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(54) Title: COMBINATION THERAPY COMPRISING A TAXANE AND A SIGMA RECEPTOR LIGAND SAUCH AS RIMCAZOLE

(57) Abstract: The present invention relates to novel combinations of a microtubule stabilising agent and a sigma receptor ligand for use in treating cancer.

COMBINATION THERAPY COMPRISING A TAXANE AND A SIGMA RECEPTOR LIGAND SAUCH AS RIMCAZOLE

TECHNICAL FIELD

The invention relates to compounds which, when used in combination, are surprisingly active against cancer. The invention also relates to methods of using these compounds, and compositions and kits that comprise these compounds.

BACKGROUND

Taxanes, a class of diterpenes originally derived from yew trees, are known to be effective in treating various cancers. They have been shown to promote the polymerisation of microtubules and thereby increase microtubule stability. The two taxanes currently licensed for use in humans are paclitaxel (Taxol™) and docetaxel (Taxotere™). Paclitaxel binds to GDP-tubulin and stops microtubule depolymerisation. This results in highly stabilised microtubules, thereby preventing normal cell function.

Paclitaxel is effective in the treatment of metastatic breast cancer (Dombernowsky *et al.*, 1995 Seminars in Oncology 22(6): 13-17) and in a range of other solid tumours (Kaye 1995 Seminars in Oncology 22(2): 30-33). *et al*

Rimcazole is a sigma receptor ligand which has been shown to be effective in inhibiting the growth of tumours in preclinical tumour xenografts models (Spruce *et al.*, 2004 Cancer Research 64: 4875-4886). Mechanistic studies (WO 00/00599) have shown that Rimcazole may synergise with agents such as colchicine, nocodazole, podophyllotoxin and vinblastine to depolymerise or destabilise microtubules.

The treatment of cancer using a taxane or a sigma receptor ligand (such as Rimcazole) has a number of problems. Administration of these agents has been associated with toxicity, leading to the use of sub-optimal doses and, in some cases, low efficacy. Furthermore, cancer therapy using these compounds in isolation can fail because cancers become resistant to the compound by mutation. In addition, further compounds are required in order to improve the selectivity of the treatment for different cancers, thereby allowing improved efficacy and/or reduced toxicity.

Accordingly, new treatments and regimens are required in order to overcome these problems and to improve the treatment of cancer. In particular, there is a need for improved treatments for cancer that have a reduced toxicity, improved efficacy and / or new anti-cancer selectivities.

SUMMARY OF INVENTION

The present inventors have surprisingly found that, when used in combination, a microtubule stabilising agent, such as a taxane, and a sigma receptor ligand, such as Rimcazole, are particularly effective in treating cancer, in particular breast cancer.

This is surprising because Rimcazole has been shown to be co-operative with microtubule destabilising agents in it's anti-tumour action (see WO 00/00599) whilst the taxanes are known stabilisers of microtubules. Given that Rimcazole is co-operative with microtubule destabilising agents, the skilled person would not have expected co-operation or synergy between Rimcazole and microtubule stabilising agents. Indeed, *in vitro* studies suggested that Rimcazole and paclitaxel have no co-operativity or synergy.

More specifically, *in vitro* experiments have showed that a combination of the present invention did not work together to improve tumour cell viability (see figure 1.) Indeed, *in vitro* studies suggested that Rimcazole and paclitaxel do not synergise to reduce MDA-MB-231 tumour cell viability *in vitro*; that Rimcazole and paclitaxel in combination reduces the percentage of cells in G2/M and subG0 arrest and that Rimcazole lacks single agent activity against large MDA-MB-231 tumours (see figures 1 – 4).

However, the inventors have surprisingly found that microtubule stabilising agents and sigma receptor ligands can be used in combination in treating cancer. Furthermore, the inventors have demonstrated that the efficacy of these compounds in combination is greater than their combined separate efficacies, i.e. the combination has an unexpected synergistic effect.

In this regard, the present invention provides a microtubule stabilising agent selected from: a taxane, or a pharmaceutically acceptable derivative thereof, and a sigma receptor ligand, for use in treating cancer, wherein said treatment involves administering said microtubule stabilising agent and said sigma receptor ligand separately, sequentially or simultaneously.

In a second aspect, the invention provides a microtubule stabilising agent selected from a taxane, or a pharmaceutically acceptable derivative thereof, for use in treating cancer in a patient, wherein the patient has been previously treated, or is currently being treated with, a sigma receptor ligand.

In a third aspect, the invention provides a microtubule stabilising agent selected from: a taxane, or a pharmaceutically acceptable derivative thereof, for use in a method of treating cancer in a patient, wherein the microtubule stabilising agent is prepared for simultaneous, separate or sequential administration with a sigma receptor ligand.

In a fourth aspect, the invention provides a sigma receptor ligand, for use in treating cancer in a patient, wherein the patient has been previously treated, or is currently being treated with a microtubule stabilising agent selected from: a taxane, or a pharmaceutically acceptable derivative thereof.

In a fifth aspect, the invention provides a sigma receptor ligand for use in treating cancer in a patient, wherein the sigma receptor ligand is prepared for simultaneous, separate or sequential administration with a microtubule stabilising agent selected from: a taxane, or a pharmaceutically acceptable derivative thereof.

In a sixth aspect, the invention provides the use of a microtubule stabilising agent selected from: a taxane, or a pharmaceutically acceptable derivative thereof, and a sigma receptor ligand, in a method of manufacturing a medicament for the treatment of cancer.

In a seventh aspect, the invention provides the use of a microtubule stabilising agent selected from: a taxane, or a pharmaceutically acceptable derivative thereof, in a method of manufacturing a medicament for the treatment of cancer, wherein said treatment comprises the administration of a sigma receptor ligand .

In an eighth aspect, the invention provides the use of a sigma receptor ligand in a method of manufacturing a medicament for the treatment of cancer, wherein said treatment comprises the administration of a microtubule stabilising agent selected from: a taxane, or a pharmaceutically acceptable derivative thereof.

In a ninth aspect, the invention provides the use of a microtubule stabilising agent selected from: a taxane, or a pharmaceutically acceptable derivative thereof, in a method of manufacturing a medicament for the treatment of a patient with cancer, wherein said patient has been previously treated, or is currently being treated with a sigma receptor ligand .

In a tenth aspect, the invention provides the use of a sigma receptor ligand in a method of manufacturing a medicament for the treatment of a patient with cancer, wherein said patient has been previously treated, or is currently being treated with a microtubule stabilising agent selected from: a taxane, or a pharmaceutically acceptable derivative thereof.

In an eleventh aspect, the invention provides a composition comprising a microtubule stabilising agent selected from: a taxane, or a pharmaceutically acceptable derivative thereof, and a sigma receptor ligand.

In a twelfth aspect, the invention provides a kit comprising a microtubule stabilising agent selected from: a taxane, or a pharmaceutically acceptable derivative thereof, and a sigma receptor ligand.

In a thirteenth aspect, the invention provides the use of any of the above compositions in therapy, wherein said therapy comprises the separate, sequential or simultaneous administration of a microtubule stabilising agent selected from: a taxane, or a pharmaceutically acceptable derivative thereof, and a sigma receptor ligand.

In a fourteenth aspect, the invention provides the use of any of the above compositions in a method of treating cancer, wherein said method comprises the separate, sequential or simultaneous administration of a microtubule stabilising agent selected from: a taxane, or a pharmaceutically acceptable derivative thereof, and a sigma receptor ligand.

In a fifteenth aspect, the invention provides a method of treatment of cancer in a patient in need thereof, wherein said method comprises administering to said patient a therapeutically effective amount of: a microtubule stabilising agent selected from: a taxane, or a pharmaceutically acceptable derivative thereof, and therapeutically effective amount of a sigma receptor ligand , wherein said a microtubule stabilising agent and said sigma receptor ligand are administered separately, sequentially or simultaneously.

In a sixteenth aspect, the invention provides a method of treatment of cancer in a patient in need thereof, wherein said method comprises administering to said patient a therapeutically effective amount of a microtubule stabilising agent selected from: a taxane, or a pharmaceutically acceptable derivative thereof, wherein a therapeutically effective amount of a sigma receptor ligand has been previously administered to said patient.

In a seventeenth aspect, the invention provides a method of treatment of cancer in a patient in need thereof, wherein said method comprises administering to said patient a therapeutically effective amount of a sigma receptor ligand , wherein a therapeutically effective amount of a microtubule stabilising agent selected from: a taxane, or a pharmaceutically acceptable derivative thereof has been previously administered to said patient.

In an eighteenth aspect, the invention provides a method of reducing the toxicity of a microtubule stabilising agent selected from: a taxane, or a pharmaceutically acceptable derivative thereof, by administering said microtubule stabilising agent in combination with a sigma receptor ligand.

In a nineteenth aspect, the invention provides a method of delaying the growth of a tumour by administering a microtubule stabilising agent selected from: a taxane, or a pharmaceutically acceptable derivative thereof in combination with a sigma receptor ligand.

In a twentieth aspect, the invention provides a method of prolonging the life span of a patient with cancer, by administrating a microtubule stabilising agent selected from: a

taxane, or a pharmaceutically acceptable derivative thereof in combination with a sigma receptor ligand.

In a twenty first aspect, the invention provides a method of treating breast cancer in a patient in need thereof, wherein said method comprises administering to said patient a therapeutically effective amount of paclitaxel, and a therapeutically effective amount of Rimcazole wherein said administration is separate, sequential or simultaneous.

In a twenty second aspect, the invention provides a method of treatment of cancer in a patient in need thereof, wherein said method comprises administering to said patient a therapeutically effective amount of A and a therapeutically effective amount of B, wherein A is a taxane, or a pharmaceutically acceptable derivative thereof, and B is a sigma receptor ligand , wherein A and B are administered separately, sequentially or simultaneously.

The microtubule stabilising agent

A microtubule stabilising agent is an agent that increases the stability of microtubules, an effect which can be observed in the microtubule stabilisation assays discussed in Shelanski *et al.* PNAS 70, 3, p765, 1973. Shelanski *et al.* describes how microtubule stabilisation may be measured by light scattering, preferably in combination with an electron microscope, and / or by using centrifugation.

The microtubule stabilising agent is a taxane or a pharmaceutically derivative thereof. Methods of synthesising microtubule stabilising agents are described in U.S. 4,924,011, U.S. 4,924,012 and U.S. 5,175,315.

The term "pharmaceutically acceptable derivative" includes pharmaceutically acceptable salts, solvates, hydrates, metabolites, prodrugs and isomers.

In any of the above aspects of the invention, the microtubule stabilising agent may be paclitaxel (taxol™), docetaxel (taxotere™), DHA-paclitaxel (taxoprexin™), polyglutimate-taxol (OPAXIO™), or a prodrug, pharmaceutically acceptable salt, solvate, hydrate, derivative, isomer or metabolite thereof. The microtubule stabilising agent is preferably paclitaxel (taxol™).

The microtubule stabilising agent can be formulated using any of the techniques known in the art. For example, it can be provided as a solid tablet, power, solution, dispersion, emulsion, or suspension. It can be formulated in liposomes, in polyethoxylated castor oil, in ethanol, bound to albumin and / or in tween 80™. In one embodiment, the agent is paclitaxel and it is formulated with polyethoxylated castor oil and / or ethanol. In another embodiment, the agent is docetaxel and it is formulated with albumin in saline solution.

Pharmaceutically acceptable salts of the taxane may include those of inorganic acids, for example, hydrohalic acids such as hydrochloric acid, hydrobromic acid or hydroiodic acid, nitric acid, sulfuric acid, phosphoric acid; and organic acids, for example aliphatic monocarboxylic acids such as formic acid, acetic acid, propionic acid and butyric acid, aliphatic hydroxy acids such as lactic acid, citric acid, tartaric acid or malic acid, dicarboxylic acids such as maleic acid or succinic acid, aromatic carboxylic acids such as benzoic acid, p-chlorobenzoic acid, diphenylacetic acid or triphenylacetic acid, aromatic hydroxy acids such as o-hydroxybenzoic acid, p-hydroxybenzoic acid, 1-hydroxynaphthalene-2-carboxylic acid or 3-hydroxynaphthalene-2-carboxylic acid, and sulfonic acids such as methanesulfonic acid or benzenesulfonic acid. These salts may be prepared by known salt-forming procedures.

If the microtubule stabilising agent contains acidic, e.g. carboxyl, groups, it may also be capable of forming salts with bases, in particular pharmaceutically acceptable bases such as those well known in the art; suitable such salts include metal salts, particularly alkali metal or alkaline earth metal salts such as sodium, potassium, magnesium or calcium salts, or salts with ammonia or pharmaceutically acceptable organic amines or heterocyclic bases such as ethanolamines, benzylamines or pyridine. These salts may be prepared by known salt-forming procedures.

The microtubule stabilising agent may be in the form of a prodrug. Said prodrug may be selected from the group consisting of esters, amides and hydrates.

The term pro-drug is also meant to include any covalently bonded carrier which releases the active compound of the invention *in vivo* when such prodrug is administered to a subject. Pro-drugs of a microtubule stabilising agent of the invention may be prepared by modifying functional groups present in the compound of the invention in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound of the invention.

Where there is an asymmetric carbon atom the compounds exist in individual optically active isomeric forms or as mixtures thereof, e.g. as racemic or diastereomeric mixtures. The optically active compounds used in the invention embrace all individual optically active R and S isomers as well as mixtures, e.g. racemic or diastereomeric mixtures, thereof.

The present invention includes pharmaceutically acceptable isotopically-labeled versions of the microtubule stabilising agents mentioned herein. Said pharmaceutically acceptable isotopically-labeled versions of the compounds are compounds wherein one or more atoms from a compound mentioned herein are replaced by atoms having the same atomic number,

but an atomic mass or mass number different from the atomic mass or mass number usually found in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention comprises isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulphur, such as ^{35}S.

Substitution with heavier isotopes such as deuterium, *i.e.* ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

Isotopically-labelled compounds mentioned herein can generally be prepared by the methods used in the art, for example, by modifying a known method for making a compound disclosed herein by using isotopically-labelled reagents.

The sigma receptor ligand

A sigma receptor ligand is a ligand that binds to the sigma receptor, an effect which can be observed in a sigma receptor binding assay (Vilner *et al.* Cancer Res 55(2):408-413, 1995 (see page 409, column 1, second paragraph). The binding of a putative sigma ligand to sites on sigma receptors, especially sigma 1 receptors can be measured by comparison to the prototypic sigma ligands such as (+)-pentazocine and 1,3-di-o-tolylguanidine (DTG). Radio- or chemically- labelled prototype sigma ligands are allowed to bind to sigma receptors in a cell preparation. The amount of labelled prototype sigma ligands displaced by the putative ligand is measured and used to calculate the affinity of the putative ligand for the sigma receptor.

If a putative sigma ligand has an affinity of less than 10μM, it is considered to be a sigma receptor ligand.

Examples of suitable sigma receptor ligands for use in the present invention include those listed in list 1 below:

List 1:

Rimcazole, Rimcazole dihydrochloride, Rimcazole hydrochloride, haloperidol, reduced haloperidol, IPAG (1-(4-iodophenyl)-3-(2-adamantyl)guanidine), BD-1047 (N(-)[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(dimethylamino)ethylamine), BD-1063 (1(-)[2-(3,4-dichlorophenyl)ethyl]-4-methylpiperazine), (+)-SKF-10047 ((+)-N-allyl normetazocine), (+)-benzomorphans including (+)-petazocine and (+)-ethylketocyclazocine, (+)-morphinans including dextrallorphan, cis isomers of U50488 and analogues, arylcyclohexamines including PCP, N,N'-diryl-substituted guanidines including DTG (1,3-di(2-tolyl)guanidine),

phenylpiperidines including (+)-3-PPP and OHBQs, steroids including progesterone and desoxycorticosterone, butryophenones, BD614,(+/-)-cis-N-methyl-N-[2-(3,4-dichlorophenyl)ethyl]-2-(1-pyrrolodinyl)cyclohexylamine, perphenazine, fluphenazine, (-)-butaclamol, acetophenazine, trifluroperazine, molindone, pimozide, thioridazine, chlorpromazine, triflupromazine, BMY14802, BMY13980, remoxipride, tiospirone, cinpuperone WY47384, and antidepressants including amitriptyline and imipramine, and pharmaceutically acceptable derivatives thereof.

More specifically, suitable sigma receptor ligands for use in the present invention are selected from list 2 below.

List 2:

Rimcazole, haloperidol, reduced haloperidol, IPAG (1-(4-iodophenyl)-3-(2-adamantyl)guanidine), DTG (1,3-di(2-tolyl)guanidine), cis isomers of U50488 and pharmaceutically acceptable derivatives thereof. In any one of the aspects of the invention, any one of the members of list 1 may be used, intended for use or formulated with paclitaxel.

In any one of the aspects of the invention, any one of the members of list 1 may be used, intended for use or formulated with docetaxel.

In any one of the aspects of the invention, any one of the members of list 1 may be used, intended for use or formulated with DHA-paclitaxel.

In any one of the aspects of the invention, any one of the members of list 1 may be used, intended for use or formulated with polyglutimate-taxol.

In any one of the aspects of the invention, any one of the members of list 2 may be used, intended for use or formulated with paclitaxel.

In any one of the aspects of the invention, any one of the members of list 2 may be used, intended for use or formulated with docetaxel.

In any one of the aspects of the invention, any one of the members of list 2 may be used, intended for use or formulated with DHA-paclitaxel.

In any one of the aspects of the invention, any one of the members of list 2 may be used, intended for use or formulated with polyglutimate-taxol.

In any of the above aspects of the invention, the sigma receptor ligand may be Rimcazole, or a pharmaceutically acceptable derivative thereof.

In any of the above aspects of the invention, the sigma receptor ligand may be specifically Rimcazole or a pharmaceutically acceptable salt thereof.

In any of the above aspects of the invention, the sigma receptor ligand may be Rimcazole.

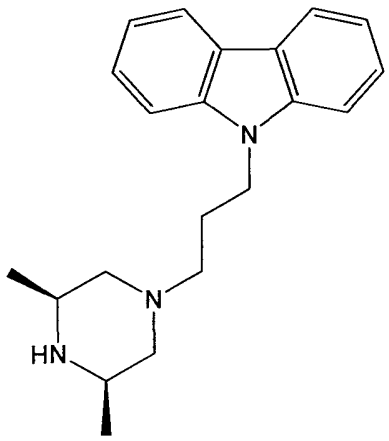
The term "pharmaceutically acceptable derivative" includes pharmaceutically acceptable salts, solvates, hydrates, metabolites, prodrugs and isomers.

Rimcazole

9-[3-[3,5-dimethylpiperazin-1-yl]propyl]carbazole (BW 234U) is known as Rimcazole. Methods of synthesising Rimcazole are known in the art, e.g. as described in EP 0 012 208, US 5,955,459 and WO01/74359.

The term "pharmaceutically acceptable derivative" when applied to Rimcazole includes pharmaceutically acceptable salts, solvates, amides and prodrugs of Rimcazole.

Rimcazole has two stereogenic centres at the 3 and 5 positions of the piperazinyl ring and, as used herein, the term "Rimcazole" includes stereoisomers of Rimcazole. In one embodiment, the stereoisomer of Rimcazole is the (3S,5R) isomer, i.e. 9-[3-[(3S,5R)-3,5-dimethylpiperazin-1-yl]propyl]carbazole having the structural formula I:

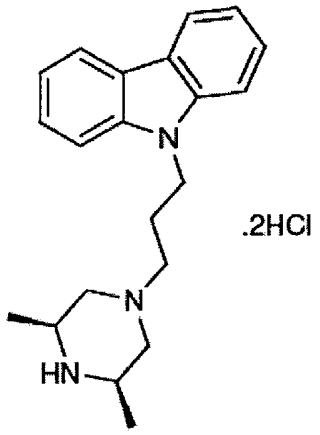


Formula I

The term "pharmaceutically acceptable salt" of Rimcazole refers to non-toxic acidic/anionic salt forms.

Suitable pharmaceutically acceptable salts include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid.

In one embodiment, the pharmaceutically acceptable salt is a hydrochloride salt of Rimcazole, typically the dihydrochloride salt (Rimcazole dihydrochloride). Preferably the salt is Rimcazole dihydrochloride, which is of structural formula II:



Formula II

The term "pharmaceutically acceptable solvate" includes hydrates or solvates formed with common organic solvents. In one embodiment, the hydrate is Rimcazole dihydrochloride monohydrate.

The Rimcazole or a pharmaceutically acceptable derivative thereof may have one or more polymorph or amorphous crystalline forms and are also included in the invention.

The term "pharmaceutically acceptable amide" includes compounds formed by the reaction of Rimcazole with a carboxylic acid, e.g. a C1-6 carboxylic acid. The use of pharmaceutically acceptable amides as prodrugs is discussed, for example, in "The Theory and Practice of Industrial Pharmacy", 2nd Edition, Lachman, Lieberman & Kanig, 1976.

The term "prodrug" means a pharmaceutically acceptable form of a functional derivative of Rimcazole (or a salt thereof), wherein the prodrug may be: 1) a relatively active precursor which converts *in vivo* to an active prodrug component; 2) a relatively inactive precursor which converts *in vivo* to an active prodrug component; or 3) a relatively less active component of the compound that contributes to therapeutic biological activity after becoming available *in vivo*. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described in, for example, EP 0 012 208.

Treatment of diseases

As discussed above, the present invention is useful in the treatment cancer. In any of the above aspects of the present invention, the cancer may be cancer of the bladder, breast (female and / or male), kidney, lung, pancreas, prostate, skin, thyroid, liver, oesophagus, stomach, ovary, brain and/or central nervous system, uterus, bone and/or connective tissue and, in addition, the cancer may be leukaemia, melanoma, non-Hodgkin Lymphoma cervical, colorectal, myeloma, mesothelioma, oral, uterine, non-small cell lung carcinoma and Kaposi's sarcoma.

In any of the above embodiments of the invention, the cancer may be specifically any one of ovarian, breast, non-small cell lung carcinoma or Kaposi's sarcoma.

In any of the above embodiments of the invention, the cancer may be specifically breast cancer. In particular, the cancer may be hormone insensitive breast cancer. Hormone insensitive breast cancer may be more particularly defined as breast cancer which does not respond to hormone based breast cancer treatments.

The compounds of the present invention may be useful as both prophylactic and therapeutic treatments for cancer.

The term "wherein said patient has been previously treated with X" as used herein describes a distinct patient subgroup. In any of the above embodiments, this term defines a patient subgroup wherein said patients have been treated with X within the last 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 20, 21, 22, 23 or 24 hours, 1 – 6 days, 1 – 2 weeks, 1 – 5 month, 6 – 11 months and / or year.

The term "wherein said patient is currently being treated with X" as used herein describes a distinct patient subgroup. In any of the above embodiments, this term defines a patient subgroup wherein said patient is currently undergoing treatment with X, i.e. at that time X is being administered to the patient. In one embodiment, X may be being administered intravenously.

The amount of any compound or composition mentioned herein (or a pharmaceutically acceptable derivative thereof) administered as part of the invention should be a therapeutically effective amount where the any compound or composition mentioned herein is used for the treatment of a disease or condition, and a prophylactically effective amount where the compound or derivative is used for the prevention of a disease or condition.

As used herein, "treatment" includes prophylactic treatment. As used herein, a "patient" means an animal, *e.g.* a mammal, typically a human, in need of treatment.

The term "therapeutically effective amount" used herein refers to the amount of any compound or composition mentioned herein (or a pharmaceutically acceptable derivative thereof) needed to treat or ameliorate a targeted disease or condition. The term "prophylactically effective amount" used herein refers to the amount of compound needed to prevent a targeted disease or condition. The exact dosage will generally be dependent on the patient's status at the time of administration. Factors that may be taken into consideration when determining dosage include the severity of the disease state in the patient, the general health of the patient, the age, weight, gender, diet, time and frequency of administration, drug combinations, reaction sensitivities and the patient's tolerance or response to therapy.

The precise amount can be determined by routine experimentation, but may ultimately lie with the judgement of the clinician.

In one embodiment, the present invention relates to taxol and Rimcazole or a pharmaceutically acceptable derivative thereof for treating cancer, in particular breast cancer.

Administration & Formulation

In some embodiments, the microtubule stabilising agent and the sigma receptor ligand are administered to the patient at the same time. In these embodiments, the microtubule stabilising agent may be administered to the patient at exactly the same time as the sigma receptor ligand (*i.e.* the two compounds are administered simultaneously). Alternatively, the microtubule stabilising agent may be administered to the patient at approximately the same time as the sigma receptor ligand (*i.e.* the two therapies are not administered at precisely the same time), *e.g.* during the same visit to a physician or healthcare professional.

In other embodiments, the microtubule stabilising agent and the sigma receptor ligand are not administered to the patient at the same time, but are administered sequentially (consecutively) in either order. In these embodiments, the methods of the present invention may comprise administering a microtubule stabilising agent to the patient before administering a sigma receptor ligand. Alternatively, the methods may comprise administering a microtubule stabilising agent to the patient after administering a sigma receptor ligand. In embodiments where the microtubule stabilising agent and the sigma receptor ligand are administered sequentially, the compounds may be administered in such a way that both compounds exert a therapeutic effect on the patient at the same time (*i.e.* the periods in which each compound is effective may overlap), although this is not essential.

In other embodiments, the microtubule stabilising agent and the sigma receptor ligand may be administered to the patient separately. Separate administration covers administering the microtubule stabilising agent and the sigma receptor ligand at substantially different points in time. For example, separate administration may include administering a first composition, waiting for a period of time "t_1", and then administering a second composition. t_1 may be in the range of 1 year to 6 months, 6 months to 1 month, 1 month to two weeks, two weeks to one week, one week to one day, 24 hours to 12 hours. In particular, t_1 may be 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 20, 21, 22, 23 or 24 hours. In a more specific embodiment, t_1 is 0.5, 1, 1.5, 2, 2.5 or 3 hours. In a more specific embodiment, t_1 is 1 hour. In a more specific embodiment, t_1 is 1 hour and the microtubule stabilising agent is given first followed by the sigma receptor ligand.

Further compositions may additionally be administered as part of the separate administration, either at the same time as the first and second compositions, or at another time. If "n" further compositions are given, they may be each given at a periods of time "t_n" after the second composition. Each t_n independently has the same possible values as t_1.

In any of the above embodiments, the microtubule stabilising agent and the sigma receptor ligand may be given in any order. In a more specific embodiment, the microtubule stabilising agent may be given first followed by a sigma receptor ligand. In a different, more specific, embodiment, the sigma receptor ligand may be given first, followed by the microtubule stabilising agent.

In any of the above embodiments, the microtubule stabilising agent may be given once or twice daily for the first 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 days of treatment. In any of the above embodiments, the microtubule stabilising agent may be given once daily for the first 1, 2, 3, 4, or 5 days of treatment. In any of these embodiments, said agent may be a taxane and it is given for the first 5 days of treatment. In a more specific embodiment, said taxane is paclitaxel and it may be administered once daily for the first 5 days of treatment.

In any of the above embodiments, the microtubule stabilising agent may be given in a metronomic regimen. A metronomic dosing regimen (also known as an anti-angiogenic dosing regimen) involves either continuous infusion or frequent administration without extended rest periods. This may be achieved by administering the drug as a continuous infusion at a low dose into the blood, or as a low dose bolus administered on a regular basis such as every day, every two days, every three days, every 4 days, every 5 days, every 6 days or every 7 days. In such embodiments, the microtubule stabilising agent may be administered once every 1, 2, 3, 4, 5 or 6 days from the start of treatment, or, more specifically, once every 3 days from the start of treatment. In any of the disclosed embodiments, paclitaxel may be given in a metronomic regimen. In such embodiments, paclitaxel may be administered once every 1, 2, 3, 4, 5 or 6 days or, more specifically, every 3 days from the start of treatment.

In some embodiments, sigma receptor ligands may be given once or twice daily as an oral tablet at a dose of up to about 800mg per tablet. In one embodiment, said sigma receptor ligand is Rimcazole, as defined above. For example, in some embodiments Rimcazole may be used or present in an amount between 0.1mg and 500 mg per day.

In some embodiments, the microtubule stabilising agent may be administered on a three weekly cycle with a regimen of 2, 3, 4 or 6 cycles of three-weekly agent at a dose of between about 75mg/m^2 and about 225mg/m^2, more specifically between about 100mg/m^2 and about 175mg/m^2, more specifically about 75mg/m^2, 100mg/m^2, 135mg/m^2, 175mg/m^2 or

225mg/m^2. In one embodiment, said agent is a taxane. In one more specific embodiment, said agent is paclitaxel, as defined above.

When the microtubule stabilising agent and the sigma receptor ligand are administered at the same time, they may be administered as a single pharmaceutical formulation or as two or more separate pharmaceutical formulations. When the microtubule stabilising agent and the sigma receptor ligand are not administered at the same time, they are administered as two or more separate pharmaceutical formulations.

Administration as separate pharmaceutical formulations

Where the microtubule stabilising agent and the sigma receptor ligand are administered as separate pharmaceutical formulations, they may be administered by enteral or parenteral routes, including intravenous, intramuscular, subcutaneous, transdermal, airway (aerosol), oral, buccal, sublingual, intranasal, rectal, vaginal, and topical administration. In particular, they may be administered by intravenous, intramuscular, subcutaneous, oral, buccal, sublingual, rectal, vaginal, and/or topical means.

Each of the microtubule stabilising agent and the sigma receptor ligand should be assessed for its biopharmaceutical properties, such as solubility and solution stability (across pH), permeability, etc., in order to select the most appropriate dosage form and route of administration for treatment of the proposed indication.

In some embodiments, each of the microtubule stabilising agent and the sigma receptor ligand may be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term "excipient" includes any ingredient other than the microtubule stabilising agent and the sigma receptor ligand which may impart either a functional (e.g drug release rate controlling) and/or a non-functional (e.g. processing aid or diluent) characteristic to the formulations. The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

Typical pharmaceutically acceptable excipients include:

- diluents, e.g. lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine;
- lubricants, e.g. silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol;
- binders, e.g. magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone;

- disintegrants, e.g. starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or
- absorbants, colorants, flavors and/or sweeteners.

A thorough discussion of pharmaceutically acceptable excipients is available in Gennaro, Remington: The Science and Practice of Pharmacy 2000, 20th edition (ISBN: 0683306472).

Oral administration

Each of the microtubule stabilising agent and/or the sigma receptor ligand may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, and/or buccal, lingual, or sublingual administration by which the compound enters the blood stream directly from the mouth.

Formulations suitable for oral administration include solid plugs, solid microparticulates, semi-solid and liquid (including multiple phases or dispersed systems) such as tablets; soft or hard capsules containing multi- or nano-particulates, liquids (e.g. aqueous solutions), emulsions or powders; lozenges (including liquid-filled); chews; gels; fast dispersing dosage forms; films; ovules; sprays; and buccal/mucoadhesive patches.

Formulations suitable for oral administration may also be designed to deliver each of the microtubule stabilising agent and/or the sigma receptor ligand in an immediate release manner or in a rate-sustaining manner, wherein the release profile can be delayed, pulsed, controlled, sustained, or delayed and sustained or modified in such a manner which optimises the therapeutic efficacy of the said compounds. Means to deliver compounds in a rate-sustaining manner are known in the art and include slow release polymers that can be formulated with each of the microtubule stabilising agent and/or the sigma receptor ligand to control its release.

Examples of rate-sustaining polymers include degradable and non-degradable polymers that can be used to release the said compounds by diffusion or a combination of diffusion and polymer erosion. Examples of rate-sustaining polymers include hydroxypropyl methylcellulose, hydroxypropyl cellulose, methyl cellulose, ethyl cellulose, sodium carboxymethyl cellulose, polyvinyl alcohol, polyvinyl pyrrolidone, xanthum gum, polymethacrylates, polyethylene oxide and polyethylene glycol.

Liquid (including multiple phases and dispersed systems) formulations include emulsions, suspensions, solutions, syrups and elixirs. Such formulations may be presented as fillers in soft or hard capsules (made, for example, from gelatin or hydroxypropylmethylcellulose) and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or

suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

Each of the microtubule stabilising agent and/or the sigma receptor ligand may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Liang and Chen, Expert Opinion in Therapeutic Patents 2001, 11(6): 981-986.

The formulation of tablets is discussed in H. Lieberman and L. Lachman, Pharmaceutical Dosage Forms: Tablets 1980, vol. 1 (Marcel Dekker, New York).

Parenteral administration

Each of the microtubule stabilising agent and/or the sigma receptor ligand can be administered parenterally.

Each of the microtubule stabilising agent and/or the sigma receptor ligand may be administered directly into the blood stream, into subcutaneous tissue, into muscle, or into an internal organ. Suitable means for administration include intravenous, intraarterial, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, intrasynovial and subcutaneous. Suitable devices for administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous or oily solutions. Where the solution is aqueous, excipients such as sugars (including but restricted to glucose, mannitol, sorbitol, etc.) salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water (WFI).

Parenteral formulations may include implants derived from degradable polymers such as polyesters (i.e. polylactic acid, polylactide, polylactide-co-glycolide, polycapro-lactone, polyhydroxybutyrate), polyorthoesters and polyanhydrides. These formulations may be administered via surgical incision into the subcutaneous tissue, muscular tissue or directly into specific organs.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

The solubility of each of the microtubule stabilising agent and/or the sigma receptor ligand used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of co-solvents and/or solubility-enhancing agents such as surfactants, micelle structures and cyclodextrins.

Inhalation & intranasal administration

Each of the microtubule stabilising agent and/or the sigma receptor ligand can be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler, as an aerosol spray from a pressurised container, pump, spray, atomiser (preferably an atomiser using electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane, or as nasal drops. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

The pressurised container, pump, spray, atomizer, or nebuliser contains a solution or suspension of the microtubule stabilising agent or the sigma receptor ligand comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilising, or extending release of the active, a propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

Prior to use in a dry powder or suspension formulation, the drug product is micronised to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenisation, or spray drying.

Capsules (made, for example, from gelatin or hydroxypropylmethylcellulose), blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as l leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified release using, for example, PGLA. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Transdermal administration

Suitable formulations for transdermal application include a therapeutically effective amount of the microtubule stabilising agent or the sigma receptor ligand with carrier. Advantageous carriers include absorbable pharmacologically acceptable solvents to assist passage through

the skin of the host. Characteristically, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound of the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

The microtubule stabilising agent or the sigma receptor ligand may be administered alone or in combination with one or more other drugs (or as any combination thereof).

Administration as a single pharmaceutical formulation

In some embodiments of the present invention, the microtubule stabilising agent and the sigma receptor ligand are administered as a single pharmaceutical formulation. Such a single pharmaceutical formulation may be administered by enteral or parenteral routes, including intravenous, intramuscular, subcutaneous, transdermal, airway (aerosol), oral, buccal, sublingual, intranasal, rectal, vaginal, and topical administration. More specifically, the single pharmaceutical agent may be formulated as an intravenous formulation, an intra-peritoneal formulation or an oral formulation. Said single formulation may be an oral formulation.

In some embodiments, the microtubule stabilising agent and the sigma receptor ligand may be administered as a single formulation in association with one or more pharmaceutically acceptable excipients. The term "excipient" is as defined above in connection with the separate pharmaceutical formulations.

Oral administration

A pharmaceutical preparation comprising a microtubule stabilising agent and a sigma receptor ligand may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, and/or buccal, lingual, or sublingual administration by which the compound enters the blood stream directly from the mouth.

Formulations suitable for oral administration include solid plugs, solid microparticulates, semi-solid and liquid (including multiple phases or dispersed systems) such as tablets; soft or hard capsules containing multi- or nano-particulates, liquids (e.g. aqueous solutions), emulsions or powders; lozenges (including liquid-filled); chews; gels; fast dispersing dosage forms; films; ovules; sprays; and buccal/mucoadhesive patches.

Formulations suitable for oral administration may also be designed to deliver each of the microtubule stabilising agentand/or the sigma receptor ligand in an immediate release manner or in a rate-sustaining manner, wherein the release profile can be delayed, pulsed, controlled, sustained, or delayed and sustained or modified in such a manner which

optimises the therapeutic efficacy of the said compounds. Means to deliver compounds in a rate-sustaining manner are known in the art and include slow release polymers that can be formulated with the microtubule stabilising agent and the sigma receptor ligand to control their release.

Examples of rate-sustaining polymers include degradable and non-degradable polymers that can be used to release the said compounds by diffusion or a combination of diffusion and polymer erosion. Examples of rate-sustaining polymers include hydroxypropyl methylcellulose, hydroxypropyl cellulose, methyl cellulose, ethyl cellulose, sodium carboxymethyl cellulose, polyvinyl alcohol, polyvinyl pyrrolidone, xanthum gum, polymethacrylates, polyethylene oxide and polyethylene glycol.

Liquid (including multiple phases and dispersed systems) formulations include emulsions, suspensions, solutions, syrups and elixirs. Such formulations may be presented as fillers in soft or hard capsules (made, for example, from gelatin or hydroxypropylmethylcellulose) and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

The combination of a microtubule stabilising agent and a sigma receptor ligand may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Liang and Chen, Expert Opinion in Therapeutic Patents 2001, 11(6): 981-986.

The formulation of tablets is discussed in H. Lieberman and L. Lachman, Pharmaceutical Dosage Forms: Tablets 1980, vol. 1 (Marcel Dekker, New York).

Parenteral administration

A pharmaceutical formulation comprising a microtubule stabilising agent and a sigma receptor ligand may be administered parenterally.

The pharmaceutical formulation may be administered directly into the blood stream, into subcutaneous tissue, into muscle, or into an internal organ. Suitable means for administration include intravenous, intraarterial, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, intrasynovial and subcutaneous. Suitable devices for administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous or oily solutions. Where the solution is aqueous, excipients such as sugars (including but restricted to glucose, mannitol, sorbitol, etc.) salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for

some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water (WFI).

Parenteral formulations may include implants derived from degradable polymers such as polyesters (i.e. polylactic acid, polylactide, polylactide-co-glycolide, polycapro-lactone, polyhydroxybutyrate), polyorthoesters and polyanhydrides. These formulations may be administered via surgical incision into the subcutaneous tissue, muscular tissue or directly into specific organs.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

The solubility of each of the microtubule stabilising agent and the sigma receptor ligand used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of co-solvents and/or solubility-enhancing agents such as surfactants, micelle structures and cyclodextrins.

Inhalation & intranasal administration

The combination of the microtubule stabilising agent and/or the sigma receptor ligand can be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler, as an aerosol spray from a pressurised container, pump, spray, atomiser (preferably an atomiser using electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane, or as nasal drops. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

The pressurised container, pump, spray, atomizer, or nebuliser contains a solution or suspension of the microtubule stabilising agent and the sigma receptor ligand comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilising, or extending release of the active, a propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

Prior to use in a dry powder or suspension formulation, the drug product is micronised to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling,

supercritical fluid processing to form nanoparticles, high pressure homogenisation, or spray drying.

Capsules (made, for example, from gelatin or hydroxypropylmethylcellulose), blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified release using, for example, PGLA. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Transdermal administration

Suitable formulations for transdermal application include a therapeutically effective amount of the microtubule stabilising agent and the sigma receptor ligand with carrier. Advantageous carriers include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. Characteristically, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound of the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

The present invention further provides a pharmaceutical composition comprising a combination of the invention and pharmaceutically acceptable excipients.

In one embodiment, the pharmaceutical composition comprising a combination of the invention is an anhydrous or lyophilised solid.

In a further embodiment, the pharmaceutical composition comprising a combination of the invention is a solution, dispersion, emulsion, or suspension. Where such compositions require a solvent, said solvent can be any known pharmaceutically acceptable solvent, including water, ethanol and saline solution.

In still another embodiment of the present invention, the pharmaceutical composition is formulated into various dosage forms selected from a group comprising tablet, troches, lozenges, aqueous or oily suspensions, ointment, patch, gel, lotion, dentifrice, capsule, emulsion, creams, spray, drops, dispersible powders or granules, emulsion in hard or soft gel capsules, syrups and elixirs.

Dosages for the methods, uses and composition of the invention will of course vary depending, for example, on the particular condition to be treated, the effect desired and the mode of administration. In general, suitable daily dosages for oral administration are of the order of 0.1 to 10 mg/kg.

The present invention further provides a kit comprising a microtubule stabilising agent selected from a taxane or a pharmaceutically acceptable derivative thereof, and a sigma receptor ligand. The kit may further comprise instructions for the separate, sequential and / or simultaneous administration of said agent and said ligand. Alternatively or in addition, the kit of the present invention may further comprise one or more devices for administering the combination therapy to a human patient such as one or more of (i) a sterile needle and syringe, (ii) a sterile container (*e.g.* a glass bottle, plastic bottle or plastic bag) and drip chamber, (iii) a sterile tube with a regulating clamp, and (iv) a catheter.

The combinations, compositions, kits and other compounds of the invention may be given by any of the routes discussed above.

In particular embodiments, any of the combined medicaments of the invention may be given orally or intravenously.

General

The term "comprising" encompasses "including" as well as "consisting" *e.g.* a composition "comprising" X may consist exclusively of X or may include something additional *e.g.* X + Y.

The word "substantially" does not exclude "completely" *e.g.* a composition which is "substantially free" from Y may be completely free from Y. Where necessary, the word "substantially" may be omitted from the definition of the invention.

The term "about" in relation to a numerical value x means, for example, $x \pm 10\%$.

The invention is further illustrated by reference to the following figures and non-limiting examples.

Description of the figures:

Figure 1 shows that Rimcazole and paclitaxel do not synergise to reduce MDA-MB-231 tumour cell viability *in vitro*;

Figure 2 shows that Rimcazole increases the percentage of cells in the G1 phase of cell cycle arrest;

Figure 3 shows that Rimcazole and paclitaxel in combination reduces the percentage of cells in G2/M and subG0 arrest;

Figure 4 shows that Rimcazole lacks single agent activity against large MDA-MB-231 tumours;

Figure 5 shows that paclitaxel administered according to a metronomic dosing schedule inhibits the growth of MDA-MB-231 xenograft tumours;

Figure 6 shows that paclitaxel inhibits the growth of MDA-MB-231 xenograft tumours when administered daily for 5 days;

Figure 7 shows that Rimcazole and paclitaxel synergise to delay tumour growth when paclitaxel is administered according to a metronomic dosing schedule;

Figure 8 shows that a combination treatment with Rimcazole (22.5mg/kg/d) and paclitaxel (30mg/kg) synergises to delay tumour growth;

Figure 9 shows that a combination treatment with Rimcazole (22.5mg/kg/d) and paclitaxel (15mg/kg) synergises to delay tumour growth; and

Figure 10 shows the effect of Rimcazole (22.5mg/kg/d) and paclitaxel (30mg/kg/days 1-5) on survival of xenografts-bearing mice.

Examples

In vitro studies

In vitro assessment of cell viability was carried out using the MTS viability assay as previously described (Malich G *et al*, Toxicology, 124(3), pp. 179-192, 1997). Assessment of cell cycle was conducted using flow cytometric analysis (FACS). This method is well known in the art and measures the percentage of cells in different phases of the cell division cycle according to DNA content, in addition to cells with subnormal DNA content (sub G0) that represent late stage apoptotic cells. For *in vitro* studies paclitaxel was used with an ethanol vehicle.

Xenografts

7-8 week old female athymic mice (NCr nu/nu) were implanted subcutaneously on Day 0 with 30 to 60mg tumour fragments using a 12-gauge trocar needle. Animals were randomized into treatment groups on Day 13. For standard paclitaxel administration studies, mean estimated tumour mass for all groups at initiation of treatment was 281mg (range of group means: 226-322mg) and paclitaxel was administered once daily for the first 5 days of treatment. For metronomic paclitaxel administration studies, mean estimated tumour mass

for all groups at initiation of treatment was 206mg (range of group means: 195-226mg) and paclitaxel was administered once every three days from the start of treatment. On days when combination treatment occurred, the animals were treated with paclitaxel first followed by treatment with Rimcazole within one hour. All animals were dosed according to individual body weight on the day of treatment (30mg/kg/d for Rimcazole and 30mg/kg every 3 days for paclitaxel). Paclitaxel metronomic administration was achieved by administering the drug once every three days. Paclitaxel was administered in cremaphor. (10%Ethanol/10%cremophor/80%water). Rimcazole was administered once daily by oral gavage as a solution in water.

Body weights and tumour measurements were recorded three times weekly. Tumour burden (mg) was estimated from calliper measurements by the formula for the volume of a prolate ellipsoid assuming unit density as: Tumour burden (mg) = (L x W2)/2, where L and W are the respective orthogonal tumour length and width measurements (mm).

Evaluation of efficacy

The following endpoints were used to evaluate the efficacy of Rimcazole and paclitaxel:

Tumour growth delay

expressed as a T-C value, where T and C are the median times in days required for the treatment and control group tumours respectively to grow to 750mg. %T/C is defined as the median tumour mass of the Treated Group divided by the median tumour mass of the Control Group x 100. In this experiment, %T/C was evaluated when the median Control reached 2g.

Tumour response

a complete response (CR) is defined as a decrease in tumour mass to an undetectable size (<50mg),

a partial response (PR) is defined as a $\geq$ 50% decrease in tumour mass from that at first treatment.

PRs are exclusive of CRs, as are Tumour–Free Survivors (TFS).

Net Log10 Tumour Cell Kill (Net Kill)

the change in tumour burden (logs) over the treatment period. The Net Kill value allows quantitative comparison of efficacy across multiple experimental protocols and across models by normalizing the efficacy data for treatment regimens of varied duration and differences in tumour growth rates between experiments or models. Positive values indicate

that an actual reduction of tumour burden had occurred at the end of therapy relative to the pre-treatment burden. Negative values indicate the tumour grew (although possibly more slowly than the control tumours) during treatment. Thus, negative Net Kill values do not necessarily imply a complete lack of activity. Tumour-free survivors and tumour-bearing survivors whose tumours had not reached the Evaluation Size by the last day of the experiment were assigned a Time to Evaluation Size of > the last day of the experiment and were included in calculations of Tumour Growth Delay and Net Kill. The calculation of Net Kill by either method requires the establishment of the tumour doubling time (Td), which is the time in days for the tumour burden to double. Doubling time (Td) was estimated from the least squares best-fit straight line from a log-linear plot of tumour burden vs. time over the period of exponential growth (~200 to ~800mg range).

Statistics

Graphical data were analysed using a standard students t-test. Results are shown in comparison to control.

Results

In vitro studies show a lack of co-operativity or synergy between Rimcazole and paclitaxel in either incuding cell death (figure 1) or in changing the cell cycle stage of the cells (figure 2) as assessed by FACS analysis. Assessment of viable cell number in cultured ER negative mammary carcinoma (MDA MB 231) cells using the MTS viabilioty assay which measures the metabolic activity of cells, exposed to Rimcazole or paclitaxel alone and in combination for a period of 24 hours revealed either no added benefit or modest antagonism between the two agents (Figure 1). Values are expressed as mean percentage viability ± SEM compared to the vehicle control. When paclitaxel 30μM and Rimcazole 10μM were combined, there was a slight increase in viable cell number compared to the value for paclitaxel alone, indicating antagonism between the two agents. When paclitaxel 10μM and Rimcazole 10μM were combined, there was a less than additive effect, again suggesting antagonism between the two.

Further evidence for antagonism between paclitaxel and Rimcazole was also revealed in an analysis of cell cycle profile. Flow cytometric analysis (FACS) was conducted on permeabilised MDA MB 231 cells that were then stained with the nucleic acid dye propidium iodide, following exposure to Rimcazole alone for 24 hours over a range of concentrations (Figure 2) or paclitaxel alone at 30μM and in combination with Rimcazole (Figure 3). Rimcazole increased the percentage of cells in the G1 phase of the cell cycle (Figure 2), indicating a partial G1 cell cycle arrest. In contrast, cells exposed to paclitaxel alone (Figure 3, left hand group of bars) displayed an increase in the percentage of cells in a

G2/M phase, indicating a G2/M cell cycle arrest compared to cells treated with no drugs (Figure 2, left hand bars). When cells were exposed to Rimcazole and paclitaxel in combination, there was a reduction in the percentage of cells in G2/M and subG0 (Figure 3), indicating antagonism of both the G2/M cell cycle arrest, as well as apoptosis induction. Together, these data teach against the combination of Rimcazole with paclitaxel.

In vivo studies with Rimcazole and paclitaxel showed surprising data, given their lack of synergy in these *in vitro* studies.

Treatment with Rimcazole, as a single agent failed to produce anti-cancer activity against MDA-MB-231 xenografts at any dosage level (30, 22.5, 10, and 3mg/kg, see figure 4). In contrast, paclitaxel administered according to a metronomic schedule whereby administration was once every three days and therefore lacking the long rest period that is characteristic of more standard paclitaxel dosing regimens resulted in a delay in tumour growth (Figure 5)

This effect was increased by administration of paclitaxel on a repeat basis for the first 5 days of the study (Figure 6). Using this administration schedule, paclitaxel produced 20% complete regressions. The animals experiencing regression remained tumour-free at termination of the experiment. Standard paclitaxel treatment resulted in tumour growth delays of $\leq$2.4 days, associated apparent net tumour cell kill values of $\leq$-0.72logs, and Day 21 T/C values of $\geq$46%. However, neither the time to evaluation size nor the Day 21 %T/C values were statistically significant. (Table 1)

Table 1. Measured tumour parameters for Rimcazole and standard paclitaxel treatment of MDA-MB-231 xenografts

	Dose	Tumour growth delay, days	Apparent net tumour cell kill, log	Day 21 %T/C	% Complete Regressions	% Partial Regressions	% Tumour-free survivors
Vehicle		N/A	N/A	100	0	0	0
Paclitaxel	15mg/kg	1.2	-0.84	57	20	0	20
Paclitaxel	30mg/kg	2.4	-0.72	46	20	0	20
Rimcazole	10mg/kg/d	0.5	-0.96	83	0	0	0
	22.5mg/kg/d	0.6	-0.93	87	0	0	0
	30mg/kg/d	0.2	-1.12	96	0	0	0
Combination	**(15P/22.5R)**	**3**	**-1.75**	**34**	**10**	**10**	**10**
	(30P/22.5R)	**8.8**	**-1.59**	**20**	**20**	**20**	**20**

Wherein XP/YR relates to X mg/kg/d of paclitaxel and Y mg/kg/d of Rimcazole.

When Rimcazole was combined with paclitaxel on a metronomic dosing schedule tumour growth was delayed by a greater margin that that seen for Rimcazole alone, which had no effect on tumour growth, and for paclitaxel alone (Figure 7).

This synergistic effect was further enhanced when paclitaxel was administered as a daily treatment for the first 5 days of the study (figures 8 and 9). Combination treatment with Rimcazole (22.5mg/kg), in combination with paclitaxel (30mg/kg), produced striking and statistically significant anti-cancer activity against MDA-MB-231 xenografts (Figure 8). The data showed that the combination of Rimcazole and paclitaxel together was able to regress tumour size back to the size of the originally implanted tumours, whilst neither Rimcazole nor paclitaxel alone were able to cause any shrinkage of tumours, or a growth delay of such magnitude. Treatment resulted in a tumour growth delay of 8.8 days and an apparent net tumour cell kill value of -1.59logs (Table 1). Treatment also resulted in a Day 21 T/C value of 20%, 20% partial regressions, 20% complete regressions, and 20% tumour-free survivors. These effects were greater than those seen with either treatment alone, which did not result in a greater number of tumour free survivors. The tumour growth delay was statistically significant compared to control and to paclitaxel alone.

A similar effect was seen when Rimcazole (22.5mg/kg/d) was administered in combination with paclitaxel at 15mg/kg (Figure 9). This treatment resulted in a tumour growth delay of 3.0 days, an associated apparent net tumour cell kill value of -1.75logs, and Day 21 T/C value of 34%. Treatment also resulted in 10% complete regressions, 10% partial regressions, and 10% tumour-free survivors. The tumour growth delay produced by treatment was statistically significant compared to the Control Group (Table 1). Neither agent alone caused an increase in tumour-free survivors. As such the action of the agents in combination was particularly surprising.

Figure 10 shows the effect of Rimcazole (22.5mg/kg/d) and paclitaxel (30mg/kg/days 1-5) on survival of xenografts-bearing mice. Combination treatment reduced tumour growth in the animals such that the time to reach the termination date was delayed.

CLAIMS:

1. A microtubule stabilising agent selected from a taxane, or a pharmaceutically acceptable derivative thereof, and a sigma receptor ligand, for use in treating cancer, wherein said treatment involves administering said microtubule stabilising agent and said sigma receptor ligand separately, sequentially or simultaneously.

2. A microtubule stabilising agent selected from a taxane or a pharmaceutically acceptable derivative thereof, for use in treating cancer in a patient, wherein the patient has been previously treated, or is currently being treated with, a sigma receptor ligand.

3. A microtubule stabilising agent selected from a taxane or a pharmaceutically acceptable derivative thereof, for use in a method of treating cancer in a patient, wherein the microtubule stabilising agent is prepared for simultaneous, separate or sequential administration with a sigma receptor ligand.

4. A microtubule stabilising agent according to any one of claims 1 to 3, wherein said agent is paclitaxel (taxol^{TM}), docetaxel (taxotere^{TM}), DHA-paclitaxel (taxoprexin^{TM}), polyglutimate-taxol (OPAXIO^{TM}), or a pharmaceutically acceptable derivative thereof.

5. A microtubule stabilising agent according to any one of claims 1 to 4, wherein said agent is paclitaxel (taxol^{TM}).

6. A microtubule stabilising agent according to any one of claims 1 to 5, wherein said sigma receptor ligand is Rimcazole, haloperidol, reduced haloperidol, IPAG (1-(4-iodophenyl)-3-(2-adamantyl)guanidine), DTG (1,3-di(2-tolyl)guanidine), cis isomers of U50488, or a pharmaceutically acceptable derivative thereof.

7. A microtubule stabilising agent according to any one of claims 1 to 6, wherein said sigma receptor ligand is Rimcazole or a pharmaceutically acceptable derivative thereof.

8. A microtubule stabilising agent according to any one of claims 1 to 7, wherein said sigma receptor ligand is Rimcazole or a pharmaceutically acceptable salt thereof.

9. A microtubule stabilising agent according to any one of claims 1 to 8, wherein said cancer is ovarian, breast, non-small cell lung carcinoma or Kaposi's sarcoma.

10. A microtubule stabilising agent according to claim 9, wherein said cancer is breast cancer.

11. A sigma receptor ligand, for use in treating cancer in a patient, wherein the patient has been previously treated, or is currently being treated with a microtubule stabilising agent selected from a taxane or a pharmaceutically acceptable derivative thereof.

12. A sigma receptor ligand for use in treating cancer in a patient, wherein the sigma receptor ligand is prepared for simultaneous, separate or sequential administration with a microtubule stabilising agent selected from a taxane, or pharmaceutically acceptable derivative thereof.

13. A sigma receptor ligand according to any one of claims 11 or 12, wherein said ligand is Rimcazole, haloperidol, reduced haloperidol, IPAG (1-(4-iodophenyl)-3-(2-adamantyl)guanidine), DTG (1,3-di(2-tolyl)guanidine), cis isomers of U50488, or a pharmaceutically acceptable derivative thereof.

14. A sigma receptor ligand according to any one of claims 11 to 13, wherein said ligand is Rimcazole or a pharmaceutically acceptable derivative thereof.

15. A sigma receptor ligand according to any one of claims 11 to 14, wherein said microtubule stabilising agent is paclitaxel (taxol™), docetaxel (taxotere™), DHA-paclitaxel (taxoprexin™), polyglutimate-taxol (OPAXIO™), or a pharmaceutically acceptable derivative thereof.

16. A sigma receptor ligand according to any one of claims 11 to 15, wherein said microtubule stabilising agent is paclitaxel (taxol™).

17. A sigma receptor ligand according to any one of claims 11 to 16, wherein said ligand is Rimcazole or a pharmaceutically acceptable salt thereof.

18. A sigma receptor ligand according to any one of claims 11 to 17, wherein said cancer is ovarian, breast, non-small cell lung carcinoma or Kaposi's sarcoma.

19. A sigma receptor ligand according to claim 18, wherein said cancer is breast cancer.

20. The use of a microtubule stabilising agent selected from a taxane or a pharmaceutically acceptable derivative thereof and a sigma receptor ligand, in a method of manufacturing a medicament for the treatment of cancer.

21. The use of a microtubule stabilising agent selected from a taxane or a pharmaceutically acceptable derivative thereof, in a method of manufacturing a medicament for the treatment of cancer, wherein said treatment comprises the administration of a sigma receptor ligand.

22. The use of a sigma receptor ligand in a method of manufacturing a medicament for the treatment of cancer, wherein said treatment comprises the administration of a microtubule stabilising agent selected from a taxane or a pharmaceutically acceptable derivative thereof.

23. The use of a microtubule stabilising agent selected from a taxane or a pharmaceutically acceptable derivative thereof, in a method of manufacturing a medicament for the treatment of a patient with cancer, wherein said patient has been previously treated, or is currently being treated with a sigma receptor ligand.

24. The use of a sigma receptor ligand in a method of manufacturing a medicament for the treatment of a patient with cancer, wherein said patient has been previously treated, or is currently being treated with a microtubule stabilising agent selected from a taxane or a pharmaceutically acceptable derivative thereof.

25. A use according to any one of claims 20 to 24, wherein said microtubule stabilising agent is paclitaxel (taxol™), docetaxel (taxotere™), DHA-paclitaxel (taxoprexin™), polyglutimate-taxol (OPAXIO™), or a pharmaceutically acceptable derivative thereof.

26. A use according to any one of claims 20 to 25, wherein said microtubule stabilising agent is paclitaxel (taxol™).

27. A use according to any one of claims 20 to 26, wherein said sigma receptor ligand is Rimcazole, haloperidol, reduced haloperidol, IPAG (1-(4-iodophenyl)-3-(2-adamantyl)guanidine), DTG (1,3-di(2-tolyl)guanidine), cis isomers of U50488, or a pharmaceutically acceptable derivative thereof.

28. A use according to any one of claims 20 to 27, wherein said sigma receptor ligand is Rimcazole or a pharmaceutically acceptable derivative thereof.

29. A use according to any one of claims 20 to 28, wherein said sigma receptor ligand is Rimcazole or a pharmaceutically acceptable salt thereof.

30. A use according to any one of claims 20 to 29, wherein said cancer is ovarian, breast, non-small cell lung carcinoma or Kaposi's sarcoma.

31. A use according to claim 30, wherein said cancer is breast cancer.

32. A composition comprising a microtubule stabilising agent selected from a taxane or a pharmaceutically acceptable derivative thereof and a sigma receptor ligand.

33. A composition according to claim 32, wherein said composition also comprises at least one pharmaceutically acceptable excipient.

34. A composition according to claim 32 or claim 33, wherein said microtubule stabilising agent is paclitaxel (taxol™), docetaxel (taxotere™), DHA-paclitaxel (taxoprexin™), polyglutimate-taxol (OPAXIO™), or a pharmaceutically acceptable derivative thereof.

35. A composition according to any one of claims 32 to 34, wherein said microtubule stabilising agent is paclitaxel (taxol™).

36. A composition according to any one of claims 32 to 35, wherein said sigma receptor ligand is Rimcazole, haloperidol, reduced haloperidol, IPAG (1-(4-iodophenyl)-3-(2-adamantyl)guanidine), DTG (1,3-di(2-tolyl)guanidine), cis isomers of U50488, or a pharmaceutically acceptable derivative thereof.

37. A composition according to any one of claims 32 to 36, wherein said sigma receptor ligand is Rimcazole or a pharmaceutically acceptable salt thereof.

38. A kit comprising a microtubule stabilising agent selected from a taxane or a pharmaceutically acceptable derivative thereof and a sigma receptor ligand.

39. A kit according to claim 38, wherein said microtubule stabilising agent is paclitaxel (taxol™), docetaxel (taxotere™), DHA-paclitaxel (taxoprexin™), polyglutimate-taxol (OPAXIO™), or a pharmaceutically acceptable derivative thereof.

40. A kit according to any one of claims 38 and 39, wherein said microtubule stabilising agent is paclitaxel (taxol™).

41. A kit according to any one of claims 38 to 40, wherein said sigma receptor ligand is Rimcazole, haloperidol, reduced haloperidol, IPAG (1-(4-iodophenyl)-3-(2-adamantyl)guanidine), DTG (1,3-di(2-tolyl)guanidine), cis isomers of U50488, or a pharmaceutically acceptable derivative thereof.

42. A kit according to any one of claims 38 to 41, wherein said sigma receptor ligand is Rimcazole or a pharmaceutically acceptable salt thereof.

43. The use of a composition of any of claims 32 to 37 in therapy, wherein said therapy comprises the separate, sequential or simultaneous administration of a microtubule stabilising agent selected from a taxane or a pharmaceutically acceptable derivative thereof and a sigma receptor ligand.

44. The use of a composition of any of claims 32 to 37 in a method of treating cancer, wherein said method comprises the separate, sequential or simultaneous administration of a microtubule stabilising agent selected from a taxane or a pharmaceutically acceptable derivative thereof and a sigma receptor ligand.

45. A method of treatment of cancer in a patient in need thereof, wherein said method comprises administering to said patient a therapeutically effective amount of: a microtubule stabilising agent selected from a taxane or a pharmaceutically acceptable derivative thereof and a therapeutically effective amount of a sigma receptor ligand, wherein said microtubule stabilising agent and said sigma receptor ligand are administered separately, sequentially or simultaneously.

46. A method of treatment of cancer in a patient in need thereof, wherein said method comprises administering to said patient a therapeutically effective amount of a microtubule stabilising agent selected from a taxane or a pharmaceutically acceptable derivative thereof, wherein a therapeutically effective amount of a sigma receptor ligand has been previously administered to said patient.

47. A method of treatment of cancer in a patient in need thereof, wherein said method comprises administering to said patient a therapeutically effective amount of a sigma receptor ligand, wherein a therapeutically effective amount of a microtubule stabilising agent selected from a taxane or a pharmaceutically acceptable derivative thereof has been previously administered to said patient.

48. A method of reducing the toxicity of a microtubule stabilising agent selected from a taxane or a pharmaceutically acceptable derivative thereof, by administering said microtubule stabilising agent in combination with a sigma receptor ligand.

49. A method of delaying the growth of a tumour by administering a microtubule stabilising agent selected from a taxane or a pharmaceutically acceptable derivative thereof, in combination with a sigma receptor ligand.

50. A method of prolonging the life span of a patient with cancer by administrating a microtubule stabilising agent selected from a taxane or a pharmaceutically acceptable derivative thereof, in combination with a sigma receptor ligand.

51. A method of any of claims 45 to 50, wherein said microtubule stabilising agent is paclitaxel (taxol™), docetaxel (taxotere™), DHA-paclitaxel (taxoprexin™), polyglutimate-taxol (OPAXIO™), or a pharmaceutically acceptable derivative thereof.

52. A method of any of claims 45 to 51, wherein said microtubule stabilising agent is paclitaxel (taxol™).

53. A method of any of claims 45 to 52, wherein said sigma receptor ligand is Rimcazole, haloperidol, reduced haloperidol, IPAG (1-(4-iodophenyl)-3-(2-adamantyl)guanidine), DTG (1,3-di(2-tolyl)guanidine), cis isomers of U50488, or a pharmaceutically acceptable derivative thereof.

54. A method according to any one of claims 45 to 53, wherein said sigma receptor ligand is Rimcazole or a pharmaceutically acceptable derivative thereof.

55. A method according to any one of claims 45 to 54, wherein said sigma receptor ligand is Rimcazole or a pharmaceutically acceptable salt thereof.

56. A method according to any one of claims 45 to 55, wherein said cancer is ovarian, breast, non-small cell lung carcinoma or Kaposi's sarcoma

57. A method according to any one of claims 45 to 56, wherein said cancer is breast cancer.

58. A method of treating breast cancer in a patient in need thereof, wherein said method comprises administering to said patient a therapeutically effective amount of paclitaxel, and a therapeutically effective amount of Rimcazole, wherein said administration is separate, sequential or simultaneous

59. A microtubule stabilising agent, sigma receptor ligand, use, composition, kit, or method of any preceding claim wherein the microtubule stabilising agent and sigma receptor ligand are formulated together for simultaneous administration, wherein said formulation is an intravenous formulation, an intra-peritoneal formulation or an oral formulation.

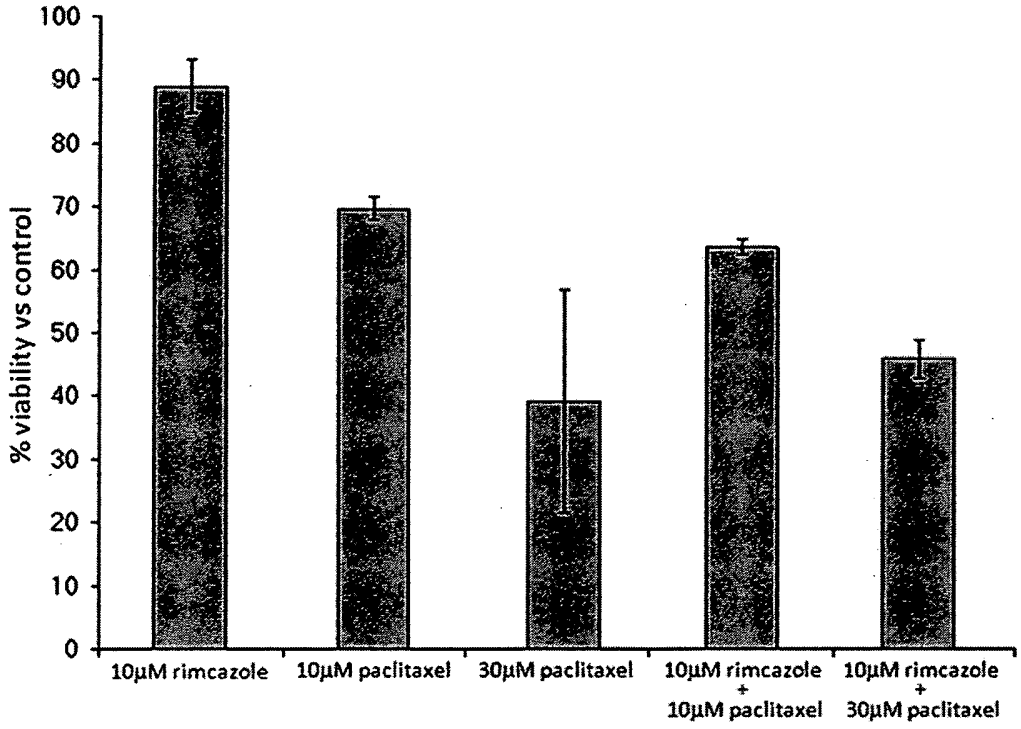

100
90
80
70
60
50
40
30
20
10
0
% viability vs control
10µM rimcazole
10µM paclitaxel
30µM paclitaxel
10µM rimcazole + 10µM paclitaxel
10µM rimcazole + 30µM paclitaxel

FIGURE 1

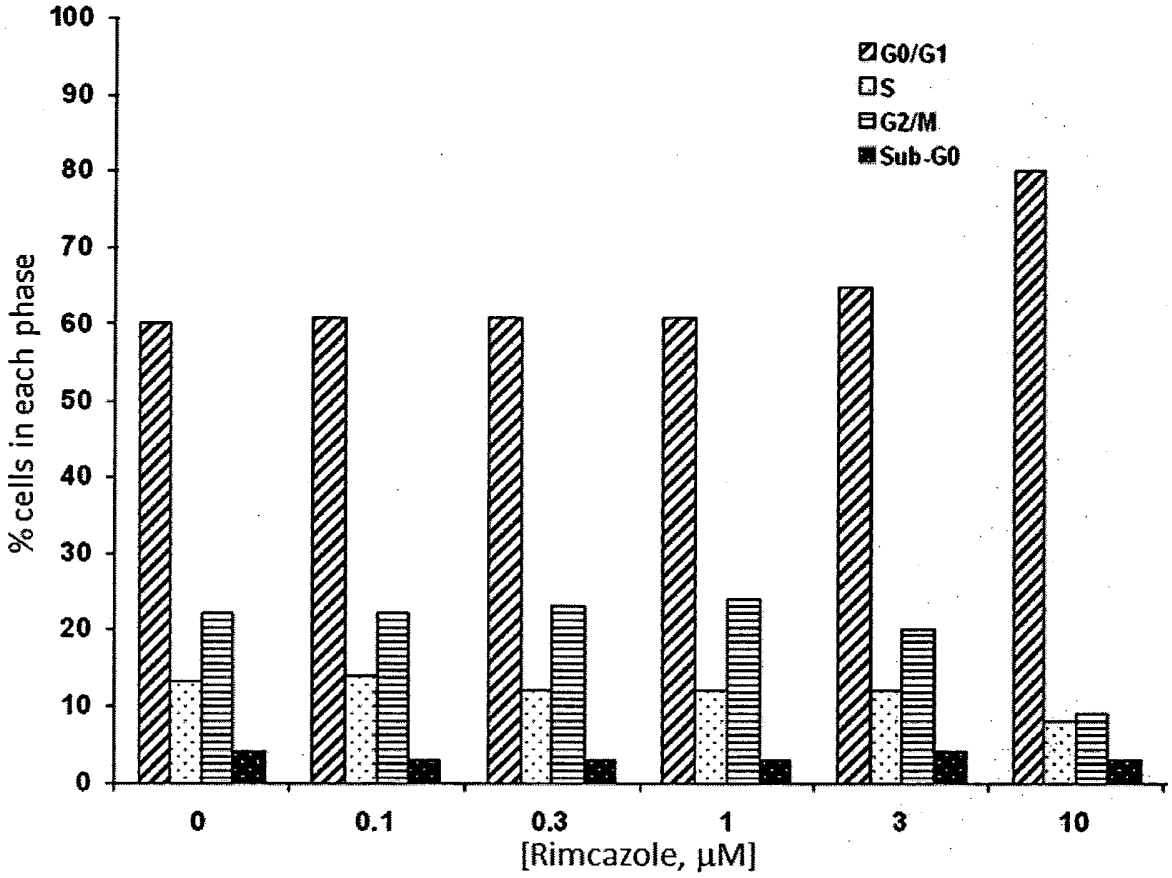

100
90
80
70
60
50
40
30
20
10
0
% cells in each phase
G0/G1
S
G2/M
Sub-G0
0
0.1
0.3
1
3
10
[Rimcazole, µM]

FIGURE 2

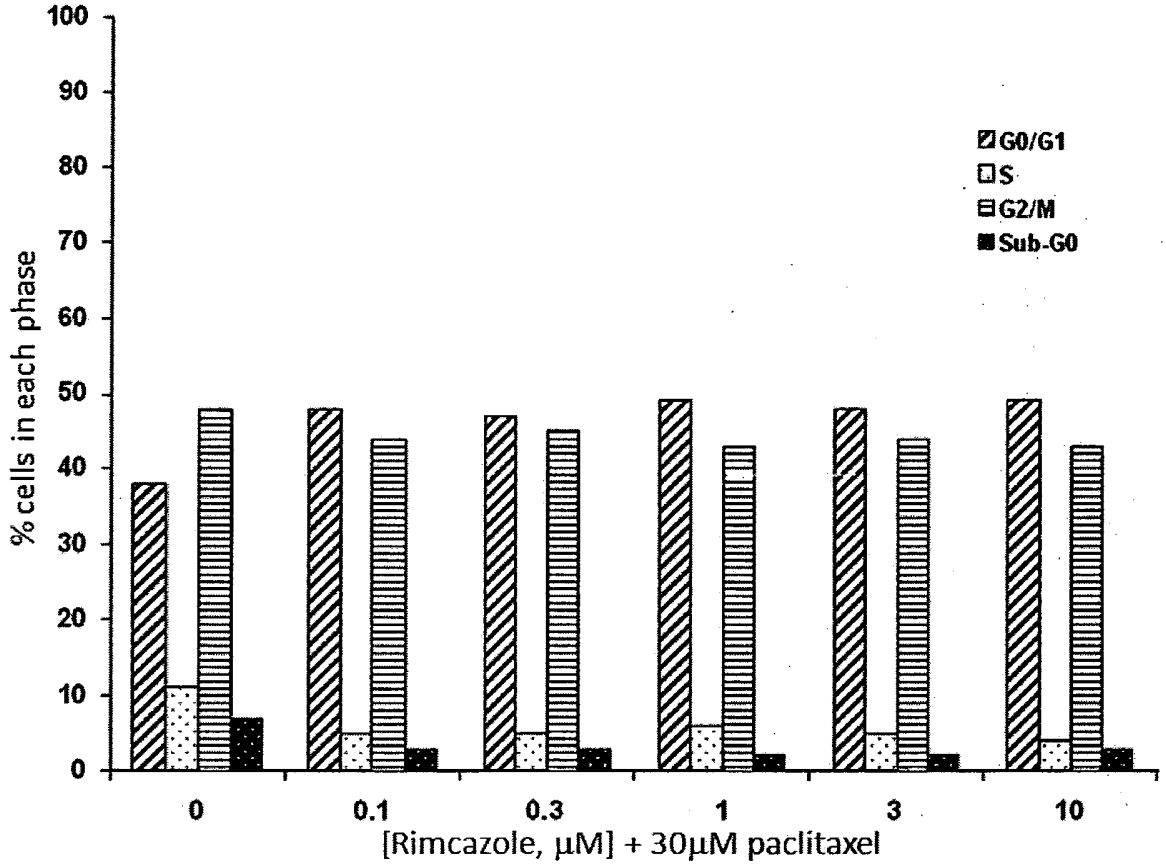

100
90
80
70
60
50
40
30
20
10
0
% cells in each phase
G0/G1
S
G2/M
Sub-G0
0
0.1
0.3
1
3
10
[Rimcazole, µM] + 30µM paclitaxel

FIGURE 3

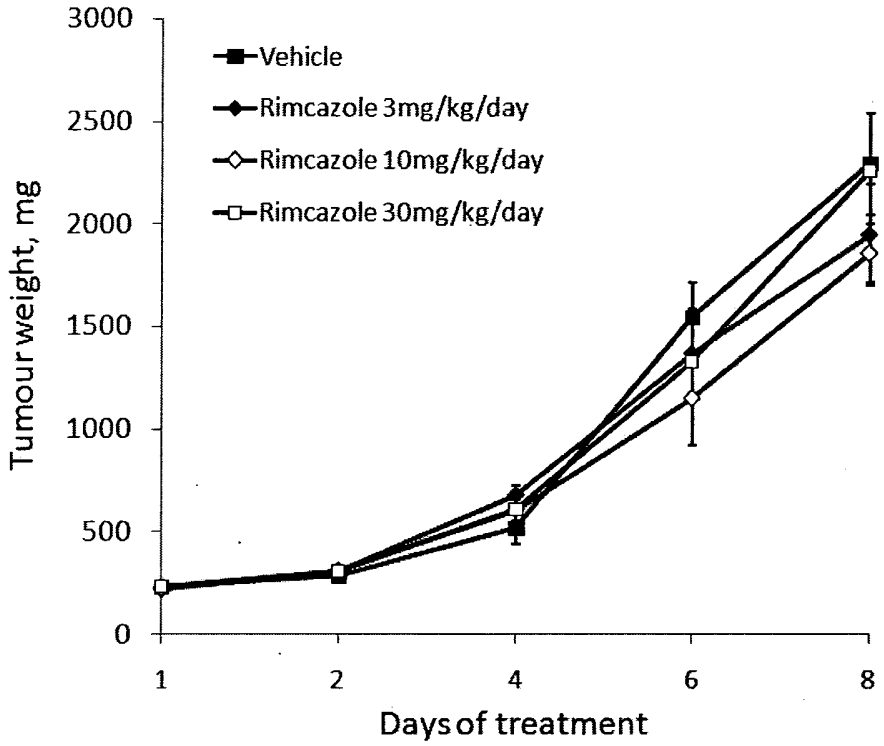

3000
2500
2000
1500
1000
500
0
Tumour weight, mg
Vehicle
Rimcazole 3mg/kg/day
Rimcazole 10mg/kg/day
Rimcazole 30mg/kg/day
1
2
4
6
8
Days of treatment

FIGURE 4

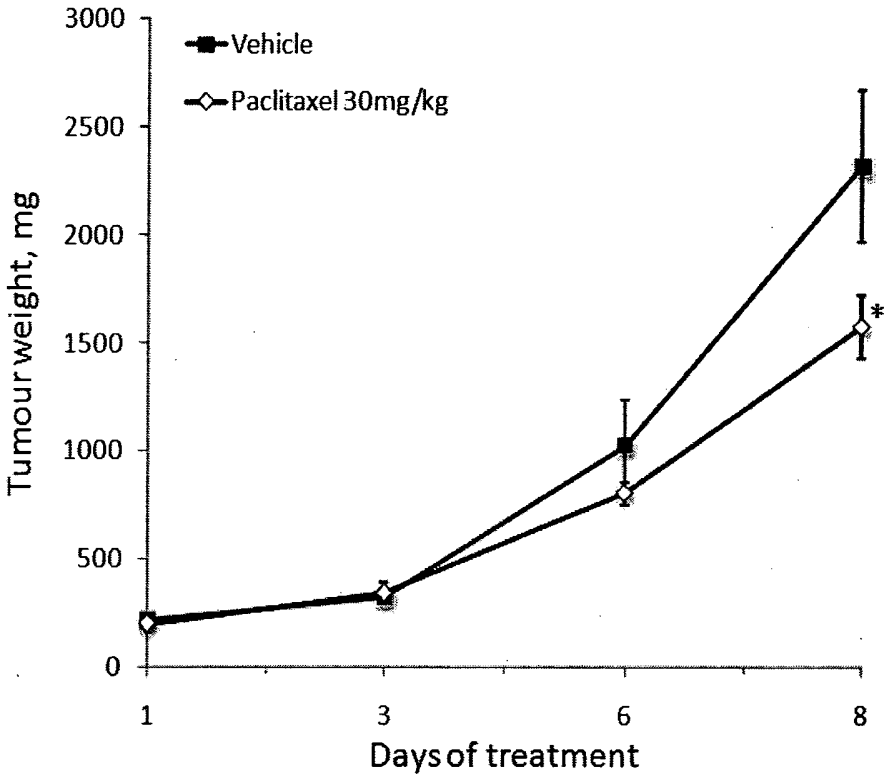

3000
2500
2000
1500
1000
500
0
Tumour weight, mg
Vehicle
Paclitaxel 30mg/kg
*
1
3
6
8
Days of treatment

FIGURE 5

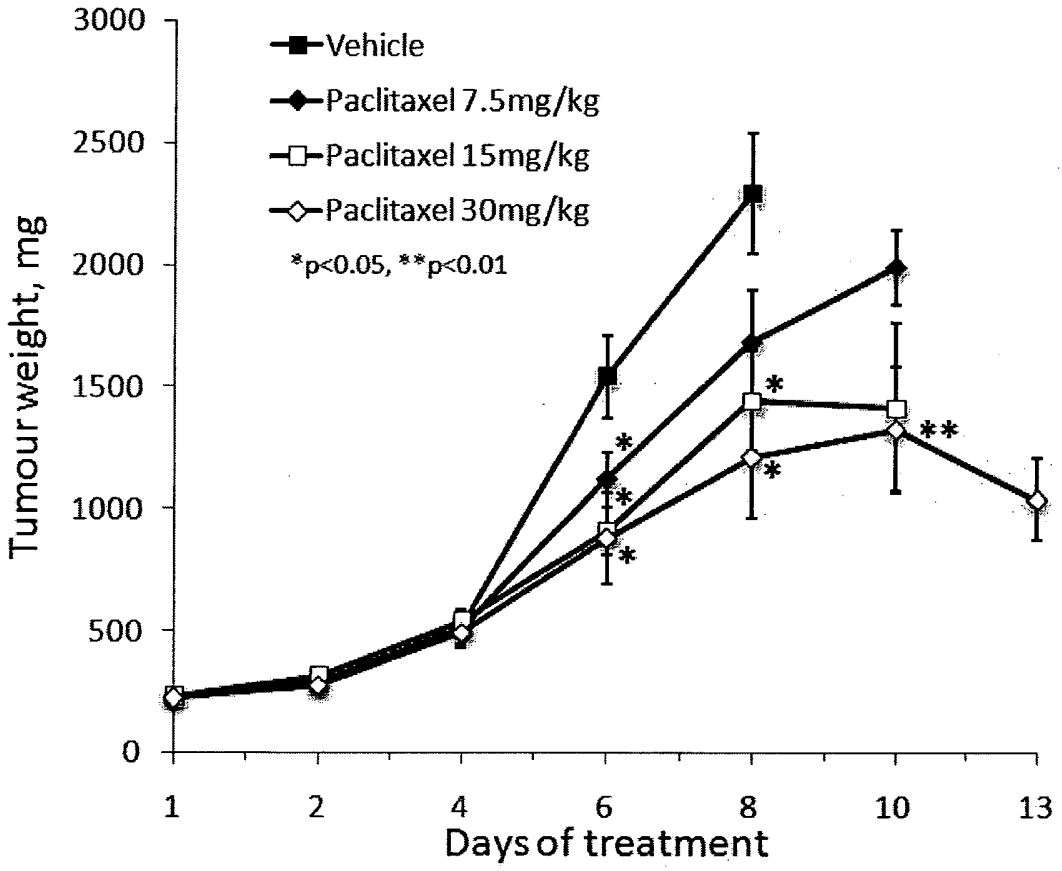

3000
2500
2000
1500
1000
500
0
Tumour weight, mg
Vehicle
Paclitaxel 7.5mg/kg
Paclitaxel 15mg/kg
Paclitaxel 30mg/kg
*p<0.05, **p<0.01
1
2
4
6
8
10
13
Days of treatment

FIGURE 6

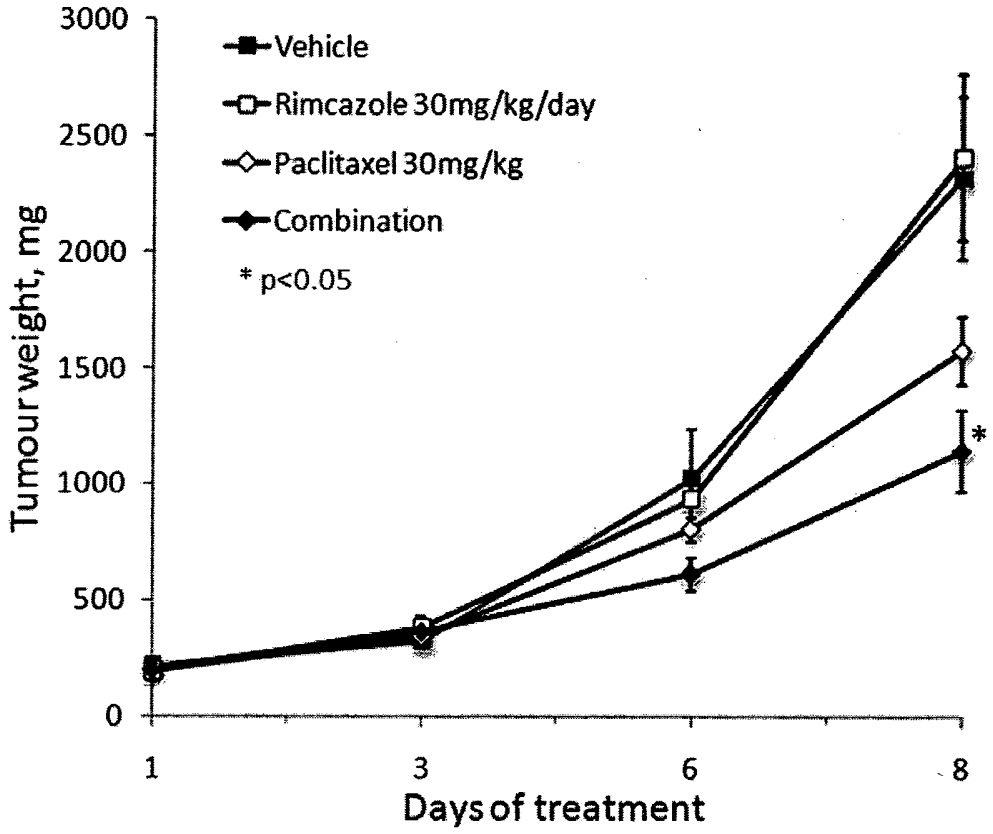

3000
2500
2000
1500
1000
500
0
Tumour weight, mg
Vehicle
Rimcazole 30mg/kg/day
Paclitaxel 30mg/kg
Combination
* p<0.05
*
1
3
6
8
Days of treatment

FIGURE 7

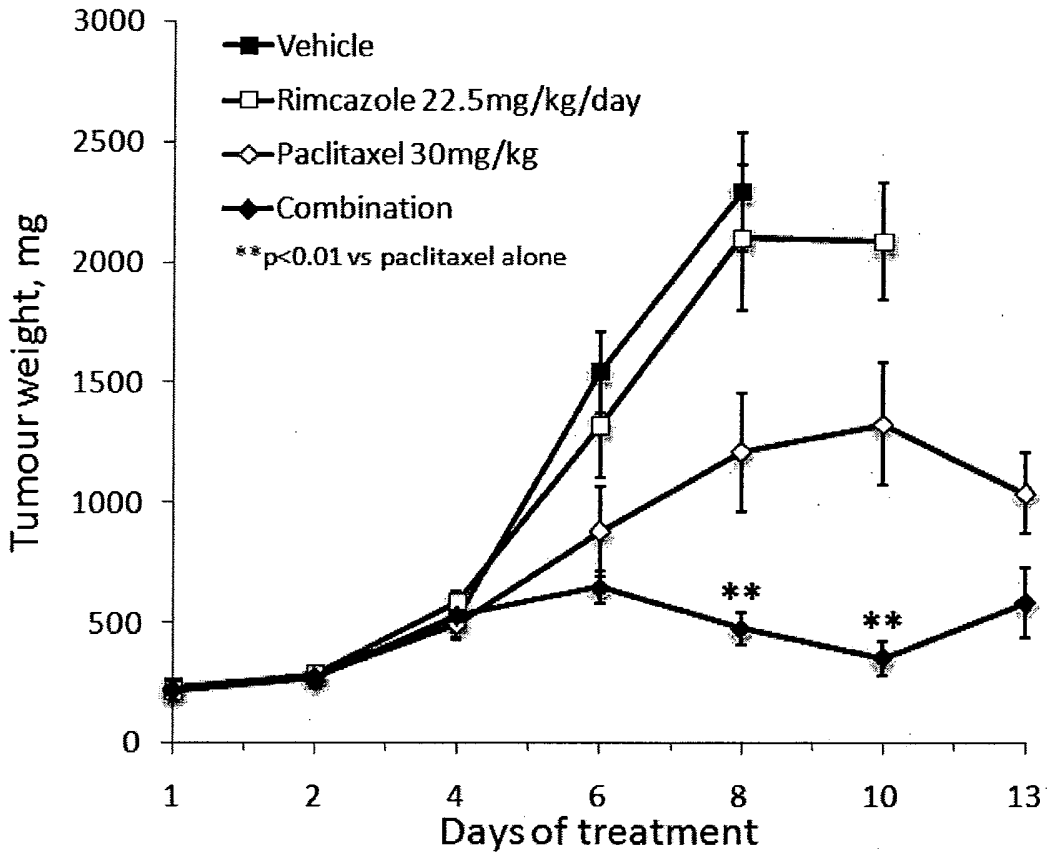

3000
2500
2000
1500
1000
500
0
Tumour weight, mg
Vehicle
Rimcazole 22.5mg/kg/day
Paclitaxel 30mg/kg
Combination
**p<0.01 vs paclitaxel alone
**
**
1
2
4
6
8
10
13
Days of treatment

FIGURE 8

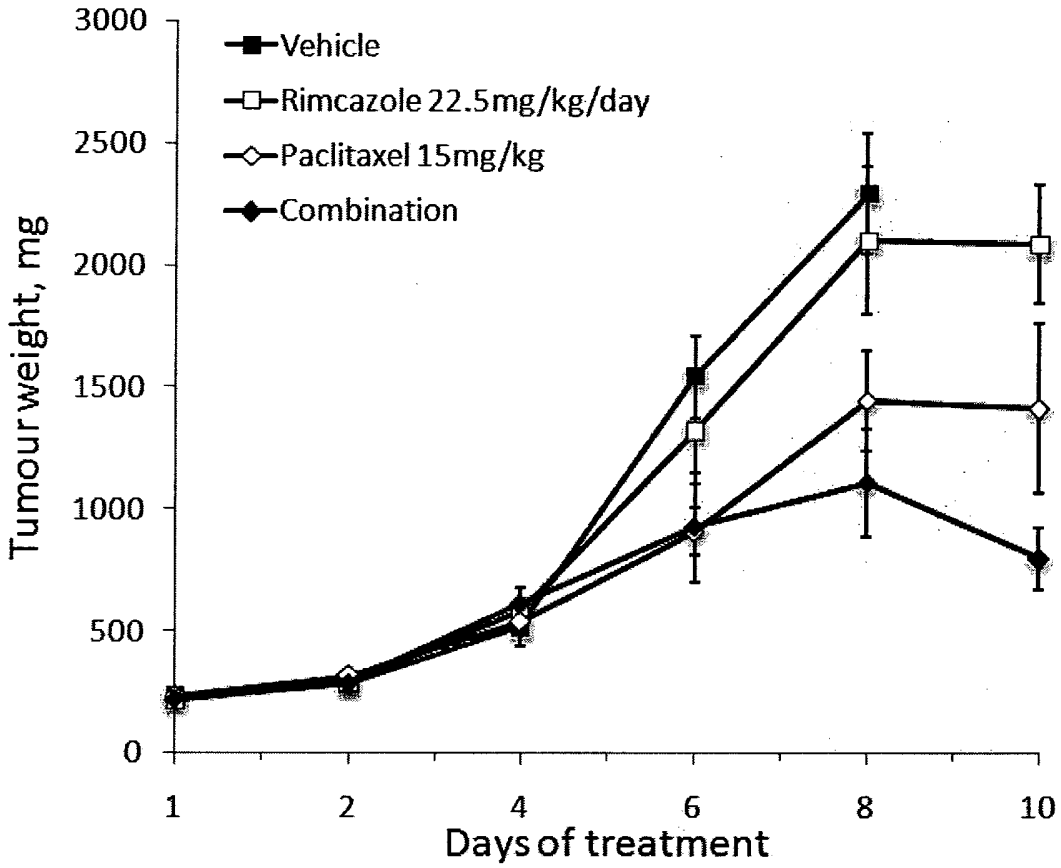

3000
2500
2000
1500
1000
500
0
Tumour weight, mg
Vehicle
Rimcazole 22.5mg/kg/day
Paclitaxel 15mg/kg
Combination
1
2
4
6
8
10
Days of treatment

FIGURE 9

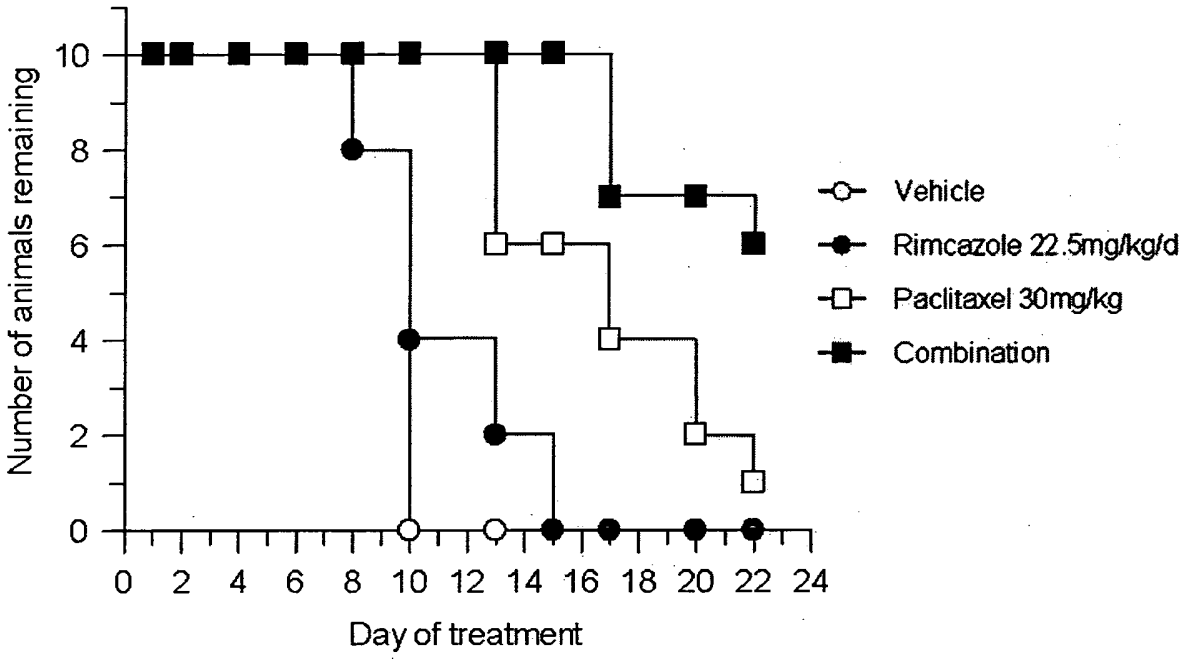

Number of animals remaining
10
8
6
4
2
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Day of treatment
Vehicle
Rimcazole 22.5mg/kg/d
Paclitaxel 30mg/kg
Combination

FIGURE 10

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2010/000926

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/337 A61K31/439 A61K31/445 A61K31/495 A61K31/496
A61K45/06 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 A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR 2 887 454 A1 (SANOFI AVENTIS SA [FR]) 29 December 2006 (2006-12-29)	1-59
Y	claim 1 page 2, lines 12-25 page 4, lines 8-11	1-59
Y	WO 01/74359 A1 (SPRUCE BARBARA [GB]; ECCLES SUZANNE [GB]; DEXTER MICHAEL [GB]) 11 October 2001 (2001-10-11) claims	1-59
X,P	WO 2009/103487 A1 (ESTEVE LABOR DR [ES]; BAEYENS-CABRERA JOSE MANUEL; BUSCHMANN HELMUT H) 27 August 2009 (2009-08-27) claims	1-59

☐ 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 document but published on or after the international filing date

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 July 2010	06/08/2010

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

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2010/000926

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR 2887454 A1	29-12-2006	NONE	
WO 0174359 A1	11-10-2001	AU 4436701 A	15-10-2001
		EP 1267875 A1	02-01-2003
		JP 2003528916 T	30-09-2003
		US 2004019060 A1	29-01-2004
WO 2009103487 A1	27-08-2009	NONE	