 5 days to about 10 days. In another specific embodiment of the invention, the daily dosage is about 210 mg, the dosing period is between about 15 days to about 25 days, and the rest period is between about 5 days to about 10 days. In another specific embodiment of the invention, the daily dosage is between about 180 mg to about 250 mg, the dosing period is about 21 days, and the rest period is about 7 days. In another specific embodiment of the invention, the daily dosage is about 210 mg, the dosing period is about 21 days, and the rest period is about 7 days.

[0059] In an embodiment of the invention, the present pharmaceutical composition for use in treating a cancer in a subject in need thereof, comprising a therapeutically effective amount of the compound of formula (II), wherein the pharmaceutical composition is orally administered to the subject for at least one cycle of a cyclical dosing schedule, wherein each cycle has a dosing period of about 15 days to about 25 days, preferably about 21 days, in which the compound or salt thereof is administered daily at a daily dosage of about 80 mg to about 100 mg, more preferably 90 mg, of the
compound, followed by a rest period of about 5 days to about 10 days, preferably about 7 days, in which the compound is not administered, is provided. In a specific embodiment of the invention, the daily dosage is about 90 mg, the dosing period is between about 15 days to about 25 days, and the rest period is between about 5 days to about 10 days. In another specific embodiment of the invention, the daily dosage is between about 80 mg to about 100 mg, the dosing period is about 21 days, and the rest period is about 7 days. In another specific embodiment of the invention, the daily dosage is about 90 mg, the dosing period is about 21 days, and the rest period is about 7 days.

[0060] In an embodiment of the invention, the present pharmaceutical composition for use in treating a cancer in a subject in need thereof, comprising a therapeutically effective amount of the compound of formula (II), wherein the pharmaceutical composition is orally administered for at least one cycle of a cyclical dosing schedule, wherein each cycle has a dosing period of about 15 days to about 25 days, preferably about 21 days, in which the compound or salt thereof is administered daily at a daily dosage of about 80 mg to about 100 mg of the compound, followed by a rest period of about 5 days to about 10 days, preferably about 7 days, in which the compound is not administered, wherein the cancer is liposarcoma such as DD or WD liposarcoma is provided. In a specific embodiment of the invention, the daily dosage is about 90 mg, the dosing period is between about 15 days to about 25 days, and the rest period is between about 5 days to about 10 days. In another specific embodiment of the invention, the daily dosage is between about 80 mg to about 100 mg, the dosing period is about 21 days, and the rest period is about 7 days. In another specific embodiment of the invention, the daily dosage is about 90 mg, the dosing period is about 21 days, and the rest period is about 7 days.

[0061] In an embodiment of the invention, the pharmaceutical composition may comprise a pharmaceutically acceptable excipient (for example, vehicles, adjuvants and additives such as bulking agent, viscosity-increasing agent, adhesive, plasticizer, binder, disintegrant, tablet lubricant, glidant, coating agent, antioxidant, preservative, humectant, opacifying agent, polishing agent, sweetening agent, aroma, flavors, and colorant) and can be prepared as a pharmaceutical composition for oral administration.
[0062] The pharmaceutical composition of the invention can be formulated by the ordinary skill in the art. The pharmaceutical composition for oral administration can be tablets, powders, granules, capsules, pills, troches, solutions, syrups, elixirs, emulsions, and oily or aqueous suspension. Pharmaceutical solutions can be made by forming acid addition salt using a pharmaceutically acceptable acid such as p-toluenesulfonate.

[0063] The compound of formula (I) or (II) can be easily prepared by those skilled in the art according to Example 70 of WO2012/121361 and Example 7 of WO2014/038606, which patent documents are incorporated by reference herein in its entirety. The compound of formula (II) may be prepared in a form of crystal.

[0064] In another aspect of the invention, a method for treating a cancer in a subject in need thereof, comprising orally and daily administering to the subject a therapeutically effective amount of the compound of formula (I) or pharmaceutically acceptable salt thereof according to a dosage schedule, wherein the dosage schedule comprises administering a daily dose of about 80 mg to about 250 mg of the compound or salt thereof to the subject. In a preferable embodiment of the dosage schedule, a daily dose of the compound or salt thereof is preferably between about 100 mg to about 140 mg, and more preferably about 120 mg. In a preferable embodiment of the dosage schedule, a daily dose of the compound or salt thereof is preferably between about 140 mg to about 180 mg, and more preferably about 160 mg. In a preferable embodiment of the dosage schedule, a daily dose of the compound or salt thereof is preferably between about 180 mg to about 250 mg, and more preferably about 210 mg. In a preferable embodiment of the dosage schedule, a daily dose of the compound or salt thereof is preferably between about 80 mg to about 100 mg, and more preferably about 90 mg. In a preferable embodiment, a cancer to be treated can be liposarcoma, especially a liposarcoma having amplified MDM2 genes in the genome of the liposarcoma. In a preferable embodiment, a pharmaceutically acceptable salt of the compound of formula (I) can be the compound of formula (II).

[0065] In an embodiment of the invention, a method for treating a cancer in a subject in need thereof, comprising orally and daily administering a therapeutically effective
amount of the compound of formula (I) or pharmaceutically acceptable salt thereof for at least one cycle of a cyclical dosing schedule, wherein each cycle has a dosing period of 15 to 25 days, in which the compound or salt thereof is administered daily at a daily dosage of about 80 mg to about 250 mg of the compound or salt thereof, followed by a rest period of 5 to 10 days in which any of the compound and salt thereof is not administered. In a preferable embodiment of the dosage schedule, a daily dose of the compound or salt thereof is preferably between about 100 mg to about 140 mg, and more preferably about 120 mg. In a preferable embodiment of the dosage schedule, a daily dose of the compound or salt thereof is preferably between about 140 mg to about 180 mg, and more preferably about 160 mg. In a preferable embodiment of the dosage schedule, a daily dose of the compound or salt thereof is preferably between about 180 mg to about 250 mg, and more preferably about 210 mg. In a preferable embodiment, a cancer to be treated can be liposarcoma, especially a liposarcoma having amplified MDM2 genes in the genome of the liposarcoma. In a preferable embodiment, a pharmaceutically acceptable salt of the compound of formula (I) can be the compound of formula (II).

[0066] The compound of formula (I) or (II) may be used in combination with additional anti-tumor agent(s). The compound of formula (I) or (II) may be used in combination with additional anti-tumor agent(s). Examples thereof include anti-tumor antibiotics, anti-tumor plant constituents, BRMs (biological response modifiers), hormones, vitamins, anti-tumor antibodies, molecular target drugs, and other anti-tumor agents. In an preferred embodiment of the invention, anti-tumor agents to be used in combination with the compound of formula (I) or (II) may be or may not be an MDM2 inhibitor.

[0067] More specifically, examples of alkylating agents include the following: alkylating agents such as nitrogen mustard, nitrogen mustard N-oxide, bendamustine and chlorambucil; amidine alkylating agents such as carboquone and thiotepa; epoxide alkylating agents such as dibromomannitol and dibromodulcitol; nitrosourea alkylating agents such as carmustine, lomustine, semustine, nimustine hydrochloride, streptozocin, chlorozotocin, and ranimustine; and busulfan, improsulfan tosylate, and dacarbazine.
Examples of various metabolic antagonists include the following: purine metabolic antagonists such as 6-mercaptopurine, 6-thioguanine, and thioinosine; pyrimidine metabolic antagonists such as fluorouracil, tegafur, tegafur-uracil, carmofur, doxifluridine, broxuridine, cytarabine, and enocitabine; and folic acid metabolic antagonists such as methotrexate and trimetrexate.

Examples of anti-tumor antibiotics include mitomycin C, bleomycin, peplomycin, daunorubicin, aclarubicin, doxorubicin, idarubicin, pirarubicin, THP-adriamycin, 4’-epidoxorubicin, and epirubicin; and chromomycin A3 and actinomycin D.

Examples of anti-tumor plant constituents and their derivatives include the following: vinca alkaloids such as vindesine, vincristine, and vinblastine; taxanes such as paclitaxel, docetaxel, and cabazitaxel; and epipodophyllotoxins such as etoposide and teniposide.

Examples of BRMs include tumor necrosis factors and indomethacin.

Examples of hormones include hydrocortisone, dexamethasone, methylprednisolone, prednisolone, prasterone, betamethasone, triamcinolone, oxmetholone, nandrolone, metenolone, fosfestril, ethinylestradiol, chlormadinone, medroxyprogesterone, and mepitiostane.

Examples of vitamins include vitamin C and vitamin A.

Examples of anti-tumor antibodies and molecular target drugs include trastuzumab, rituximab, cetuximab, nimotuzumab, denosumab, bevacizumab, infliximab, ipilimumab, nivolumab, pembrolizumab, avelumab, pidilizumab, atezolizumab, ramucirumab imatinib mesilate, dasatinib, gefitinib, erlotinib, sunitinib, lapatinib, vemurafenib, dabrafenib, trametinib, pazopanib, palbociclib, panobinostat, sorafenib, ibritinib, bortezomib, carfilzomib, ixazomib, and quizartinib.

Examples of other anti-tumor agents include cisplatin, carboplatin, oxaliplatin, tamoxifen, letrozole, anastrozole, exemestane, toremifene citrate, fulvestrant, bicalutamide, flutamide, mitotane, leuprolrelin, goserelin acetate, camptothecin,
ifosfamide, cyclophosphamide, melphalan, L-asparaginase, aceglatone, sizofuran, picibanil, procarbazine, pipobroman, neocarzinostatin, hydroxyurea, ubenimex, azacytidine, decitabine, thalidomide, lenalidomide, pomalidomide, eribulin, tretinoin, and krestin.

Hereinafter, the following examples are provided only for illustrative purposes and it is understood that the invention is not limited the examples.

**Examples**

**Example 1**

This Example describes the clinical study wherein the specific dosage regimen for the test compound (also referred to as "Compound 2") shown unexpectedly good results in treating cancers.

**Test compound**

(3'R,4'S,5'R)-N-[(3R,6S)-6-carbamoyltetrahydro-2H-pyran-3-yl]-6"-chloro-4'-(2-chloro-3-fluoropyridin-4-yl)-4,4-dimethyl-2"-oxo-1",2"-dihydrodispiro[cyclohexane-1,2'-pyrro lidine-3',3"-indole]-5'-carboxamide mono(4-methylbenzenesulfonate) monohydrate (Compound 2) was prepared as described in WO2012/121361 and WO2014/038606, which are incorporated by reference herein in its entirety.

**Subject Eligibility Criteria**

**Inclusion Criteria for Solid Tumor/Lymphoma Subject:**

1. Has a histologically or cytologically documented advanced solid tumor or lymphoma that has relapsed from or is refractory to standard treatment, or for which no standard treatment is available.

2. Man or woman ≥ 18 years old.

3. Has an Eastern Cooperative Oncology Group (ECOG) performance status 0-1.

4. Has adequate bone marrow function, adequate renal function, adequate hepatic
function, and adequate blood clotting function.

[0080] The demographic/characteristics of the subjects enrolled in the dose escalation part of the study were as summarized in Table 1.

Table 1: Subject Demographics and Baseline

<table>
<thead>
<tr>
<th>Demographic/Characteristics</th>
<th>Total (N=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at informed consent (years)</strong></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>59.5</td>
</tr>
<tr>
<td>Minimum</td>
<td>42</td>
</tr>
<tr>
<td>Maximum</td>
<td>79</td>
</tr>
<tr>
<td><strong>Gender (n, %)</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>15 (44.1)</td>
</tr>
<tr>
<td>Female</td>
<td>19 (55.9)</td>
</tr>
<tr>
<td><strong>Number of Prior Regimens</strong></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>3.0</td>
</tr>
<tr>
<td>Minimum</td>
<td>0.0</td>
</tr>
<tr>
<td>Maximum</td>
<td>11.0</td>
</tr>
<tr>
<td><strong>Cancer Type (n, %)</strong></td>
<td></td>
</tr>
<tr>
<td>Liposarcoma</td>
<td>15 (44.1)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>4 (11.8)</td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>2 (5.9)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>2 (5.9)</td>
</tr>
<tr>
<td>Adenoid cystic</td>
<td>2 (5.9)</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>2 (5.9)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Renal</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Long</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Chordoma</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Salivary adenocarcinoma</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Adrenocortical carcinoma</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Maxillary sinus adenocarcinoma</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td><strong>TP53 Genotyping (n, %)</strong></td>
<td></td>
</tr>
<tr>
<td>Wild type</td>
<td>26 (76.5)</td>
</tr>
<tr>
<td>Mutant</td>
<td>6 (17.6)</td>
</tr>
<tr>
<td>Not available</td>
<td>2 (5.9)</td>
</tr>
</tbody>
</table>

[0081] **Dosage regimen** Compound 2 was administered as an oral capsule comprising a pharmaceutically acceptable carrier (diluting agent, plasticizer, disintegrator and lubricant). Compound 2 was administered to the subjects once daily on Days 1 to 21 of a 28-day cycle (QD21/28). An alternative drug administration schedule was considered after establishing the maximum tolerated dose (MTD) of Compound 2 in solid tumor and/or lymphoma subjects using the above schedule, and upon review of the human safety. Subjects were administered Compound 2 in fasting conditions by
avoiding food for 2 hours before and 1 hour after drug administration. Dose-escalation of Compound 2 to determine the MTD was guided by the modified continuous reassessment method (mCRJVI) using a Bayesian logistic regression model (BLRM) following escalation with overdose control (EWOC) principle. Dose escalation began in subjects with advanced solid tumors or lymphomas with a starting dose of Compound 2 at 15 mg/day based on the Highest Non-Severely Toxic Dose (HNSTD) of 3mg/kg in dogs.

[0082] **Dose Limiting Toxicity Definition** A DLT was defined as any treatment-emergent adverse event (TEAE) not attributable to disease or disease-related processes that occurred during the observation period (Cycle 1) in each dose-level cohort and was grade 3 or higher according to NCI CTCAE, version 4. Subjects who were unable to complete at least 75% of the prescribed doses (i.e., 16 days) of Compound 2 in the first 21 days as a result of nondisease-related ≥ grade 2 adverse event (AE) were considered to have a DLT.

[0083] **Tumor assessment** Tumor assessment was performed at baseline, within every 2 cycles while the subject remained on study for the first 9 cycles and then every 3 cycles thereafter (start of Cycles 3, 5, 7, and 9, then Cycles 12, 15, etc.).

[0084] **Tumor rebiopsy** To search for possible mechanisms of acquired resistance to Compound 2, an optional tumor rebiopsy was performed within 30 days following the last dose of Compound 2 treatment for subjects who had achieved an initial complete response/partial response by standard response criteria but later developed progressive disease while on therapy, preferably prior to initiating new therapy.

[0085] **TP53 genotyping, subject enrollment and early discontinuation option** Tumor TP53 genotyping was performed using archived formalin-fixed paraffin-embedded (FFPE) or frozen samples in all enrolled subjects. Confirmation of TP53 wildtype status was not required prior to Compound 2 dosing. During the study, in the event when a subject was found to contain a nonsynonymous mutation, insertion or deletion in the TP53 gene after Compound 2 had begun, the investigator and subject was informed about the genotyping result and given the option to discontinue study drug early.
Study Duration

The number of treatment cycles was not fixed in this study. Subjects, who continued to derive clinical benefit from treatment in the absence of withdrawal of subject consent, progression, or unacceptable toxicity, continued treatment at the physicians' discretion. Continuing treatment was given in a separate extension phase of the protocol and data collected from those patients were captured in a separate database.

Treatment Arms

In this open-label, single-arm, dose escalation study, each subject received Compound 2 orally once daily on Days 1 to 21 of a 28-day cycle.

Safety Parameters

The safety profile was based on AEs, physical examination findings, vital sign measurements, clinical laboratory measurements, and ECG recordings. All subjects receiving at least 1 dose of Compound 2 were included in the safety analyses.

Tumor Response

Response assessment was performed according to the Schedule of Events or if disease progression was suspected. Radiographic assessment included computerized tomography (CT) of all affected sites. In addition, subjects with lymphoma underwent a \(^{18}\text{F}\) fluorodeoxyglucose-positron emission tomography FDG-PET scan. Tumor responses were assessed by the physicians according to RECIST 1.1 criteria for subjects with solid tumors and revised IWG criteria for subjects with lymphoma. Descriptive statistics for the greatest percent change in the sum of longest dimensions (SLD) of measurable tumors were provided. A waterfall plot of the greatest percent change from screening in the SLD for each subject was presented for subjects with advanced solid malignancies and lymphomas. In addition, descriptive statistics for FDG-PET scans were provided for lymphoma subjects according to revised IWG criteria.

Results

34 subjects were enrolled in the dose escalation part of the phase 1 study, 31 of which were evaluable for dose limiting toxicities (DLT). The subjects ranged in age between 42 years and 79 years, with a median age of 59.5 years. Subjects with thirteen different tumors types, of which 76.5 % were TP53 wild-type, were enrolled in
the study, with liposarcoma subjects being the most frequent (n=15; 44.1%). The drug was studied at 7 increasing dose levels starting from 15 mg through 30, 60, 120 and 160mg to the highest tested dose of 240 mg in a QD schedule in 21 days out of 28 day cycles (QD 21/28). A 90 mg dose in an alternate schedule of everyday administration in 28 day cycles (QD 28/28) was also tested. The maximum tolerated dose (MTD) was determined to be 120 mg with 2 DLTs out of 13 subjects in the QD 21/28 schedule. The 90 mg in QD 28/28 schedule was also determined to be an MTD in this dosing schedule with one out of 9 subjects experiencing a DLT.

[0091] Twenty three subjects were evaluable for efficacy based on RECIST v1.1 in this study. Most subjects (21 out of 23) experienced stable disease (SD) as the best tumor response with >10% tumor shrinkage in 3 subjects (Figure 1). Durable stable disease was seen for many subjects with the median progression free survival (PFS) for the overall population at 5.72 months. Interestingly, the greatest tumor shrinkage and most durable stable disease were seen in subjects with well-differentiated or de-differentiated (WD/DD) liposarcoma (Table 2, Figure 2). The 3- and 6-month PFS rate in the liposarcoma subjects were 91.7% and 76.4%, respectively (Table 2). Further attention should be drawn to the result that the 12-month PFS rate in the liposarcoma subjects was 57.3% (Table 2). The European Organization of Research and Treatment of Cancer (EORTC) has defined the criterion for an active agent in second line soft tissue sarcoma as one with a 12-week PFS > 40%. Thus, our efficacy results in liposarcoma compare favorably to historical data.
## Table 2: Evaluation of Progression Free survival for the study populations

<table>
<thead>
<tr>
<th></th>
<th>Liposarcoma (N=13)</th>
<th>Non-Liposarcoma (N=14)</th>
<th>Overall (N=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subjects with Events (n, %)</strong></td>
<td>3 (23.1)</td>
<td>9 (64.3)</td>
<td>12 (44.4)</td>
</tr>
<tr>
<td><strong>Subjects without Events (Censored) (n, %)</strong></td>
<td>10 (76.9)</td>
<td>5 (35.7)</td>
<td>15 (55.6)</td>
</tr>
<tr>
<td><strong>Progression-Free Survival (months)</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (95% CI)</td>
<td>-</td>
<td>4.04 (1.68, 8.57)</td>
<td>5.72 (4.04, -)</td>
</tr>
<tr>
<td>Log-Rank p-value (Liposarcoma vs. Non-Liposarcoma)</td>
<td>0.0394</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rate (%) of Being Alive Without Progression at Least</strong> *</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 months (95% CI)</td>
<td>91.7 (53.9, 98.8)</td>
<td>58.4 (26.2, 80.6)</td>
<td>74.5 (51.4, 87.8)</td>
</tr>
<tr>
<td>6 months (95% CI)</td>
<td>76.4 (30.9, 94.0)</td>
<td>35.4 (3.8, 52.5)</td>
<td>47.4 (22.5, 68.8)</td>
</tr>
<tr>
<td>9 months (95% CI)</td>
<td>57.3 (14.6, 85.1)</td>
<td>11.7 (0.7, 39.9)</td>
<td>29.7 (8.7, 54.5)</td>
</tr>
<tr>
<td>12 months (95% CI)</td>
<td>57.3 (14.6, 85.1)</td>
<td>11.7 (0.7, 39.9)</td>
<td>29.7 (8.7, 54.5)</td>
</tr>
</tbody>
</table>

* Kaplan-Meier estimate.

- = not estimable (i.e., median PFS has not been reached).
Treatment emergent adverse events (TEAE) of any grade at any treatment cycle irrespective of causality were observed in 97.1% of the subjects, 55.9% of which were grade 3 or higher in severity. The most common TEAEs irrespective of causality were neutropenia (17.6%), thrombocytopenia (32.4%), anemia (38.2%), nausea (64.7%), vomiting (35.3%), diarrhea (35.3%), constipation (23.5), decreased appetite (50.0%), dysgeusia (20.6%), fatigue (52.9%), dyspnoea (26.5%), hypoalbuminemia (32.4%), peripheral edema (17.6%) and hyperglycemia (29.4%). The most common drug-related TEAEs were hematological (thrombocytopenia, anemia, neutropenia), gastrointestinal (nausea, vomiting and diarrhea), and fatigue, consistent with on-target toxic effects of MDM2 inhibitors [Lillian L. Siu, et al, J Clin Oncol 32:5s, 2014 (suppl; abstr 2535) and Isabelle Ray-Coquard, et al, The Lancet Oncology, 13(11):1133-1140 (November 2012)]. Prolonged thrombocytopenia resulting in more than 4 weeks dose interruption or discontinuation was seen in 8 subjects, 2 were treated at the MTD of 120 mg QD 21/28. Nine out of 13 subjects at 120 mg QD 21/28 and 6 out of 9 subjects at 90 mg QD 28/28 (MTD at the two dosing schedules) experienced Common Terminology Criteria for Adverse Events (CTCAE) v4.0 grade ≥3 TEAEs, thrombocytopenia being the most predominant (Table 3). A total of 6 subjects experienced DLTs, all of which were at MTD or higher doses (Table 4). All the 3 DLTs at the MTD arose due to thrombocytopenia that resulted in >1 week delay in starting cycle 2. The patients with hematological malignancies tolerated 160 mg.
Table 3: Incidence of CTCAE v4.0 Grade >3 TEAEs at MTD (120 mg QD 21/28 and 90 mg OD 28/28)

<table>
<thead>
<tr>
<th>MTD Dose</th>
<th>Subject</th>
<th>Adverse Event</th>
<th>DLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>120 mg QD 21/28</td>
<td>Patient 5</td>
<td>Anemia</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Patient 11</td>
<td>Vomiting, Nausea, Hypokalemia, Thrombocytopenia</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Patient 24</td>
<td>Thrombocytopenia, shortness of breath</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Patient 21</td>
<td>Thrombocytopenia</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Patient 19</td>
<td>Pulmonary Embolism</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Patient 12</td>
<td>Thrombocytopenia</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Patient 16</td>
<td>Fatigue, Hypotension</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Patient 9</td>
<td>Fatigue, Hypotension, Thrombocytopenia, Anemia</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Patient 22</td>
<td>Leucopenia, Thrombocytopenia, Neutropenia</td>
<td>No</td>
</tr>
<tr>
<td>90 mg QD 28/28</td>
<td>Patient 4</td>
<td>Thrombocytopenia, Hypokalemia</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Patient 25</td>
<td>Thrombocytopenia</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Patient 10</td>
<td>Neutropenia</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Patient 26</td>
<td>Lymphocyte count decreased</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Patient 18</td>
<td>Leucopenia, Neutropenia, Thrombocytopenia, Anemia, Lymphocytopenia</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Patient 20</td>
<td>Thrombocytopenia</td>
<td>No</td>
</tr>
</tbody>
</table>
Table 4: Dose limiting toxicities experienced by the subjects and their corresponding doses, grades and actions taken

<table>
<thead>
<tr>
<th>Dose (Schedule)</th>
<th>Subject</th>
<th>Adverse Event</th>
<th>CTCAE Grade</th>
<th>SAE</th>
<th>Action Taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>90mg (QD28/28)</td>
<td>Patient 4</td>
<td>Thrombocytopenia</td>
<td>3*</td>
<td>No</td>
<td>Drug Withdrawn (due to disease progression)</td>
</tr>
<tr>
<td>120mg (QD21/28)</td>
<td>Patient 21</td>
<td>Thrombocytopenia</td>
<td>2*</td>
<td>No</td>
<td>Drug Interrupted</td>
</tr>
<tr>
<td></td>
<td>Patient 24</td>
<td>Thrombocytopenia</td>
<td>3*</td>
<td>No</td>
<td>Drug Interrupted</td>
</tr>
<tr>
<td>160mg (QD21/28)</td>
<td>Patient 27</td>
<td>Anorexia</td>
<td>3</td>
<td>No</td>
<td>Drug Interrupted</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nausea</td>
<td>3</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vomiting</td>
<td>3</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patient 23</td>
<td>Neutropenia</td>
<td>4</td>
<td>No</td>
<td>Drug Interrupted and Dose Reduced</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thrombocytopenia</td>
<td>2</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>240mg (QD21/28)</td>
<td>Patient 28</td>
<td>Thrombocytopenia</td>
<td>4</td>
<td>Yes</td>
<td>Dose Reduced</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Febrile Neutropenia</td>
<td>4</td>
<td>Yes</td>
<td>Dose Reduced</td>
</tr>
</tbody>
</table>

*A delay of ≥ 1 week in initiating Cycle 2 secondary to a non disease-related ≥ grade 2 adverse event will be considered a DLT.
CLAIMS

[Claim 1]

A pharmaceutical composition for use in treating a cancer in a subject in need thereof, comprising a therapeutically effective amount of the compound of formula (I) or pharmaceutically acceptable salt thereof, wherein the pharmaceutical composition is orally administered according to a dosage schedule comprising administering a daily dose of about 80 mg to about 250 mg of the compound or salt thereof to the subject.

[Chem. 1]

(3'i?,4'S,5'i?)-N-[(3'i?,6'S)-6-Carbamoyltetrahydro-2'H-pyran-3-yl]-6''-chloro-4'-[(2-chloro-3-fluoropyridin-4-yl)-4,4-dimethyl-2''-oxo-1'',2''-dihydrodispiro[cyclohexane-1,2''-pyrroldidine-3'3''-indole]-5''-carboxamide

[Claim 2]

A pharmaceutical composition according to claim 1, wherein the dosage schedule comprises administering a daily dose of about 80 mg to about 140 mg of the compound or salt thereof to the subject.

[Claim 3]

A pharmaceutical composition according to claim 1, wherein the dosage schedule comprises administering a daily dose of about 80 mg to about 100 mg of the
compound or salt thereof to the subject.

[Claim 4]

A pharmaceutical composition according to claim 1, wherein the dosage schedule comprises administering a daily dose of about 90 mg of the compound or salt thereof to the subject.

[Claim 5]

A pharmaceutical composition according to claim 1, wherein the dosage schedule comprises administering a daily dose of about 100 mg to about 140 mg of the compound or salt thereof to the subject.

[Claim 6]

A pharmaceutical composition according to claim 1, wherein the dosage schedule comprises administering a daily dose of about 120 mg of the compound or salt thereof to the subject.

[Claim 7]

A pharmaceutical composition for use in treating a cancer in a subject in need thereof according to any one of claims 1 to 6, wherein the cancer is liposarcoma.

[Claim 8]

A pharmaceutical composition for use in treating a cancer in a subject in need thereof according to claim 7, wherein the cancer is a liposarcoma having amplified MDM2 genes in the genome of the liposarcoma.

[Claim 9]

A pharmaceutical composition for use in treating a cancer in a subject in need thereof, comprising a therapeutically effective amount of the compound of formula (I) or pharmaceutically acceptable salt thereof, wherein the pharmaceutical composition is orally administered for at least one cycle of a cyclical dosing schedule, wherein each
cycle has a dosing period of at least 10 days, in which the compound or salt thereof is administered daily at a daily dosage of about 80 mg to about 250 mg.

[Claim 10]

A pharmaceutical composition according to claim 9, wherein the compound or salt thereof is administered daily at a daily dosage of about 80 mg to about 140 mg.

[Claim 11]

A pharmaceutical composition according to claim 9, wherein the compound or salt thereof is administered daily at a daily dosage of about 80 mg to about 100 mg.

[Claim 12]

A pharmaceutical composition according to claim 9, wherein the compound or salt thereof is administered daily at a daily dosage of about 90 mg.

[Claim 13]

A pharmaceutical composition according to claim 9, wherein the compound or salt thereof is administered daily at a daily dosage of about 100 mg to about 140 mg.

[Claim 14]

A pharmaceutical composition according to claim 9, wherein the compound or salt thereof is administered daily at a daily dosage of about 120 mg.

[Claim 15]

A pharmaceutical composition according to claim 9, wherein the compound or salt thereof is administered daily at a daily dosage of about 140 mg to about 180 mg, more preferably about 160 mg.

[Claim 16]

A pharmaceutical composition according to claim 9, wherein the compound or salt thereof is administered daily at a daily dosage of about 160 mg.
[Claim 17]

A pharmaceutical composition according to claim 9, wherein the compound or salt thereof is administered daily at a daily dosage of about 180 mg to about 250 mg, more preferably about 210 mg.

[Claim 18]

A pharmaceutical composition according to claim 9, wherein the compound or salt thereof is administered daily at a daily dosage of about 210 mg.

[Claim 19]

A pharmaceutical composition for use in treating a cancer in a subject in need thereof, comprising a therapeutically effective amount of the compound of formula (I) or pharmaceutically acceptable salt thereof, wherein the pharmaceutical composition is orally administered for at least one cycle of a cyclical dosing schedule, wherein each cycle has a dosing period of about 15 days to about 25 days, in which the compound or salt thereof is administered daily at a daily dosage of about 80 mg to about 250 mg of the compound or salt thereof, followed by a rest period of about 5 days to about 10 days in which any of the compound and salt thereof is not administered.

[Chem. 1]

(3'?,4.S,5.S)-N-{(3'i?,6'S)-6-Carbamoyltetrahydro-2'H-pyran-3-yl]-6"-chloro-4'- (2-chloro-3-fluoropyridin-4-yl)-4,4-dimethyl-2"-oxo-1" ,2"-dihydrodipsir[ cyclohexane-1,2'-pyrrolidine-3',3'-indole]-5'-carboxamide

[Claim 20]
A pharmaceutical composition according to any one of claims 9 to 19, wherein each cycle has a dosing period of about 15 days to about 25 days, in which the compound or salt thereof is administered daily at a daily dosage of about 100 mg to about 140 mg, followed by a rest period of about 5 days to about 10 days, in which any of the compound and salt thereof is not administered.

[Claim 21]

A pharmaceutical composition according to any one of claims 9 to 19, wherein each cycle has a dosing period of about 15 days to about 25 days, in which the compound or salt thereof is administered daily at a daily dosage of about 120 mg, followed by a rest period of about 5 days to about 10 days, in which any of the compound and salt thereof is not administered.

[Claim 22]

A pharmaceutical composition according to any one of claims 9 to 19, wherein each cycle has a dosing period of about 15 days to about 25 days, in which the compound or salt thereof is administered daily at a daily dosage of about 140 mg to about 180 mg, followed by a rest period of about 5 days to about 10 days, in which any of the compound and salt thereof is not administered.

[Claim 23]

A pharmaceutical composition according to any one of claims 9 to 19, wherein each cycle has a dosing period of about 15 days to about 25 days, in which the compound or salt thereof is administered daily at a daily dosage of about 160 mg, followed by a rest period of about 5 days to about 10 days, in which any of the compound and salt thereof is not administered.

[Claim 24]

A pharmaceutical composition according to any one of claims 9 to 19, wherein each cycle has a dosing period of about 15 days to about 25 days, in which the compound or salt thereof is administered daily at a daily dosage of about 180 mg to
about 250 mg, followed by a rest period of about 5 days to about 10 days, in which any
of the compound and salt thereof is not administered.

[Claim 25]

A pharmaceutical composition according to any one of claims 9 to 19, wherein
each cycle has a dosing period of about 15 days to about 25 days, in which the
compound or salt thereof is administered daily at a daily dosage of about 210 mg,
followed by a rest period of about 5 days to about 10 days, in which any of the
compound and salt thereof is not administered.

[Claim 26]

A pharmaceutical composition according to any one of claims 9 to 19, wherein
each cycle has a dosing period of about 21 days, in which the compound or salt thereof
is administered daily at a daily dosage of about 100 mg to about 140 mg, followed by a
rest period of about 7 days, in which any of the compound and salt thereof is not
administered.

[Claim 27]

A pharmaceutical composition according to any one of claims 9 to 19, wherein
each cycle has a dosing period of about 21 days, in which the compound or salt thereof
is administered daily at a daily dosage of about 140 mg to about 180 mg, followed by a
rest period of about 7 days, in which any of the compound and salt thereof is not
administered.

[Claim 28]

A pharmaceutical composition according to any one of claims 9 to 19, wherein
each cycle has a dosing period of about 21 days, in which the compound or salt thereof
is administered daily at a daily dosage of about 180 mg to about 250 mg, followed by a
rest period of about 7 days, in which any of the compound and salt thereof is not
administered.

[Claim 29]
A pharmaceutical composition according to any one of claims 9 to 19, wherein each cycle has a dosing period of about 15 days to about 25 days, in which the compound or salt thereof is administered daily at a daily dosage of about 80 mg to about 100 mg, preferably about 90 mg, followed by a rest period of about 5 days to about 10 days, in which any of the compound and salt thereof is not administered.

[Claim 30]

A pharmaceutical composition according to any one of claims 9 to 19, wherein each cycle has a dosing period of about 15 days to about 25 days, in which the compound or salt thereof is administered daily at a daily dosage of about 90 mg, followed by a rest period of about 5 days to about 10 days, in which any of the compound and salt thereof is not administered.

[Claim 31]

A pharmaceutical composition according to any one of claims 9 to 19, wherein each cycle has a dosing period of about 21 days, in which the compound or salt thereof is administered daily at a daily dosage of about 80 mg to about 100 mg, followed by a rest period of about 7 days, in which any of the compound and salt thereof is not administered.

[Claim 32]

A pharmaceutical composition according to any one of claims 9 to 19, wherein each cycle has a dosing period of about 21 days, in which the compound or salt thereof is administered daily at a daily dosage of about 120 mg of the compound or salt thereof, followed by a rest period of about 7 days, in which any of the compound and salt thereof is not administered.

[Claim 33]

A pharmaceutical composition according to any one of claims 9 to 19, wherein each cycle has a dosing period of about 21 days, in which the compound or salt thereof is administered daily at a daily dosage of about 160 mg of the compound or salt thereof,
followed by a rest period of about 7 days, in which any of the compound and salt thereof is not administered.

[Claim 34]

A pharmaceutical composition according to any one of claims 9 to 19, wherein each cycle has a dosing period of about 21 days, in which the compound or salt thereof is administered daily at a daily dosage of about 210 mg of the compound or salt thereof, followed by a rest period of about 7 days, in which any of the compound and salt thereof is not administered.

[Claim 35]

A pharmaceutical composition according to any one of claims 9 to 19, wherein each cycle has a dosing period of about 21 days, in which the compound or salt thereof is administered daily at a daily dosage of about 90 mg of the compound or salt thereof, followed by a rest period of about 7 days, in which any of the compound and salt thereof is not administered.

[Claim 36]

A pharmaceutical composition for use in treating a cancer in a subject in need thereof according to any one of claims 9 to 35, wherein the cancer is liposarcoma.

[Claim 37]

A pharmaceutical composition for use in treating a cancer in a subject in need thereof according to claim 36, wherein the cancer is a liposarcoma having amplified MDM2 genes in the genome of the liposarcoma.

[Claim 38]

A pharmaceutical composition for use in treating a cancer in a subject in need thereof according to any one of claims 1 to 37, wherein the compound or salt thereof is in a form of p-toluenesulfonic acid salt monohydrate as shown in formula (II).
A pharmaceutical composition for use in treating liposarcoma, comprising
(3′R,4′S,5′S)-N-[(3′R,6′S)-6-Carbamoyltetrahydro-2H-pyran-3-yl]-6′-chloro-4′-(2-chloro-3-fluoropyridin-4-yl)-4,4-dimethyl-2″-oxo-1′,2″-dihydrodispiro[cyclohexane-1,2′-pyrrole-3′,3″-indole]-5″-carboxamide or pharmaceutically acceptable salt thereof.

A pharmaceutical composition according to claim 39, wherein liposarcoma has amplified MDM2 genes in the genome of the liposarcoma.
[Fig. 1]

*TP53 Mutant

Best % Change in SD from Baseline

Patient 23 (160mg/613d)
Patient 22 (120mg/19d)
Patient 21 (120mg/7d)
Patient 20 (90mg/99d)
Patient 19 (120mg/399d)
Patient 18 (90mg/147d)
Patient 17 (90mg/18d)
Patient 16 (120mg/204d)
Patient 15 (160mg/18d)
Patient 14 (120mg/80d)
Patient 13 (120mg/336d)
Patient 12 (120mg/168d)
Patient 11 (120mg/13d)
Patient 10 (90mg/50d)
Patient 9 (120mg/127d)
Patient 8 (30mg/188d)
Patient 7 (160mg/77d)
Patient 6 (150mg/167d)
Patient 5 (120mg/43d)
Patient 4 (90mg/28d)
Patient 3 (120mg/82d)
Patient 2 (120mg/21d)
Patient 1 (60mg/43d)
[Fig. 2]

WD: Well-differentiated; DD: De-differentiated

Best % change in Jopp from baseline

PD → | ← SD → |

Patient 23 (160mg/61d)
Patient 22 (120mg/19d)
Patient 21 (120mg/17d)
Patient 19 (120mg/399d)
Patient 18 (90mg/14d)
Patient 17 (90mg/18d)
Patient 16 (120mg/204d)
Patient 11 (120mg/193d)
Patient 9 (120mg/127d)
Patient 8 (50mg/188d)
Patient 4 (90mg/28d)
Patient 3 (120mg/82d)
Patient 2 (120mg/21d)

* TP53 Mutant
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/4439 A61P35/00

ADD.

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 database consulted during the international search (name of database and, where practicable, search terms used)

EPO-Internal, BIOSIS, CHEM ABS Data, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>US 2012/264738 AI (SUGIMOTO YUICHI [JP]) cited in the application on page 1, paragraphs 5, 8 page 15, paragraph 193 page 16, paragraphs 195, 198 page 57; example 70</td>
<td>1-40</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C.

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 application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which establishes 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

"A" document member of the same patent family

Date of the actual completion of the international search

19 January 2017

Date of mailing of the international search report

01/02/2017

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk

Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

Authorized officer

Terenzi, Carl a
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>page 3, paragraph 16 - page 4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>page 10, paragraph 46</td>
<td></td>
</tr>
<tr>
<td></td>
<td>page 16, paragraph 67</td>
<td></td>
</tr>
<tr>
<td></td>
<td>page 24, paragraph 95 - page 25</td>
<td></td>
</tr>
<tr>
<td></td>
<td>page 28, paragraph 104</td>
<td></td>
</tr>
<tr>
<td></td>
<td>page 1, paragraph 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>page 5, paragraph 13 - page 9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>page 25, paragraph 41</td>
<td></td>
</tr>
<tr>
<td></td>
<td>page 27, paragraph 46 - page 28, paragraph 47</td>
<td></td>
</tr>
<tr>
<td></td>
<td>page 4, paragraph 11 - page 7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>page 15, paragraph 34</td>
<td></td>
</tr>
<tr>
<td></td>
<td>page 17, paragraph 40</td>
<td></td>
</tr>
<tr>
<td>Patent document cited in search report</td>
<td>Publication date</td>
<td>Patent family member(s)</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>-----------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>US 2012264738 AI</td>
<td>18-10-2012</td>
<td>AU 2012226890 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BR 112013023175 A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2829188 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 103635473 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 105753872 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CO 6781539 A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 2684880 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 5792279 B2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KR 20140059161 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NZ 614218 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RU 2013145310 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SG 193002 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SG 10201601802Y A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TW 201249842 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2012264738 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2014121196 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 2012121361 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 104812757 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HK 1210172 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 6016284 B2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP W02014038606 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KR 20150048140 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RU 2015112098 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TW 201410681 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2015210707 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2016244458 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 2014038606 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2016333419 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 2015108175 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WO 2016133194 AI</td>
<td>25-08-2016</td>
<td>NONE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WO 2016167236 AI</td>
<td>20-10-2016</td>
<td>NONE</td>
</tr>
</tbody>
</table>