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(54) Title: COMBINATION TREATMENT

(57) Abstract: The present specification relates to the use of combinations comprising 1-(4-(5-(5- amino-6-(5-tert-butyl-1,3,4-oxadiazol-2-yl)pyrazin-2-yl)-1-ethyl-1H-1,2,4-triazol-3- yl)piperidin-1-yl)-3-hydroxypropan-1-one (Compound [I]) or a pharmaceutically acceptable salt thereof, and either a cyclin-dependent kinase (CDK) inhibitor or an anti- estrogen agent, or both a CDK inhibitor and an anti-estrogen agent, in the treatment or prophylaxis of cancer; pharmaceutical compositions comprising Compound [I] or a pharmaceutically acceptable salt thereof and either or both of a CDK inhibitor and an anti- estrogen agent; kits comprising Compound [I] or a pharmaceutically acceptable salt thereof and either or both of a CDK inhibitor and an anti-estrogen agent, optionally with instructions for use; methods of treatment comprising the simultaneous, sequential or separate administration of Compound [I] or a pharmaceutically acceptable salt thereof and either or both of a CDK inhibitor and an anti-estrogen agent, to a warm-blooded animal, such as man; and the intermittent dosing of Compound [I] or a pharmaceutically acceptable salt thereof either alone or in combination with either or both of a CDK inhibitor and an anti-estrogen agent.

COMBINATION TREATMENT

The present specification relates to the use of combinations comprising 1-(4-(5-(5-amino-6-(5-tert-butyl-1,3,4-oxadiazol-2-yl)pyrazin-2-yl)-1-ethyl-1H-1,2,4-triazol-3-yl)piperidin-1-yl)-3-hydroxypropan-1-one (hereafter "Compound [I]") or a pharmaceutically acceptable salt thereof and a cyclin-dependent kinase (CDK) inhibitor in the treatment or prophylaxis of cancer. The specification also relates to pharmaceutical compositions comprising Compound [I] or a pharmaceutically acceptable salt thereof and a CDK inhibitor; and to kits comprising Compound [I] or a pharmaceutically acceptable salt thereof and a CDK inhibitor, optionally with instructions for use. The specification further relates to methods of treatment comprising the simultaneous, sequential or separate administration of Compound [I] or a pharmaceutically acceptable salt thereof and a CDK inhibitor, to a warm-blooded animal, such as man. The specification further relates to combinations comprising Compound [I] or a pharmaceutically acceptable salt thereof and an anti-estrogen agent in the treatment or prophylaxis of cancer, and to pharmaceutical compositions, kits and methods of treatment thereof. The specification further relates to the use of combinations comprising Compound [I] or a pharmaceutically acceptable salt thereof, a cyclin-dependent kinase (CDK) inhibitor, and an anti-estrogen agent in the treatment or prophylaxis of cancer, and to pharmaceutical compositions, kits and methods of treatment thereof. The specification further relates to the intermittent dosing of Compound [I] in the treatment or prophylaxis of cancer, both alone and in combination with a CDK inhibitor and/or an anti-estrogen agent.

In the area of cancer it has in recent years been discovered that a cell may become cancerous by virtue of the transformation of a portion of its DNA into an oncogene, that is a gene which, on activation, leads to the formation of malignant tumour cells (Bradshaw, Mutagenesis, 1986, 1, 91). Several such oncogenes give rise to the production of peptides, which are Kinases, a class of enzymes that are capable of phosphorylating their protein or lipid substrates. There are several classes of kinases.

Firstly, tyrosine kinases, which may be receptor tyrosine kinases or non receptor tyrosine kinases. Various classes of receptor tyrosine kinases are known (Wilks, Advances in Cancer Research, 1993, 60, 43-73) based on families of growth factors, that can bind to the extracellular surface of different receptor tyrosine kinases; as an example the

classification includes Class I receptor tyrosine kinases comprising the EGF family of receptor tyrosine kinases. Non-receptor tyrosine kinases are located intracellularly; various classes of non-receptor tyrosine kinases are known including the Src family such as the Src, Lyn, Fyn and Yes tyrosine kinases.

Secondly, certain kinases belong to the class of serine/threonine kinases which are also located intracellularly. Serine/threonine kinase signalling pathways include the Raf-MEK-ERK cascade and those downstream of PI3-kinase such as PDK-1, AKT and mTOR (Blume-Jensen and Hunter, Nature, 2001, 411, 355).

It is also known that certain other kinases belong to the class of lipid kinases, which are located intracellularly and are, as for the above mentioned kinases, involved in the transmission of biochemical signals such as those that influence tumour cell growth and invasiveness. Various classes of lipid kinases are known including the aforementioned PI3-kinase family.

It is now well understood that deregulation of oncogenes and tumour-suppressor genes contributes to the formation of malignant tumours, for example by way of increased cell proliferation or increased cell survival. It is also now known that signalling pathways mediated by the PI3-kinase family have a central role in a number of cell processes including proliferation and survival, and deregulation of these pathways is a causative factor across a wide spectrum of human cancers and other diseases (Katso et al., Annual Rev. Cell Dev. Biol., 2001, 17: 615-617 and Foster et al., J. Cell Science, 2003, 116: 3037-3040).

The PI3-kinase family of lipid kinases is a group of enzymes that phosphorylate the 3-position of the inositol ring of phosphatidylinositol (PI). Three major groups of PI3-kinase enzymes are known which are classified according to their physiological substrate specificity (Vanhaesebroeck et al., Trends in Biol. Sci., 1997, 22, 267; Engleman et al., Nature Review Genetics, 2006, 7, 607). Class III PI3-kinase enzymes phosphorylate PI alone. In contrast, Class II PI3-kinase enzymes phosphorylate both PI and PI4-phosphate [abbreviated hereinafter to PI(4)P]. Class I PI3-kinase enzymes phosphorylate PI, PI(4)P and PI4,5-bisphosphate [abbreviated hereinafter to PI(4,5)P2], although only PI(4,5)P2 is believed to be the physiological cellular substrate. Phosphorylation of PI(4,5)P2 produces the lipid second messenger PI3,4,5-triphosphate [abbreviated hereinafter to PI(3,4,5)P3]. More distantly related members of this superfamily are Class IV kinases such as mTOR

and DNA-dependent protein kinase that phosphorylate serine/threonine residues within protein substrates. The most studied and understood of these lipid kinases are the Class I PI3-kinase enzymes.

Class I PI3-kinases are heterodimers consisting of a p110 catalytic subunit and a regulatory subunit, and the family is further divided into Class Ia and Class Ib enzymes on the basis of regulatory partners and mechanism of regulation (Engleman et al., Nature Review Genetics, 2006, 7, 607). Class Ia enzymes consist of three distinct catalytic subunits (p110α, p110β and p110δ, by nomenclature define the PI3-Kinase isoform as α, β or δ respectively) that dimerise with five distinct regulatory subunits (p85α, p55α, p50α, p85β and p55γ), with all catalytic subunits being able to interact with all regulatory subunits to form a variety of heterodimers. Class Ia PI3-kinase enzymes are generally activated in response to growth factor-stimulation of receptor tyrosine kinases, *via* interaction of the regulatory subunit SH2 domains with specific phospho-tyrosine residues of the activated receptor or adaptor proteins such as IRS-1. Both p110α and p110β are widely expressed across cell types and tissues, whereas p110δ expression is more restricted to leukocyte populations and some epithelial cells. In contrast, the single Class Ib enzyme consists of a p110γ catalytic subunit that interacts with a p101 regulatory subunit. Furthermore, the Class Ib enzyme is activated in response to G-protein coupled receptor (GPCR) systems as well as by the mechanisms described above.

There is now considerable evidence indicating that Class Ia PI3-kinase enzymes, contribute to tumourigenesis in a wide variety of human cancers, either directly or indirectly (Vivanco and Sawyers, Nature Reviews Cancer, 2002, 2, 489-501). In particular, the PIK3CA gene which encodes the p110α catalytic subunit of PI3-kinase is widely implicated in tumourigenesis. Activating point mutations, most frequently found in the helical or catalytic domains of p110α, increase the PI3-kinase activity of the holoenzyme and can transform cells. They have been reported, particularly, as somatically occurring mutations at significant frequencies across a wide range of tumour types (Samuels et al., Science, 2004, 304, 554; Samuels et al., Cancer Cell, 2005, 7, 561; Engleman et al., Nature Review Genetics, 2006, 7, 607; Zhao L and Vogt PK, Oncogene 2008, 27 5486). Tumour-related mutations in p85α have also been identified in cancers such as those of the ovary and colon (Philp et al., Cancer Research, 2001, 61, 7426-7429).

Furthermore, the p110α subunit is amplified in some tumours such as those of the ovary (Shayesteh et al., Nature Genetics, 1999, 21, 99-102) and cervix (Ma et al., Oncogene, 2000, 19, 2739-2744).

In addition to direct effects, it is believed that activation of Class Ia PI-3 kinase contributes to tumourigenic events that occur upstream in signalling pathways, for example by way of ligand-dependent or ligand-independent activation of receptor tyrosine kinases, GPCR systems or integrins (Vara et al., Cancer Treatment Reviews, 2004, 30, 193-204). Examples of such upstream signalling pathways include over-expression of the receptor tyrosine kinase Erb2 in a variety of tumours leading to activation of PI 3-kinase-mediated pathways (Harari et al., Oncogene, 2000, 19, 6102-6114) and over-expression of the oncogene Ras (Kauffmann-Zeh et al., Nature, 1997, 385, 544-548). In addition, Class Ia PI3-kinases may contribute to tumourigenesis caused by various downstream signalling events. For example, loss of the effect of the PTEN tumour-suppressor phosphatase that catalyses conversion of PI(3,4,5)P3 back to PI(4,5)P2 is associated with a very broad range of tumours *via* deregulation of PI3-kinase-mediated production of PI(3,4,5)P3 (Simpson and Parsons, Exp. Cell Res., 2001, 264, 29-41). Furthermore, augmentation of the effects of other PI3-kinase-mediated signalling events is believed to contribute to a variety of cancers, for example by activation of Akt (Nicholson and Anderson, Cellular Signalling, 2002, 14, 381-395).

Hence the common deregulation of PI3-kinase together with those of upstream and downstream signalling pathways collectively make it one of the most commonly deregulated pathways in human cancer (Hennessey et al., Nature Reviews Drug Discovery, 2005, 4, 988).

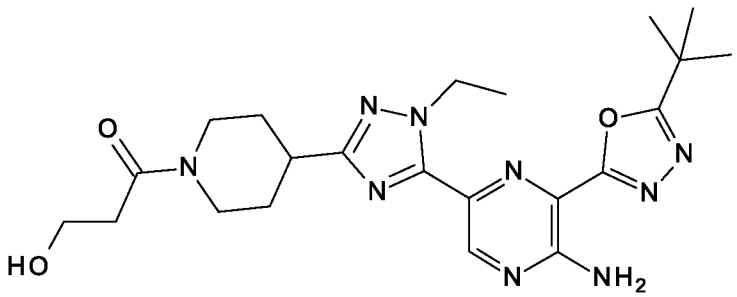
In addition to a role in mediating proliferative and survival signalling in tumour cells, there is evidence that Class I PI3K enzymes also contribute to tumourigenesis *via* their functions in tumour-associated stromal cells. For example, class I PI3K enzymes play an important role in the regulation of immune cells with PI3K activity contributing to pro-tumourigenic effects of inflammatory cells (Coussens and Werb, Nature, 2002, 420, 860-867). More recent developments include the finding in pre-clinical models of solid tumours that that PI3Kδ can restrain the antitumour immune response by promoting the action of suppressive immune cells. Indeed, deletion or pharmacological inhibition of PI3Kδ can prolong survival in pre-clinical tumour models as a result of blockade of

Regulatory T cells (Treg) cell activity and the accumulation of tumour killing CD8+ T cells (Ali et al, Nature, 2014, 510, 407-411).

In addition, the Class Ia PI3-kinase enzyme, PI3-kinase δ, is particularly implicated in tumourigenesis in haematological malignancies, such as Chronic Lymphoctyic Leukaemia (CLL), Acute Lymphoblastic Leukaemia (ALL) and Mantle Cell Lymphoma (MCL). Elevated -signalling of PI3K (mainly p110δ) is reported in a wide range of malignant lymphoid cells (Herman et al., Blood, 2010, 116. 2078; Ikeda et al., Blood, 2010, 116, 1460; Uddin et al., Blood, 2006, 108, 4178; Rudelius et al., Blood 2006, 108, 1668; Garcia-Martinez., Br J Cancer, 2011, 104, 1116; Renne et al., Leukemia, 2007, 2,780). This has led to the development of agents targeting PI3-kinase δ, with promising initial clinical results in haematological malignancies. (Castillo et al., Expert Opinion on Investigational Drugs, 2012, 21, 15).

These findings suggest that pharmacological inhibitors of Class I PI3-kinase enzymes should be of therapeutic value for treatment of the various forms of the disease of cancer comprising solid tumours such as carcinomas and sarcomas and the leukaemias and lymphoid malignancies.

Compound [I] is a selective inhibitor of Class I PI3-kinase enzymes, particularly by way of inhibition of a subset of the Class Ia PI3-kinase enzymes, more particularly by way of inhibition of the PI3K-α and -δ isoforms, and Compound [I] is disclosed amongst a number of other Examples in international patent application publication number WO2014/114928. Compound [I] has the following structure:



Compound [I]

In WO2014/114928 it is stated that the compounds disclosed therein "may be applied as a sole therapy or may involve, in addition to the compound of the specification, conventional surgery or radiotherapy or chemotherapy". WO2014/114928 then lists many

potential anti-tumour agents for use in such chemotherapy. However, WO2014/114928 does not list an inhibitor of CDK as a potential anti-tumour agent for use in chemotherapy.

It has now been found that the use of Compound [I] in combination with a CDK inhibitor, or in combination with a CDK inhibitor and an anti-estrogen agent, provides a synergistic effect, and may therefore provide an improved method of treating cancer compared to the use of either Compound [I] or a CDK inhibitor or an anti-estrogen agent alone.

A combination treatment may be considered to provide a synergistic effect if the effect is therapeutically superior, as measured by, for example, the extent of the response, the response rate, the time to disease progression or the survival period, to that achievable on dosing one or other of the components of the combination treatment at their conventional dose. For example, the effect of the combination treatment is synergistic if the use of the combination is superior to the effect achievable with Compound [I] or one of the specified combination partners, when used alone. In particular, the effect of the combination treatment is synergistic if efficacy can be maintained during combination treatment at a lower dose of one or more of the combination partners than is required for the corresponding monotherapy treatment. Further, the effect of the combination treatment is synergistic if a beneficial effect is obtained in a group of patients that does not respond (or responds poorly) to Compound [I] or one of the specified combination partners, when used alone.

A combination treatment may also be considered to provide a synergistic effect if one or both of the components may be dosed less frequently than the dosing schedule used for conventional dosing of each component when used alone, while not adversely impacting the beneficial effect otherwise achieved by the use of conventional amounts of an agent used alone. In particular, synergy is deemed to be present if the frequency of dosing of Compound [I] and/or a specified combination partner may be reduced relative to what would otherwise be conventional/required when using one of the combination partners alone, without detriment to one or more factors such as: extent of the response, the response rate, the time to disease progression and survival data and in particular without detriment to the duration of the response. Decreasing the dosing amount and frequency for a particular compound can lead to fewer and/or less troublesome side-effects than those that occur when conventional scheduling/doses are used.

In a first embodiment of the specification there is provided a combination comprising Compound [I] or a pharmaceutically acceptable salt thereof and a CDK inhibitor, for use in the treatment of cancer.

A further embodiment is any one of the embodiments hereinafter described, wherein Compound [I] is 1-(4-(5-(5-amino-6-(5-tert-butyl-1,3,4-oxadiazol-2-yl)pyrazin-2-yl)-1-ethyl-1H-1,2,4-triazol-3-yl)piperidin-1-yl)-3-hydroxypropan-1-one.

A further embodiment is any one of the embodiments hereinafter described, wherein Compound [I] is a pharmaceutically acceptable salt of 1-(4-(5-(5-amino-6-(5-tert-butyl-1,3,4-oxadiazol-2-yl)pyrazin-2-yl)-1-ethyl-1H-1,2,4-triazol-3-yl)piperidin-1-yl)-3-hydroxypropan-1-one.

A pharmaceutically acceptable salt is, for example, an acid-addition salt with an inorganic or organic acid, for example hydrochloric acid, hydrobromic acid, methanesulphonic acid, sulphuric acid or trifluoroacetic acid.

Herein where the term "CDK inhibitor" is used it is to be understood that this may refer to any chemical analogue which exerts its anticancer effect by inhibition of one or more of the cyclin-dependent kinases.

In one embodiment the CDK inhibitor that may be combined with Compound [I] is one which predominantly targets CDK4 and/or CDK6 (a "CDK4/6 inhibitor").

A further embodiment is any one of the embodiments hereinafter described wherein the CDK inhibitor comprises a CDK4/6 inhibitor.

Examples of CDK4/6 inhibitors that may be combined with Compound (I) include:

palbociclib (PD-0332991) also described by the chemical name 6-acetyl-8-cyclopentyl-5-methyl-2-{[5-(piperazin-1-yl)pyridin-2yl]amino}pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;

abemaciclib (LY2835219) also described by the chemical name N-(5-((4-ethylpiperazin-1-yl)methyl)pyridin-2-yl)-5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-amine;

LEE011 also described by the chemical name 7-cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide; and

7-cyclopentyl-N,N-dimethyl-2-(5-((1R,6S)-9-methyl-4-oxo-3,9-diazabicyclo[4.2.1]nonan-3-yl)pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide.

In a further embodiment the CDK inhibitor that may be combined with Compound [I] is palbociclib.

A further embodiment is any one of the embodiments hereinafter described wherein the CDK inhibitor comprises palbociclib.

In a further embodiment, there is provided a combination comprising Compound [I] or a pharmaceutically acceptable salt thereof, a CDK inhibitor, and an anti-estrogen agent, for use in the treatment of cancer.

Herein where the term "anti-estrogen agent" is used it is understood that this may refer to any chemical analogue which exerts its anticancer effect by either (1) reducing the amount of estrogen in the body, or by (2) reducing the binding of estrogen to estrogen receptors (hereafter an estrogen receptor inhibitor), or by (3) otherwise impacting on estrogen receptor function and/or expression.

An example of an anti-estrogen agent which exerts its anticancer effect by reducing the amount of estrogen in the body is an aromatase inhibitor, and in one embodiment, the anti-estrogen agent comprises an aromatase inhibitor.

A further embodiment is any one of the embodiments hereinafter described wherein the anti-estrogen agent comprises an aromatase inhibitor.

Examples of aromatase inhibitors that may be combined with Compound [I] include:

anastrozole also described by the chemical name 1,3-benzenediacetonitrile,a,a,a',a'-tetramethyl-5-(1H-1,2,4-triazol-1-ylmethyl);

exemestane also described by the chemical name 6-methylenandrosta-1,4-diene-3,17-dione;

letrozole also described by the chemical name 4,4'-(1H-1,2,4-triazol-1-ylmethylene)dibenzonitrile;

fadrozole also described by the chemical name 4-(5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridin-5-yl)benzonitrile; and

formestane also described by the chemical name 4-(5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridin-5-yl)benzonitrile (8*R*,9*S*,10*R*,13*S*,14*S*)-4-hydroxy-10,13-dimethyl-2,6,7,8,9,11,12,14,15,16-decahydro-1*H*-cyclopenta[*a*]phenanthrene-3,17-dione;

In a further embodiment the anti-estrogen agent that may be combined with Compound [I] comprises anastrozole.

A further embodiment is any one of the embodiments hereinafter described wherein the anti-estrogen agent comprises anastrozole.

Example of estrogen receptor inhibitors are selective estrogen receptor modulators (hereafter "SERMs") and selective estrogen receptor downregulators (hereafter "SERDs"), and in one embodiment the anti-estrogen agent is a SERM or a SERD.

A further embodiment is any one of the embodiments hereinafter described wherein the anti-estrogen agent is a SERM or a SERD.

Herein where the term "SERM" is used it is understood that this may refer to any chemical analogue which exerts its anticancer effect by binding to the estrogen receptor and possessing an ability to act either as an estrogen receptor agonist or antagonist depending on the cellular and promoter context as well as the estrogen receptor isoform targeted.

Examples of SERMs that may be combined with Compound [I] include:

tamoxifen also described by the chemical name (*Z*)-2-[4-(1,2-diphenylbut-1-enyl)phenoxy]-*N*,*N*-dimethylethanamine;

lasofoxifene also described by the chemical name 5R,6S)-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol;

toremifene also described by the chemical name 2-{4-[(1*Z*)-4-chloro-1,2-diphenyl-but-1-en-1-yl]phenoxy}-*N*,*N*-dimethylethanamine; and

raloxifene also described by the chemical name 6-hydroxy-2-(4-hydroxyphenyl)-benzothiophen-3-yl]- [4-[2-(1-piperidyl)ethoxy]phenyl]-methanone.

In one embodiment the anti-estrogen agent comprises a SERM.

A further embodiment is any one of the embodiments hereinafter described wherein the anti-estrogen agent comprises a SERM.

In a further embodiment the anti-estrogen agent that may be combined with Compound [I] comprises tamoxifen.

A further embodiment is any one of the embodiments hereinafter described wherein the anti-estrogen agent comprises tamoxifen.

Herein where the term "SERD" is used it is to be understood that this may refer to any chemical analogue which exerts its anticancer effect by, at a minimum, the down-regulation of estrogen receptor alpha ("ERα").

Examples of SERDs that may be combined with Compound [I] include:

fulvestrant also described by the chemical name 7-alpha-[9-(4,4,5,5,5-penta fluoropentylsulphinyl)nonyl]estra-1,3,5-(10)-triene-3,17beta-diol;

RG6046 (GDC-0810, ARN-810); and

(E)-3-(3,5-difluoro-4-((1R,3R)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenyl)acrylic acid (hereafter "Compound A").

In one embodiment the anti-estrogen agent comprises a SERD.

A further embodiment is any one of the embodiments hereinafter described wherein the anti-estrogen agent comprises a SERD.

In a further embodiment the anti-estrogen agent that may be combined with Compound [I] comprises fulvestrant. In another embodiment the anti-estrogen agent that may be combined with Compound [I] comprises Compound A.

A further embodiment is any one of the embodiments hereinafter described wherein the anti-estrogen agent comprises fulvestrant. Another embodiment is any one of the embodiments hereinafter described wherein the anti-estrogen agent comprises Compound A.

A further embodiment is any one of the embodiments hereinafter described wherein the CDK inhibitor comprises palbociclib and the anti-estrogen agent comprises fulvestrant. A further embodiment is any one of the embodiments hereinafter described wherein the CDK inhibitor comprises palbociclib and the anti-estrogen agent comprises Compound A.

Herein, where the term "combination" is used it is to be understood that this may refer to simultaneous, separate or sequential administration of the components of the combination.

In one embodiment "combination" refers to simultaneous administration of the components of the combination.

In one embodiment "combination" refers to separate administration of the components of the combination.

In one embodiment "combination" refers to sequential administration of the components of the combination.

In one embodiment there is provided a combination comprising Compound [I] or a pharmaceutically acceptable salt thereof and palbociclib, for use in the treatment of cancer.

In one embodiment there is provided a combination comprising a pharmaceutically acceptable salt of Compound [I] and palbociclib, for use in the treatment of cancer.

In a further embodiment there is provided a combination comprising Compound [I] or a pharmaceutically acceptable salt thereof, palbociclib, and an anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A), for use in the treatment of cancer.

In one embodiment there is provided a combination comprising a pharmaceutically acceptable salt of Compound [I], palbociclib, and an anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A), for use in the treatment of cancer.

As shown hereinafter, there are benefits in combining Compound [I] or a pharmaceutically acceptable salt thereof with a CDK inhibitor (such as palbociclib), and optionally an anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A). Furthermore, as also shown herein, benefits in regulating tumour size may be achieved through intermittent dosage of Compound [I] or a pharmaceutically acceptable salt thereof in combination with a CDK inhibitor (such as palbociclib), and optionally an anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A).

Therefore, in one embodiment there is provided a combination comprising Compound [I] or a pharmaceutically acceptable salt thereof, and a CDK inhibitor (such as palbociclib), for use in the treatment of cancer, wherein the Compound [I] or a pharmaceutically acceptable salt thereof is dosed intermittently.

In one embodiment there is provided a combination comprising Compound [I] or a pharmaceutically acceptable salt thereof, a CDK inhibitor (such as palbociclib), and an anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A), for use in the treatment of cancer, wherein the Compound [I] or a pharmaceutically acceptable salt thereof is dosed intermittently.

As the skilled person will be aware, medicaments which are used in the treatment of cancer may be administered in dosage cycles. In one embodiment the dosage cycle comprises the intermittent dosage of Compound [I] or a pharmaceutically acceptable salt thereof.

For the avoidance of doubt, intermittent dosage of Compound [I] or a pharmaceutically acceptable salt thereof means that in a given dosage cycle there will be one or more days (for example 1, 2, 3, 4, 5, 6 or 7 days) where no Compound [I] or a pharmaceutically acceptable salt thereof is administered.

It may be advantageous, within a given dosage cycle, to administer one specific component of the combination before the other, i.e. to dose sequentially.

In one embodiment, Compound [I] or a pharmaceutically acceptable salt thereof is administered prior to the CDK inhibitor (such as palbociclib).

In one embodiment, the CDK inhibitor (such as palbociclib) is administered prior to Compound [I] or a pharmaceutically acceptable salt thereof.

In one embodiment, the order of administration is Compound [I] or a pharmaceutically acceptable salt thereof followed by the CDK inhibitor (such as palbociclib) followed by an anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A).

In one embodiment, the order of administration is the CDK inhibitor (such as palbociclib) followed by Compound [I] or a pharmaceutically acceptable salt thereof followed by an anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A).

In one embodiment, the order of administration is Compound [I] or a pharmaceutically acceptable salt thereof followed by an anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A) followed by the CDK inhibitor (such as palbociclib).

In one embodiment, the order of administration is the CDK inhibitor (such as palbociclib) followed by an anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A) followed by Compound [I] or a pharmaceutically acceptable salt thereof.

In one embodiment, the order of administration is an anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A) followed by Compound [I] or a pharmaceutically acceptable salt thereof followed by the CDK inhibitor (such as palbociclib).

In one embodiment, the order of administration is an anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A) followed by the CDK inhibitor (such as palbociclib) followed by Compound [I] or a pharmaceutically acceptable salt thereof.

In one embodiment, the dosage cycle comprises Compound [I] or a pharmaceutically acceptable salt thereof being dosed for 1, 2 or 3 consecutive days followed by 2, 3, 4, 5 or 6 days with no dose in a dosage cycle.

In one embodiment, the dosage cycle comprises Compound [I] or a pharmaceutically acceptable salt thereof being dosed for 1 day followed by no dose for 2, 3 or 4 days.

In one embodiment, the dosage cycle comprises Compound [I] or a pharmaceutically acceptable salt thereof being dosed for 1 day followed by no dose for 2 or 3 days.

In one embodiment, the dosage cycle comprises at least one 7 day period, in which during each 7 day period Compound [I] or a pharmaceutically acceptable salt thereof is dosed on two separate days, with no dose on the remaining 5 days.

In one embodiment, the dosage cycle comprises one 7 day period, in which Compound [I] or a pharmaceutically acceptable salt thereof is dosed on two separate days, with no dose on the remaining 5 days.

In one embodiment, the dosage cycle comprises two 7 day periods, in which during each 7 day period Compound [I] or a pharmaceutically acceptable salt thereof is dosed on two separate days, with no dose on the remaining 5 days.

In one embodiment, the dosage cycle comprises three 7 day periods, in which during each 7 day period Compound [I] or a pharmaceutically acceptable salt thereof is dosed on two separate days, with no dose on the remaining 5 days.

In one embodiment, the dosage cycle comprises four 7 day periods, in which during each 7 day period Compound [I] or a pharmaceutically acceptable salt thereof is dosed on two separate days, with no dose on the remaining 5 days.

In one embodiment, the dosage cycle comprises Compound [I] or a pharmaceutically acceptable salt thereof being dosed for 1 day followed by no dose for 6 days.

In one embodiment, the dosage cycle comprises at least one 7 day period, in which during each 7 day period Compound [I] or a pharmaceutically acceptable salt thereof is dosed on one day, with no dose on the remaining 6 days.

In one embodiment, the dosage cycle comprises one 7 day period, in which Compound [I] or a pharmaceutically acceptable salt thereof is dosed on one day, with no dose on the remaining 6 days.

In one embodiment, the dosage cycle comprises two 7 day periods, in which during each 7 day period Compound [I] or a pharmaceutically acceptable salt thereof is dosed on one day, with no dose on the remaining 6 days.

In one embodiment, the dosage cycle comprises three 7 day periods, in which during each 7 day period Compound [I] or a pharmaceutically acceptable salt thereof is dosed on one day, with no dose on the remaining 6 days.

In one embodiment, the dosage cycle comprises four 7 day periods, in which during each 7 day period Compound [I] or a pharmaceutically acceptable salt thereof is dosed on one day, with no dose on the remaining 6 days.

In one embodiment, during any 7 day period, Compound [I] or a pharmaceutically acceptable salt thereof is dosed on days 1 and 4 only.

In one embodiment, during any 14 day period, Compound [I] or a pharmaceutically acceptable salt thereof is dosed on days 1, 4, 8 and 11 only.

In one embodiment, during any 21 day period, Compound [I] or a pharmaceutically acceptable salt thereof is dosed on days 1, 4, 8, 11, 15 and 18 only.

In one embodiment, during any 28 day period, Compound [I] or a pharmaceutically acceptable salt thereof is dosed on days 1, 4, 8, 11, 15, 18, 22 and 25 only.

In one embodiment, during any 7 day period, Compound [I] or a pharmaceutically acceptable salt thereof is dosed on days 1 and 2 only.

In one embodiment, during any 14 day period, Compound [I] or a pharmaceutically acceptable salt thereof is dosed on days 1, 2, 8 and 9 only.

In one embodiment, during any 21 day period, Compound [I] or a pharmaceutically acceptable salt thereof is dosed on days 1, 2, 8, 9, 15 and 16 only.

In one embodiment, during any 28 day period, Compound [I] or a pharmaceutically acceptable salt thereof is dosed on days 1, 2, 8, 9, 15, 16, 22 and 23 only.

In one embodiment, Compound [I] or a pharmaceutically acceptable salt thereof and the CDK inhibitor (such as palbociclib) are administered in a dosage cycle of 7-28 days in length.

In one embodiment, the dosage cycle is 7-28 days long and comprises a daily dosing of the CDK inhibitor (such as palbociclib) and intermittent dosing of Compound [I] or a pharmaceutically acceptable salt thereof.

In one embodiment, the dosage cycle is 7-28 days long and comprises a daily dosing of the CDK inhibitor (such as palbociclib) and dosing of Compound [I] or a pharmaceutically acceptable salt thereof on two separate days of each 7 day period, with no dose on the remaining 5 days of each 7 day period.

In one embodiment, the dosage cycle is 7-28 days long and comprises a daily dosing of the CDK inhibitor (such as palbociclib) and dosing of Compound [I] or a pharmaceutically acceptable salt thereof on days 1 and 4 only of each 7 day period. In another embodiment, Compound [I] or a pharmaceutically acceptable salt thereof is dosed on days 1 and 2 only of each 7 day period.

In one embodiment, the dosage cycle is 22-28 days long and comprises a daily dosing of the CDK inhibitor (such as palbociclib) for the first 21 days followed by no dose on the remaining days and intermittent dosing of Compound [I] or a pharmaceutically acceptable salt thereof.

In one embodiment, the dosage cycle is 22-28 days long and comprises a daily dosing of the CDK inhibitor (such as palbociclib) for the first 21 days followed by no dose on the remaining days and dosing of Compound [I] or a pharmaceutically acceptable salt thereof on two separate days of each 7 day period, with no dose on the remaining 5 days of each 7 day period.

In one embodiment, the dosage cycle is 22-28 days long and comprises a daily dosing of the CDK inhibitor (such as palbociclib) for the first 21 days followed by no dose on the remaining days and dosing of Compound [I] or a pharmaceutically acceptable salt thereof on days 1 and 4 only of each 7 day period. In another embodiment, Compound [I] or a pharmaceutically acceptable salt thereof is dosed on days 1 and 2 only of each 7 day period.

In one embodiment, the dosage cycle is 28 days long and comprises a daily dosing of the CDK inhibitor (such as palbociclib) for the first 21 days followed by no dose on the remaining days and intermittent dosing of Compound [I] or a pharmaceutically acceptable salt thereof.

In one embodiment, the dosage cycle is 28 days long and comprises a daily dosing of the CDK inhibitor (such as palbociclib) for the first 21 days followed by no dose on the remaining days and dosing of Compound [I] or a pharmaceutically acceptable salt thereof on two separate days of each 7 day period, with no dose on the remaining 5 days of each 7 day period.

In one embodiment, the dosage cycle is 28 days long and comprises a daily dosing of the CDK inhibitor (such as palbociclib) for the first 21 days followed by no dose on the remaining days and dosing of Compound [I] or a pharmaceutically acceptable salt thereof

on days 1 and 4 only of each 7 day period. In another embodiment, Compound [I] or a pharmaceutically acceptable salt thereof is dosed on days 1 and 2 only of each 7 day period.In one embodiment the dosage cycle comprises the following steps:

a) Days 1-21: administration of the CDK inhibitor (such as palbociclib);
b) Days 1, 4, 8, 11, 15, 18, 22 and 25: administration of Compound [I] or a pharmaceutically acceptable salt thereof;
c) Days 23-24 and 26-28: no administration of either Compound [I] or a pharmaceutically acceptable salt thereof or the CDK inhibitor (such as palbociclib).

In another embodiment, Compound [I] or a pharmaceutically acceptable salt thereof is administered on Days 1, 2, 8, 9, 15, 16, 22 and 23 in step b) above.

In one embodiment the dosage cycle comprises the following steps:

a) Days 1-21: administration of the CDK inhibitor (such as palbociclib);
b) Days 1, 4, 8, 11, 15, and 18: administration of Compound [I] or a pharmaceutically acceptable salt thereof;
c) Days 22-28: no administration of either Compound [I] or a pharmaceutically acceptable salt thereof or the CDK inhibitor (such as palbociclib).

In another embodiment, Compound [I] or a pharmaceutically acceptable salt thereof is administered on Days 1, 2, 8, 9, 15 and 16 in step b) above.

In one embodiment, Compound [I] or a pharmaceutically acceptable salt thereof, the CDK inhibitor (such as palbociclib), and the anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A) are administered in a dosage cycle of 7-28 days in length.

In one embodiment, the dosage cycle is 7-28 days long and comprises a daily dosing of the CDK inhibitor (such as palbociclib), intermittent dosing of an anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A), and intermittent dosing of Compound [I] or a pharmaceutically acceptable salt thereof. In another embodiment the anti-estrogen agent is dosed daily.

In one embodiment, the dosage cycle is 7-28 days long and comprises a daily dosing of the CDK inhibitor (such as palbociclib), dosing of an anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A) on two separate days in the first dosage cycle and once monthly thereafter, and dosing of Compound [I] or a

pharmaceutically acceptable salt thereof on two separate days of each 7 day period, with no dose on the remaining 5 days of each 7 day period. In another embodiment the anti-estrogen agent is dosed daily.

In one embodiment, the dosage cycle is 15-28 days long and comprises a daily dosing of the CDK inhibitor (such as palbociclib), dosing of an anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A) on days 1 and 15 of the first dosage cycle followed by once monthly thereafter, and dosing of Compound [I] or a pharmaceutically acceptable salt thereof on days 1 and 4 only of each 7 day period. In another embodiment the anti-estrogen agent is dosed daily. In another embodiment, Compound [I] or a pharmaceutically acceptable salt thereof is dosed on days 1 and 2 only of each 7 day period.

In one embodiment, the dosage cycle is 22-28 days long and comprises a daily dosing of the CDK inhibitor (such as palbociclib) for the first 21 days followed by no dose on the remaining days, intermittent dosing of an anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A), and intermittent dosing of Compound [I] or a pharmaceutically acceptable salt thereof. In another embodiment the anti-estrogen agent is dosed daily.

In one embodiment, the dosage cycle is 22-28 days long and comprises a daily dosing of the CDK inhibitor (such as palbociclib) for the first 21 days followed by no dose on the remaining days, dosing of an anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A) on two separate days in the first dosage cycle and once monthly thereafter, and dosing of Compound [I] or a pharmaceutically acceptable salt thereof on two separate days of each 7 day period, with no dose on the remaining 5 days of each 7 day period. In another embodiment the anti-estrogen agent is dosed daily.

In one embodiment, the dosage cycle is 22-28 days long and comprises a daily dosing of the CDK inhibitor (such as palbociclib) for the first 21 days followed by no dose on the remaining days, dosing of an anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A) on days 1 and 15 of the first dosage cycle followed by once monthly thereafter, and dosing of Compound [I] or a pharmaceutically acceptable salt thereof on days 1 and 4 only of each 7 day period. In another embodiment the anti-estrogen agent is dosed daily. In another embodiment, Compound [I] or a pharmaceutically acceptable salt thereof is dosed on days 1 and 2 only of each 7 day period.

In one embodiment, the dosage cycle is 28 days long and comprises a daily dosing of the CDK inhibitor (such as palbociclib) for the first 21 days followed by no dose on the remaining days, intermittent dosing of an anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A), and intermittent dosing of Compound [I] or a pharmaceutically acceptable salt thereof. In another embodiment the anti-estrogen agent is dosed daily.

In one embodiment, the dosage cycle is 28 days long and comprises a daily dosing of the CDK inhibitor (such as palbociclib) for the first 21 days followed by no dose on the remaining days, dosing of an anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A) on two separate days in the first dosage cycle and once monthly thereafter, and dosing of Compound [I] or a pharmaceutically acceptable salt thereof on two separate days of each 7 day period, with no dose on the remaining 5 days of each 7 day period. In another embodiment the anti-estrogen agent is dosed daily.

In one embodiment, the dosage cycle is 28 days long and comprises a daily dosing of the CDK inhibitor (such as palbociclib) for the first 21 days followed by no dose on the remaining days, dosing of an anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A) on days 1 and 15 of the first dosage cycle followed by once monthly thereafter, and dosing of Compound [I] or a pharmaceutically acceptable salt thereof on days 1 and 4 only of each 7 day period. In another embodiment the anti-estrogen agent is dosed daily. In another embodiment, Compound [I] or a pharmaceutically acceptable salt thereof is dosed on days 1 and 2 only of each 7 day period.

In one embodiment the dosage cycle comprises the following steps:

a) Days 1-21: administration of the CDK inhibitor (such as palbociclib);
b) Days 1 and 15: administration of the anti-estrogen agent (such as fulvestrant) during the first dosage cycle, said agent to be dosed only once per each subsequent dosage cycle;
c) Days 1, 4, 8, 11, 15, 18, 22 and 25: administration of Compound [I] or a pharmaceutically acceptable salt thereof;
d) Days 23-24 and 26-28: no administration of either Compound [I] or a pharmaceutically acceptable salt thereof or the CDK inhibitor (such as palbociclib) or the anti-estrogen agent (such as fulvestrant).

In another embodiment, Compound [I] or a pharmaceutically acceptable salt thereof is administered on Days 1, 2, 8, 9, 15, 16, 22 and 23 in step c) above.

In one embodiment the dosage cycle comprises the following steps:

a) Days 1-21: administration of the CDK inhibitor (such as palbociclib);
b) Days 1 and 15: administration of the anti-estrogen agent (such as fulvestrant) during the first dosage cycle, said agent to be dosed only once per each subsequent dosage cycle;
c) Days 1, 4, 8, 11, 15 and 18: administration of Compound [I] or a pharmaceutically acceptable salt thereof;
d) Days 22-28: no administration of either Compound [I] or a pharmaceutically acceptable salt thereof or the CDK inhibitor (such as palbociclib) or the anti-estrogen agent (such as fulvestrant).

In another embodiment, Compound [I] or a pharmaceutically acceptable salt thereof is administered on Days 1, 2, 8, 9, 15 and 16 in step b) above.

In one embodiment the dosage cycle comprises the following steps:

a) A first dosage cycle in which the anti-estrogen agent (such as fulvestrant) is dosed on days 1 and 15 only;
b) One or more subsequent dosage cycles which comprise:
    a. Day 1: administration of the anti-estrogen agent (such as fulvestrant);
    b. Days 1-21: administration of the CDK inhibitor (such as palbociclib);
    c. Days 1, 4, 8, 11, 15, 18, 22 and 25: administration of Compound [I] or a pharmaceutically acceptable salt thereof;
    d. Days 23-24 and 26-28: no administration of either Compound [I] or a pharmaceutically acceptable salt thereof or the CDK inhibitor (such as palbociclib) or the anti-estrogen agent (such as fulvestrant).

In another embodiment, Compound [I] or a pharmaceutically acceptable salt thereof is administered on Days 1, 2, 8, 9, 15, 16, 22 and 23 in step b) above.

In one embodiment the dosage cycle comprises the following steps:

a) A first dosage cycle in which the anti-estrogen agent (such as fulvestrant) is dosed on days 1 and 15 only;
b) One or more subsequent dosage cycles which comprise:
    a. Day 1: administration of the anti-estrogen agent (such as fulvestrant);

b. Days 1-21: administration of the CDK inhibitor (such as palbociclib);
c. Days 1, 4, 8, 11, 15 and 18: administration of Compound [I] or a pharmaceutically acceptable salt thereof;
d. Days 22-28: no administration of either Compound [I] or a pharmaceutically acceptable salt thereof or the CDK inhibitor (such as palbociclib) or the anti-estrogen agent (such as fulvestrant).

In another embodiment, Compound [I] or a pharmaceutically acceptable salt thereof is administered on Days 1, 2, 8, 9, 15 and 16 in step b) above.

In one embodiment the dosage cycle comprises the following steps:

a) Days 1-21: administration of the CDK inhibitor (such as palbociclib);
b) Days 1-21: administration of the anti-estrogen agent (such as Compound A);
c) Days 1, 4, 8, 11, 15, 18, 22 and 25: administration of Compound [I] or a pharmaceutically acceptable salt thereof;
d) Days 23-24 and 26-28: no administration of either Compound [I] or a pharmaceutically acceptable salt thereof or the CDK inhibitor (such as palbociclib) or the anti-estrogen agent (such as Compound A).

In another embodiment, Compound [I] or a pharmaceutically acceptable salt thereof is administered on Days 1, 2, 8, 9, 15, 16, 22 and 23 in step c) above.

In one embodiment the dosage cycle comprises the following steps:

a) Days 1-21: administration of the CDK inhibitor (such as palbociclib);
b) Days 1-21: administration of the anti-estrogen agent (such as Compound A);
c) Days 1, 4, 8, 11, 15 and 18: administration of Compound [I] or a pharmaceutically acceptable salt thereof;
d) Days 22-28: no administration of either Compound [I] or a pharmaceutically acceptable salt thereof or the CDK inhibitor (such as palbociclib) or the anti-estrogen agent (such as Compound A).

In another embodiment, Compound [I] or a pharmaceutically acceptable salt thereof is administered on Days 1, 2, 8, 9, 15 and 16 in step c) above.

A further embodiment is any of the dosage cycles described herein, wherein the CDK inhibitor (such as palbociclib) is dosed daily for the first 21 day period followed by no dose during the next 7 day period.

A further embodiment is any of the dosage cycles described herein, wherein the dosage cycle is 28 days long and wherein the CDK inhibitor (such as palbociclib) is dosed daily on each day of the 28 day period.

A further embodiment is any of the dosage cycles described herein, wherein Compound [I] or a pharmaceutically acceptable salt thereof is dosed intermittently during the first 21 day period (such as on Days 1, 4, 8, 11, 15, and 18, or on Days 1, 2, 8, 9, 15 and 16) followed by no dose during the next 7 day period.

A further embodiment is any of the dosage cycles described herein, wherein prior to the first dosage cycle, the anti-estrogen agent (such as fulvestrant) is administered on two separate occasions (such as days 1 and 15), and is thereafter dosed once per month.

In one embodiment, Compound [I] or a pharmaceutically acceptable salt thereof is administered once daily on the days of a dosage cycle when it is dosed.

In one embodiment, Compound [I] or a pharmaceutically acceptable salt thereof is administered twice daily on the days of a dosage cycle when it is dosed.

For the avoidance of doubt, dosage cycles may be separated by a number of days (for example 1, 2, 3, 4, 5, 6 or 7 days) where none of the active combination components are administered.

According to a further embodiment, there is provided a pharmaceutical composition which comprises Compound [I] or a pharmaceutically acceptable salt thereof and a CDK inhibitor (such as palbociclib) in association with a pharmaceutically acceptable diluent or carrier.

According to a further embodiment there is provided a pharmaceutical composition which comprises Compound [I] or a pharmaceutically acceptable salt thereof, a CDK inhibitor (such as palbociclib), and an anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A) in association with a pharmaceutically acceptable diluent or carrier.

Pharmaceutical compositions may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository. In general the above compositions may be prepared in a conventional manner using conventional excipients.

A compound such as Compound [I] may normally be administered to a warm-blooded animal at a unit dose within the range 5-5000 mg/m^2 body area of the animal, i.e. approximately 0.1-200 mg/kg, and this normally provides a therapeutically-effective dose. For a single dosage form, the active ingredients may be compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. A unit dose form such as a tablet or capsule will usually contain, for example 100-1000 mg of active ingredient, such as 100-750 mg of active ingredient. Normally a daily dose in the range of 0.1-50 mg/kg is employed, for example 0.5-25 mg/kg administered twice daily. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the practitioner who is treating any particular patient may determine the optimum dosage.

A CDK inhibitor (such as palbociclib) will normally be administered to a warm-blooded animal at a unit dose known to the skilled practitioner as a therapeutically effective dose. For a single dosage form, the active ingredients may be compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 20 mg to about 500 mg of active ingredient, such as 70 mg to 130 mg. Normally a daily dose in the range of 0.1-100 mg/kg is employed, for example 0.1-50 mg/kg administered once daily. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

An anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A) will normally be administered to a warm-blooded animal at a unit dose known to the skilled practitioner as a therapeutically effective dose. For a single dosage form, the active ingredients may be compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 750 mg of active ingredient. Where the anti-estrogen agent (such as Compound A) is to be administered orally, dosage unit forms will generally contain about 5 mg to about 1000 mg, such as about 30 mg to 700 mg. Normally a daily dose in the range of 0.1-100 mg/kg is employed, for example 0.1 to

50 mg/kg. Where the anti-estrogen agent (such as fulvestrant) is to be administered via parenteral injection, the active ingredient will be provided as a sterile solution at a concentration in the range of 10-100 mg/mL, such as 50 mg/mL. Where the anti-estrogen agent is fulvestrant, the dosage unit form will generally comprise about 250 mg to 500 mg of active ingredient, and normally a dose in the range of 250 mg to 500 mg is delivered per administration. Where the anti-estrogen agent is fulvestrant, the dose of between 250 mg and 500 mg is normally administered via intramuscular injection three separate times in the first month of treatment (such as on days 1, 15 and 29) followed by once monthly injection thereafter. However the dose of the anti-estrogen agent will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

The dosage of each of the drugs and their proportions have to be composed so that the best possible treatment effects, as defined by national and international guidelines (which are periodically reviewed and re-defined), will be met.

In a further embodiment there is provided a pharmaceutical composition which comprises Compound [I], or a pharmaceutically acceptable salt thereof; and a CDK inhibitor (such as palbociclib) in association with a pharmaceutically acceptable diluent or carrier, for use in the treatment of cancer.

In a further embodiment there is provided a pharmaceutical composition which comprises Compound [I], or a pharmaceutically acceptable salt thereof; a CDK inhibitor (such as palbociclib); and an anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A), in association with a pharmaceutically acceptable diluent or carrier, for use in the treatment of cancer.

In a further embodiment there is provided a pharmaceutical composition which comprises Compound [I], or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier; in combination with a pharmaceutical composition which comprises a CDK inhibitor (such as palbociclib), in association with a pharmaceutically acceptable diluent or carrier, for use in the treatment of cancer.

In a further embodiment there is provided a pharmaceutical composition which comprises Compound [I], or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier; in combination with a pharmaceutical

composition which comprises a CDK inhibitor (such as palbociclib), in association with a pharmaceutically acceptable diluent or carrier; and in combination with a pharmaceutical composition which comprises an anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A), in association with a pharmaceutically acceptable diluent or carrier, for use in the treatment of cancer.

In one embodiment there is provided a pharmaceutical product comprising:

(i) a pharmaceutical composition which comprises Compound [I], or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier; and

(ii) a pharmaceutical composition which comprises a CDK inhibitor (such as palbociclib), in association with a pharmaceutically acceptable diluent or carrier.

In one embodiment there is provided a pharmaceutical product comprising:

(i) a pharmaceutical composition which comprises Compound [I], or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier;

(ii) a pharmaceutical composition which comprises a CDK inhibitor (such as palbociclib), in association with a pharmaceutically acceptable diluent or carrier; and

(iii) a pharmaceutical composition which comprises an anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A), in association with a pharmaceutically acceptable diluent or carrier.

In one embodiment there is provided a method of treating cancer, in a warm-blooded animal, such as a human, which comprises administering to said animal an effective amount of Compound [I], or a pharmaceutically acceptable salt thereof, in combination with an effective amount of a CDK inhibitor (such as palbociclib).

In one embodiment there is provided a method of treating cancer, in a warm-blooded animal, such as a human, which comprises administering to said animal an effective amount of Compound [I], or a pharmaceutically acceptable salt thereof, in combination with an effective amount of a CDK inhibitor (such as palbociclib) and an effective amount of an anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A).

Where the treatment of cancer is indicated, it is to be understood that this may refer to the prevention of metastases and the treatment of metastases, i.e. cancer spread. Therefore the combination of the present specification might be used to treat a patient who has no metastases to stop them occurring, or to lengthen the time period before they occur, and to a patient who already has metastases to treat the metastases themselves. Furthermore the treatment of cancer may refer to treatment of an established primary tumour or tumours and developing primary tumour or tumours.

Therefore, in one embodiment the treatment of cancer relates to the prevention of metastases.

In another embodiment the treatment of cancer relates to the treatment of metastases.

In another embodiment the treatment of cancer relates to treatment of an established primary tumour or tumours or developing primary tumour or tumours.

Herein, the treatment of cancer may refer to the prevention of cancer *per se*.

In a further embodiment, there is provided a combination which comprises Compound [I], or a pharmaceutically acceptable salt thereof and a CDK inhibitor (such as palbociclib) for use as a medicament.

In a further embodiment, there is provided a combination which comprises Compound [I], or a pharmaceutically acceptable salt thereof, a CDK inhibitor (such as palbociclib), and an anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A), for use as a medicament.

In a further embodiment, there is provided the use of Compound [I], or a pharmaceutically acceptable salt thereof, in combination with a CDK inhibitor (such as palbociclib), in the manufacture of a medicament for the treatment of cancer.

In a further embodiment, there is provided the use of Compound [I], or a pharmaceutically acceptable salt thereof, in combination with a CDK inhibitor (such as palbociclib), and an anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A), in the manufacture of a medicament for the treatment of cancer.

It may be convenient or medically appropriate for a physician to determine the exact dosage and scheduling for use of a combination product, such that the active components of the combination product may necessarily not be present together within a single dosage form at a fixed dose. Therefore a physician or pharmacist may prepare a

combination medicament comprising the active combination products in readiness for simultaneous, separate or sequential combination use in medicine, for example to treat cancer in a warm-blooded animal, such as human.

According to another embodiment there is provided the use of Compound [I], or a pharmaceutically acceptable salt thereof, in combination with a CDK inhibitor (such as palbociclib), in the preparation of a combination medicament for use in medicine.

According to another embodiment there is provided the use of Compound [I], or a pharmaceutically acceptable salt thereof, in combination with a CDK inhibitor (such as palbociclib), and an anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A), in the preparation of a combination medicament for use in medicine.

According to another embodiment there is provided the use of Compound [I], or a pharmaceutically acceptable salt thereof, in combination with a CDK inhibitor (such as palbociclib), in the preparation of a combination medicament for the treatment of cancer.

According to another embodiment there is provided the use of Compound [I], or a pharmaceutically acceptable salt thereof, in combination with a CDK inhibitor (such as palbociclib), and an anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A), in the preparation of a combination medicament for the treatment of cancer.

According to another embodiment there is provided the use of Compound [I], or a pharmaceutically acceptable salt thereof, in combination with a CDK inhibitor (such as palbociclib), in the preparation of a combination medicament for simultaneous, separate or sequential combination use in medicine.

According to another embodiment there is provided the use of Compound [I], or a pharmaceutically acceptable salt thereof, in combination with a CDK inhibitor (such as palbociclib), and an anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A) in the preparation of a combination medicament for simultaneous, separate or sequential combination use in medicine.

According to another embodiment there is provided the use of Compound [I], or a pharmaceutically acceptable salt thereof, in combination with a CDK inhibitor (such as palbociclib), in the preparation of a combination medicament for simultaneous, separate or sequential combination use for the treatment of cancer.

According to another embodiment there is provided the use of Compound [I], or a pharmaceutically acceptable salt thereof, in combination with a CDK inhibitor (such as

palbociclib), and an anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A), in the preparation of a combination medicament for simultaneous, separate or sequential combination use for the treatment of cancer.

According to another embodiment there is provided the use of Compound [I], or a pharmaceutically acceptable salt thereof, in combination with a CDK inhibitor (such as palbociclib), in the preparation of a combination medicament for separate combination use for the treatment of cancer.

According to another embodiment there is provided the use of Compound [I], or a pharmaceutically acceptable salt thereof, in combination with a CDK inhibitor (such as palbociclib), and an anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A), in the preparation of a combination medicament for separate combination use for the treatment of cancer.

According to another embodiment there is provided the use of Compound [I], or a pharmaceutically acceptable salt thereof, in combination with a CDK inhibitor (such as palbociclib), in the preparation of a combination medicament for sequential combination use for the treatment of cancer.

According to another embodiment there is provided the use of Compound [I], or a pharmaceutically acceptable salt thereof, in combination with a CDK inhibitor (such as palbociclib), and an anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A), in the preparation of a combination medicament for sequential combination use for the treatment of cancer.

In one embodiment there is provided a method for the production of an anti-cancer effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of Compound [I] or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable diluent or carrier; before, after or simultaneously with an effective amount of a CDK inhibitor (such as palbociclib), optionally together with a pharmaceutically acceptable diluent or carrier.

In one embodiment there is provided a method for the production of an anti-cancer effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of Compound [I] or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable diluent or carrier; before, after or simultaneously with an effective amount of a CDK inhibitor (such as palbociclib), and an

effective amount of an anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A), optionally together with a pharmaceutically acceptable diluent or carrier.

In one embodiment, where cancer is referred to, it may refer to tumours which are sensitive to inhibition of PI3K-α and/or -δ enzymes that are involved in the signal transduction steps which lead to the proliferation, survival, invasiveness and migratory ability of tumour cells.

In one embodiment, the cancer is one which carries mutation in the PIK3CA gene.

In one embodiment, the cancer is one which displays PIK3CA-dependency, based on mutation, amplification, or other aberration.

In one embodiment, the cancer is selected from the Breast, Stomach (Gastric) and Oesophagus cancers, Non Small Cell Lung Cancer (NSCLC) including squamous cell carcinomas (SCC) and adenocarcinoma, SCC of the Head and Neck (H&N), Gynaecological cancers (including Endometrial, Ovarian and Cervical) and of Haematological cancers such as multiple myeloma, lymphomas and leukemias (including Chronic Lymphoctyic Leukaemia (CLL), Acute Lymphoblastic Leukaemia (ALL) and Mantle Cell Lymphoma (MCL).

In one embodiment, the cancer is selected from cancer of the Bladder, Brain/CNS, Colorectum, Lung (all other forms), Gallbladder and Bile duct, and Skin.

In one embodiment, the cancer is selected from cancer of the Prostate, Bone, Kidney, Liver, Melanoma, Gastrointestinal tissue, Pancreas, Testes, Thyroid, Penile, Vulva, and other tumour types with a PI3-kinase dependency through mutation, amplification or other aberrations.

In one embodiment the cancer is breast cancer.

In one embodiment the cancer is Estrogen Receptor +ve breast cancer.

In one embodiment the cancer is in a metastatic state

In one embodiment the cancer is in a non-metastatic state.

According to a further embodiment, there is provided a kit comprising Compound [I], or a pharmaceutically acceptable salt thereof, and a CDK inhibitor (such as palbociclib), optionally with instructions for use.

In one embodiment, there is provided a kit comprising Compound [I], or a pharmaceutically acceptable salt thereof, a CDK inhibitor (such as palbociclib), and an

anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A), optionally with instructions for use.

In one embodiment, there is provided a kit comprising:

a) Compound [I], or a pharmaceutically acceptable salt thereof, in a first unit dosage form;

b) a CDK inhibitor (such as palbociclib), in a second unit dosage form;

c) container means for containing said first and second dosage forms; and optionally

d) instructions for use.

In one embodiment, there is provided a kit comprising:

a) Compound [I], or a pharmaceutically acceptable salt thereof, in a first unit dosage form;

b) a CDK inhibitor (such as palbociclib), in a second unit dosage form;

c) an anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A), in a third unit dosage form;

d) container means for containing said first, second and third dosage forms; and optionally

e) instructions for use.

An example of a unit dosage form is a tablet for oral administration. Another example of a unit dosage form is a sterile solution, suspension or emulsion suitable for parenteral injection (such as intramuscular injection).

According to a further embodiment there is provided a kit comprising Compound [I], or a pharmaceutically acceptable salt thereof and a CDK inhibitor (such as palbociclib); optionally with instructions for use; for use in the treatment of cancer.

In one embodiment there is provided a kit comprising Compound [I], or a pharmaceutically acceptable salt thereof, a CDK inhibitor (such as palbociclib), and an anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A); optionally with instructions for use; for use in the treatment of cancer.

In one embodiment there is provided a kit comprising:

a) Compound [I], or a pharmaceutically acceptable salt thereof, in a first unit dosage form;

b) a CDK inhibitor (such as palbociclib), in a second unit dosage form;

c) container means for containing said first and second dosage forms; and optionally

d) instructions for use;

for use in the treatment of cancer.

In one embodiment there is provided a kit comprising:

a) Compound [I], or a pharmaceutically acceptable salt thereof, in a first unit dosage form;

b) a CDK inhibitor (such as palbociclib), in a second unit dosage form;

c) an anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A), in a third unit dosage form;

d) container means for containing said first, second and third dosage forms; and optionally

e) instructions for use;

for use in the treatment of cancer.

As shown hereinafter, there are benefits in combining Compound [I] or a pharmaceutically acceptable salt thereof with an anti-estrogen agent (such as a SERD, for example fulvestrant or Compound A).

Therefore, in another embodiment there is provided a combination comprising Compound [I] or a pharmaceutically acceptable salt thereof and an anti-estrogen agent (such as a SERM or a SERD, for example a SERD, such as fulvestrant or Compound A), for use in the treatment of cancer.

In one embodiment there is provided a combination comprising Compound [I] or a pharmaceutically acceptable salt thereof, and an anti-estrogen agent (such as a SERM or a SERD, for example a SERD, such as fulvestrant or Compound A), for use in the treatment of cancer, wherein the Compound [I] or a pharmaceutically acceptable salt thereof is dosed intermittently.

In one embodiment, Compound [I] or a pharmaceutically acceptable salt thereof, and the anti-estrogen agent (such as a SERM or a SERD, for example a SERD, such as fulvestrant or Compound A) are administered in a dosage cycle of 7-28 days in length.

In one embodiment, the dosage cycle is 7-28 days long and comprises intermittent dosing of an anti-estrogen agent (such as a SERM or a SERD, for example a SERD, such as fulvestrant or Compound A), and intermittent dosing of Compound [I] or a pharmaceutically acceptable salt thereof. In another embodiment, the anti-estrogen agent (such as Compound A) is dosed daily.

In one embodiment, the dosage cycle is 7-28 days long and comprises dosing of an anti-estrogen agent (such as a SERM or a SERD, for example fulvestrant) on two separate days in the first dosage cycle and once monthly thereafter, and dosing of Compound [I] or

a pharmaceutically acceptable salt thereof on two separate days of each 7 day period, with no dose on the remaining 5 days of each 7 day period. In another embodiment, Compound [I] or a pharmaceutically acceptable salt thereof is dosed on days 1 and 4 only of each 7 day period. In another embodiment, Compound [I] or a pharmaceutically acceptable salt thereof is dosed on days 1 and 2 only of each 7 day period.

In one embodiment, the dosage cycle is 7-28 days long and comprises dosing of an anti-estrogen agent (such as a SERM or a SERD, for example Compound A) on a daily basis, and dosing of Compound [I] or a pharmaceutically acceptable salt thereof on two separate days of each 7 day period, with no dose on the remaining 5 days of each 7 day period. In another embodiment, Compound [I] or a pharmaceutically acceptable salt thereof is dosed on days 1 and 4 only of each 7 day period. In another embodiment, Compound [I] or a pharmaceutically acceptable salt thereof is dosed on days 1 and 2 only of each 7 day period.

In one embodiment, the dosage cycle is 28 days long and comprises dosing of an anti-estrogen agent (such as a SERM or a SERD, for example fulvestrant) on days 1 and 15 of the first dosage cycle followed by once monthly thereafter, and dosing of Compound [I] or a pharmaceutically acceptable salt thereof on days 1 and 4 only of each 7 day period. In another embodiment, Compound [I] or a pharmaceutically acceptable salt thereof is dosed on days 1 and 2 only of each 7 day period.

In one embodiment, the dosage cycle is 28 days long and comprises dosing of an anti-estrogen agent (such as a SERM or a SERD, for example Compound A) on a daily basis, and dosing of Compound [I] or a pharmaceutically acceptable salt thereof on days 1 and 4 only of each 7 day period. In another embodiment, Compound [I] or a pharmaceutically acceptable salt thereof is dosed on days 1 and 2 only of each 7 day period.

In one embodiment, Compound [I] or a pharmaceutically acceptable salt thereof is administered once daily on the days of a dosage cycle when it is dosed.

In one embodiment, Compound [I] or a pharmaceutically acceptable salt thereof is administered twice daily on the days of a dosage cycle when it is dosed.

In one embodiment there is provided a pharmaceutical composition which comprises Compound [I] or a pharmaceutically acceptable salt thereof, and an anti-

estrogen agent (such as a SERM or a SERD, for example a SERD, such as fulvestrant or Compound A) in association with a pharmaceutically acceptable diluent or carrier.

In one embodiment there is provided a combination comprising Compound [I] or a pharmaceutically acceptable salt thereof and an anti-estrogen agent (such as a SERM or a SERD, for example a SERD, such as fulvestrant or Compound A), for use in the treatment of cancer, wherein the cancer is selected from a cancer with a PI3-kinase dependency through mutation, amplification or other aberrations.

In one embodiment there is provided a method for the production of an anti-cancer effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of Compound [I], or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable diluent or carrier; before, after or simultaneously with an effective amount of an anti-estrogen agent (such as a SERM or a SERD, for example a SERD, such as fulvestrant or Compound A), optionally together with a pharmaceutically acceptable diluent or carrier.

In one embodiment there is provided the use of Compound [I], or a pharmaceutically acceptable salt thereof in combination with an anti-estrogen agent (such as a SERM or a SERD, for example a SERD, such as fulvestrant or Compound A), in the manufacture of a medicament for the treatment of cancer.

In one embodiment there is provided a kit comprising:

Compound [I], or a pharmaceutically acceptable salt thereof, in a first unit dosage form;

an anti-estrogen agent (such as a SERM or a SERD, for example a SERD, such as fulvestrant or Compound A), in a second unit dosage form;

container means for containing said first and second dosage forms; and optionally instructions for use.

As shown hereinafter, when administered as a monotherapy, the intermittent dosing of Compound [I] or a pharmaceutically acceptable salt thereof is at least as effective in producing sustained anti-tumour activity as continuous daily dosing.

Therefore in another embodiment there is provided a method for the production of an anti-cancer effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of Compound [I] or a pharmaceutically

acceptable salt thereof, wherein the Compound [I] or a pharmaceutically acceptable salt thereof is dosed intermittently.

In one embodiment there is provided the use of Compound [I] or a pharmaceutically acceptable salt thereof in the treatment of cancer, wherein the Compound [I] or a pharmaceutically acceptable salt thereof is dosed intermittently.

In one embodiment there is provided a dosage cycle which comprises the intermittent dosage of Compound [I] or a pharmaceutically acceptable salt thereof.

In one embodiment, the dosage cycle comprises Compound [I] or a pharmaceutically acceptable salt thereof being dosed for 1, 2 or 3 consecutive days followed by 2, 3, 4, 5 or 6 days with no dose in a dosage cycle.

In one embodiment, the dosage cycle comprises Compound [I] or a pharmaceutically acceptable salt thereof being dosed for 1 day followed by no dose for 2, 3 or 4 days.

In one embodiment, the dosage cycle comprises Compound [I] or a pharmaceutically acceptable salt thereof being dosed for 1 day followed by no dose for 2 or 3 days.

In one embodiment, the dosage cycle comprises at least one 7 day period, in which during each 7 day period Compound [I] or a pharmaceutically acceptable salt thereof is dosed on two separate days, with no dose on the remaining 5 days.

In one embodiment, the dosage cycle comprises one 7 day period, in which Compound [I] or a pharmaceutically acceptable salt thereof is dosed on two separate days, with no dose on the remaining 5 days.

In one embodiment, the dosage cycle comprises two 7 day periods, in which during each 7 day period Compound [I] or a pharmaceutically acceptable salt thereof is dosed on two separate days, with no dose on the remaining 5 days.

In one embodiment, the dosage cycle comprises three 7 day periods, in which during each 7 day period Compound [I] or a pharmaceutically acceptable salt thereof is dosed on two separate days, with no dose on the remaining 5 days.

In one embodiment, the dosage cycle comprises four 7 day periods, in which during each 7 day period Compound [I] or a pharmaceutically acceptable salt thereof is dosed on two separate days, with no dose on the remaining 5 days.

In one embodiment, the dosage cycle comprises Compound [I] or a pharmaceutically acceptable salt thereof being dosed for 1 day followed by no dose for 6 days.

In one embodiment, the dosage cycle comprises at least one 7 day period, in which during each 7 day period Compound [I] or a pharmaceutically acceptable salt thereof is dosed on one day, with no dose on the remaining 6 days.

In one embodiment, the dosage cycle comprises one 7 day period, in which Compound [I] or a pharmaceutically acceptable salt thereof is dosed on one day, with no dose on the remaining 6 days.

In one embodiment, the dosage cycle comprises two 7 day periods, in which during each 7 day period Compound [I] or a pharmaceutically acceptable salt thereof is dosed on one day, with no dose on the remaining 6 days.

In one embodiment, the dosage cycle comprises three 7 day periods, in which during each 7 day period Compound [I] or a pharmaceutically acceptable salt thereof is dosed on one day, with no dose on the remaining 6 days.

In one embodiment, the dosage cycle comprises four 7 day periods, in which during each 7 day period Compound [I] or a pharmaceutically acceptable salt thereof is dosed on one day, with no dose on the remaining 6 days.

In one embodiment, during any 7 day period, Compound [I] or a pharmaceutically acceptable salt thereof is dosed on days 1 and 4 only.

In one embodiment, during any 14 day period, Compound [I] or a pharmaceutically acceptable salt thereof is dosed on days 1, 4, 8 and 11 only.

In one embodiment, during any 21 day period, Compound [I] or a pharmaceutically acceptable salt thereof is dosed on days 1, 4, 8, 11, 15 and 18 only.

In one embodiment, during any 28 day period, Compound [I] or a pharmaceutically acceptable salt thereof is dosed on days 1, 4, 8, 11, 15, 18, 22 and 25 only.

In one embodiment, during any 7 day period, Compound [I] or a pharmaceutically acceptable salt thereof is dosed on days 1 and 2 only.

In one embodiment, during any 14 day period, Compound [I] or a pharmaceutically acceptable salt thereof is dosed on days 1, 2, 8 and 9 only.

In one embodiment, during any 21 day period, Compound [I] or a pharmaceutically acceptable salt thereof is dosed on days 1, 2, 8, 9, 15 and 16 only.

In one embodiment, during any 28 day period, Compound [I] or a pharmaceutically acceptable salt thereof is dosed on days 1, 2, 8, 9, 15, 16, 22 and 23 only.

In one embodiment, Compound [I] or a pharmaceutically acceptable salt thereof is administered once daily on the days of a dosage cycle when it is dosed.

In one embodiment, Compound [I] or a pharmaceutically acceptable salt thereof is administered twice daily on the days of a dosage cycle when it is dosed.

Experimental Details

Compound [I] may be prepared according to the procedures described in WO2014/114928, relevant details of which are incorporated herein by reference.

Compound A may be prepared according to the procedures described in WO2014/191726, relevant details of which are incorporated herein by reference.

Female Swiss athymic nude mice (swiss nu/nu) were transplanted subcutaneously (s.c.) with human breast tumour cell line BT474c (derived from BT474 (ATCC HTB-20)) tumours passaged in mice). Mice were implanted with 0.36mg 60 day oestrogen pellet (Innovative Research of America #SE-121) 24 hours prior to cell implantation. On day zero, 5 X 10^6 cells in 50% Matrigel™ (BD Bioscience #354234) were injected s.c. on the left flank of the animals.

Male SCID mice were transplanted s.c. with human breast tumour cell line MCF7 (ICRF London). Mice were implanted with a 0.5mg 21 day oestrogen pellet (Innovative Research of America) 24 hours prior to cell implantation. 5 X 10^6 cells in 50% matrigel (BD Bioscience) were injected s.c. on the left flank of the animals.

Compound [I] in free base form was formulated in HPMC/Tween (0.5% Methocel (hydroxypropyl methocellulose) /0.1% Polysorbate 80) and dosed per oral once (qd) / twice (bid) daily at a dose volume of 0.1ml/10g mouse. For twice daily dosing Compound [I] was administered 6 – 8 hours apart.

Fulvestrant was formulated in peanut oil (Sigma) and dosed 3 times weekly subcutaneously at 5mg/mouse at dose volume of 0.1ml/mouse.

Compound A was formulated in 40% Polyethylene glycol (PEG) / 30% Captisol® and protected from light. It was dosed per oral once daily at 5mg/kg at a dose volume of 0.1ml/10g mouse. Where dosed in combination, it was dosed 1hr after the morning dose of Compound I.

Palbociclib was formulated in HPMC/Tween (as for Compound [I]) and co-formulated when dosed with Compound [I]. It was dosed per oral once daily (qd) at a dose volume of 0.1ml/10g mouse in the morning dose.

For efficacy studies, animals were randomised into groups of 8-15 when average tumour volume reached a volume of ~200-500 mm^3. Animals were dosed for 2-4 weeks by peroral route with compound in a suitable vehicle at defined doses and schedules. Tumours were measured two – three times weekly by caliper and volume of tumours calculated using elliptical formula (pi/6 x width x width x length).

Growth inhibition from the start of treatment was assessed by comparison of the geometric mean change in tumour volume for the control and treated groups. Regression was calculated as the percentage reduction in tumour volume from baseline (pre-treatment) value - % Regression = (1 – RTV)*100 % where RTV = Geometric Mean Relative Tumour Volume. Statistical significance was evaluated using a one-tailed, t-test.

List of Figures

FIG. 1 - Anti-tumour Activity of Intermittent Dosing of Compound [I] in Combination with Palbociclib in a Xenograft Model grown in Mouse using the Human Tumour Cell Line MCF7.

This figure shows the change in tumour volume in a MCF7 (a human breast cancer cell line carrying mutation in PIK3CA gene) mouse xenograft model over a 19-day period when treated with:

i. Compound [I] alone at a dose of 50 mg/kg twice daily (bid), wherein Compound [I] was administered on days 1 and 4 of each 7 day period only, with no agent administered on the remaining 5 days;
ii. Palbociclib alone at a dose of 50 mg/kg qd, wherein palbociclib was administered daily throughout each 7 day period;
iii. A combination of Compound [I] at a dose of 50 mg/kg bid and palbociclib at a dose of 50 mg/kg qd, wherein Compound [I] was administered on days 1 and 4 of each 7 day period and palbociclib was administered daily throughout each 7 day period.

Fig. 1 shows that use of the combination of Compound [I] and palbociclib achieves marked additional tumour shrinkage, even when Compound [I] is dosed intermittently, compared to the use of either Compound [I] or palbociclib alone.

Fig. 1 further shows that use of Compound [I] alone can achieve marked tumour shrinkage, even when dosed intermittently.

FIG. 2 - Anti-tumour Activity of Intermittent Dosing of Compound [I] in Combination with Fulvestrant in a Xenograft Model grown in Mouse using the Human Tumour Cell Line MCF7.

This figure shows the change in tumour volume in a MCF7 (a human breast cancer cell line carrying mutation in PIK3CA gene) mouse xenograft model over an 18-day period when treated with:

i. Compound [I] alone at a dose of 50 mg/kg bid, wherein Compound [I] was administered on days 1 and 4 of each 7 day period only, with no agent administered on the remaining 5 days;
ii. Fulvestrant alone at a dose of 5 mg/mouse qd, wherein fulvestrant was administered on days 1, 3 and 5 of each 7 day period only, with no agent administered on the remaining 4 days;
iii. A combination of Compound [I] at a dose of 50 mg/kg bid, and fulvestrant at a dose of 5 mg/mouse qd, wherein Compound [I] was administered on days 1 and 4 of each 7 day period, and fulvestrant was administered on days 1, 3 and 5 of each 7 day period.

FIG. 3 - Anti-tumour Activity of Intermittent Dosing of Compound [I] in Combination with Fulvestrant in a Xenograft Model grown in Mouse using the Human Tumour Cell Line BT474c.

This figure shows the change in tumour volume in a BT474c (a human breast cancer cell line carrying mutation in PIK3CA gene) mouse xenograft model over an 18-day period when treated with:

i. Compound [I] alone at a dose of 100 mg/kg bid, wherein Compound [I] was administered on days 1 and 4 of each 7 day period only, with no agent administered on the remaining 5 days;
ii. Fulvestrant alone at a dose of 5 mg/mouse qd, wherein fulvestrant was administered on days 1, 3 and 5 of each 7 day period only, with no agent administered on the remaining 4 days;
iii. A combination of Compound [I] at a dose of 100 mg/kg bid, and fulvestrant at a dose of 5 mg/mouse qd, wherein Compound [I] was administered on days 1 and 4 of each 7 day period, and fulvestrant was administered on days 1, 3 and 5 of each 7 day period.

Figs. 2 and 3 show that use of the combination of Compound [I] and fulvestrant achieves marked additional tumour shrinkage, even when Compound [I] is dosed intermittently, compared to the use of either Compound [I] or fulvestrant alone.

Fig. 2 and 3 further show that use of Compound [I] alone can achieve marked tumour shrinkage, even when dosed intermittently.

FIG. 4 - Anti-tumour Activity of Intermittent Dosing of Compound [I] in Combination with Palbociclib and with Fulvestrant in a Xenograft Model grown in Mouse using the Human Tumour Cell Line MCF7.

This figure shows the change in tumour volume in a MCF7 (a human breast cancer cell line carrying mutation in PIK3CA gene) mouse xenograft model over an 18-day period when treated with:

i. Compound [I] alone at a dose of 50 mg/kg bid, wherein Compound [I] was administered on days 1 and 4 of each 7 day period only, with no agent administered on the remaining 5 days;

ii. Palbociclib alone at a dose of 50 mg/kg qd, wherein palbociclib was administered daily throughout each 7 day period;

iii. Fulvestrant alone at a dose of 5 mg/mouse qd, wherein fulvestrant was administered on days 1, 3 and 5 of each 7 day period only, with no agent administered on the remaining 4 days;

iv. A combination of Compound [I] at a dose of 50 mg/kg bid, palbociclib at a dose of 50 mg/kg qd, and fulvestrant at a dose of 5 mg/mouse qd, wherein Compound [I] was administered on days 1 and 4 of each 7 day period, palbociclib was administered daily throughout each 7 day period, and fulvestrant was administered on days 1, 3 and 5 of each 7 day period.

FIG. 5 - Anti-tumour Activity of Intermittent Dosing of Compound [I] in Combination with Palbociclib and/or with Fulvestrant in a Xenograft Model grown in Mouse using the Human Tumour Cell Line MCF7.

This figure shows the change in tumour volume in a MCF7 (a human breast cancer cell line carrying mutation in PIK3CA gene) mouse xenograft model over a 29-day period when treated with:

i. Compound [I] alone at a dose of 50 mg/kg bid, wherein Compound [I] was administered on days 1 and 4 of each 7 day period only, with no agent administered on the remaining 5 days;

ii. Palbociclib alone at a dose of 50 mg/kg qd, wherein palbociclib was administered daily throughout each 7 day period;

iii. Fulvestrant alone at a dose of 5 mg/mouse qd, wherein fulvestrant was administered on days 1, 3 and 5 of each 7 day period only, with no agent administered on the remaining 4 days;

iv. A combination of Compound [I] at a dose of 50 mg/kg bid and palbociclib at a dose of 50 mg/kg qd, wherein Compound [I] was administered on days 1 and 4 of each 7 day period and palbociclib was administered daily throughout each 7 day period.

v. A combination of Compound [I] at a dose of 50 mg/kg bid, and fulvestrant at a dose of 5 mg/mouse qd, wherein Compound [I] was administered on days 1 and 4 of each 7 day period, and fulvestrant was administered on days 1, 3 and 5 of each 7 day period.

vi. A combination of palbociclib at a dose of 50 mg/kg qd, and fulvestrant at a dose of 5 mg/mouse qd, wherein palbociclib was administered daily throughout each 7 day period, and fulvestrant was administered on days 1, 3 and 5 of each 7 day period.

vii. A combination of Compound [I] at a dose of 50 mg/kg bid, palbociclib at a dose of 50 mg/kg qd, and fulvestrant at a dose of 5 mg/mouse qd, wherein Compound [I] was administered on days 1 and 4 of each 7 day period, palbociclib was administered daily throughout each 7 day period, and fulvestrant was administered on days 1, 3 and 5 of each 7 day period.

Figs. 4 and 5 show that use of the triplet combination of Compound [I], palbociclib, and fulvestrant achieves marked additional tumour shrinkage, even when Compound [I] is dosed intermittently, compared to the use of either Compound [I], palbociclib, or fulvestrant alone.

Fig. 5 further shows that use of the triplet combination of Compound [I], palbociclib, and fulvestrant achieves marked additional tumour shrinkage, even when Compound [I] is dosed intermittently, compared to the doublet combinations of either Compound [I] and palbociclib, of palbociclib and fulvestrant, and of Compound [I] and fulvestrant.

FIG. 6 - Anti-tumour Activity of Intermittent Dosing of Compound [I] in a Xenograft Model grown in Mouse using the Human Tumour Cell Line BT474c.

This figure shows the change in tumour volume in a BT474c (a human breast cancer cell line carrying mutation in PIK3CA gene) mouse xenograft model over an 18-day period when treated with:

i. Compound [I] alone at a dose of 25 mg/kg bid, wherein Compound [I] was administered daily throughout each 7 day period;

ii. Compound [I] alone at a dose of 50 mg/kg bid, wherein Compound [I] was administered on days 1 and 2 of each 7 day period only, with no agent administered on the remaining 5 days; and

iii. Compound [I] alone at a dose of 100 mg/kg qd, wherein Compound [I] was administered on days 1 and 4 of each 7 day period only, with no agent administered on the remaining 5 days.

FIG. 7 - Anti-tumour Activity of Intermittent Dosing of Compound [I] in a Xenograft Model grown in Mouse using the Human Tumour Cell Line BT474c.

This figure shows the change in tumour volume in a BT474c (a human breast cancer cell line carrying mutation in PIK3CA gene) mouse xenograft model over a 22-day period when treated with:

i. Compound [I] alone at a dose of 100 mg/kg bid, wherein Compound [I] was administered on days 1 and 4 of each 7 day period only, with no agent administered on the remaining 5 days.

Figs. 6 and 7 show that intermittent dosage of Compound [I] is at least as effective in producing sustained anti-tumour activity as continuous daily dosing.

FIG. 8 - Anti-tumour Activity of Intermittent Dosing of Compound [I] in Combination with Palbociclib and/or with Compound A in a Xenograft Model grown in Mouse using the Human Tumour Cell Line MCF7.

This figure shows the change in tumour volume in a MCF7 (a human breast cancer cell line carrying mutation in PIK3CA gene) mouse xenograft model over a 29-day period when treated with:

i. Compound [I] alone at a dose of 50 mg/kg bid, wherein Compound [I] was administered on days 1 and 4 of each 7 day period only, with no agent administered on the remaining 5 days;

ii. Palbociclib alone at a dose of 50 mg/kg qd, wherein palbociclib was administered daily throughout each 7 day period;

iii. Compound A alone at a dose of 5 mg/kg qd, wherein Compound A was administered daily throughout each 7 day period;

iv. A combination of Compound [I] at a dose of 50 mg/kg bid and palbociclib at a dose of 50 mg/kg qd, wherein Compound [I] was administered on days 1 and 4 of each 7 day period and palbociclib was administered daily throughout each 7 day period.

v. A combination of Compound [I] at a dose of 50 mg/kg bid, and Compound A at a dose of 5 mg/kg qd, wherein Compound [I] was administered on days 1 and 4 of each 7 day period, and Compound A was administered daily throughout each 7 day period.

vi. A combination of palbociclib at a dose of 50 mg/kg qd, and Compound A at a dose of 5 mg/kg qd, wherein both palbociclib and Compound A were administered daily throughout each 7 day period.

vii. A combination of Compound [I] at a dose of 50 mg/kg bid, palbociclib at a dose of 50 mg/kg qd, and Compound A at a dose of 5 mg/kg qd, wherein Compound [I] was administered on days 1 and 4 of each 7 day period, and both palbociclib and Compound A were administered daily throughout each 7 day period.

Fig. 8 shows that use of the triplet combination of Compound [I], palbociclib, and Compound A achieves marked additional tumour shrinkage, even when Compound [I] is dosed intermittently, compared to the use of either Compound [I], palbociclib, or Compound A alone.

Fig. 8 further shows that use of the triplet combination of Compound [I], palbociclib, and Compound A achieves marked additional tumour shrinkage, even when Compound [I] is dosed intermittently, compared to the doublet combinations of either Compound [I] and palbociclib, of palbociclib and Compound A, and of Compound [I] and Compound A.

FIG. 9 - Anti-tumour Activity of Intermittent Dosing of Compound [I] in Combination with Fulvestrant (F) in a Xenograft Model grown in Mouse using the Human Tumour Cell Line MCF7.

This figure shows the change in tumour volume in a MCF7 (a human breast cancer cell line carrying mutation in PIK3CA gene) mouse xenograft model over a 22-day period when treated with:

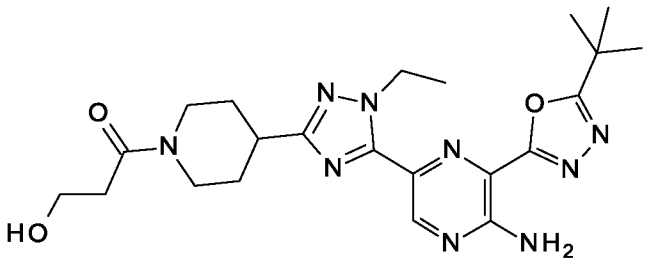
i. Compound [I] alone at a dose of 50 mg/kg bid, wherein Compound [I] was administered on days 1 and 2 of each 7 day period only, with no agent administered on the remaining 5 days;
ii. Fulvestrant alone at a dose of 5 mg/mouse qd, wherein fulvestrant was administered on days 1, 3 and 5 of each 7 day period only, with no agent administered on the remaining 4 days;
iii. A combination of Compound [I] at a dose of 50 mg/kg bid, and fulvestrant at a dose of 5 mg/mouse qd, wherein Compound [I] was administered on days 1 and 2 of each 7 day period, and fulvestrant was administered on days 1, 3 and 5 of each 7 day period.
iv. Compound [I] alone at a dose of 50 mg/kg bid, wherein Compound [I] was administered on days 1 and 4 of each 7 day period only, with no agent administered on the remaining 5 days;
v. A combination of Compound [I] at a dose of 50 mg/kg bid, and fulvestrant at a dose of 5 mg/mouse qd, wherein Compound [I] was administered on days 1 and 4 of each 7 day period, and fulvestrant was administered on days 1, 3 and 5 of each 7 day period.

Fig. 9 shows that intermittent dosage of Compound [I] alone on days 1 and 2 is at least as effective in producing sustained anti-tumour activity as intermittent dosage of Compound [I] alone on days 1 and 4.

Fig. 9 further shows that use of the combination of Compound [I] and fulvestrant achieves marked additional tumour shrinkage, even when Compound [I] is dosed intermittently, compared to the use of either Compound [I] or fulvestrant alone.

CLAIMS

1. A combination comprising Compound [I]:



Compound [I]

or a pharmaceutically acceptable salt thereof, and a CDK inhibitor, for use in the treatment of cancer.

2. A combination as claimed in claim 1, wherein the CDK inhibitor comprises palbociclib.

3. A combination as claimed in claim 1 or claim 2, which further comprises an anti-estrogen agent.

4. A combination as claimed in claim 3, wherein the anti-estrogen agent is a SERM or a SERD.

5. A combination as claimed in claim 4, wherein the anti-estrogen agent comprises fulvestrant.

6. A combination as claimed in claim 4, wherein the anti-estrogen agent comprises (E)-3-(3,5-difluoro-4-((1R,3R)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenyl)acrylic acid.

7. A combination for use in the treatment of cancer as claimed in any one of the preceding claims, wherein the Compound [I] or a pharmaceutically acceptable salt thereof is dosed intermittently.

8. A combination for use in the treatment of cancer as claimed in any one of the preceding claims, wherein Compound [I] or a pharmaceutically acceptable salt thereof and the CDK inhibitor are administered in a dosage cycle of 7-28 days in length.

9. A combination for use in the treatment of cancer as claimed in claim 8, which further comprises an anti-estrogen agent.

10. A combination for use in the treatment of cancer as claimed in any one of the preceding claims, wherein the dosage cycle is 28 days long and comprises a daily dosing of the CDK inhibitor for the first 21 days followed by no dose on the remaining days, and intermittent dosing of Compound [I] or a pharmaceutically acceptable salt thereof.

11. A combination for use in the treatment of cancer as claimed in claim 10, which further comprises the intermittent dosing of an anti-estrogen agent.

12. A combination for use in the treatment of cancer as claimed in any one of the preceding claims, wherein Compound [I] or a pharmaceutically acceptable salt thereof is administered twice daily on the days of a dosage cycle when it is dosed.

13. A combination for use in the treatment of cancer as claimed in any one of the preceding claims, wherein Compound [I] or a pharmaceutically acceptable salt thereof is dosed at 0.5-25 mg/kg twice daily on the days when it is dosed.

14. A combination for use in the treatment of cancer as claimed in any one of the preceding claims, wherein the cancer is selected from a cancer with a PI3-kinase dependency through mutation, amplification or other aberrations.

15. A method for the production of an anti-cancer effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of Compound [I], or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable diluent or carrier; before, after or simultaneously with an

effective amount of a CDK inhibitor, optionally together with a pharmaceutically acceptable diluent or carrier.

16. A method for the production of an anti-cancer effect in a warm-blooded animal such as a human, which comprises administering to said animal an effective amount of Compound [I], or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable diluent or carrier; before, after or simultaneously with an effective amount of a CDK inhibitor, optionally together with a pharmaceutically acceptable diluent or carrier, and an effective amount of an anti-estrogen agent, optionally together with a pharmaceutically acceptable diluents or carrier.

17. The use of Compound [I], or a pharmaceutically acceptable salt thereof in combination with a CDK inhibitor, and optionally an anti-estrogen agent, in the manufacture of a medicament for the treatment of cancer.

18. A pharmaceutical composition which comprises Compound [I], or a pharmaceutically acceptable salt thereof, a CDK inhibitor, and optionally an anti-estrogen agent, in association with a pharmaceutically acceptable diluent or carrier.

19. A kit comprising:
Compound [I], or a pharmaceutically acceptable salt thereof, in a first unit dosage form;
a CDK inhibitor, in a second unit dosage form;
container means for containing said first and second dosage forms; and optionally instructions for use.

20. A kit comprising:
Compound [I], or a pharmaceutically acceptable salt thereof, in a first unit dosage form;
a CDK inhibitor, in a second unit dosage form;
an anti-estrogen agent, in a third unit dosage form;
container means for containing said first, second and third dosage forms; and optionally instructions for use.

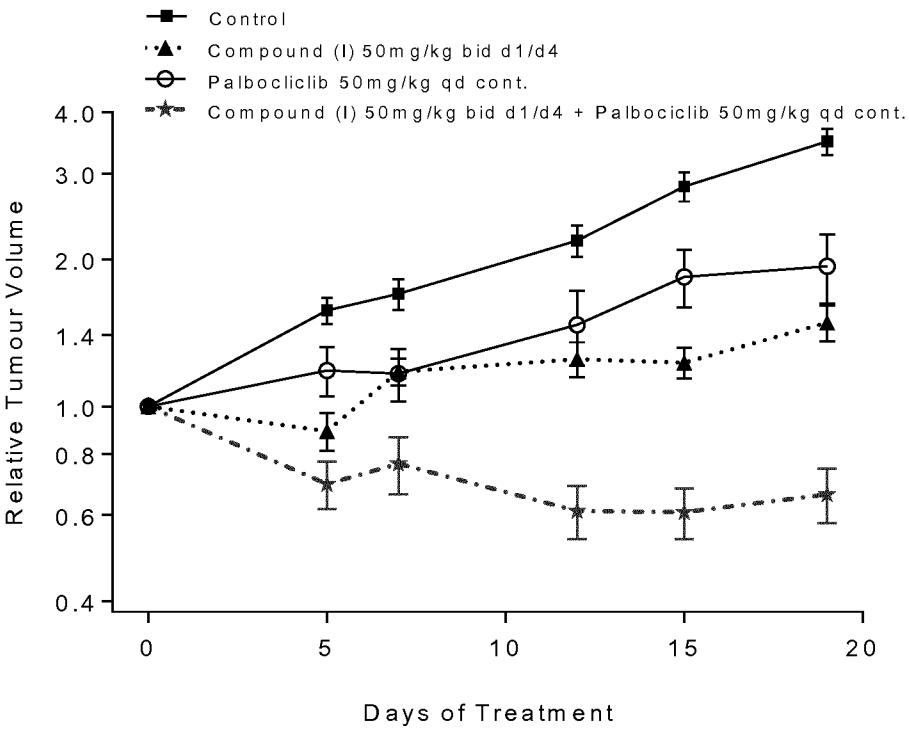

Control
Compound (I) 50mg/kg bid d1/d4
Palbocliclib 50mg/kg qd cont.
Compound (I) 50mg/kg bid d1/d4 + Palbociclib 50mg/kg qd cont.
Relative Tumour Volume
4.0
3.0
2.0
1.4
1.0
0.8
0.6
0.4
0
5
10
15
20
Days of Treatment

Figure 1

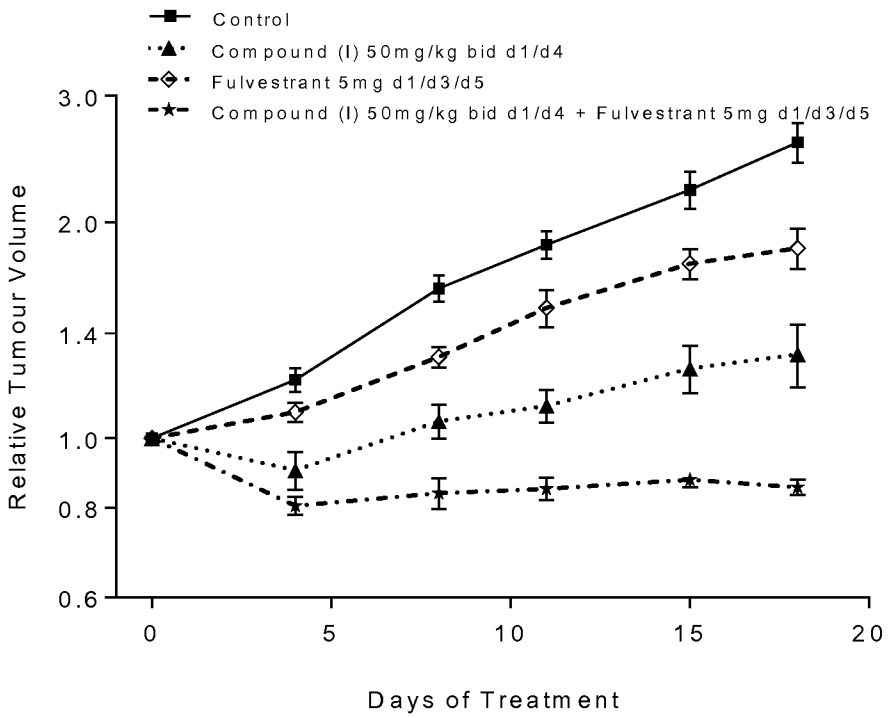

Control
Compound (I) 50mg/kg bid d1/d4
Fulvestrant 5mg d1/d3/d5
Compound (I) 50mg/kg bid d1/d4 + Fulvestrant 5mg d1/d3/d5
Relative Tumour Volume
3.0
2.0
1.4
1.0
0.8
0.6
0
5
10
15
20
Days of Treatment

Figure 2

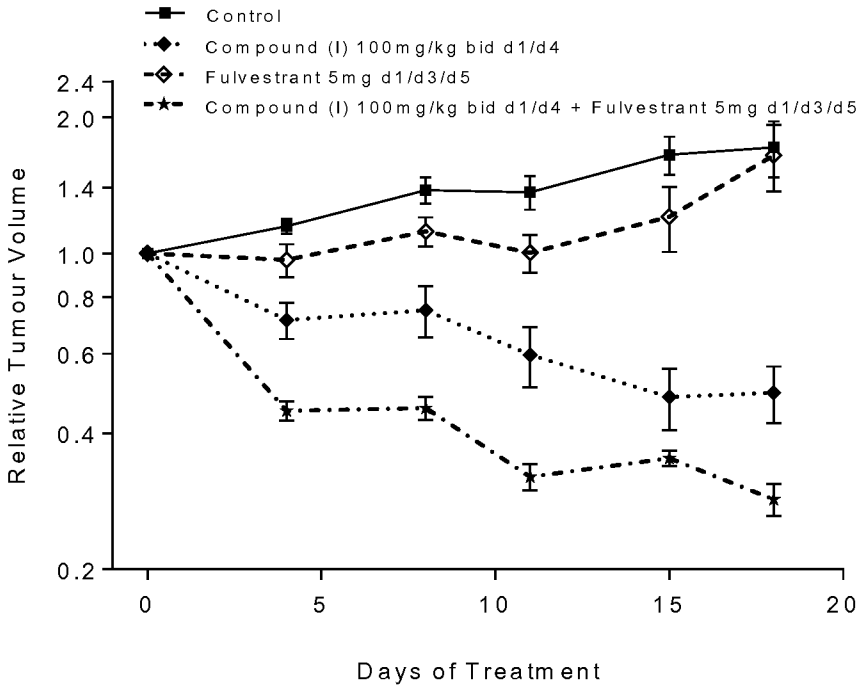

Control
Compound (I) 100mg/kg bid d1/d4
Fulvestrant 5mg d1/d3/d5
Compound (I) 100mg/kg bid d1/d4 + Fulvestrant 5mg d1/d3/d5
Relative Tumour Volume
2.4
2.0
1.4
1.0
0.8
0.6
0.4
0.2
0
5
10
15
20
Days of Treatment

Figure 3

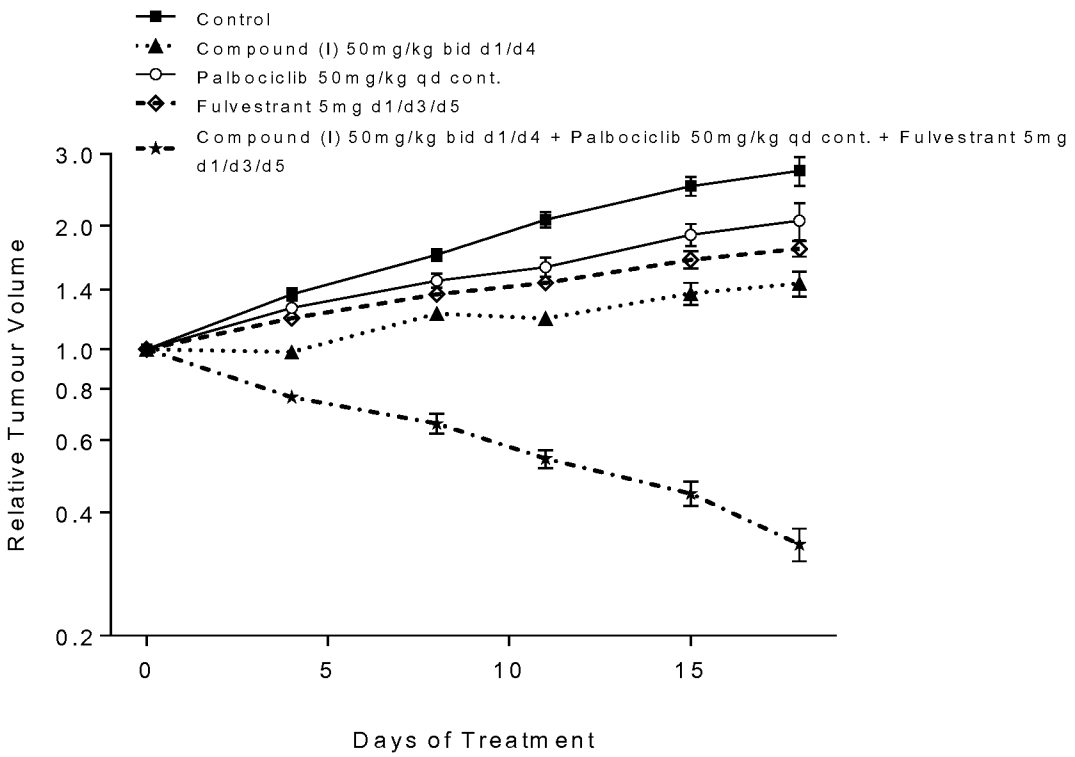

Control
Compound (I) 50mg/kg bid d1/d4
Palbociclib 50mg/kg qd cont.
Fulvestrant 5mg d1/d3/d5
Compound (I) 50mg/kg bid d1/d4 + Palbociclib 50mg/kg qd cont. + Fulvestrant 5mg d1/d3/d5
Relative Tumour Volume
3.0
2.0
1.4
1.0
0.8
0.6
0.4
0.2
0
5
10
15
Days of Treatment

Figure 4

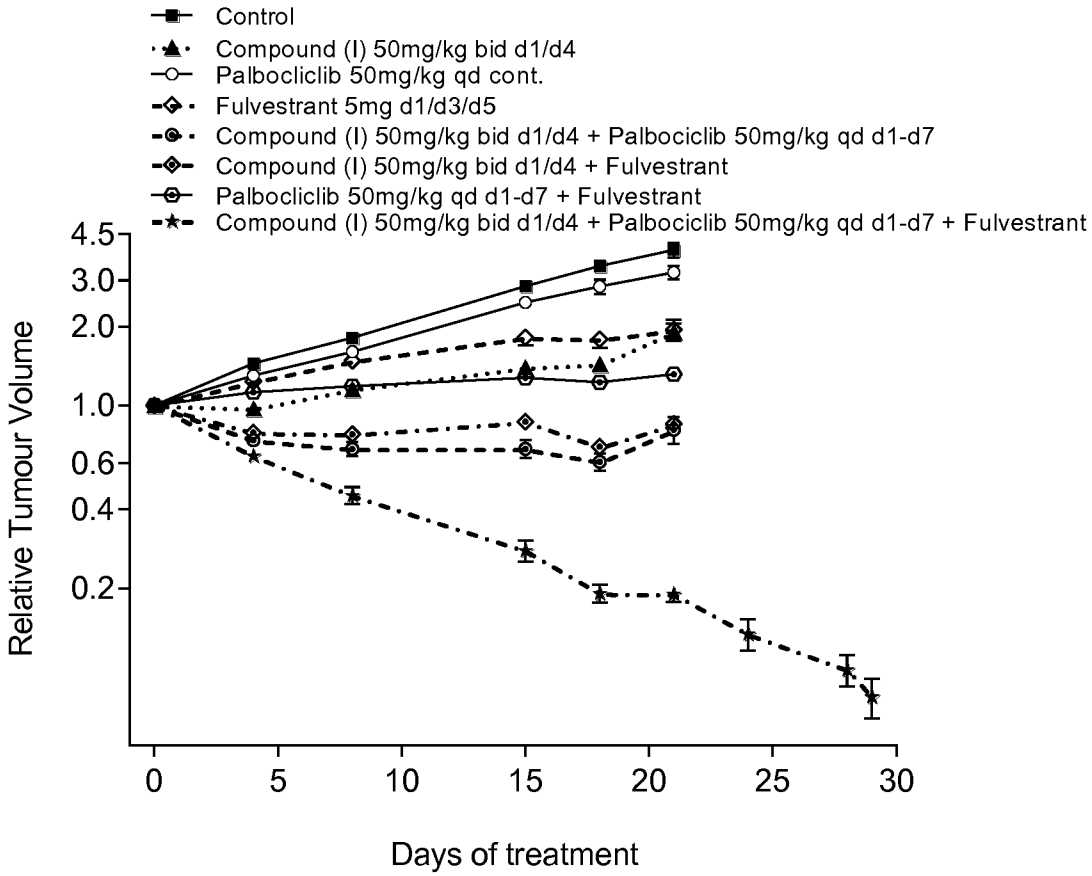

Control
Compound (I) 50mg/kg bid d1/d4
Palbociclib 50mg/kg qd cont.
Fulvestrant 5mg d1/d3/d5
Compound (I) 50mg/kg bid d1/d4 + Palbociclib 50mg/kg qd d1-d7
Compound (I) 50mg/kg bid d1/d4 + Fulvestrant
Palbociclib 50mg/kg qd d1-d7 + Fulvestrant
Compound (I) 50mg/kg bid d1/d4 + Palbociclib 50mg/kg qd d1-d7 + Fulvestrant
Relative Tumour Volume
4.5
3.0
2.0
1.0
0.6
0.4
0.2
0
5
10
15
20
25
30
Days of treatment

Figure 5

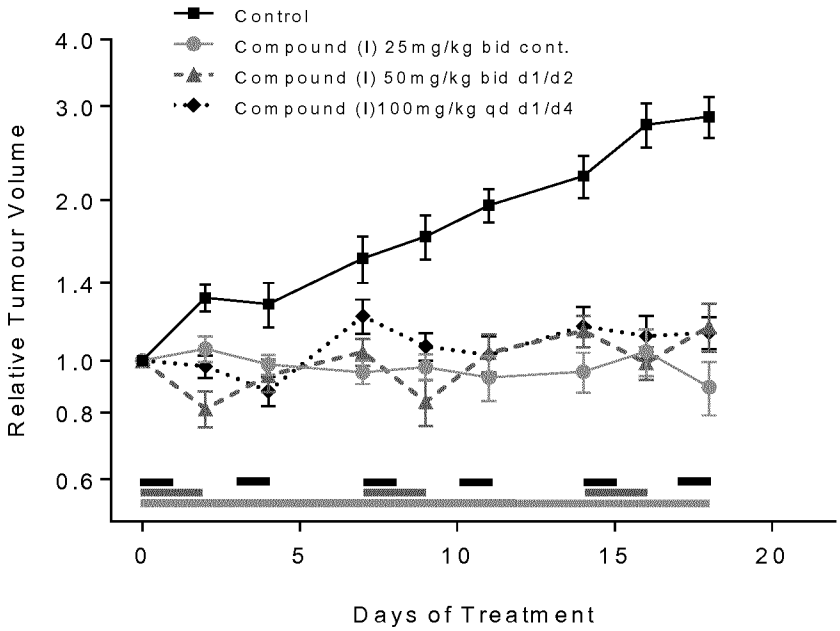

Control
Compound (I) 25mg/kg bid cont.
Compound (I) 50mg/kg bid d1/d2
Compound (I)100mg/kg qd d1/d4
Relative Tumour Volume
4.0
3.0
2.0
1.4
1.0
0.8
0.6
0
5
10
15
20
Days of Treatment

Figure 6

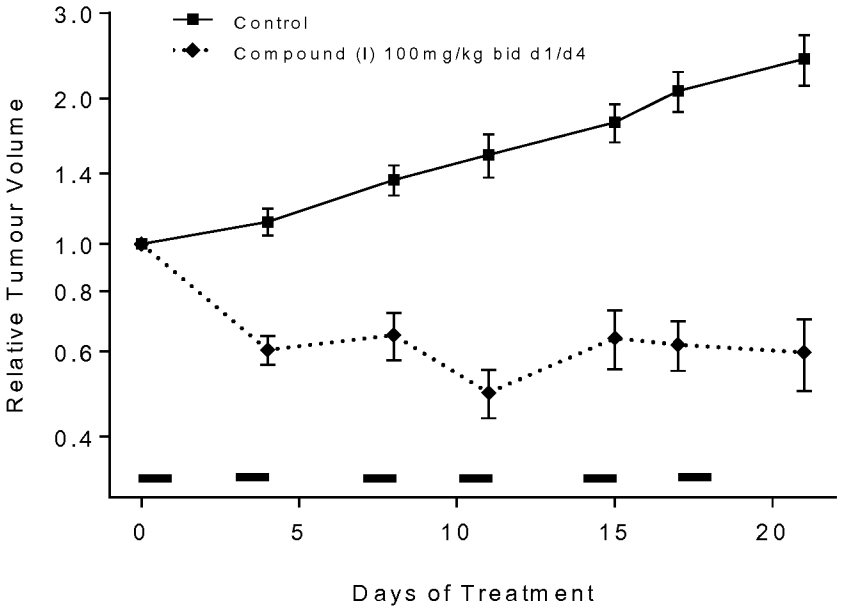

Control
Compound (I) 100mg/kg bid d1/d4
Relative Tumour Volume
3.0
2.0
1.4
1.0
0.8
0.6
0.4
0
5
10
15
20
Days of Treatment

Figure 7

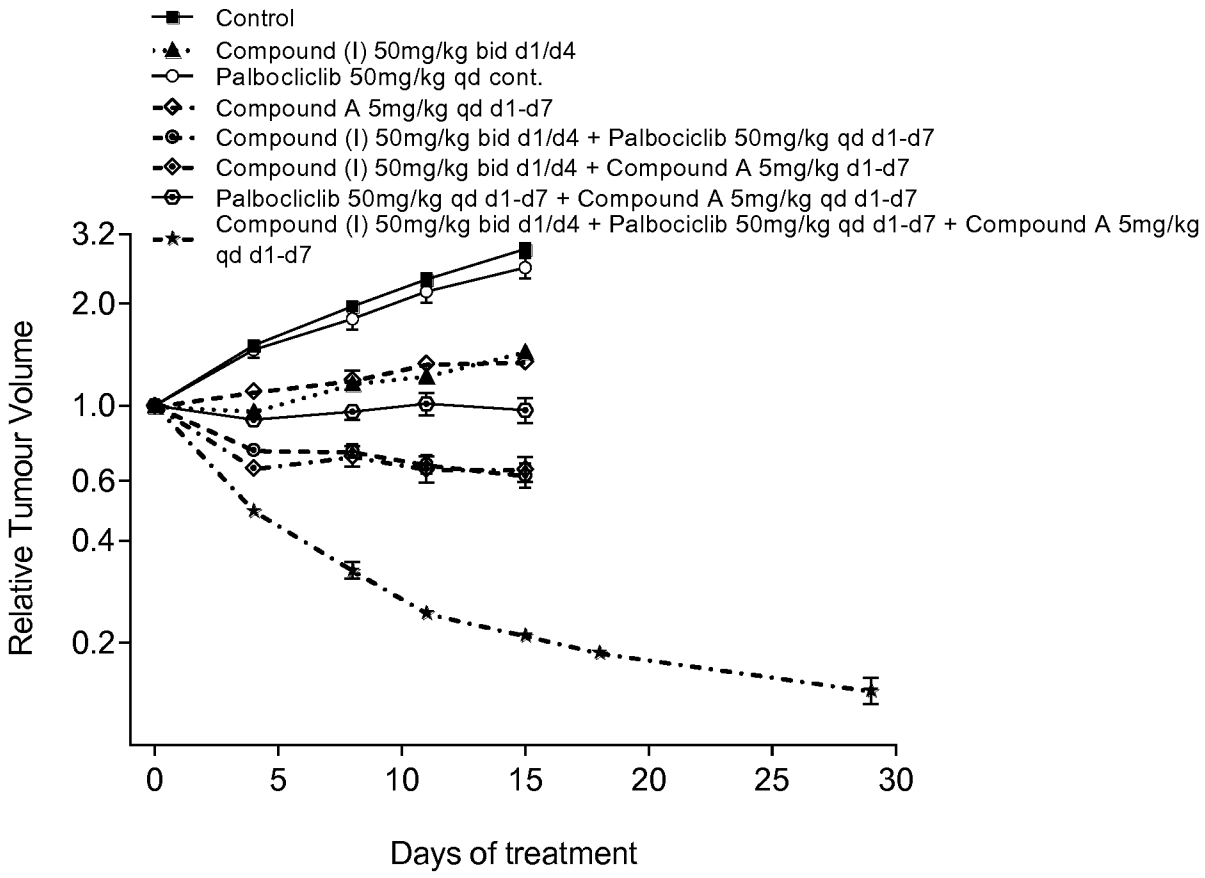

Control
Compound (I) 50mg/kg bid d1/d4
Palbociclib 50mg/kg qd cont.
Compound A 5mg/kg qd d1-d7
Compound (I) 50mg/kg bid d1/d4 + Palbociclib 50mg/kg qd d1-d7
Compound (I) 50mg/kg bid d1/d4 + Compound A 5mg/kg d1-d7
Palbociclib 50mg/kg qd d1-d7 + Compound A 5mg/kg qd d1-d7
Compound (I) 50mg/kg bid d1/d4 + Palbociclib 50mg/kg qd d1-d7 + Compound A 5mg/kg qd d1-d7
Relative Tumour Volume
3.2
2.0
1.0
0.6
0.4
0.2
0
5
10
15
20
25
30
Days of treatment

Figure 8

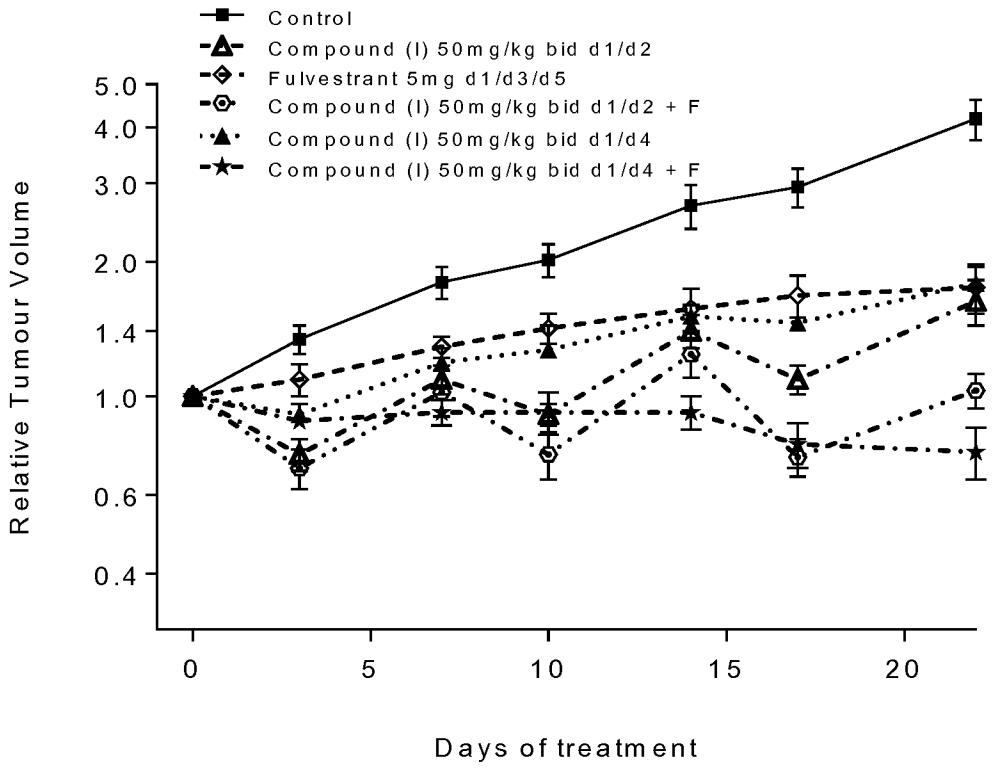

Control
Compound (I) 50mg/kg bid d1/d2
Fulvestrant 5mg d1/d3/d5
Compound (I) 50mg/kg bid d1/d2 + F
Compound (I) 50mg/kg bid d1/d4
Compound (I) 50mg/kg bid d1/d4 + F
Relative Tumour Volume
5.0
4.0
3.0
2.0
1.4
1.0
0.6
0.4
0
5
10
15
20
Days of treatment

Figure 9

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/055467

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K45/06 A61K31/138 A61K31/40 A61K31/4196 A61K31/437
A61K31/4535 A61K31/497 A61K31/506 A61K31/519 A61K31/55
A61K31/565 A61K31/5685 A61P35/00 A61P35/02 A61P35/04

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2014/114928 A1 (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]) 31 July 2014 (2014-07-31) cited in the application abstract page 11, line 13 - page 15, line 3 page 56, line 13 - page 57, line 25 page 82, line 15 - page 84, line 8 example 3 figures 9-13 claims 1-15 ----- -/--	1,3-20

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

[X] See patent family annex.

* Special categories of cited documents :

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

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

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"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

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"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
11 April 2016	18/04/2016

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	Taylor, Mark

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2014/191726 A1 (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]) 4 December 2014 (2014-12-04) cited in the application abstract page 8, line 5 - page 9, line 9 example 1 figures 1-12 claims 1-16	1-20
A	CUIXIAN LI ET AL: "Sensitization of Glioma Cells to Tamoxifen-Induced Apoptosis by Pl3-Kinase Inhibitor through the GSK-3[beta]/[beta]-Catenin Signaling Pathway", PLOS ONE, vol. 6, no. 10, 27 October 2011 (2011-10-27), page e27053, XP055263814, DOI: 10.1371/journal.pone.0027053 the whole document	1-20
A	METIN KURTOGLU ET AL: "Elevating the Horizon: Emerging Molecular and Genomic Targets in the Treatment of Advanced Urothelial Carcinoma", CLINICAL GENITOURINARY CANCER, vol. 13, no. 5, 5 March 2015 (2015-03-05), pages 410-420, XP055263796, US ISSN: 1558-7673, DOI: 10.1016/j.clgc.2015.02.009 abstract table 1	1-20
T	BARLAAM BERNARD ET AL: "Discovery of 1-(4-(5-(5-amino-6-(5-tert-butyl-1,3,4-oxadiazol-2-yl)pyrazin-2-yl)-1-ethyl-1,2,4-triazol-3-yl)piperidin-1-yl)-3-hydroxypropan-1-one (AZD8835): A potent and selective inhibitor of PI3K[alpha] and PI3K[delta] for the treatment of cancers", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 25, no. 22, 9 October 2015 (2015-10-09), pages 5155-5162, XP029321433, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2015.10.002 the whole document	1-20

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2016/055467

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		CA 2911859 A1	04-12-2014
		CN 105229004 A	06-01-2016
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		SG 11201509393V A	30-12-2015
		TW 201536779 A	01-10-2015
		US 2014357661 A1	04-12-2014
		UY 35590 A	28-11-2014
		WO 2014191726 A1	04-12-2014