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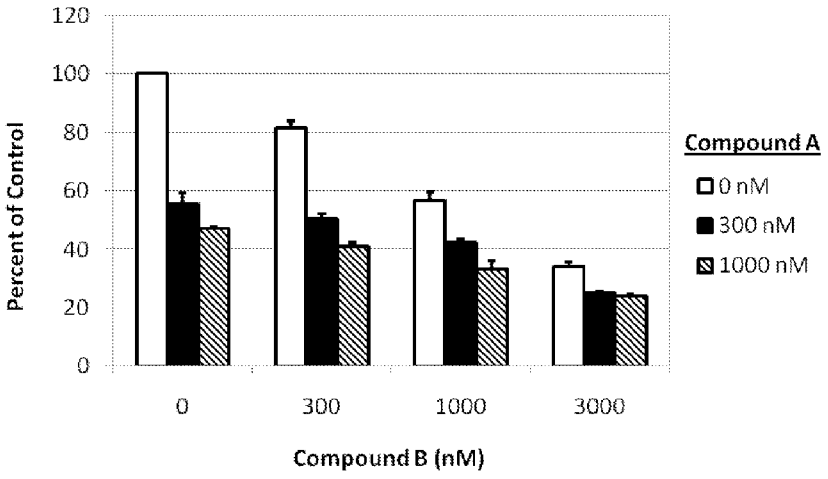
[Continued on next page]

(54) Title: COMBINATION DRUG THERAPY

FIGURE 1



(57) Abstract: A novel combination comprising the androgen receptor inhibitor, 4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-*N*-methylbenzamide or a pharmaceutically acceptable salt or solvate thereof, with a PI3Kß inhibitor, 2-methyl-1-{[2-methyl-3-(trifluoromethyl)phenyl]methyl}-6-(4-morpholinyl)-1H-benzimidazole-4-carboxylic acid, or a pharmaceutically acceptable salt thereof, pharmaceutical compositions comprising the same and methods of using such combinations and compositions in the treatment of conditions in which the inhibition of androgen receptor and/or PI3Kß is beneficial, e.g., cancer.

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COMBINATION DRUG THERAPY

FIELD OF INVENTION

The present invention relates to a method of treating cancer and to combinations useful in such treatment. In particular, the method relates to a novel combination comprising the androgen receptor inhibitor, 4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-*N*-methylbenzamide or a pharmaceutically acceptable salt or solvate thereof, with a PI3Kβ inhibitor, 2-methyl-1-{[2-methyl-3-(trifluoromethyl)phenyl]methyl}-6-(4-morpholinyl)-1H-benzimidazole-4-carboxylic acid, or a pharmaceutically acceptable salt thereof, pharmaceutical compositions comprising the same and methods of using such combinations and compositions in the treatment of conditions in which the inhibition of the androgen receptor and/or PI3Kβ is beneficial, e.g., cancer.

BACKGROUND OF THE INVENTION

Effective treatment of hyperproliferative disorders including cancer is a continuing goal in the oncology field. Generally, cancer results from the deregulation of the normal processes that control cell division, differentiation and apoptotic cell death and is characterized by the proliferation of malignant cells which have the potential for unlimited growth, local expansion and systemic. Deregulation of normal processes includes abnormalities in signal transduction pathways and response to factors which differ from those found in normal cells.

Prostate cancer is characterized by its dependence on the androgen receptor and genetic alterations in the androgen receptor pathway. The primary mode of treatment for metastatic prostate cancer has historically focused on targeting androgen–androgen receptor signaling by decreasing the amount of ligand (androgens) available for binding to the androgen receptor.

Androgen antagonists, also known as antiandrogens alter the androgen pathway by blocking the receptor, competing for binding sites on the cell's surface or affecting androgen production. The most common antiandrogens are androgen receptor antagonists which act on the target cell level and competitively bind to androgen

receptors. By competing with circulating androgens for binding sites on prostate cell receptors, antiandrogens promote apoptosis and inhibit prostate cancer growth.

Recent studies reveal that inhibition of androgen receptors promotes the activation of phosphoinositide 3-kinase (PI3K). (Rini, B.I., and Small, E.J., Hormone-refractory prostate cancer. *Curr.Treat. Options Oncol.* 2002; 3:437; Singh, P., Yam, M., Russell, P.J., and Khatri, A., Molecular and traditional chemotherapy: a united front against prostate cancer. *Cancer Lett.* 2010; 293:1). The PI3K pathway is among the most commonly activated in human cancer and the importance in carcinogenesis is well established (Samuels Y and Ericson K. Oncogenic PI3K and its role in cancer. *Current Opinion in Oncology,* 2006; 18:77-82). Initiation of signaling begins with the phosphorylation of phosphatidylinositol-4, 5-bisphosphate (PIP2) to produce phosphatidylinositol-3, 4, 5-P3 (PIP3). PIP3 is a critical second messenger which recruits proteins that contain pleckstrin homology domains to the cell membrane where they are activated. The most studied of these proteins is AKT which promotes cell survival, growth, and proliferation.

The PI3K family consists of 15 proteins that share sequence homology, particularly within their kinase domains, but have distinct substrate specificities and modes of regulation (Vivanco I and Sawyers CL. The phosphatidylinositol 3-kinase-AKT pathway in human cancer. *Nature Reviews Cancer,* 2002; 2:489-501). Class I PI3Ks are heterodimers consisting of a p110 catalytic subunit complexed to one of several regulatory subunits collectively referred to as p85 and have been the most extensively studied in the context of tumorgenesis. The class 1A PI3K catalytic subunits comprise the p110α, p110β, and p110δ isoforms, which associate with one of five different regulatory subunits encoded by three separate genes. A single class 1B PI3K catalytic isoform p110γ interacts with one of two associated regulatory subunits (Crabbe T, Welham MJ, Ward SG, The PI3K inhibitor arsenal: choose your weapon *Trends in Biochem Sci*, 2007; 32:450-456). Class 1 PI3Ks are primarily responsible for phosphorylating the critical PIP2 signaling molecule.

The link between the PI3K pathway and cancer was confirmed by a study which identified somatic mutations in the PIK3CA gene encoding the p110α protein. Subsequently, mutations in PIK3CA have been identified in numerous cancers including

colorectal, breast, glioblastomas ovarian and lung. In contrast to PIK3CA, no somatic mutations in the β isoform have been identified. However, in overexpression studies, the PI3Kβ isoform has been implicated as necessary for transformation induced by the loss or inactivation of the PTEN tumor suppressor both *in vitro* and *in vivo* (Torbett NE, Luna A, Knight ZA, et al., A chemical screen in diverse breast cancer cell lines reveals genetic enhancers and suppressors of sensitivity to PI3K isotype-selective inhibition. *Biochem J* 2008; 415:97-110; Zhao JJ, Liu Z, Wang L, Shin E, Loda MF, Roberts TM, The oncogenic properties of mutant p110α and p110β phosphatidylinositol 3-kinases in human mammary epithelial cells. *Proc Natl Acad Sci USA* 2005; 102:18443-8). Consistent with this finding, overexpression of the PIK3CB gene has been identified in some bladder, colon, glioblastomas and leukemias and siRNA mediated knockdown of p110β in glioblastoma cell lines results in suppression of tumor growth *in vitro* and *in vivo* (Pu P, Kang C, Zhang Z, et al., Downregulation of PIK3CB by siRNA suppresses malignant glioma cell growth in vitro and in vivo. *Technolo Cancer Res Treat* 2006; 5:271-280). More recent data using shRNA demonstrated that downregulation of p110β and not p110α resulted in PI3K pathway inactivation and subsequent inactivation of tumor cell growth in PTEN deficient cancers cells both *in vitro* and *in vivo* (Wee S, Wiederschain, Maira S-M, Loo A, Miller C, et al., PTEN-deficient cancers depend on PIK3CB. *Proc Natl Acad Sci* 2008; 105:13057-13062). Consistent with a role of PI3Kβ signaling in PTEN null tumors, p110β was reported to be essential to the transformed phenotype in a PTEN-null prostate cancer model (Jia S, Liu Z, Zhang S, Liu P, Zhang L, et al., Essential roles of PI(3)K-p110b in cell growth, metabolism and tumorgenesis. *Nature* 2008; 10:1038).

It has been reported that fibrogenesis, including systemic sclerosis (SSc), arthritis, nephropahty, liver cirrhosis, and some cancers, are related to PTEN deficiency and corresponding PI3K-Akt overexpression (Parapuram, S.K., et al., Loss of PTEN expression by dermal fibroblasts causes skin fibrosis. J. of Investigative Dermatology, advance online publication 9 June 2011; doi: 10.1038/jid.2011.156). Taken together, these findings indicate PI3K p110β as a promising target for cancer and other syndromes related to PTEN loss (Hollander, M. Christine; Blumenthal, Gideon M.; Dennis, Phillip

P.; PTEN loss in the continuum of common cancers, rare syndromes and mouse models. *Nature Reviews/Cancer* 2011; 11: 289-301).

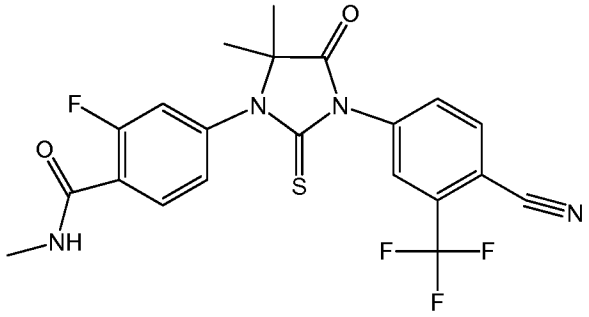
Further, studies have revealed reciprocal feedback regulation of PI3K and androgen receptor signaling in PTEN-deficient prostate cancer. Specifically, inhibition of either PI3K or the androgen receptor activated the other, thereby maintaining tumor cell survival. (Carver, Brett, S., Chapinski, C., Wongvipat, J., Hieronymus, H., Chen, Y., et al., Reciprocal Feeback Regulation of P13K and Androgen Receptor Signaling in PTEN-Deficient Prostate Cancer, *Cancer Cell* 2011; 19:575). Androgen deprivation therapy remains the standard of care for treatment of advanced prostate cancer. Despite an initial favorable response, almost all patients invariably progress to a more aggressive, castrate-resistant phenotype. Evidence indicates that the development of castrate-resistant prostate cancer is causally related to continue signaling of the androgen receptor.

Thus, although there have been many recent advances in the treatment of cancer with compounds such as androgen receptor there remains a need for more effective and/or enhanced treatment for an individual suffering the effects of cancer.

SUMMARY OF THE INVENTION

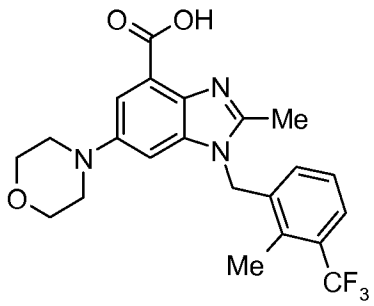
The present inventors have identified a combination of chemotherapeutic agents that provides increased activity over monotherapy. The invention includes a drug combination that includes an androgen receptor inhibitor and a PI3Kβ inhibitor. In particular, the drug combination that includes the androgen receptor inhibitor, particularly 4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-*N*-methylbenzamide or or a pharmaceutically acceptable salt or solvate thereof, with the PI3Kβ inhibitor, 2-methyl-1-{[2-methyl-3-(trifluoromethyl)phenyl]methyl}-6-(4-morpholinyl)-1H-benzimidazole-4-carboxylic acid, or a pharmaceutically acceptable salt is described.

The androgen inhibitor of the invention is represented by the structure of formula (I):



, or a pharmaceutically acceptable salt or solvate thereof (collectively referred to herein as "compound A"),

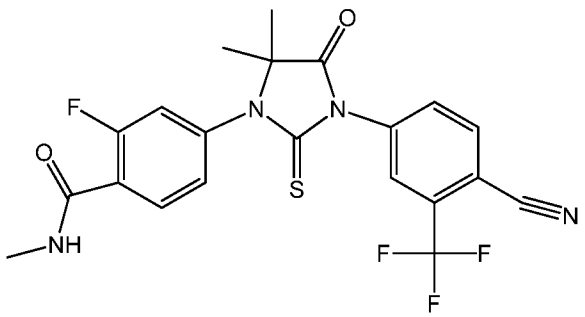
The PI3Kβ inhibitor of the invention is represented by the structure of formula (II):



, or a pharmaceutically acceptable salt or solvate thereof (collectively referred to herein as "compound B"),

In a first aspect of the present invention, there is provided a combination comprising:

(i) a compound of formula (I)

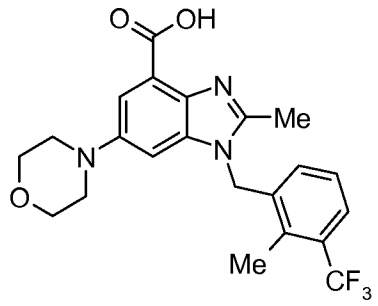


(I)

or a pharmaceutically acceptable salt or solvate thereof

and

(ii) a compound of formula (II)



(II)

or a pharmaceutically acceptable salt thereof.

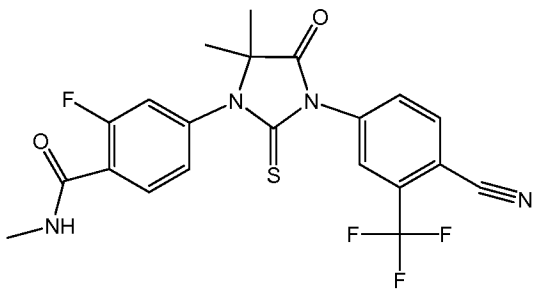
In one aspect of the invention, the P13K inhibitor compound of formula II is in a salt form. In a preferred embodiment, the salt form of the P13K inhibitor compound of formula II is in the form of Tris salt.

In another aspect of the invention, there is provided a combination comprising 4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-*N*-methylbenzamide solvent form and 2-methyl-1-{[2-methyl-3-(trifluoromethyl)phenyl]methyl}-6-(4-morpholinyl)-1H-benzimidazole-4-carboxylic acid Tris salt form.

In another aspect of the invention, there is provided a combination comprising 4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-*N*-methylbenzamide dimethyl sulfoxide (solvent) and 2-methyl-1-{[2-methyl-3-(trifluoromethyl)phenyl]methyl}-6-(4-morpholinyl)-1H-benzimidazole-4-carboxylic acid 2-amino-2-(hydroxymethyl)-1,3-propanediol.

In another aspect of the present invention, there is provided a combination comprising:

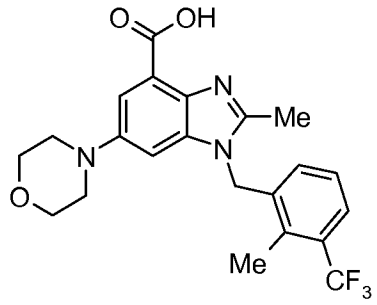
(i) a compound of formula (I):



(I)

or a pharmaceutically acceptable salt or solvate thereof and

(ii) a compound of formula (II):

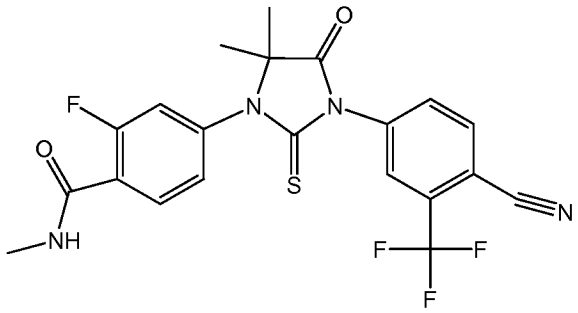


(II)

or a pharmaceutically acceptable salt thereof for use in therapy.

In another aspect of the present invention, there is provided a combination comprising:

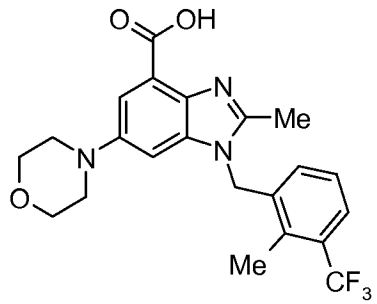
(i) a compound of formula (I):



(I)

or a pharmaceutically acceptable salt or solvate thereof and

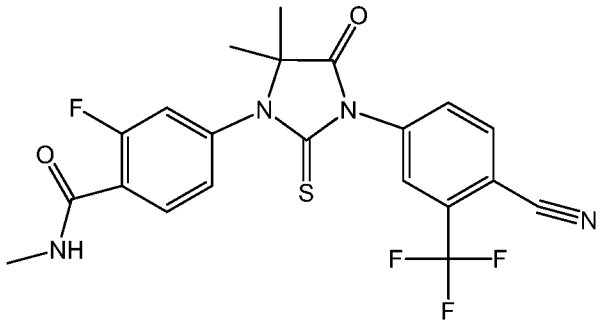
(ii) a compound of formula (II):



or a pharmaceutically acceptable salt thereof, for use in treatment of cancer.

In another aspect of the present invention, there is provided a combination comprising:

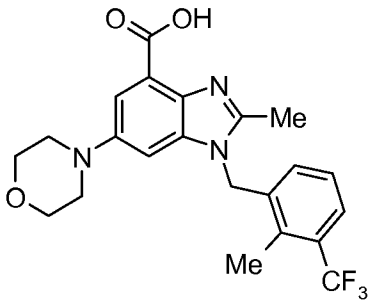
(i) a compound of formula (I):



(I)

or a pharmaceutically acceptable salt or solvate thereof and

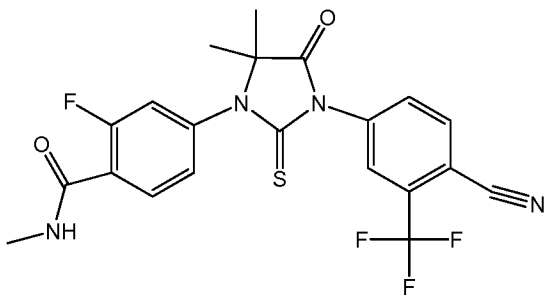
(ii) a compound of formula (II):



or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

In another aspect of the present invention, there is provided a combination comprising:

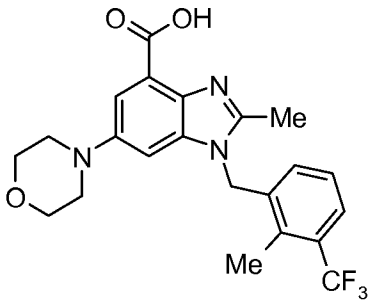
(i) a compound of formula (I):



(I)

or a pharmaceutically acceptable salt or solvate thereof and

(ii) a compound of formula (II):

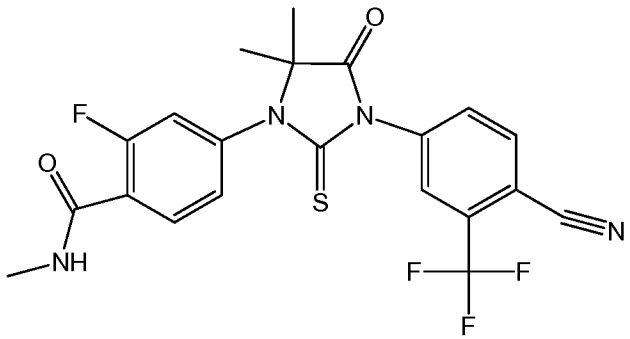


(II)

or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of cancer.

In another aspect of the present invention, there is provided a method of treatment of cancer in a mammal comprising administering to said mammal:

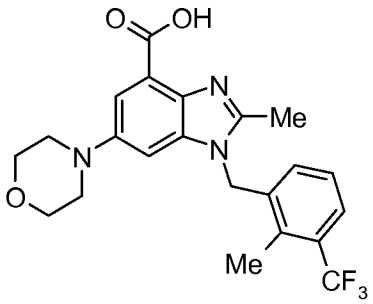
(i) a therapeutically effective amount of a compound of formula (I)



(I)

or a pharmaceutically acceptable salt or solvate thereof and

(ii) a compound of formula (II):



or a pharmaceutically acceptable salt thereof.

In another aspect, there is provided a method of treating cancer in a human in need thereof comprising the administration of a therapeutically effective amount of a combination of 4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-

thioxoimidazolidin-1-yl)-2-fluoro-*N*-methylbenzamide or a pharmaceutically acceptable salt or solvate thereof, and 2-methyl-1-{[2-methyl-3-(trifluoromethyl)phenyl]methyl}-6-(4-morpholinyl)-1H-benzimidazole-4-carboxylic acidor a pharmaceutically acceptable salt thereof.

In another aspect, there is provided a method of treating cancer in a human in need thereof comprising the administration of a therapeutically effective amount of a combination 4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-*N*-methylbenzamide dimethyl sulfoxide solvate, and 2-methyl-1-{[2-methyl-3-(trifluoromethyl)phenyl]methyl}-6-(4-morpholinyl)-1H-benzimidazole-4-carboxylic 2-amino-2-(hydroxymethyl)-1,3-propanediol Tris salt form.

In a further aspect of this invention is provided a method of treating cancer in a human in need thereof which comprises administering a therapeutically effective amount of a combination of the invention wherein the combination is administered within a specific period, and for a duration of time.

BRIEF DESCRIPTION OF THE FIGURES

FIGURE 1 is a graph showing the anti-proliferative effect of an androgen receptor inhibitor, Compound A and PI3Kβ inhibitor, Compound B, and combination thereof in prostate cancer cells.

FIGURE 2 is an immunoblot showing the effect of an androgen receptor inhibitor, Compound A and PI3Kβ inhibitor, Compound B, and combination thereof on cell signaling in prostate cancer cells.

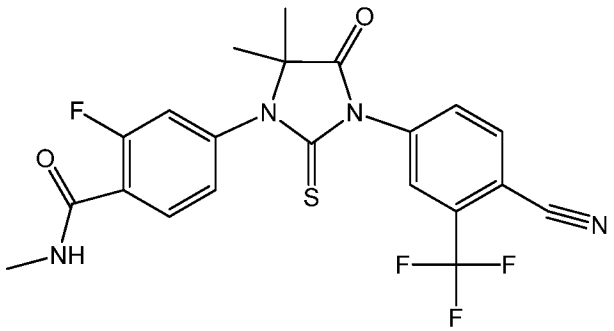
FIGURE 3 is a graph showing the effect of an androgen receptor inhibitor, Compound A and PI3Kβ inhibitor, Compound B, and combination thereof on caspase 3/7 induction in prostate cancer cells.

DETAILED DESCRIPTION OF THE INVENTION

This section presents a detailed description of the invention and its applications. This description is by way of several exemplary illustrations, in increasing detail and specificity, of the general methods of this invention. These examples are non-limiting and related variants will be apparent to one of skill in the art.

As used herein, the androgen receptor inhibitor, 4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-*N*-

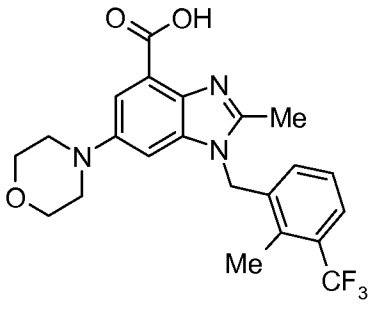
methylbenzamide or a pharmaceutically acceptable salt or solvate thereof, is represented by a compound of formula (I):



(I)

or a pharmaceutically acceptable salt or solvate thereof. For convenience, the group of possible compound and salts or solvates is collectively referred to as Compound A, meaning that reference to Compound A will refer to any of the compound or pharmaceutically acceptable salt or solvate thereof in the alternative. Depending on naming convention, the compound of formula (I) may also properly be referred to as 4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-*N*-methylbenzamide.

As used herein, the PI3Kβ inhibitor, 2-methyl-1-{[2-methyl-3-(trifluoromethyl)phenyl]methyl}-6-(4-morpholinyl)-1H-benzimidazole-4-carboxylic acid, or a pharmaceutically acceptable salt or solvate thereof, is represented by a compound of formula (II):



(II)

or pharmaceutically acceptable salt or solvate thereof. For convenience, the group of possible compound and salts or solvates is collectively referred to as Compound B, meaning that reference to Compound B will refer to any of the compound or pharmaceutically acceptable salt or solvate thereof in the alternative.

As used herein the term "combination of the invention" refers to a combination comprising Compound A and Compound B.

As used herein the term "neoplasm" refers to an abnormal growth of cells or tissue and is understood to include benign, i.e., non-cancerous growths, and malignant, i.e., cancerous growths. The term "neoplastic" means of or related to a neoplasm.

As used herein the term "agent" is understood to mean a substance that produces a desired effect in a tissue, system, animal, mammal, human, or other subject. Accordingly, the term "anti-neoplastic agent" is understood to mean a substance producing an anti-neoplastic effect in a tissue, system, animal, mammal, human, or other subject. It is also to be understood that an "agent" may be a single compound or a combination or composition of two or more compounds.

By the term "treating" and derivatives thereof as used herein, is meant therapeutic therapy. In reference to a particular condition, treating means: (1) to ameliorate the condition or one or more of the biological manifestations of the condition, (2) to interfere with (a) one or more points in the biological cascade that leads to or is responsible for the condition or (b) one or more of the biological manifestations of the condition (3) to alleviate one or more of the symptoms, effects or side effects associated with the condition or one or more of the symptoms, effects or side effects associated with the condition or treatment thereof, or (4) to slow the progression of the condition or one or more of the biological manifestations of the condition.

As used herein, "prevention" is understood to refer to the prophylactic administration of a drug to substantially diminish the likelihood or severity of a condition or biological manifestation thereof, or to delay the onset of such condition or biological manifestation thereof. The skilled artisan will appreciate that "prevention" is not an absolute term. Prophylactic therapy is appropriate, for example, when a subject is considered at high risk for developing cancer, such as when a subject has a strong family history of cancer or when a subject has been exposed to a carcinogen.

As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician. Furthermore, the term "therapeutically effective amount" means any amount which, as

compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function.

Compounds A and/or B may contain one or more chiral atoms, or may otherwise be capable of existing as enantiomers. Accordingly, the compounds of this invention include mixtures of enantiomers as well as purified enantiomers or enantiomerically enriched mixtures. Also, it is understood that all tautomers and mixtures of tautomers are included within the scope of Compound A and Compound B.

Also, it is understood that compounds A and B may be presented, separately or both, as solvates. As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute in this invention, compounds of formula (I) or (II) or a salt thereof and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, methanol, dimethyl sulforide, ethanol and acetic acid. In one embodiment, the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include, without limitation, water, ethanol and acetic acid. In another embodiment, the solvent used is water.

Compounds A and B may have the ability to crystallize in more than one form, a characteristic, which is known polymorphism, and it is understood that such polymorphic forms ("polymorphs") are within the scope of Compounds A and B. Polymorphism generally can occur as a response to changes in temperature or pressure or both and can also result from variations in the crystallization process. Polymorphs can be distinguished by various physical characteristics known in the art such as x-ray diffraction patterns, solubility, and melting point.

Compound A is disclosed and claimed, along with pharmaceutically acceptable salts thereof, and also as solvates thereof, as being useful as an inhibitor of androgen receptor activity, particularly, in treatment of cancer, in U.S. Patent No. 7,709,517. Compound A is the compound of Example 56. Compound A can be prepared as described in U.S. Patent No. 7,709,517.

Suitably, Compound A is in the form of a dimethyl sulfoxide solvate. Suitably, Compound A is in the form of an acetate salt. Suitably, Compound A is in the form of a solvate selected from: hydrate, acetic acid, ethanol, nitromethane, chlorobenzene, 1-pentancol, isopropyl alcohol, ethylene glycol and 3-methyl-1-butanol. These solvates and salt forms can be prepared by one of skill in the art from the description in U.S. Patent No. 7,709,517.

By the term "androgen receptor inhibitor" and derivatives thereof, as used herein, unless otherwise defined, is meant the class of compounds that alters the androgen pathway by blocking the receptor, competing for binding sites on the cell's surface or affecting androgen production. The most common antiandrogens are androgen receptor antagonists which act on the target cell level and competitively bind to androgen receptors. By competing with circulating androgens for binding sites on prostate cell receptors, antiandrogens promote apoptosis and inhibit prostate cancer growth. Several androgen receptor inhibitors are marketed or are being studied in the treatment of cancer. In one embodiment of the present invention Compound A is replaced by an alternate androgen receptor inhibitor.

The invention includes androgen receptor inhibitors that are structurally and chemically similar to Compound A, 4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-*N*-methylbenzamide. Compound ARN-509 is a structural analog of Compound A.

In some embodiments of the invention, the androgen receptor inhibitor is ARN-509. ARN-509 is a compound currently in phase III clinical development that can be named as 4-{7-[6-Cyano-5-(trifluoromethyl)-3-pyridinyl]-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl}-2-fluoro-N-methylbenzamide. US2011/003839 to Jung et al., which incorporated herein by reference in its entirely, discloses compound ARN-509 and methods of preparing and using the compound. ARN-509 is also known as A52. See *Cancer Res.* 72(6), 1494-1503 (Mar. 15, 2012).

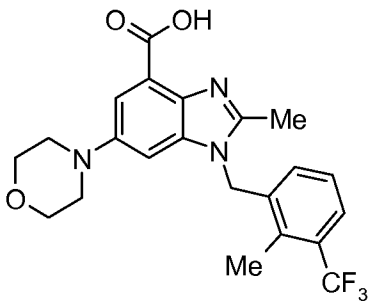
The invention includes androgen receptor inhibitors that are biologically similar to Compound A, 4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-*N*-methylbenzamide. Compound ODM-201 is a biological analog of Compound A

In some embodiments of the invention, the androgen receptor inhibitor is ODM-201. Currently in phase II clinical development trials, the structure for ODM-201 is unavailable. Studies reveal that ODM-201 has a high affinity for the androgen receptor and anti-proliferative activity in prostate cancer xenograft models. See Fizazi K, et al. An open-label, phase I/II safety, pharmacokinetic, and proof-of-concept study of ODM-201 in patients with progressive metastatic castration-resistant prostate cancer.). *Proceedings of ESMO Congress, Vienna, Austria, ESMO* 2013; Abstract 2853. ODM-201 is manufactured by Orion Pharma.

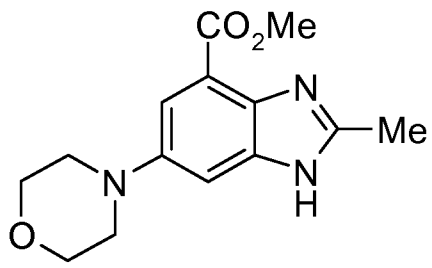
Compound B is disclosed and claimed, along with pharmaceutically acceptable salts thereof, as being useful as an inhibitor of PI3Kβ activity, particularly in the treatment of cancer, in U.S. Patent No. 8,435,988. Compound B is embodied in Examples 31 and 86 of U.S. Patent No. 8,435,988, and is hereby incorporated by reference.

More particularly, Compound B may be prepared according to the methods below:

Method 1: Compound B: 2-methyl-1-{[2-methyl-3-(trifluoromethyl)phenyl]methyl}-6-(4-morpholinyl)-1H-benzimidazole-4-carboxylic acid

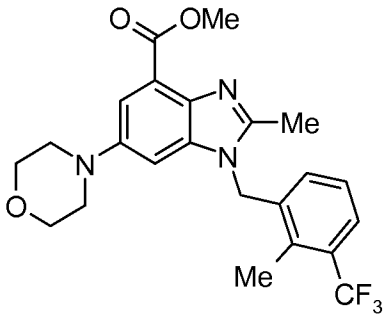


Step A: Preparation of methyl 2-methyl-5-(4-morpholinyl)-1H-benzimidazole-7-carboxylate.



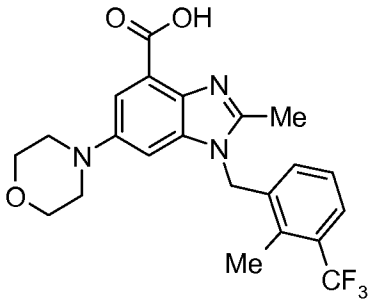
To a solution of methyl 3-amino-5-(4-morpholinyl)-2-nitrobenzoate (22 g) stirring at reflux in HOAc (400 mL) was added iron powder in portions (13 g). After the addition, the mixture was stirred at reflux for 5 h. It was cooled to room temperature and the solvent was removed in-vacuo. The residue was neutralized with aqueous Na_2CO_3 solution (1 L). It was extracted with EtOAc (500 mL ×3). The combined organic layers were then concentrated in-vacuo and the residue was purified by silica gel chromatography eluted with MeOH : DCM = 1 : 30 to afford the desired product as a solid (16.6 g, yield 77%). ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 2.67 (s, 3H), 3.17 (t, 4H, J= 4.8 Hz), 3.90 (t, 4H, J= 4.8 Hz), 3.98 (s, 3H), 7.44 (d, 1H, J= 1.8 Hz), 7.54 (d, 1H, J= 1.8 Hz); LC-MS: m/e = 276 $[M+1]^+$.

Step B: Preparation of methyl 2-methyl-1-{[2-methyl-3-(trifluoromethyl)phenyl]methyl}-6-(4-morpholinyl)-1H-benzimidazole-4-carboxylate



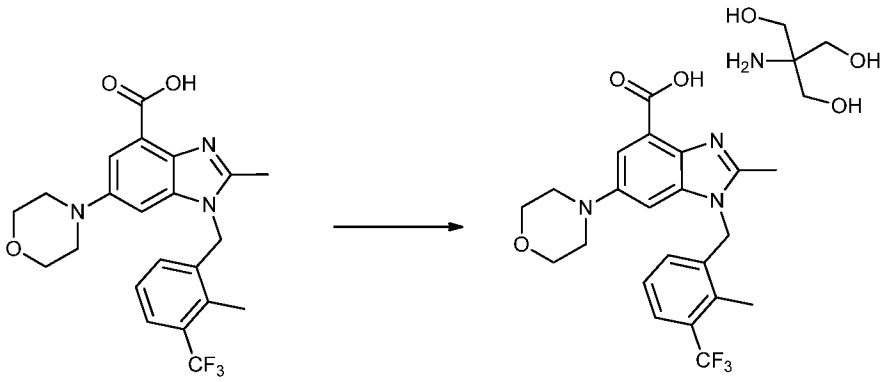
A solution of methyl 2-methyl-5-(4-morpholinyl)-1H-benzimidazole-7-carboxylate was prepared as described above, (500mg, 1.8 mmol), 1-(bromomethyl)-2-methyl-3-(trifluoromethyl)benzene (483 mg, 1.9 mmol) and K_2CO_3 (497 mg, 3.6 mmol) in DMF (50 mL) was stirred at 80° C for 3 h. The reaction mixture was cooled to rt and poured into water (50 mL), extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The resulting residue was purified by silica gel chromatography eluted with DCM : MeOH = 50 : 1 to give the crude product (230 mg, yield 29%), as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 2.39 (s, 3H), 2.54 (s, 3H), 3.08 (t, 4H, J=4.8 Hz), 3.72 (t, 4H, J=4.8 Hz), 3.89 (s, 3H), 5.57 (s, 2H), 6.27 (d, 1H, J=7.5 Hz), 7.22 (t, 1H, J=7.5 Hz), 7.27 (d, 1H, J=2.4 Hz), 7.38 (d, 1H, J=2.4 Hz) 7.60 (d, 1H, J=7.5 Hz); LC-MS: m/e = 448 $[M+1]^+$

Step C: Preparation of 2-methyl-1-{[2-methyl-3-(trifluoromethyl)phenyl]methyl}-6-(4-morpholinyl)-1H-benzimidazole-4-carboxylic acid



An aqueous solution of 2 N LiOH (1.2 mL) was added to a solution of methyl 2-methyl-1-{[2-methyl-3-(trifluoromethyl)phenyl]methyl}-6-(4-morpholinyl)-1H-benzimidazole-4-carboxylate, prepared as described above, (180 mg, 0.4 mmol) in THF (10 mL) and stirred at 50° C for 1 h. When TLC showed no starting material remaining, the mixture was cooled to rt and THF was removed under reduced pressure. The pH of the mixture was acidified to pH 3. The suspension was filtered and the filtrate was collected, and washed with water (10mL) to give the product as a white solid (152 mg, yield 88%). ^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 2.46 (s, 3H), 2.54 (s, 3H), 3.10 (t, 4H, J=4.8 Hz), 3.73 (t, 4H, J=4.8 Hz), 5.63 (s, 2H), 6.37 (d, 1H, J=7.8 Hz), 7.26 (t, 1H, J=7.8 Hz), 7.35 (d, 1H, J=2.4 Hz), 7.44 (d, 1H, J=2.4 Hz), 7.62 (d, 1H, J=7.8 Hz); LC-MS: m/e = 434 $[M+1]^+$.

Method 2: Compound B (Tris salt): 2-methyl-1-{[2-methyl-3-(trifluoromethyl)phenyl]methyl}-6-(4-morpholinyl)-1H-benzimidazole-4-carboxylic acid 2-amino-2-(hydroxymethyl)-1,3-propanediol salt



Seed crystal preparation - Batch 1: To the 2-methyl-1-{[2-methyl-3-(trifluoromethyl)phenyl]methyl}-6-(4-morpholinyl)-1H-benzimidazole-4-carboxylic acid (52.9 mg, 0.122 mmol), methanol (2.0 mL) was added. To the slurry, tromethamine (2-amino-2-(hydroxymethyl)-1,3-propanediol) (3.0 M solution in water, 1.0 equivalent) was added. The slurry was heated to 60C and kept stirring at 60C for 3 hours. The slurry was then cooled slowly (0.1C/min) to 20C. Once the temperature of the slurry reached 20C, the slurry was kept stirring at 20C for 8 hours. The crystalline solids were isolated by vacuum filtration. The yield of the desired salt was 57.2 mg (85% yield).

Seed crystal preparation - Batch 2: To the 2-methyl-1-{[2-methyl-3-(trifluoromethyl)phenyl]methyl}-6-(4-morpholinyl)-1H-benzimidazole-4-carboxylic acid (353.0 mg), methanol (14.0 mL) was added. The slurry was heated to 60C and tromethamine (3.0 M solution in water, 1.0 equivalent) was added in four aliquots over 15 minutes followed by the addition of crystalline seeds of crystalline tromethamine salt from batch 1. The slurry was stirred at 60C for 3 hours, cooled (1C/min) to 20C, and stirred at 20C for 8 hours. The solids were isolated by vacuum filtration, dried at 60C under vacuum for 5 hours. The yield of the tromethamine salt was 401.5 mg (~88.9% yield).

Batch 3: 2-methyl-1-{[2-methyl-3-(trifluoromethyl)phenyl]methyl}-6-(4-morpholinyl)-1H-benzimidazole-4-carboxylic acid (40.0 g, 92 mmol) was suspended in Methanol (1.6 L) in a 3L rounded-bottom flask. The resulting slurry was heated to 60°C mixing on a buchii rotary evaporator water bath and tris(hydroxymethyl)aminomethane (3M solution

in water) (0.031 L, 92 mmol) was added in four aliquots over 15 minutes followed by the addition of seed crystals as produced by method analogous to Batch 2, above (108 mg). This slurry was stirred (flask rotated on buchii rotovap) at 60 °C for 3 hours, then cooled (~1 °C/min) to 20 °C (room temperature), then finally magnetically stirred at 20 °C (room temperature) for 8 hours. The resulting white solid was isolated by vacuum filtration, dried under vacuum at 60 °C for 8 hours to provide 2-methyl-1-{[2-methyl-3-(trifluoromethyl)phenyl]methyl}-6-(4-morpholinyl)-1H-benzimidazole-4-carboxylic acid - 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1) (47.76 g, 86 mmol, 93 % yield) as a white solid. Both proton NMR and LCMS are consistent with the proposed structure. 1H NMR (400 MHz, DMSO-d6) δ ppm 7.61 (d, J=7.83 Hz, 1 H) 7.37 (d, J=2.27 Hz, 1 H) 7.17 - 7.33 (m, 2 H) 6.33 (d, J=7.83 Hz, 1 H) 5.59 (s, 2 H) 3.66 - 3.80 (m, 4 H) 2.98 - 3.15 (m, 4 H) 2.50 - 2.58 (m, 10 H) 2.43 (s, 3 H); LCMS m/z MH+ =434.3.

Typically, the salts of the present invention are pharmaceutically acceptable salts. Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention. Salts of the compounds of the present invention may comprise acid addition salts derived from a nitrogen on a substituent in a compound of the present invention. Representative salts include the following salts: acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, monopotassium maleate, mucate, napsylate, nitrate, N-methylglucamine, oxalate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, potassium, salicylate, sodium, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, trimethylammonium and valerate. Other salts, which are not pharmaceutically acceptable, may be useful in the preparation of compounds of this invention and these form a further aspect of the invention. Salts may be readily prepared by a person skilled in the art.

While it is possible that, for use in therapy, compounds A and B may be administered as the raw chemical, it is possible to present the active ingredient as a pharmaceutical composition. Accordingly, the invention further provides pharmaceutical compositions, which include a compound A and/or a compound B, and one or more pharmaceutically acceptable carriers, diluents, or excipients. The compounds A and B are as described above. The carrier(s), diluent(s) or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation, capable of pharmaceutical formulation, and not deleterious to the recipient thereof. In accordance with another aspect of the invention there is also provided a process for the preparation of a pharmaceutical composition including admixing a Compound A and/or Compound B, with one or more pharmaceutically acceptable carriers, diluents or excipients. Such elements of the pharmaceutical compositions utilized may be presented in separate pharmaceutical combinations or formulated together in one pharmaceutical composition. Accordingly, the invention further provides a combination of pharmaceutical compositions one of which includes Compound A and one or more pharmaceutically acceptable carriers, diluents, or excipients and a pharmaceutical composition containing Compound B and one or more pharmaceutically acceptable carriers, diluents, or excipients.

Compound A and Compound B are as described above and may be utilized in any of the compositions described above.

Pharmaceutical compositions may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. As is known to those skilled in the art, the amount of active ingredient per dose will depend on the condition being treated, the route of administration and the age, weight and condition of the patient. Preferred unit dosage compositions are those containing a daily dose or sub-dose, or an appropriate fraction thereof, of an active ingredient. Furthermore, such pharmaceutical compositions may be prepared by any of the methods well known in the pharmacy art.

Compounds A and B may be administered by any appropriate route. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal, and parenteral (including subcutaneous, intramuscular, intraveneous, intradermal, intrathecal, and epidural). It will be appreciated that the preferred route may vary with, for example,

the condition of the recipient of the combination and the cancer to be treated. It will also be appreciated that each of the agents administered may be administered by the same or different routes and that the Compounds A and B may be compounded together in a pharmaceutical composition.

Pharmaceutical compositions adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing and coloring agent can also be present.

Capsules are made by preparing a powder mixture as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. Tablets are

formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginate, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or an absorption agent such as bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acadia mucilage or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined with free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or natural sweeteners or saccharin or other artificial sweeteners, and the like can also be added.

Where appropriate, compositions for oral administration can be microencapsulated. The composition can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax or the like.

The agents for use according to the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large

unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Agents for use according to the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

Pharmaceutical compositions adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in Pharmaceutical Research, 3(6), 318 (1986).

Pharmaceutical compositions adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oils.

For treatments of the eye or other external tissues, for example mouth and skin, the compositions are preferably applied as a topical ointment or cream. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in-oil base.

Pharmaceutical compositions adapted for topical administrations to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent.

Pharmaceutical compositions adapted for topical administration in the mouth include lozenges, pastilles and mouth washes.

Pharmaceutical compositions adapted for rectal administration may be presented as suppositories or as enemas.

Pharmaceutical compositions adapted for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable compositions wherein the carrier is a liquid, for administration as a nasal spray or as nasal drops, include aqueous or oil solutions of the active ingredient.

Pharmaceutical compositions adapted for administration by inhalation include fine particle dusts or mists that may be generated by means of various types of metered dose pressurised aerosols, nebulizers or insufflators.

Pharmaceutical compositions adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray compositions.

Pharmaceutical compositions adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The compositions may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

It should be understood that in addition to the ingredients particularly mentioned above, the compositions may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

Unless otherwise defined, in all dosing protocols described herein, the regimen of compounds administered does not have to commence with the start of treatment and terminate with the end of treatment, it is only required that the number of consecutive days in which both compounds are administered and the optional number of consecutive

days in which only one of the component compounds is administered, or the indicated dosing protocol – including the amount of compound administered, occur at some point during the course of treatment.

Compounds A and B may be employed in combination in accordance with the invention by administration simultaneously in a unitary pharmaceutical composition including both compounds. Alternatively, the combination may be administered separately in separate pharmaceutical compositions, each including one of the compounds A and B in a sequential manner wherein, for example, Compound A or Compound B is administered first and the other second. Such sequential administration may be close in time (eg. simultaneously) or remote in time. Furthermore, it does not matter if the compounds are administered in the same dosage form, e.g. one compound may be administered topically and the other compound may be administered orally. Suitably, both compounds are administered orally.

Thus in one embodiment, one or more doses of Compound A are administered simultaneously or separately with one or more doses of Compound B.

Unless otherwise defined, in all dosing protocols described herein, the regimen of compounds administered does not have to commence with the start of treatment and terminate with the end of treatment, it is only required that the number of consecutive days in which both compounds are administered and the optional number of consecutive days in which only one of the component compounds is administered, or the indicated dosing protocol – including the amount of compound administered, occur at some point during the course of treatment.

In one embodiment, multiple doses of Compound A are administered simultaneously or separately with multiple doses of Compound B.

In one embodiment, multiple doses of Compound A are administered simultaneously or separately with one dose of Compound B.

In one embodiment, one dose of Compound A is administered simultaneously or separately with multiple doses of Compound B.

In one embodiment one dose of Compound A is administered simultaneously or separately with one dose of Compound B.

In all the above embodiments Compound A may be administered first or Compound B may be administered first.

The combinations may be presented as a combination kit. By the term "combination kit" "or kit of parts" as used herein is meant the pharmaceutical composition or compositions that are used to administer Compound A and Compound B according to the invention. When both compounds are administered simultaneously, the combination kit can contain Compound A and Compound B in a single pharmaceutical composition, such as a tablet, or in separate pharmaceutical compositions. When Compounds A and B are not administered simultaneously, the combination kit will contain Compound A and Compound B in separate pharmaceutical compositions either in a single package or Compound A and Compound B in separate pharmaceutical compositions in separate packages.

In one aspect there is provided a kit of parts comprising components:

Compound A in association with a pharmaceutically acceptable excipients, diluents or carrier; and
Compound B in association with a pharmaceutically acceptable excipients, diluents or carrier.

In one embodiment of the invention the kit of parts comprising the following components:

Compound A in association with a pharmaceutically acceptable excipients, diluents or carrier; and
Compound B in association with a pharmaceutically acceptable excipients, diluents or carrier,

wherein the components are provided in a form which is suitable for sequential, separate and/or simultaneous administration.

In one embodiment the kit of parts comprises:

a first container comprising Compound A in association with a pharmaceutically acceptable excipient, diluent or carrier; and

a second container comprising Compound B in association with a pharmaceutically acceptable excipient, diluent or carrier, and a container means for containing said first and second containers.

The combination kit can also be provided by instruction, such as dosage and administration instructions. Such dosage and administration instructions can be of the kind that are provided to a doctor, for example, by a drug product label, or they can be of the kind that are provided by a doctor, such as instructions to a patient.

The term "maintenance dose" as used herein will be understood to mean a dose that is serially administered (for example; at least twice), and which is intended to either slowly raise blood concentration levels of the compound to a therapeutically effective level, or to maintain such a therapeutically effective level. The maintenance dose is generally administered once per day and the daily dose of the maintenance dose is lower than the total daily dose of the loading dose.

The term "loading dose" as used herein will be understood to mean a single dose or short duration regimen of a combination of the invention, suitably Compound A or Compound B having a dosage higher than the maintenance dose administered to the subject to rapidly increase the blood concentration level of the drug. Suitably, a short duration regimen for use herein will be from: 1 to 14 days; suitably from 1 to 7 days; suitably from 1 to 3 days; suitably for three days; suitably for two days; suitably for one day. In some embodiments, the "loading dose" can increase the blood concentration of the drug to a therapeutically effective level. In some embodiments, the "loading dose" can increase the blood concentration of the drug to a therapeutically effective level in conjunction with a maintenance dose of the drug. The "loading dose" can be administered once per day, or more than once per day (e.g., up to 4 times per day). Suitably the "loading dose" will be administered once a day. Suitably, the loading dose will be an amount from 2 to 100 times the maintenance dose; suitably from 2 to 10 times; suitably from 2 to 5 times; suitably 2 times; suitably 3 times; suitably 4 times; suitably 5

times. Suitably, the loading dose will be administered for from 1 to 7 days; suitably from 1 to 5 days; suitably from 1 to 3 days; suitably for 1 day; suitably for 2 days; suitably for 3 days, followed by a maintenance dosing protocol.

Suitably the combinations of this invention are administered within a "specified period".

By the term "specified period" and derivatives thereof, as used herein is meant the interval of time between the administration of one of Compound A and Compound B and the other of Compound A and Compound B. Unless otherwise defined, the specified period can include simultaneous administration. When both compounds of the invention are administered once a day the specified period refers to administration of Compound A and Compound B during a single day. When one or both compounds of the invention are administered more than once a day, the specified period is calculated based on the first administration of each compound on a specific day. All administrations of a compound of the invention that are subsequent to the first during a specific day are not considered when calculating the specific period.

Suitably, if the compounds are administered within a "specified period" and not administered simultaneously, they are both administered within about 24 hours of each other – in this case, the specified period will be about 24 hours; suitably they will both be administered within about 12 hours of each other – in this case, the specified period will be about 12 hours; suitably they will both be administered within about 11 hours of each other – in this case, the specified period will be about 11 hours; suitably they will both be administered within about 10 hours of each other – in this case, the specified period will be about 10 hours; suitably they will both be administered within about 9 hours of each other – in this case, the specified period will be about 9 hours; suitably they will both be administered within about 8 hours of each other – in this case, the specified period will be about 8 hours; suitably they will both be administered within about 7 hours of each other – in this case, the specified period will be about 7 hours; suitably they will both be administered within about 6 hours of each other – in this case, the specified period will be about 6 hours; suitably they will both be administered within about 5 hours of each other – in this case, the specified period will be about 5 hours; suitably they will both be administered within about 4 hours of each other – in this case, the specified period will be

about 4 hours; suitably they will both be administered within about 3 hours of each other – in this case, the specified period will be about 3 hours; suitably they will be administered within about 2 hours of each other – in this case, the specified period will be about 2 hours; suitably they will both be administered within about 1 hour of each other – in this case, the specified period will be about 1 hour. As used herein, the administration of Compound A and Compound B in less than about 45 minutes apart is considered simultaneous administration.

Suitably, when the combination of the invention is administered for a "specified period", the compounds will be co-administered for a "duration of time".

By the term "duration of time" and derivatives thereof, as used herein is meant that both compounds of the invention are administered for an indicated number of consecutive days.

Regarding "specified period" administration:

Suitably, both compounds will be administered within a specified period for at least one day – in this case, the duration of time will be at least one day; suitably, during the course to treatment, both compounds will be administered within a specified period for at least 3 consecutive days – in this case, the duration of time will be at least 3 days; suitably, during the course to treatment, both compounds will be administered within a specified period for at least 5 consecutive days – in this case, the duration of time will be at least 5 days; suitably, during the course to treatment, both compounds will be administered within a specified period for at least 7 consecutive days – in this case, the duration of time will be at least 7 days; suitably, during the course to treatment, both compounds will be administered within a specified period for at least 14 consecutive days – in this case, the duration of time will be at least 14 days; suitably, during the course to treatment, both compounds will be administered within a specified period for at least 30 consecutive days – in this case, the duration of time will be at least 30 days.

Further regarding "specified period" administration:

Suitably, during the course of treatment, Compound A and Compound B will be administered within a specified period for from 1 to 4 days over a 7 day period, and during the other days of the 7 day period Compound A will be administered alone.

Suitably, this 7 day protocol is repeated for 2 cycles or for 14 days; suitably for 4 cycles or 28 days; suitably for continuous administration.

Suitably, during the course of treatment, Compound A and Compound B will be administered within a specified period for from 1 to 4 days over a 7 day period, and during the other days of the 7 day period Compound B will be administered alone. Suitably, this 7 day protocol is repeated for 2 cycles or for 14 days; suitably for 4 cycles or 28 days; suitably for continuous administration. Suitably, Compound B is administered for consecutive days during the 7 day period. Suitably, Compound B is administered in a pattern of every other day during each 7 day period.

Suitably, during the course of treatment, Compound A and Compound B will be administered within a specified period for 3 days over a 7 day period, and during the other days of the 7 day period Compound B will be administered alone. Suitably, this 7 day protocol is repeated for 2 cycles or for 14 days; suitably for 4 cycles or 28 days; suitably for continuous administration. Suitably, Compound A will be administered 3 consecutive days during the 7 day period.

Suitably, during the course of treatment, Compound A and Compound B will be administered within a specified period for 2 days over a 7 day period, and during the other days of the 7 day period Compound B will be administered alone. Suitably, this 7 day protocol is repeated for 2 cycles or for 14 days; suitably for 4 cycles or 28 days; suitably for continuous administration. Suitably, Compound A will be administered 2 consecutive days during the 7 day period.

Suitably, during the course of treatment, Compound A and Compound B will be administered within a specified period for 1 day during a 7 day period, and during the other days of the 7 day period Compound B will be administered alone. Suitably, this 7 day protocol is repeated for 2 cycles or for 14 days; suitably for 4 cycles or 28 days; suitably for continuous administration.

Suitably, if the compounds are not administered during a "specified period", they are administered sequentially. By the term "sequential administration", and derivates thereof, as used herein is meant that one of Compound A and Compound B is administered for two or more consecutive days and the other of Compound A and Compound B is subsequently administered for two or more consecutive days. Also,

contemplated herein is a drug holiday utilized between the sequential administration of one of Compound A and Compound B and the other of Compound A and Compound B. As used herein, a drug holiday is a period of days after the sequential administration of one of Compound A and Compound B and before the administration of the other of Compound A and Compound B where neither Compound A nor Compound B is administered. Suitably the drug holiday will be a period of days selected from: 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days and 14 days.

Regarding sequential administration:

Suitably, one of Compound A and Compound B is administered for from 1 to 30 consecutive days, followed by an optional drug holiday, followed by administration of the other of Compound A and Compound B for from 1 to 30 consecutive days. Suitably, one of Compound A and Compound B is administered for from 2 to 21 consecutive days, followed by an optional drug holiday, followed by administration of the other of Compound A and Compound B for from 2 to 21 consecutive days. Suitably, one of Compound A and Compound B is administered for from 2 to 14 consecutive days, followed by a drug holiday of from 1 to 14 days, followed by administration of the other of Compound A and Compound B for from 2 to 14 consecutive days. Suitably, one of Compound A and Compound B is administered for from 3 to 7 consecutive days, followed by a drug holiday of from 3 to 10 days, followed by administration of the other of Compound A and Compound B for from 3 to 7 consecutive days.

Suitably, Compound B will be administered first in the sequence, followed by an optional drug holiday, followed by administration of Compound A. Suitably, Compound B is administered for from 1 to 21 consecutive days, followed by an optional drug holiday, followed by administration of Compound A for from 1 to 21 consecutive days. Suitably, Compound B is administered for from 3 to 21 consecutive days, followed by a drug holiday of from 1 to 14 days, followed by administration of Compound A for from 3 to 21 consecutive days. Suitably, Compound B is administered for from 3 to 21 consecutive days, followed by a drug holiday of from 3 to 14 days, followed by administration of Compound A for from 3 to 21 consecutive days. Suitably, Compound B is administered for 21 consecutive days, followed by an optional drug holiday,

followed by administration of Compound A for 14 consecutive days. Suitably, Compound B is administered for 14 consecutive days, followed by a drug holiday of from 1 to 14 days, followed by administration of Compound A for 14 consecutive days. Suitably, Compound B is administered for 7 consecutive days, followed by a drug holiday of from 3 to 10 days, followed by administration of Compound A for 7 consecutive days. Suitably, Compound B is administered for 3 consecutive days, followed by a drug holiday of from 3 to 14 days, followed by administration of Compound A for 7 consecutive days. Suitably, Compound B is administered for 3 consecutive days, followed by a drug holiday of from 3 to 10 days, followed by administration of Compound A for 3 consecutive days.

Suitably, Compound A will be administered first in the sequence, followed by an optional drug holiday, followed by administration of Compound B. Suitably, Compound A is administered for from 1 to 21 consecutive days, followed by an optional drug holiday, followed by administration of Compound B for from 1 to 21 consecutive days. Suitably, Compound A is administered for from 3 to 21 consecutive days, followed by a drug holiday of from 1 to 14 days, followed by administration of Compound B for from 3 to 21 consecutive days. Suitably, Compound A is administered for from 3 to 21 consecutive days, followed by a drug holiday of from 3 to 14 days, followed by administration of Compound B for from 3 to 21 consecutive days. Suitably, Compound A is administered for 21 consecutive days, followed by an optional drug holiday, followed by administration of Compound B for 14 consecutive days. Suitably, Compound A is administered for 14 consecutive days, followed by a drug holiday of from 1 to 14 days, followed by administration of Compound B for 14 consecutive days. Suitably, Compound A is administered for 7 consecutive days, followed by a drug holiday of from 3 to 10 days, followed by administration of Compound B for 7 consecutive days. Suitably, Compound A is administered for 3 consecutive days, followed by a drug holiday of from 3 to 14 days, followed by administration of Compound B for 7 consecutive days. Suitably, Compound A is administered for 3 consecutive days, followed by a drug holiday of from 3 to 10 days, followed by administration of Compound B for 3 consecutive days.

It is understood that a "specified period" administration and a "sequential" administration can be followed by repeat dosing or can be followed by an alternate dosing protocol, and a drug holiday may precede the repeat dosing or alternate dosing protocol.

Suitably, the amount of Compound A (based on weight of free base amount) administered as part of the combination according to the present invention will be an amount selected from about 40 mg to about 160 mg; suitably, the amount will be selected from about 40 mg to about 120 mg; suitably, the amount will be about 80 mg. Accordingly, the amount of Compound A administered as part of the combination according to the present invention will be an amount selected from about 40 mg to about 160 mg. For example, the amount of Compound A administered as part of the combination according to the present invention can be 40 mg, 80 mg, 120 mg, 160 mg.

Suitably, the amount of ARN-509, the analog of Compound A, (based on weight of free base amount) administered as part of the combination according to the present invention will be an amount selected from about 120 mg to about 300 mg; suitably, the amount will be selected from about 120 mg to about 240 mg; suitably, the amount will be about 180 mg. Accordingly, the amount of ARN-509 administered as part of the combination according to the present invention will be an amount selected from about 120 mg to about 300 mg. For example, the amount of ARN-509 administered as part of the combination according to the present invention can be 120 mg, 180 mg, 240 mg, 300 mg. Suitably, ARN-509 is administered once daily.

Suitably, the amount of ODM-201, the analog of Compound A, (based on weight of free base amount) administered as part of the combination according to the present invention will be an amount selected from about 100 mg to about 700 mg; suitably, the amount will be selected from about 200 mg to about 600 mg; suitably, the amount will be selected from about 300 mg to about 500 mg; suitably, the amount will be about 400 mg. Accordingly, the amount of ODM-201 administered as part of the combination according to the present invention will be an amount selected from about 100 mg to about 700 mg. For example, the amount of ODM-201 administered as part of the combination according to the present invention can be 100 mg, 180 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg and 700 mg. Suitably, the ODM-201 is administered twice daily.

Suitably, the amount of Compound B (based on weight of free base amount) administered as part of the combination according to the present invention will be an amount selected from about 50 mg to about 400 mg. Suitably, the amount will be selected from about 50 mg to about 350 mg; suitably, the amount will be selected from about 100 mg to about 300 mg; suitably, the amount will be selected from about 150mg to 250 mg; the amount will be 200 mg. Accordingly, the amount of Compound B administered as part of the combination according to the present invention will be an amount selected from about 50 mg to about 400 mg. For example, the amount of Compound B administered as part of the combination according to the present invention is suitably selected from 50 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg. Suitably, selected amount of Compound B is administered once a day. Suitably, the selected amount of Compound B is administered from 1 to 4 times a day. Suitably, Compound B is administered at an amount of 400 mg once a day.

As used herein, all amounts specified for Compound A, Compound B, and analogs of Compound A are indicated as the amount of free or unsalted compound.

Method of Treatment

The combinations of the invention are believed to have utility in disorders wherein the inhibition of the PI3Kβ and androgen receptor is beneficial.

The present invention thus also provides a combination of the invention, for use in therapy, particularly in the treatment of disorders wherein the inhibition of PI3Kβ and/or androgen receptor activity is beneficial, particularly cancer.

A further aspect of the invention provides a method of treatment of a disorder wherein to inhibition of PI3Kβ and/or androgen receptor is beneficial, comprising administering a combination of the invention.

A further aspect of the present invention provides the use of a combination of the invention in the manufacture of a medicament for the treatment of a disorder wherein the inhibition of PI3Kβ and/or androgen receptor is beneficial.

Typically, the disorder is a cancer such that inhibition of PI3Kβ and/or androgen receptor has a beneficial effect. Examples of cancers that are suitable for treatment with combination of the invention include, but are limited to, both primary and metastatic forms of head and neck, breast, lung, colon, ovary, and prostate cancers. Suitably the

cancer is selected from: brain (gliomas), glioblastomas, astrocytomas, glioblastoma multiforme, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, inflammatory breast cancer, Wilm's tumor, Ewing's sarcoma, Rhabdomyosarcoma, ependymoma, medulloblastoma, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, prostate, sarcoma, osteosarcoma, giant cell tumor of bone, thyroid cancer, lymphoblastic T cell leukemia, Chronic myelogenous leukemia, Chronic lymphocytic leukemia, Hairy-cell leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, AML, Chronic neutrophilic leukemia, Acute lymphoblastic T cell leukemia, plasmacytoma, Immunoblastic large cell leukemia, Mantle cell leukemia, Multiple myeloma Megakaryoblastic leukemia, multiple myeloma, acute megakaryocytic leukemia, promyelocytic leukemia, Erythroleukemia, malignant lymphoma, hodgkins lymphoma, non-hodgkins lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma, follicular lymphoma, neuroblastoma, bladder cancer, urothelial cancer, lung cancer, vulval cancer, cervical cancer, endometrial cancer, renal cancer, mesothelioma, esophageal cancer, salivary gland cancer, hepatocellular cancer, gastric cancer, nasopharangeal cancer, buccal cancer, cancer of the mouth, GIST (gastrointestinal stromal tumor) and testicular cancer.

Additionally, examples of a cancer to be treated include Barret's adenocarcinoma; billiary tract carcinomas; breast cancer; cervical cancer; cholangiocarcinoma; central nervous system tumors including primary CNS tumors such as glioblastomas, astrocytomas (e.g., glioblastoma multiforme) and ependymomas, and secondary CNS tumors (i.e., metastases to the central nervous system of tumors originating outside of the central nervous system); colorectal cancer including large intestinal colon carcinoma; gastric cancer; carcinoma of the head and neck including squamous cell carcinoma of the head and neck; hematologic cancers including leukemias and lymphomas such as acute lymphoblastic leukemia, acute myelogenous leukemia (AML), myelodysplastic syndromes, chronic myelogenous leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, megakaryoblastic leukemia, multiple myeloma and erythroleukemia; hepatocellular carcinoma; lung cancer including small cell lung cancer and non-small cell lung cancer; ovarian cancer; endometrial cancer; pancreatic cancer; pituitary adenoma;

prostate cancer; renal cancer; sarcoma; skin cancers including melanomas; and thyroid cancers.

In one embodiment, the cancer described here is PTEN deficient. As used herein, the phrase "PTEN deficient" or "PTEN deficiency" shall describe tumors with deficiencies of the tumor suppressor function of PTEN (Phosphatase and Tensin Homolog). Such deficiency includes mutation in the PTEN gene, reduction or absence of PTEN proteins when compared to PTEN wild-type, or mutation or absence of other genes that cause suppression of PTEN function.

Suitably, the present invention relates to a method for treating or lessening the severity of a cancer selected from: brain (gliomas), glioblastomas, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, prostate, sarcoma and thyroid.

Suitably, the present invention relates to a method for treating or lessening the severity of a cancer selected from ovarian, breast, pancreatic and prostate.

The combination of the invention may be used alone or in combination with one or more other therapeutic agents. The invention thus provides in a further aspect a further combination comprising a combination of the invention with a further therapeutic agent or agents, compositions and medicaments comprising the combination and use of the further combination, compositions and medicaments in therapy, in particular in the treatment of diseases susceptible to inhibition of PI3Kβ and/or androgen receptor.

In the embodiment, the combination of the invention may be employed with other therapeutic methods of cancer treatment. In particular, in anti-neoplastic therapy, combination therapy with other chemotherapeutic, hormonal, antibody agents as well as surgical and/or radiation treatments other than those mentioned above are envisaged. Combination therapies according to the present invention thus include the administration of Compound A and Compound B as well as optional use of other therapeutic agents including other anti-neoplastic agents. Such combination of agents may be administered together or separately and, when administered separately this may occur simultaneously or sequentially in any order, both close and remote in time. In one embodiment, the pharmaceutical combination includes Compound A and Compound B, and optionally at least one additional anti-neoplastic agent.

As indicated, therapeutically effective amounts of Compound A and Compound B are discussed above. The therapeutically effective amount of the further therapeutic agents of the present invention will depend upon a number of factors including, for example, the age and weight of the mammal, the precise condition requiring treatment, the severity of the condition, the nature of the formulation, and the route of administration. Ultimately, the therapeutically effective amount will be at the discretion of the attendant physician or veterinarian. The relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

In one embodiment, the further anti-cancer therapy is surgical and/or radiotherapy.

In one embodiment, the further anti-cancer therapy is at least one additional anti-neoplastic agent.

Any anti-neoplastic agent that has activity versus a susceptible tumor being treated may be utilized in the combination. Typical anti-neoplastic agents useful include, but are not limited to, anti-microtubule agents such as diterpenoids and vinca alkaloids; platinum coordination complexes; alkylating agents such as nitrogen mustards, oxazaphosphorines, alkylsulfonates, nitrosoureas, and triazenes; antibiotic agents such as anthracyclins, actinomycins and bleomycins; topoisomerase II inhibitors such as epipodophyllotoxins; antimetabolites such as purine and pyrimidine analogues and anti-folate compounds; topoisomerase I inhibitors such as camptothecins; hormones and hormonal analogues; signal transduction pathway inhibitors; non-receptor tyrosine angiogenesis inhibitors; immunotherapeutic agents; proapoptotic agents; late stage development drug treatments including conjugates which are antibodies against prostate cancer targets that are chemically conjugated to potent microtubule inhibitors such as monomethylauristatin E (MMAE) and the maytansinoids (DM1, DM4), or DNA binding agents such as the pyrrolobenzodiazepine dimmers; and cell cycle signaling inhibitors; and cell cycle signaling inhibitors.

Cabazitaxel, 2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-9-(((2R,3S)-3-((tert-butoxycarbonyl)amino)-2-hydroxy-3-phenylpropanoyl)oxy)-11-hydroxy-4,6-dimethoxy-4a,8,13,13-tetramethyl-5-oxo-

2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-12-yl benzoate is a treatment option for hormone-refractory prostate cancer. Cabazitaxel is a semi-synthetic derivative of the natural taxoid 10-deacetylbaccatin III with potential antineoplastic activity. Cabazitaxel binds to and stabilizes tubulin, resulting in the inhibition of microtubule depolymerization and cell division, cell cycle arrest in the G2/M phase, and the inhibition of tumor cell proliferation.

Anti-microtubule or anti-mitotic agents: Anti-microtubule or anti-mitotic agents are phase specific agents active against the microtubules of tumor cells during M or the mitosis phase of the cell cycle. Examples of anti-microtubule agents include, but are not limited to, diterpenoids and vinca alkaloids.

Diterpenoids, which are derived from natural sources, are phase specific anti - cancer agents that operate at the G_2/M phases of the cell cycle. It is believed that the diterpenoids stabilize the β-tubulin subunit of the microtubules, by binding with this protein. Disassembly of the protein appears then to be inhibited with mitosis being arrested and cell death following. Examples of diterpenoids include, but are not limited to, paclitaxel and its analog docetaxel.

Paclitaxel, 5β,20-epoxy-1,2α,4,7β,10β,13α-hexa-hydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine; is a natural diterpene product isolated from the Pacific yew tree *Taxus brevifolia* and is commercially available as an injectable solution TAXOL®. It is a member of the taxane family of terpenes. Paclitaxel has been approved for clinical use in the treatment of refractory ovarian cancer in the United States (Markman et al., *Yale Journal of Biology and Medicine*, 64:583, 1991; McGuire et al., *Ann. lntem, Med.*, 111:273, 1989) and for the treatment of breast cancer (Holmes et al., *J. Nat. Cancer Inst.*, 83:1797,1991.) It is a potential candidate for treatment of neoplasms in the skin (Einzig et. al., *Proc. Am. Soc. Clin. Oncol.*, 20:46, 2001) and head and neck carcinomas (Forastire et. al., *Sem. Oncol.*, 20:56, 1990). The compound also shows potential for the treatment of polycystic kidney disease (Woo et. al., *Nature*, 368:750. 1994), lung cancer and malaria. Treatment of patients with paclitaxel results in bone marrow suppression (multiple cell lineages, Ignoff, R.J. et. al, *Cancer Chemotherapy Pocket Guide*, 1998) related to the duration of

dosing above a threshold concentration (50nM) (Kearns, C.M. et. al., *Seminars in Oncology*, 3(6) p.16-23, 1995).

Docetaxel, (2R,3S)- N-carboxy-3-phenylisoserine,N-*tert*-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate; is commercially available as an injectable solution as TAXOTERE®. Docetaxel is indicated for the treatment of breast cancer. Docetaxel is a semisynthetic derivative of paclitaxel *q.v.*, prepared using a natural precursor, 10-deacetyl-baccatin III, extracted from the needle of the European Yew tree.

Vinca alkaloids are phase specific anti-neoplastic agents derived from the periwinkle plant. Vinca alkaloids act at the M phase (mitosis) of the cell cycle by binding specifically to tubulin. Consequently, the bound tubulin molecule is unable to polymerize into microtubules. Mitosis is believed to be arrested in metaphase with cell death following. Examples of vinca alkaloids include, but are not limited to, vinblastine, vincristine, and vinorelbine.

Vinblastine, vincaleukoblastine sulfate, is commercially available as VELBAN® as an injectable solution. Although, it has possible indication as a second line therapy of various solid tumors, it is primarily indicated in the treatment of testicular cancer and various lymphomas including Hodgkin's Disease; and lymphocytic and histiocytic lymphomas. Myelosuppression is the dose limiting side effect of vinblastine.

Vincristine, vincaleukoblastine, 22-oxo-, sulfate, is commercially available as ONCOVIN® as an injectable solution. Vincristine is indicated for the treatment of acute leukemias and has also found use in treatment regimens for Hodgkin's and non-Hodgkin's malignant lymphomas. Alopecia and neurologic effects are the most common side effect of vincristine and to a lesser extent myelosupression and gastrointestinal mucositis effects occur.

Vinorelbine, 3',4'-didehydro -4'-deoxy-C'-norvincaleukoblastine [R-(R*,R*)-2,3-dihydroxybutanedioate (1:2)(salt)], commercially available as an injectable solution of vinorelbine tartrate (NAVELBINE®), is a semisynthetic vinca alkaloid. Vinorelbine is indicated as a single agent or in combination with other chemotherapeutic agents, such as cisplatin, in the treatment of various solid tumors, particularly non-small cell lung,

advanced breast, and hormone refractory prostate cancers. Myelosuppression is the most common dose limiting side effect of vinorelbine.

Platinum coordination complexes: Platinum coordination complexes are non-phase specific anti-cancer agents, which are interactive with DNA. The platinum complexes enter tumor cells, undergo, aquation and form intra- and interstrand crosslinks with DNA causing adverse biological effects to the tumor. Examples of platinum coordination complexes include, but are not limited to, oxaliplatin, cisplatin and carboplatin.

Cisplatin, cis-diamminedichloroplatinum, is commercially available as PLATINOL® as an injectable solution. Cisplatin is primarily indicated in the treatment of metastatic testicular and ovarian cancer and advanced bladder cancer.

Carboplatin, platinum, diammine [1,1-cyclobutane-dicarboxylate(2-)-O,O'], is commercially available as PARAPLATIN® as an injectable solution. Carboplatin is primarily indicated in the first and second line treatment of advanced ovarian carcinoma.

Alkylating agents: Alkylating agents are non-phase anti-cancer specific agents and strong electrophiles. Typically, alkylating agents form covalent linkages, by alkylation, to DNA through nucleophilic moieties of the DNA molecule such as phosphate, amino, sulfhydryl, hydroxyl, carboxyl, and imidazole groups. Such alkylation disrupts nucleic acid function leading to cell death. Examples of alkylating agents include, but are not limited to, nitrogen mustards such as cyclophosphamide, melphalan, and chlorambucil; alkyl sulfonates such as busulfan; nitrosoureas such as carmustine; and triazenes such as dacarbazine.

Cyclophosphamide, 2-[bis(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide monohydrate, is commercially available as an injectable solution or tablets as CYTOXAN®. Cyclophosphamide is indicated as a single agent or in combination with other chemotherapeutic agents, in the treatment of malignant lymphomas, multiple myeloma, and leukemias.

Melphalan, 4-[bis(2-chloroethyl)amino]-L-phenylalanine, is commercially available as an injectable solution or tablets as ALKERAN®. Melphalan is indicated for

the palliative treatment of multiple myeloma and non-resectable epithelial carcinoma of the ovary. Bone marrow suppression is the most common dose limiting side effect of melphalan.

Chlorambucil, 4-[bis(2-chloroethyl)amino]benzenebutanoic acid, is commercially available as LEUKERAN® tablets. Chlorambucil is indicated for the palliative treatment of chronic lymphatic leukemia, and malignant lymphomas such as lymphosarcoma, giant follicular lymphoma, and Hodgkin's disease.

Busulfan, 1,4-butanediol dimethanesulfonate, is commercially available as MYLERAN® TABLETS. Busulfan is indicated for the palliative treatment of chronic myelogenous leukemia.

Carmustine, 1,3-[bis(2-chloroethyl)-1-nitrosourea, is commercially available as single vials of lyophilized material as BiCNU®. Carmustine is indicated for the palliative treatment as a single agent or in combination with other agents for brain tumors, multiple myeloma, Hodgkin's disease, and non-Hodgkin's lymphomas.

Dacarbazine, 5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide, is commercially available as single vials of material as DTIC-Dome®. Dacarbazine is indicated for the treatment of metastatic malignant melanoma and in combination with other agents for the second line treatment of Hodgkin's Disease.

Antibiotic anti-neoplastics: Antibiotic anti-neoplastics are non-phase specific agents, which bind or intercalate with DNA. Typically such action results in stable DNA complexes or strand breakage, which disrupts ordinary function of the nucleic acids leading to cell death. Examples of antibiotic anti-neoplastic agents include, but are not limited to, actinomycins such as dactinomycin, anthrocyclins such as daunorubicin and doxorubicin; and bleomycins.

Dactinomycin, also know as Actinomycin D, is commercially available in injectable form as COSMEGEN®. Dactinomycin is indicated for the treatment of Wilm's tumor and rhabdomyosarcoma.

Daunorubicin, (8S-cis-)-8-acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12

naphthacenedione hydrochloride, is commercially available as a liposomal injectable form as DAUNOXOME® or as an injectable as CERUBIDINE®. Daunorubicin is indicated for remission induction in the treatment of acute nonlymphocytic leukemia and advanced HIV associated Kaposi's sarcoma.

Doxorubicin, (8S, 10S)-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-8-glycoloyl, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12 naphthacenedione hydrochloride, is commercially available as an injectable form as RUBEX® or ADRIAMYCIN RDF®. Doxorubicin is primarily indicated for the treatment of acute lymphoblastic leukemia and acute myeloblastic leukemia, but is also a useful component in the treatment of some solid tumors and lymphomas.

Bleomycin, a mixture of cytotoxic glycopeptide antibiotics isolated from a strain of *Streptomyces verticillus*, is commercially available as BLENOXANE®. Bleomycin is indicated as a palliative treatment, as a single agent or in combination with other agents, of squamous cell carcinoma, lymphomas, and testicular carcinomas.

Topoisomerase II inhibitors: Topoisomerase II inhibitors include, but are not limited to, epipodophyllotoxins.

Epipodophyllotoxins are phase specific anti-neoplastic agents derived from the mandrake plant. Epipodophyllotoxins typically affect cells in the S and G_2 phases of the cell cycle by forming a ternary complex with topoisomerase II and DNA causing DNA strand breaks. The strand breaks accumulate and cell death follows. Examples of epipodophyllotoxins include, but are not limited to, etoposide and teniposide.

Etoposide, 4'-demethyl-epipodophyllotoxin 9[4,6-0-(R)-ethylidene-β-D-glucopyranoside], is commercially available as an injectable solution or capsules as VePESID® and is commonly known as VP-16. Etoposide is indicated as a single agent or in combination with other chemotherapy agents in the treatment of testicular and non-small cell lung cancers.

Teniposide, 4'-demethyl-epipodophyllotoxin 9[4,6-0-(R)-thenylidene-β-D-glucopyranoside], is commercially available as an injectable solution as VUMON® and is commonly known as VM-26. Teniposide is indicated as a single agent or in

combination with other chemotherapy agents in the treatment of acute leukemia in children.

Antimetabolite neoplastic agents: Antimetabolite neoplastic agents are phase specific anti-neoplastic agents that act at S phase (DNA synthesis) of the cell cycle by inhibiting DNA synthesis or by inhibiting purine or pyrimidine base synthesis and thereby limiting DNA synthesis. Consequently, S phase does not proceed and cell death follows. Examples of antimetabolite anti-neoplastic agents include, but are not limited to, fluorouracil, methotrexate, cytarabine, mecaptopurine, thioguanine, and gemcitabine.

5-fluorouracil, 5-fluoro-2,4- (1H,3H) pyrimidinedione, is commercially available as fluorouracil. Administration of 5-fluorouracil leads to inhibition of thymidylate synthesis and is also incorporated into both RNA and DNA. The result typically is cell death. 5-fluorouracil is indicated as a single agent or in combination with other chemotherapy agents in the treatment of carcinomas of the breast, colon, rectum, stomach and pancreas. Other fluoropyrimidine analogs include 5-fluoro deoxyuridine (floxuridine) and 5-fluorodeoxyuridine monophosphate.

Cytarabine, 4-amino-1-β-D-arabinofuranosyl-2 (1H)-pyrimidinone, is commercially available as CYTOSAR-U® and is commonly known as Ara-C. It is believed that cytarabine exhibits cell phase specificity at S-phase by inhibiting DNA chain elongation by terminal incorporation of cytarabine into the growing DNA chain. Cytarabine is indicated as a single agent or in combination with other chemotherapy agents in the treatment of acute leukemia. Other cytidine analogs include 5-azacytidine and 2',2'-difluorodeoxycytidine (gemcitabine).

Mercaptopurine, 1,7-dihydro-6H-purine-6-thione monohydrate, is commercially available as PURINETHOL®. Mercaptopurine exhibits cell phase specificity at S-phase by inhibiting DNA synthesis by an as of yet unspecified mechanism. Mercaptopurine is indicated as a single agent or in combination with other chemotherapy agents in the treatment of acute leukemia. A useful mercaptopurine analog is azathioprine.

Thioguanine, 2-amino-1,7-dihydro-6H-purine-6-thione, is commercially available as TABLOID®. Thioguanine exhibits cell phase specificity at S-phase by inhibiting

DNA synthesis by an as of yet unspecified mechanism. Thioguanine is indicated as a single agent or in combination with other chemotherapy agents in the treatment of acute leukemia. Other purine analogs include pentostatin, erythrohydroxynonyladenine, fludarabine phosphate, and cladribine.

Gemcitabine, 2'-deoxy-2', 2'-difluorocytidine monohydrochloride (β-isomer), is commercially available as GEMZAR®. Gemcitabine exhibits cell phase specificity at S-phase and by blocking progression of cells through the G1/S boundary. Gemcitabine is indicated in combination with cisplatin in the treatment of locally advanced non-small cell lung cancer and alone in the treatment of locally advanced pancreatic cancer.

Methotrexate, N-[4[(2,4-diamino-6-pteridinyl) methyl]methylamino] benzoyl]-L-glutamic acid, is commercially available as methotrexate sodium. Methotrexate exhibits cell phase effects specifically at S-phase by inhibiting DNA synthesis, repair and/or replication through the inhibition of dyhydrofolic acid reductase which is required for synthesis of purine nucleotides and thymidylate. Methotrexate is indicated as a single agent or in combination with other chemotherapy agents in the treatment of choriocarcinoma, meningeal leukemia, non-Hodgkin's lymphoma, and carcinomas of the breast, head, neck, ovary and bladder.

Topoisomerase I inhibitors: Camptothecins, including, camptothecin and camptothecin derivatives are available or under development as Topoisomerase I inhibitors. Camptothecins cytotoxic activity is believed to be related to its Topoisomerase I inhibitory activity. Examples of camptothecins include, but are not limited to irinotecan, topotecan, and the various optical forms of 7-(4-methylpiperazino-methylene)-10,11-ethylenedioxy-20-camptothecin described below.

Irinotecan HCl, (4S)-4,11-diethyl-4-hydroxy-9-[(4-piperidinopiperidino) carbonyloxy]-1H-pyrano[3',4',6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione hydrochloride, is commercially available as the injectable solution CAMPTOSAR®. Irinotecan is a derivative of camptothecin which binds, along with its active metabolite SN-38, to the topoisomerase I – DNA complex. It is believed that cytotoxicity occurs as a result of irreparable double strand breaks caused by interaction of the topoisomerase I :

DNA : irintecan or SN-38 ternary complex with replication enzymes. Irinotecan is indicated for treatment of metastatic cancer of the colon or rectum.

Topotecan HCl, (S)-10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1H-pyrano[3',4',6,7]indolizino[1,2-b]quinoline-3,14-(4H,12H)-dione monohydrochloride, is commercially available as the injectable solution HYCAMTIN®. Topotecan is a derivative of camptothecin which binds to the topoisomerase I – DNA complex and prevents religation of singles strand breaks caused by Topoisomerase I in response to torsional strain of the DNA molecule. Topotecan is indicated for second line treatment of metastatic carcinoma of the ovary and small cell lung cancer.

Hormones and hormonal analogues: Hormones and hormonal analogues are useful compounds for treating cancers in which there is a relationship between the hormone(s) and growth and/or lack of growth of the cancer. Examples of hormones and hormonal analogues useful in cancer treatment include, but are not limited to, adrenocorticosteroids such as prednisone and prednisolone which are useful in the treatment of malignant lymphoma and acute leukemia in children ; aminoglutethimide and other aromatase inhibitors such as anastrozole, letrazole, vorazole, and exemestane useful in the treatment of adrenocortical carcinoma and hormone dependent breast carcinoma containing estrogen receptors; progestrins such as megestrol acetate useful in the treatment of hormone dependent breast cancer and endometrial carcinoma; estrogens, androgens, and anti-androgens such as flutamide, nilutamide, bicalutamide, cyproterone acetate and 5α-reductases such as finasteride and dutasteride, useful in the treatment of prostatic carcinoma and benign prostatic hypertrophy; anti-estrogens such as tamoxifen, toremifene, raloxifene, droloxifene, iodoxyfene, as well as selective estrogen receptor modulators (SERMS) such those described in U.S. Patent Nos. 5,681,835, 5,877,219, and 6,207,716, useful in the treatment of hormone dependent breast carcinoma and other susceptible cancers; and gonadotropin-releasing hormone (GnRH) and analogues thereof which stimulate the release of leutinizing hormone (LH) and/or follicle stimulating hormone (FSH) for the treatment prostatic carcinoma, for instance, LHRH agonists and antagagonists such as goserelin acetate and luprolide.

Signal transduction pathway inhibitors: Signal transduction pathway inhibitors are those inhibitors, which block or inhibit a chemical process which evokes an intracellular change. As used herein this change is cell proliferation or differentiation. Signal tranduction inhibitors useful in the present invention include inhibitors of receptor tyrosine kinases, non-receptor tyrosine kinases, SH2/SH3domain blockers, serine/threonine kinases, phosphotidyl inositol-3 kinases, myo-inositol signaling, and Ras oncogenes.

Several protein tyrosine kinases catalyse the phosphorylation of specific tyrosyl residues in various proteins involved in the regulation of cell growth. Such protein tyrosine kinases can be broadly classified as receptor or non-receptor kinases.

Receptor tyrosine kinases are transmembrane proteins having an extracellular ligand binding domain, a transmembrane domain, and a tyrosine kinase domain. Receptor tyrosine kinases are involved in the regulation of cell growth and are generally termed growth factor receptors. Inappropriate or uncontrolled activation of many of these kinases, i.e. aberrant kinase growth factor receptor activity, for example by over-expression or mutation has been shown to result in uncontrolled cell growth. Accordingly, the aberrant activity of such kinases has been linked to malignant tissue growth. Consequently, inhibitors of such kinases could provide cancer treatment methods. Growth factor receptors include, for example, epidermal growth factor receptor (EGFr), platelet derived growth factor receptor (PDGFr), erbB2, erbB4, ret, vascular endothelial growth factor receptor (VEGFr), tyrosine kinase with immunoglobulin-like and epidermal growth factor homology domains (TIE-2), insulin growth factor –I (IGFI) receptor, macrophage colony stimulating factor (cfms), BTK, ckit, cmet, fibroblast growth factor (FGF) receptors, Trk receptors (TrkA, TrkB, and TrkC), ephrin (eph) receptors, and the RET protooncogene. Several inhibitors of growth receptors are under development and include ligand antagonists, antibodies, tyrosine kinase inhibitors and anti-sense oligonucleotides. Growth factor receptors and agents that inhibit growth factor receptor function are described, for instance, in Kath, John C., *Exp. Opin. Ther. Patents* (2000) 10(6):803-818; Shawver et al *DDT* Vol 2, No. 2 February 1997; and Lofts, F. J. et al, "Growth factor receptors as targets", New Molecular Targets for Cancer Chemotherapy, ed. Workman, Paul and Kerr, David, CRC press 1994, London.

Tyrosine kinases, which are not growth factor receptor kinases are termed non-receptor tyrosine kinases. Non-receptor tyrosine kinases useful in the present invention, which are targets or potential targets of anti-cancer drugs, include cSrc, Lck, Fyn, Yes, Jak, cAbl, FAK (Focal adhesion kinase), Brutons tyrosine kinase, and Bcr-Abl. Such non-receptor kinases and agents which inhibit non-receptor tyrosine kinase function are described in Sinh, S. and Corey, S.J., (1999) *Journal of Hematotherapy and Stem Cell Research* 8 (5): 465 – 80; and Bolen, J.B., Brugge, J.S., (1997) *Annual Review of Immunology*. 15: 371-404.

SH2/SH3 domain blockers are agents that disrupt SH2 or SH3 domain binding in a variety of enzymes or adaptor proteins including, PI3-K p85 subunit, Src family kinases, adaptor molecules (Shc, Crk, Nck, Grb2) and Ras-GAP. SH2/SH3 domains as targets for anti-cancer drugs are discussed in Smithgall, T.E. (1995), *Journal of Pharmacological and Toxicological Methods*. 34(3) 125-32.

Inhibitors of Serine/Threonine Kinases including MAP kinase cascade blockers which include blockers of Raf kinases (rafk), Mitogen or Extracellular Regulated Kinase (MEKs), and Extracellular Regulated Kinases (ERKs); and Protein kinase C family member blockers including blockers of PKCs (alpha, beta, gamma, epsilon, mu, lambda, iota, zeta). IkB kinase family (IKKa, IKKb), PKB family kinases, akt kinase family members and TGF beta receptor kinases. Such Serine/Threonine kinases and inhibitors thereof are described in Yamamoto, T., Taya, S., Kaibuchi, K., (1999), *Journal of Biochemistry* 126 (5) 799-803; Brodt, P, Samani, A., and Navab, R. (2000), Biochemical Pharmacology, 60. 1101-1107; Massague, J., Weis-Garcia, F. (1996) Cancer Surveys. 27:41-64; Philip, P.A., and Harris, A.L. (1995), *Cancer Treatment and Research* 78: 3-27, Lackey, K. et al., *Bioorganic and Medicinal Chemistry Letters*, (10), 2000, 223-226; U.S. Patent No. 6,268,391; and Martinez-Iacaci, L., et al, *Int. J. Cancer* (2000), 88(1), 44-52.

Inhibitors of Phosphotidyl inositol-3 Kinase family members including blockers of PI3-kinase, ATM, DNA-PK, and Ku are also useful in the present invention. Such kinases are discussed in Abraham, R.T. (1996), *Current Opinion in Immunology* 8 (3) 412-8; Canman, C.E., Lim, D.S. (1998), *Oncogene* 17 (25) 3301-3308; Jackson, S.P.

(1997), *International Journal of Biochemistry and Cell Biology* 29 (7):935-8; and Zhong, H. et al, *Cancer Res*, (2000) 60(6), 1541-1545.

Also useful in the present invention are Myo-inositol signaling inhibitors such as phospholipase C blockers and Myoinositol analogues. Such signal inhibitors are described in Powis, G., and Kozikowski A., (1994) New Molecular Targets for Cancer Chemotherapy ed., Paul Workman and David Kerr, CRC press 1994, London.

Another group of signal transduction pathway inhibitors are inhibitors of Ras Oncogene. Such inhibitors include inhibitors of farnesyltransferase, geranyl-geranyl transferase, and CAAX proteases as well as anti-sense oligonucleotides, ribozymes and immunotherapy. Such inhibitors have been shown to block ras activation in cells containing wild type mutant ras , thereby acting as antiproliferation agents. Ras oncogene inhibition is discussed in Scharovsky, O.G., Rozados, V.R., Gervasoni, S.I. Matar, P. (2000), *Journal of Biomedical Science* 7(4) 292-8; Ashby, M.N. (1998), *Current Opinion in Lipidology* 9 (2) 99 – 102; and *BioChim. Biophys. Acta*, (19899) 1423(3):19-30.

As mentioned above, antibody antagonists to receptor kinase ligand binding may also serve as signal transduction inhibitors. This group of signal transduction pathway inhibitors includes the use of humanized antibodies to the extracellular ligand binding domain of receptor tyrosine kinases. For example Imclone C225 EGFR specific antibody (see Green, M.C. et al, *Monoclonal Antibody Therapy for Solid Tumors, Cancer Treat. Rev.*, (2000), 26(4), 269-286); Herceptin ® erbB2 antibody (see Tyrosine Kinase Signalling in Breast cancer:erbB Family Receptor Tyrosine Kinases, Breast cancer Res., 2000, 2(3), 176-183); and 2CB VEGFR2 specific antibody (see Brekken, R.A. et al, Selective Inhibition of VEGFR2 Activity by a monoclonal Anti-VEGF antibody blocks tumor growth in mice, *Cancer Res*. (2000) 60, 5117-5124).

Anti-angiogenic agents: Anti-angiogenic agents including non-receptorMEKngiogenesis inhibitors may alo be useful. Anti-angiogenic agents such as those which inhibit the effects of vascular edothelial growth factor, (for example the anti-vascular endothelial cell growth factor antibody bevacizumab [Avastin™], and compounds that work by other mechanisms (for example linomide, inhibitors of integrin $\alpha v\beta 3$ function, endostatin and angiostatin);

Immunotherapeutic agents: Agents used in immunotherapeutic regimens may also be useful in combination with the compounds of formula (I). Immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenecity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies

Proapoptotoc agents: Agents used in proapoptotic regimens (e.g., bcl-2 antisense oligonucleotides) may also be used in the combination of the present invention.

Cell cycle signalling inhibitors: Cell cycle signalling inhibitors inhibit molecules involved in the control of the cell cycle. A family of protein kinases called cyclin dependent kinases (CDKs) and their interaction with a family of proteins termed cyclins controls progression through the eukaryotic cell cycle. The coordinate activation and inactivation of different cyclin/CDK complexes is necessary for normal progression through the cell cycle. Several inhibitors of cell cycle signalling are under development. For instance, examples of cyclin dependent kinases, including CDK2, CDK4, and CDK6 and inhibitors for the same are described in, for instance, Rosania et al, *Exp. Opin. Ther. Patents* (2000) 10(2):215-230.

In one embodiment, the combination of the present invention comprises a compound of formula I or a salt or solvate thereof and at least one anti-neoplastic agent selected from anti-microtubule agents, platinum coordination complexes, alkylating agents, antibiotic agents, topoisomerase II inhibitors, antimetabolites, topoisomerase I inhibitors, hormones and hormonal analogues, signal transduction pathway inhibitors, non-receptor tyrosine MEK angiogenesis inhibitors, immunotherapeutic agents, proapoptotic agents, and cell cycle signaling inhibitors.

In one embodiment, the combination of the present invention comprises a compound of formula I or a salt or solvate thereof and at least one anti-neoplastic agent which is an anti-microtubule agent selected from diterpenoids and vinca alkaloids.

In a further embodiment, the at least one anti-neoplastic agent agent is a diterpenoid.

In a further embodiment, the at least one anti-neoplastic agent is a vinca alkaloid.

In one embodiment, the combination of the present invention comprises a compound of formula I or a salt or solvate thereof and at least one anti-neoplastic agent, which is a platinum coordination complex.

In a further embodiment, the at least one anti-neoplastic agent is paclitaxel, carboplatin, or vinorelbine.

In a further embodiment, the at least one anti-neoplastic agent is carboplatin.

In a further embodiment, the at least one anti-neoplastic agent is vinorelbine.

In a further embodiment, the at least one anti-neoplastic agent is paclitaxel.

In one embodiment, the combination of the present invention comprises a compound of formula I and salts or solvates thereof and at least one anti-neoplastic agent which is a signal transduction pathway inhibitor.

In a further embodiment the signal transduction pathway inhibitor is an inhibitor of a growth factor receptor kinase VEGFR2, TIE2, PDGFR, BTK, erbB2, EGFr, IGFR-1, TrkA, TrkB, TrkC, or c-fms.

In a further embodiment the signal transduction pathway inhibitor is an inhibitor of a serine/threonine kinase rafk, akt, or PKC-zeta.

In a further embodiment the signal transduction pathway inhibitor is an inhibitor of a non- receptor tyrosine kinase selected from the src family of kinases.

In a further embodiment the signal transduction pathway inhibitor is an inhibitor of c-src.

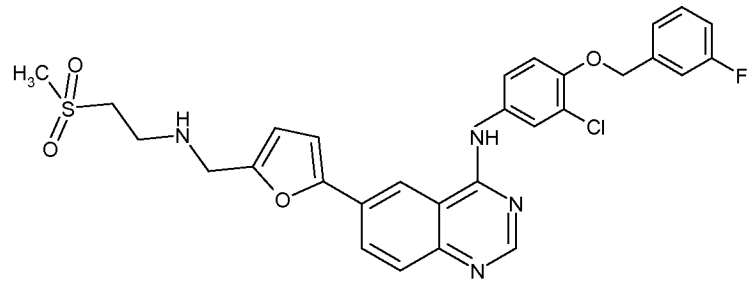
In a further embodiment the signal transduction pathway inhibitor is an inhibitor of the androgen receptor.

In a further embodiment the signal transduction pathway inhibitor is an inhibitor of Ras oncogene selected from inhibitors of farnesyl transferase and geranylgeranyl transferase.

In a further embodiment the signal transduction pathway inhibitor is an inhibitor of a serine/threonine kinase selected from the group consisting of PI3K.

In a further embodiment the signal transduction pathway inhibitor is a dual EGFr/erbB2 inhibitor, for example N-{3-Chloro-4-[(3-fluorobenzyl) oxy]phenyl}-6-[5-

({[2-(methanesulphonyl) ethyl]amino}methyl)-2-furyl]-4-quinazolinamine (structure below):



In one embodiment, the combination of the present invention comprises a compound of formula I or a salt or solvate thereof and at least one anti-neoplastic agent which is a cell cycle signaling inhibitor.

In further embodiment, cell cycle signaling inhibitor is an inhibitor of CDK2, CDK4 or CDK6.

In one embodiment the mammal in the methods and uses of the present invention is a human.

Suitably, the present invention relates to a method of treating or lessening the severity of a cancer that is either wild type or mutant for each of Raf, Ras, MEK, and PI3K/Pten. This includes but is not limited to patients having cancers that are mutant for RAF, wild type for RAS, wild type for MEK, and wild type for PI3K/PTEN; mutant for RAF, mutant for RAS, wild type for MEK, and wild type for PI3K/PTEN; mutant for RAF, mutant for RAS, mutant for MEK, and wild type for PI3K/PTEN; and mutant for RAF, wild type for RAS, mutant for MEK, and wild type PI3K/PTEN.

The term “wild type” as is understood in the art refers to a polypeptide or polynucleotide sequence that occurs in a native population without genetic modification. As is also understood in the art, a "mutant" includes a polypeptide or polynucleotide sequence having at least one modification to an amino acid or nucleic acid compared to the corresponding amino acid or nucleic acid found in a wild type polypeptide or polynucleotide, respectively. Included in the term mutant is Single Nucleotide Polymorphism (SNP) where a single base pair distinction exists in the sequence of a nucleic acid strand compared to the most prevalently found (wild type) nucleic acid strand.

Cancers that are either wild type or mutant for Raf, Ras, MEK, or mutant for PI3K/Pten are identified by known methods. For example, wild type or mutant tumor cells can be identified by DNA amplification and sequencing techniques, DNA and RNA detection techniques, including, but not limited to Northern and Southern blot, respectively, and/or various biochip and array technologies. Wild type and mutant polypeptides can be detected by a variety of techniques including, but not limited to immunodiagnostic techniques such as ELISA, Western blot or immunocytochemistry. Suitably, Pyrophosphorolysis-activated polymerization (PAP) and/or PCR methods may be used. Liu, Q et al, *Human Mutation* 23:426-436 (2004).

The most common system for determining how far cancer has spread is the four-stage tumor/nodes/metastases system. Several different hormonal approaches are used in the management of various stages of prostate cancer including bilateral orchiectomy, estrogen therapy, luteinizing hormone-releasing hormone agonist therapy, antiandrogen therapy, androgen deprivation therapy and antiadrenal therapy. Radical prostatectomy is usually reserved for patients who are good health and elect surgical intervention and have tumor confined to the prostate gland (stage I and stage II). Patients who are considered poor medical candidates for radical prostatectomy and have confirmed pathologic diagnosis of stages I, II and III are candidates for radiation therapy.

According, the compounds of the present invention may be combined with prostate cancer treatment therapy including radical prostatectomy, radiation therapy, bilateral orchiectomy, estrogen therapy, luteinizing hormone-releasing hormone agonist therapy, antiandrogen therapy, androgen deprivation therapy and/or antiandrenal therapy.

While the preferred embodiments of the invention are illustrated by the above, it is to be understood that the invention is not limited to the precise instructions herein disclosed and that the right to all modifications coming within the scope of the following claims is reserved.

Because the combinations of the present invention are active in the above assays they exhibit advantageous therapeutic utility in treating cancer.

Suitably, the present invention relates to a method for treating or lessening the severity of prostate cancer.

The invention includes a drug combination that includes an androgen receptor inhibitor and a PI3Kβ inhibitor. This invention provides a combination comprising 4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-*N*-methylbenzamide or a pharmaceutically acceptable salt thereof, and 2-methyl-1-{[2-methyl-3-(trifluoromethyl)phenyl]methyl}-6-(4-morpholinyl)-1H-benzimidazole-4-carboxylic acid, or a pharmaceutically acceptable salt, suitably the hydrochloride salt, thereof, and optional additional antineoplastic agents.

This invention also provides for a combination comprising 4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-*N*-methylbenzamide or a pharmaceutically acceptable salt thereof, and 2-methyl-1-{[2-methyl-3-(trifluoromethyl)phenyl]methyl}-6-(4-morpholinyl)-1H-benzimidazole-4-carboxylic acid, or a pharmaceutically acceptable salt, suitably the hydrochloride salt, thereof.

This invention also provides for a combination comprising 4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-*N*-methylbenzamide or a pharmaceutically acceptable salt thereof, and 2-methyl-1-{[2-methyl-3-(trifluoromethyl)phenyl]methyl}-6-(4-morpholinyl)-1H-benzimidazole-4-carboxylic acid, or a pharmaceutically acceptable salt, suitably the hydrochloride salt, thereof, for use in treating cancer.

This invention also provides a pharmaceutical composition comprising a combination of 4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-*N*-methylbenzamide or a pharmaceutically acceptable salt thereof, and 2-methyl-1-{[2-methyl-3-(trifluoromethyl)phenyl]methyl}-6-(4-morpholinyl)-1H-benzimidazole-4-carboxylic acid, or a pharmaceutically acceptable salt, suitably the hydrochloride salt, thereof.

This invention also provides a combination kit comprising 4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-*N*-methylbenzamide or a pharmaceutically acceptable salt thereof, and 2-methyl-1-{[2-methyl-3-(trifluoromethyl)phenyl]methyl}-6-(4-morpholinyl)-1H-benzimidazole-4-carboxylic acid, or a pharmaceutically acceptable salt, suitably the hydrochloride salt, thereof, and optional additional antineoplastic agents.

This invention also provides for the use of a combination comprising 4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-*N*-methylbenzamide or a pharmaceutically acceptable salt thereof, and 2-methyl-1-{[2-methyl-3-(trifluoromethyl)phenyl]methyl}-6-(4-morpholinyl)-1H-benzimidazole-4-carboxylic acid, or a pharmaceutically acceptable salt, suitably the hydrochloride salt, thereof, in the manufacture of a medicament.

This invention also provides for the use of a combination comprising 4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-*N*-methylbenzamide or a pharmaceutically acceptable salt thereof, and 2-methyl-1-{[2-methyl-3-(trifluoromethyl)phenyl]methyl}-6-(4-morpholinyl)-1H-benzimidazole-4-carboxylic acid, or a pharmaceutically acceptable salt, suitably the hydrochloride salt, thereof, in the manufacture of a medicament to treat cancer.

This invention also provides a method of treating cancer which comprises administering a combination of 4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-*N*-methylbenzamide or a pharmaceutically acceptable salt thereof, and 2-methyl-1-{[2-methyl-3-(trifluoromethyl)phenyl]methyl}-6-(4-morpholinyl)-1H-benzimidazole-4-carboxylic acid, or a pharmaceutically acceptable salt, suitably the hydrochloride salt, thereof, and optional additional antineoplastic agents to a subject in need thereof.

EXAMPLES

The following examples are intended for illustration only and are not intended to limit the scope of the invention in any way.

Example 1

Anti-proliferative effect of Compound A and Compound B in prostate cancer cells

LNCaP prostate cancer cells are androgen receptor positive and are dependent on androgen for cell growth. Cells were grown in charcoal-stripped serum to deplete potential androgen from serum. Under these conditions, cell growth is dependent on exogenous androgen (e.g., R1881). In presence of synthetic androgen (0.1 nM R1881), LNCaP cell growth was inhibited by androgen receptor antagonist, compound A, in a concentration-dependent manner. Similarly, compound B also inhibited the growth of

LNCaP cells under these conditions. When LNCaP cells were treated concomitantly with both compounds, there was an additive anti-proliferative effect (Figure 1).

Cell Proliferation Assay

Androgen-dependent prostate cancer cell line, LNCaP, were grown in RPMI 1640 culture medium supplemented with 10% charcoal-stripped fetal bovine serum for 24 hours in 96-well tissue culture plates at a density of 1,000 cells per well. Cells were treated with various concentrations of compounds A or B alone and in combination in the presence of synthetic androgen (R1881, Sigma-Aldrich, St. Louis, MO). After 7 days, total cellular ATP was measured using the CellTiter-Glo Luminescent Cell Viability Assay (Promega, Madison, WI) on an EnVision plate reader. Background counts from wells containing no cells were subtracted and the data is presented as a percentage of the DMSO-treated control cells.

Example 2

Effect of Compound A and Compound B on cell signaling in prostate cancer cells

LNCaP cells were treated with Compound B (3 or 10 uM) alone or in presence of compound A (3 uM), all in presence of 0.1 nM synthetic androgen (R1881).

Compound B inhibited AKT phosphorylation suggesting inhibition of PI3 kinase activity in cells. AKT inhibitor used as a control in this experiment, either alone or in combination with Compound A, also labeled as ENZA showed a decrease in phosphorylation of downstream signaling as evidenced by a decrease in phospho-PRAS40 and phospho-S6. Compound B treatment alone as well as in presence of Compound A showed inhibition of phospho-S6, a marker of downstream pathway modulation.

The combination of two compounds resulted in greater decrease in phospho-S6 level than compound B alone. Decrease in S6 phosphorylation has been associated with greater anti-proliferative effect as well as clinical benefit with targeted inhibitors (Elkabets et al., mTORC1 Inhibition is Required for Sensitivity to PI3k p110α inhibitors in *PIK3CA*-Mutant Breast Cancer, (2013) *Sci Transl Med.* 5(196)); Corcoran et al., TORC1 Suppression Predicts Responsiveness to RAF and MEK Inhibition in BRAF-Mutant Melanoma, (2013) *Sci Transl Med.* 5(196)). These results provide a potential

mechanism for enhanced anti-proliferative effects observed with the combination of Compounds A and B in these cells (Figure 2).

Immunoblot Assay

LNCaP cells were grown in RPMI 1640 culture medium supplemented with 10% charcoal-stripped fetal bovine serum for 48 hours in 6-well tissue culture plates at a density of 500,000 cells per well. Cells were treated with the indicated compounds for six hours, washed with PBS, and whole cell lysates were prepared in RIPA buffer (Teknova, Hollister, CA). Cell lysates were clarified by centrifugation at 20,000 relative centrifugal force, 4 °C, and protein was quantified using the BCA Protein Assay Kit (Pierce, Rockford, IL). Equal amounts of protein lysates were separated by SDS-PAGE using a 4-12% Bis-Tris polyacrylamide gel (Life Technologies) and transferred to a nitrocellulose membrane and incubated with antibodies against total and phospho-AKT, phospho-PRAS40, total and phospho-S6, androgen receptor, and FKBP5. Following incubation with primary antibody, blots were washed and incubated with IRDye-800 anti-mouse or IRDye-680 anti-rabbit antibodies for 1 h. Following thorough washing, blots were analyzed using an infrared imaging system (LI-COR).

Example 3

Effect of Compound A and Compound B on caspase 3/7 induction in prostate cancer cells

Caspase 3/7 activity, a marker of apoptosis, was measured using luminescent caspase 3/7 assays in LNCaP cells treated with Compound A (5 uM), Compound B (5 uM), or both. Caspase 3/7 activity was normalized and plotted as a percentage of the untreated control samples. Data for 2 independent experiments (N=1, N=2) is shown and represents mean ± std dev from duplicate treatments.

In LNCaP cells, there was minimal induction of caspase 3/7 activity after five days of treatment with Compound B or Compound A, while treatment with the combination had a further increase (1.4 to 2.0 fold in growth media, 2.5 to 4 fold in CSS media) (Figure 3).

Luminescent Caspase 3/7 Assay

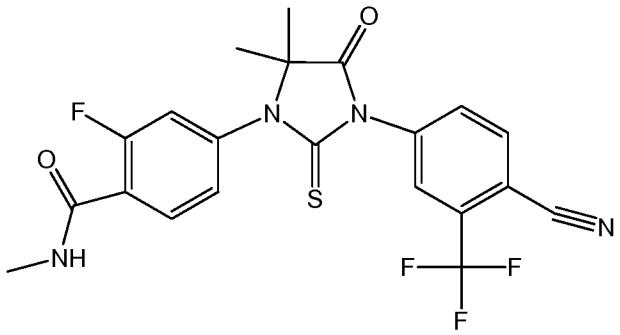
Tumor cells were seeded in 96-well white tissue culture plates in 100 µL growth media (media with 10% FBS) or CSS media (media with 10% charcoal stripped fetal bovine serum). LNCaP cells were seeded at a density of 1,000 cells per well.

Approximately 24 hr after plating, duplicate or triplicate plates of cells were treated with indicated compounds for both luminescent caspase-3/7 and CTG readings. At the end of the 5 days of incubations, half of the plates were lysed and caspase-3/7 activity was measured using the Caspase-Glo® 3/7 Assay (Promega) according to the manufacturer's protocol. Caspase-Glo reagent was added to each plate, incubated for at least 45 minutes, and luminescent signal was read on the EnVision Multilabel Plate Reader with a 0.1 sec integration time. The remaining plates were lysed and ATP levels were measured using the CTG assay. The caspase-3/7 signal was normalized to the ATP signal. The normalized values were expressed as a percentage of the control wells.

WHAT IS CLAIMED IS:

1. A combination comprising:

(i) a compound of formula (I)

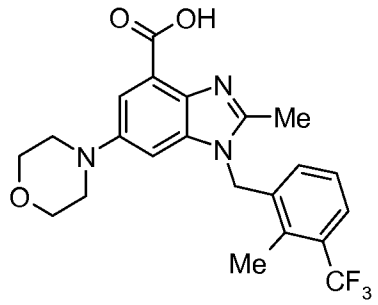


(I)

or a pharmaceutically acceptable salt or solvate thereof;

and

(ii) a compound of formula (II)



(II)

or a pharmaceutically acceptable salt thereof.

2. A combination according to claim 1, wherein compound (i) is in the form of a solvate selected from a group consisting of: dimethyl sulfoxide; hydrate, acetic acid, ethanol, nitromethane, chlorobenzene, 1-pentancol, isopropyl alcohol, ethylene glycol and 3-methyl-1-butanol.

3. A combination according to claim 1, wherein compound (ii) is in the form of the Tris salt.

4. A combination kit comprising a combination according claims 1, 2 or 3 together with a pharmaceutically acceptable carrier or carriers.

5. Use of a combination according to any of claims 1 to 3 in the manufacture of a medicament for the treatment of cancer.

6. A combination according to any of claims 1 to 3 for use in therapy.

7. A combination according to any of claims 1 to 3 for use in treating cancer.

8. A pharmaceutical composition comprising a combination according to claims 1 to 3 together with a pharmaceutically acceptable diluent or carrier.

9. An orally ingestible solid compound or a sterile injectable compound comprising a solid or liquid pharmaceutically acceptable carrier or diluents, and compound of formula I and compound of formula II as defined by claim 1.

10. An orally ingestible solid compound or a sterile injectable compound comprising a solid or liquid pharmaceutically acceptable carrier or diluents, and compound of formula I and compound of formula II as defined by claim 1.

11. A combination according to claim 1 or claim 2 or of a combination kit according to claim 4 where the amount of the compound of Structure (I) is an amount selected from 40mg to 160mg, and that amount is suitable for administration once per day in one or more doses, and the amount of the compound of Structure (II) is an amount selected from 50mg to 400mg, and that amount is suitable for administration once per day.

12. A combination or combination kit for use in the treatment of cancer, comprising a therapeutically effective amount of a combination of 4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-*N*-methylbenzamide or a pharmaceutically acceptable salt thereof, and 2-methyl-1-{[2-

methyl-3-(trifluoromethyl)phenyl]methyl}-6-(4-morpholinyl)-1H-benzimidazole-4-carboxylic acid, or a pharmaceutically acceptable salt thereof,

wherein the combination is administered within a specified period, and

wherein the combination is administered for a duration of time.

13. A combination or combination kit according to claim 12 wherein an amount of 4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-*N*-methylbenzamide is selected from about 40mg to about 160mg, and that amount is suitable for daily administration in one or more doses, and the amount of 2-methyl-1-{[2-methyl-3-(trifluoromethyl)phenyl]methyl}-6-(4-morpholinyl)-1H-benzimidazole-4-carboxylic acid, is selected from about 50mg to about 400mg, and that amount is suitable for administration once per day.

14. A combination or combination kit according to claim 13 wherein 4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-*N*-methylbenzamide and2-methyl-1-{[2-methyl-3-(trifluoromethyl)phenyl]methyl}-6-(4-morpholinyl)-1H-benzimidazole-4-carboxylic acid, are administered for at least 7 consecutive days.

15. A combination or combination kit according to claim 13 wherein 4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-*N*-methylbenzamide or a pharmaceutically acceptable salt or solvate thereof, and 2-methyl-1-{[2-methyl-3-(trifluoromethyl)phenyl]methyl}-6-(4-morpholinyl)-1H-benzimidazole-4-carboxylic acid or a pharmaceutically acceptable salt thereof, are administered within 12 hours of each other for at least 5 consecutive days.

16. A combination or combination kit according to claim 15 wherein 4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-*N*-methylbenzamide and2-methyl-1-{[2-methyl-3-(trifluoromethyl)phenyl]methyl}-6-(4-morpholinyl)-1H-benzimidazole-4-carboxylic acid, are administered for at least 14 consecutive days.

17. A combination or combination kit according to claim 1 or claim 4 wherein the compound 4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-*N*-methylbenzamide is first administered in a loading dose for from 1 to 3 days followed by maintenance dose administration of the compound, and/or the compound 2-methyl-1-{[2-methyl-3-(trifluoromethyl)phenyl]methyl}-6-(4-morpholinyl)-1H-benzimidazole-4-carboxylic acid is first administered in a loading dose for from 1 to 3 days followed by maintenance dose administration of the compound.

18. A combination comprising an analog of 4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-*N*-methylbenzamide and 2-methyl-1-{[2-methyl-3-(trifluoromethyl)phenyl]methyl}-6-(4-morpholinyl)-1H-benzimidazole-4-carboxylic acid.

19. A combination of claim 18 wherein the analog is 4-[7- (6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide.

20. A combination of claim 18 wherein 4-[7- (6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N- methylbenzamide is in the form of the dimethyl sulfoxide solvate.

21. A combination kit comprising a combination according claims 18 or 19 together with a pharmaceutically acceptable carrier or carriers.

23. Use of a combination according to any of claims 18 or 19 in the manufacture of a medicament for the treatment of cancer.

24. A combination according to claims 18 or 19 for use in therapy.

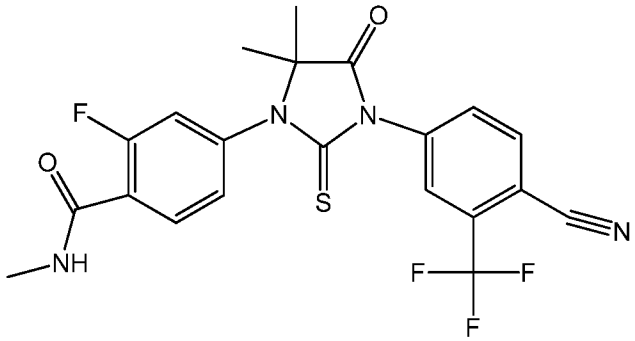
25. A combination according to claims 18 or 19 for use in treating cancer.

26. A pharmaceutical composition comprising a combination according to claims 18 or 19 together with a pharmaceutically acceptable diluent or carrier.

27. A combination of claim 18 wherein the analog is ODM-201.

28. A method of treating cancer in a human in need thereof which comprises the administration of a therapeutically effective amount of

(i) a compound of formula (I)

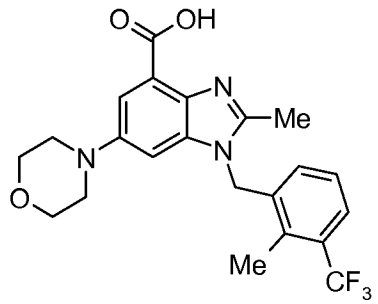


(I)

or a pharmaceutically acceptable salt or solvate thereof;

and

(ii) a compound of formula (II)



(II)

or a pharmaceutically acceptable salt thereof for use in therapy.

29. The method of claim 28, wherein the cancer is selected from head and neck cancer, breast cancer, lung cancer, colon cancer, ovarian cancer, prostate cancer, gliomas, glioblastoma, astrocytomas, glioblastoma multiforme, Bannayan-Zonana syndrome,

Cowden disease, Lhermitte-Duclos disease, inflammatory breast cancer, Wilm's tumor, Ewing's sarcoma, Rhabdomyosarcoma, ependymoma, medulloblastoma, kidney cancer, liver cancer, melanoma, pancreatic cancer, sarcoma, osteosarcoma, giant cell tumor of bone, thyroid cancer, lymphoblastic T cell leukemia, Chronic myelogenous leukemia, Chronic lymphocytic leukemia, Hairy-cell leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, AML, Chronic neutrophilic leukemia, Acute lymphoblastic T cell leukemia, plasmacytoma, Immunoblastic large cell leukemia, Mantle cell leukemia, Multiple myeloma Megakaryoblastic leukemia, multiple myeloma, acute megakaryocytic leukemia, promyelocytic leukemia, Erythroleukemia, malignant lymphoma, hodgkins lymphoma, non-hodgkins lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma, follicular lymphoma, neuroblastoma, bladder cancer, urothelial cancer, vulval cancer, cervical cancer, endometrial cancer, renal cancer, mesothelioma, esophageal cancer, salivary gland cancer, hepatocellular cancer, gastric cancer, nasopharangeal cancer, buccal cancer, cancer of the mouth, GIST (gastrointestinal stromal tumor), and testicular cancer.

30. The method of claims 28 or 29, wherein the cancer is prostate.

31. The method of claims 28 or 29, wherein the cancer is PTEN deficient cancer.

32. The method of any of claims 28-31, wherein compound (i) is in the form of the dimethyl sulfoxide solvate and the compound (ii) is in the form of the Tris salt.

33. The method of treating cancer in a human in need thereof which comprises administering a therapeutically effective amount of a combination of particularly 4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-*N*-methylbenzamide or a pharmaceutically acceptable salt or solvate thereof, and 2-methyl-1-{[2-methyl-3-(trifluoromethyl)phenyl]methyl}-6-(4-morpholinyl)-1H-benzimidazole-4-carboxylic acid, or a pharmaceutically acceptable salt thereof, to a human in need thereof, wherein the combination is administered within a specified period, and wherein the combination is administered for a duration of time.

34. The method of claim 33, wherein 4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-*N*-methylbenzamide is in the form of the dimethyl sulfoxide solvate.

35. The method of claim 33, wherein 2-methyl-1-{[2-methyl-3-(trifluoromethyl)phenyl]methyl}-6-(4-morpholinyl)-1H-benzimidazole-4-carboxylic acid is in the form of the Tris salt.

36. The method of treating cancer in a human in need thereof which comprises administering a therapeutically effective amount of a combination of an analog of 4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-*N*-methylbenzamide or a pharmaceutically acceptable salt or solvate thereof, and 2-methyl-1-{[2-methyl-3-(trifluoromethyl)phenyl]methyl}-6-(4-morpholinyl)-1H-benzimidazole-4-carboxylic acid, or a pharmaceutically acceptable salt thereof, to a human in need thereof, wherein the combination is administered within a specified period, and wherein the combination is administered for a duration of time.

37. The method of claim 36, wherein the analog is 4-[7- (6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide.

38. The method of claim 37, wherein 4-[7- (6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N- methylbenzamide is in the form of the dimethyl sulfoxide solvate.

39. The method of claim 36, wherein the analog is ODM-201.

FIGURE 1

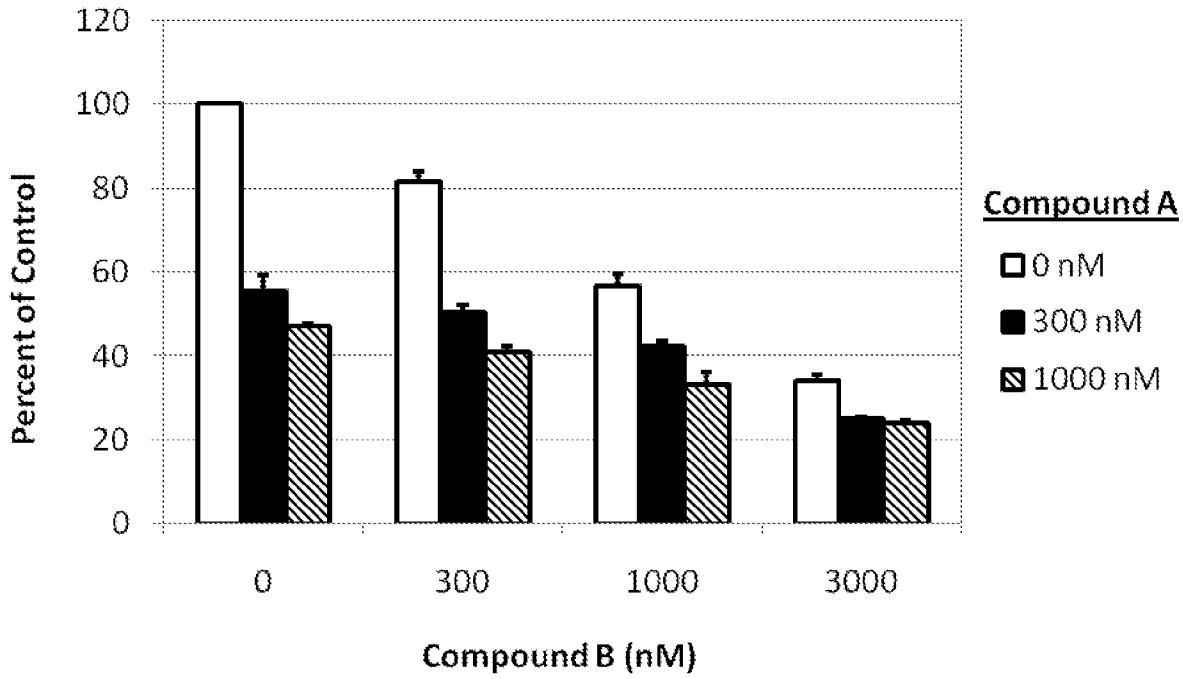

120
100
80
60
40
20
0
Percent of Control
0
300
1000
3000
Compound B (nM)
Compound A
0 nM
300 nM
1000 nM

FIGURE 2

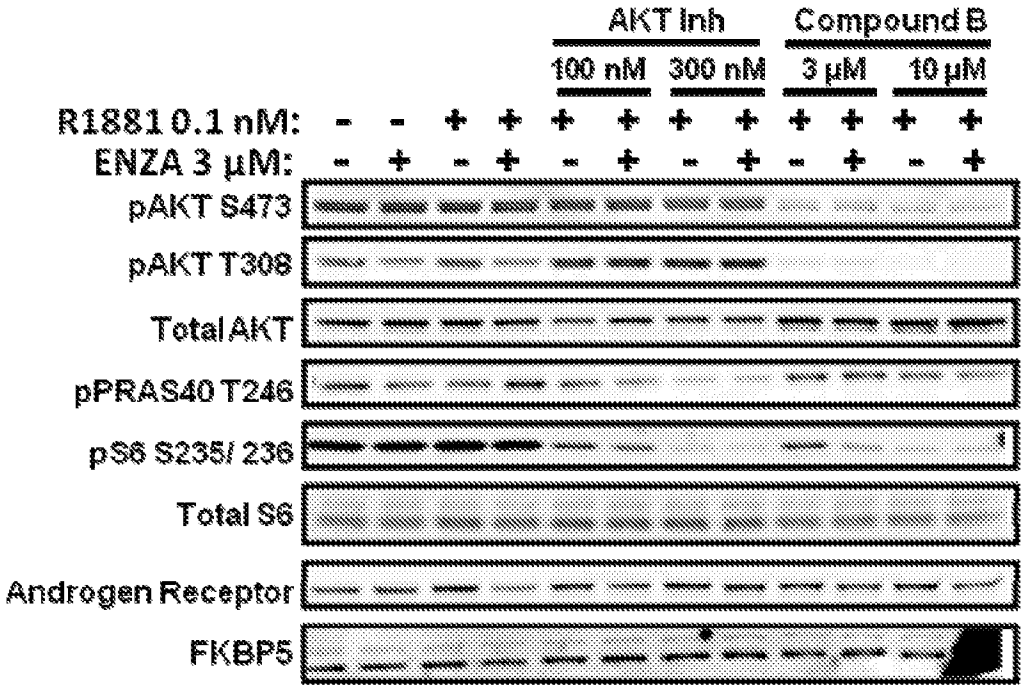
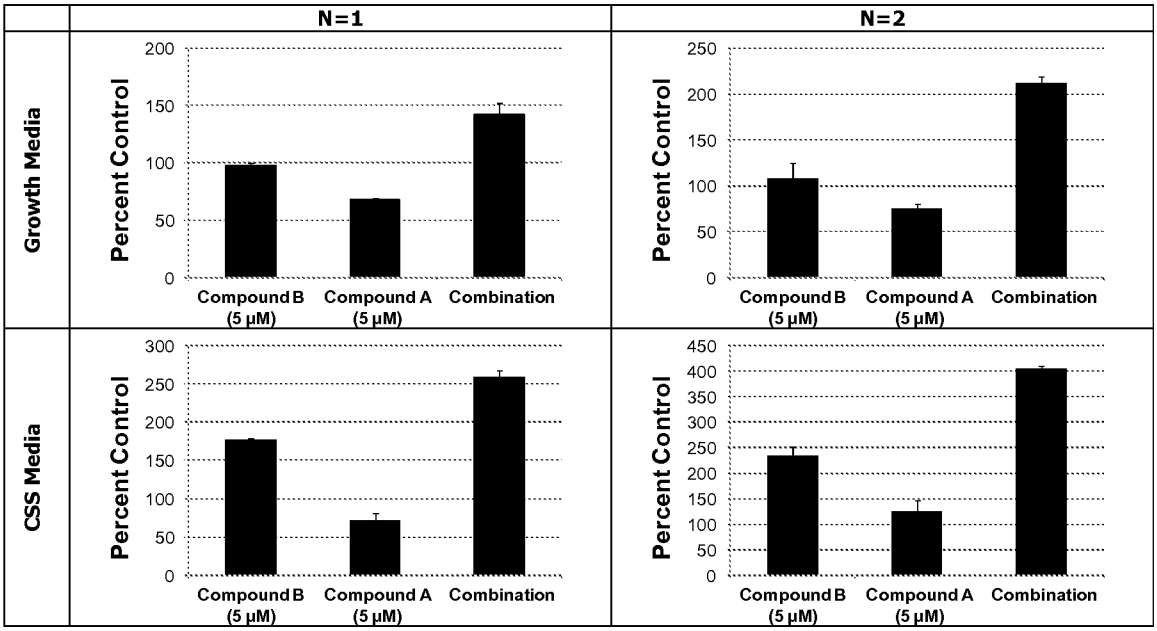

AKT Inh
Compound B
100 nM
300 nM
3 µM
10 µM
R1881 0.1 nM: - - + + + + + + + + + +
ENZA 3 µM: - + - + - + - + - + - +
pAKT S473
pAKT T308
Total AKT
pPRAS40 T246
pS6 S235/ 236
Total S6
Androgen Receptor
FKBP5

Figure 3


N=1
N=2
Growth Media
CSS Media
Percent Control
200
150
100
50
0
250
300
450
400
350
Compound B (5 µM)
Compound A (5 µM)
Combination

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/55816

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/4166, 31/535; C07D 233/86, 413/10 (2014.01)
CPC - C07D233/70; C07D235/00, C07D233/74; C07D233/86; C07D413/10; C07D417/04; C07D413/04
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)
IPC: A61K 31/4166, 31/535; C07D 233/86, 413/10 (2014.01)
CPC: C07D233/70; C07D235/00; C07D233/74; C07D233/86; C07D413/10; C07D417/04; C07D413/04

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/391, 548/301.4, 548/321.1; 514/234.5, 544/139 (see search words below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PATBASE: Full-text = AU BE BR CA CH CN DE DK EP ES FI FR GB IN JP KR SE TH TW US WO
Google: Scholar/Patents: androgen antagonists pi3 kinase inhibitor combination thioxo imidazoline dimethyl diazaspiro methylbenzamide prostate cancer DMSO solvate trifluoromethylphenyl morpholinyl benzimidazole ODM-201 diarylhydrantoin

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 7,709,517 B2 (SAWYERS et al.) 04 May 2010 (04.05.2010) Col 2, ln 49-53 ; Col 5,ln 35-45;Col 14, ln 5-12; Col 14, ln 21-24; Col 112, ln 58-61; Col 116, Claim 12	1-7;9;10;12-16;28-31;33-35
Y	US 2012/0088767 A1 (QU et al.) 12 April 2012 (12.04.2012) para [0247];[0308];[0314];[0316];[0448];[0588];[0589]	1-7;9;10;12-16;18-21; 23-31;33-39
Y	US 2009/0175868 A1 (LUDWIG et al.) 09 July 2009 (09.07.2009) para [0010];[0017];[0025];[0028];[0040]; [0075];[0079];[0081];[0085];[0093];[0094];[0232]	1-7;9;10;12-16;18-21; 23-31;33-39
Y	US 2011/0003839 A1 (JUNG et al.) 06 January 2011 (06.01.2011) para [0055];[0141]	18-21; 23-27; 36-39
Y	CENSITS et al. Chemotherapy and Targeted Therapies:Are We Making Progress in Castrate-Resistant Prostate Cancer, Seminars in Oncology, June 2013, Vol 40, No 3, pp 361-374; pg 362, Col 2, para 3 to pg 363, Col 1, para 1	27;39

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 November 2014 (13.11.2014)	10 DEC 2014

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/55816

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

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

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

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

3. ☒ Claims Nos.: 8, 11, 17, 32
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

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

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

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

Remark on Protest

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

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

☐ No protest accompanied the payment of additional search fees.