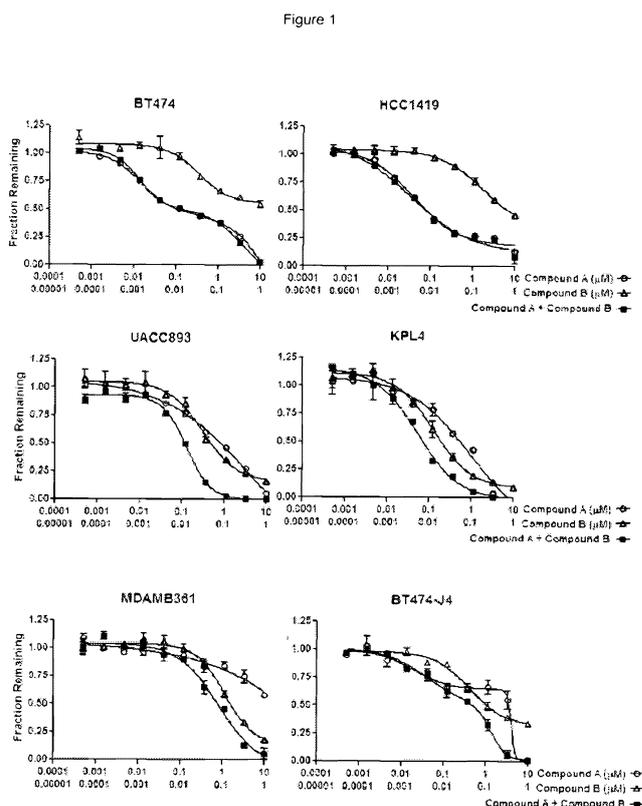




- (51) International Patent Classification:
A61K 31/501 (2006.01) *A61K 31/517* (2006.01)
- (21) International Application Number:
PCT/US2013/065827
- (22) International Filing Date:
21 October 2013 (21.10.2013)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
61/716,780 22 October 2012 (22.10.2012) US
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- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.
- (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,

[Continued on next page]

(54) Title: COMBINATION



(57) Abstract: The present invention relates to a method of treating cancer in a human and to pharmaceutical combinations useful in such treatment. In particular, the method relates to a cancer treatment method that includes administering N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({2-(methanesulfonyl)ethyl}amino)methyl]-2-furyl]-4-quinazolinamine, or a pharmaceutically acceptable hydrate and/or salt thereof, and N{(1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1 H-pyrazol-5-yl)-2-furancarboxamide, or a pharmaceutically acceptable salt thereof, to a human in need thereof.

EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU,
LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK,
SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, KM, ML, MR, NE, SN, TD, TG).

Published:

- *with international search report (Art. 21(3))*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

Declarations under Rule 4.17:

- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
- *of inventorship (Rule 4.17(iv))*

COMBINATION

FIELD OF THE INVENTION

The present invention relates to a method of treating cancer in a mammal and to
5 combinations useful in such treatment. In particular, the method relates to a novel
combination comprising the dual EGF-R/erbB-2 inhibitor: N-{3-Chloro-4-[(3-
fluorobenzyl)oxy]phenyl}-6-[5-{{[2-(methanesulphonyl)ethyl]amino}methyl}-2-furyl]-4-
quinazolinamine, or a pharmaceutically acceptable hydrate and/or salt thereof, and the
Akt inhibitor: N-{{(1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-
10 methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide, or a pharmaceutically acceptable salt
thereof, pharmaceutical compositions comprising the same, and methods of using such
combinations in the treatment of cancer.

BACKGROUND OF THE INVENTION

15

Generally, cancer results from the deregulation of the normal processes that
control cell division, differentiation and apoptotic cell death. Apoptosis (programmed cell
death) plays essential roles in embryonic development and pathogenesis of various
diseases, such as degenerative neuronal diseases, cardiovascular diseases and cancer.
20 One of the most commonly studied pathways, which involves kinase regulation of
apoptosis, is cellular signaling from growth factor receptors at the cell surface to the
nucleus (Crews and Erikson, Cell, 74:215-17, 1993).

25

Protein tyrosine kinases (PTKs) catalyze the phosphorylation of specific tyrosyl
residues in various proteins involved in the regulation of cell growth and differentiation.
(A.F. Wilks, Progress in Growth Factor Research, 1990, 2, 97-111; S.A. Courtneidge,
Dev. Supp.l, 1993, 57-64; J.A. Cooper, Semin. Cell Biol., 1994, 5(6), 377-387; R.F.
Paulson, Semin. Immunol., 1995, 7(4), 267-277; A.C. Chan, Curr. Opin. Immunol., 1996,
30 8(3), 394-401). Inappropriate or uncontrolled activation of many PTKs, i.e. aberrant PTK
activity, for example by over-expression or mutation, has been shown to result in
uncontrolled cell growth.

Aberrant protein tyrosine kinase (PTK) activity has been implicated in a variety of
35 disorders including psoriasis, rheumatoid arthritis, bronchitis, as well as cancer.

Development of effective treatments for such disorders is a constant and ongoing enterprise in the medical field. The ErbB family of PTKs, which includes ErbB-2, EGFR, ErbB-3 and ErbB-4, is one group of PTKs that has attracted interest as a therapeutic target. Currently, of special interest, is the role of ErbB family PTKs in hyperproliferative disorders, particularly human malignancies. Elevated EGFR activity has, for example, been implicated in non-small cell lung, bladder, and head and neck cancers. Furthermore, increased ErbB-2 activity has been implicated in breast, ovarian, gastric and pancreatic cancers. Overexpression of HRG and/or HER3 has been reported in numerous cancers, including gastric, ovarian, prostate, bladder, and breast tumors and is associated with poor prognosis (B.Tanner, *J Clin Oncol.* 2006, 24(26):4317-23; M. Hayashi, *Clin. Cancer Res.* 2008.14(23):7843-9.; H. Kaya, *Eur J Gynaecol Oncol.* 2008;29(4):350-6;). Consequently, inhibition of ErbB family PTKs should provide a treatment for disorders characterized by aberrant ErbB family PTK activity. The biological role of ErbB family PTKs and their implication in various disease states is discussed, for instance in U.S. patent 5,773,476; International Patent Application WO 99/35146; M.C. Hung et al, *Seminars in Oncology*, 26: 4, Suppl. 12 (August) 1999, 51-59; Ullrich et al, *Cell*, 61: 203-212, April 20, 1990; Modjtahedi et al, *Int'l. J. of Oncology*, 13: 335-342, 1998; and J.R. Woodburn, *Pharmacol. Ther.*, 82: 2-3, 241-250, 1999, it is generally accepted that inhibitors of ErbB family kinases will be useful for the treatment of such cancers or other condition associated with ErbB family kinases.

Apoptosis (programmed cell death) plays essential roles in embryonic development and pathogenesis of various diseases, such as degenerative neuronal diseases, cardiovascular diseases and cancer. Recent work has led to the identification of various pro- and anti-apoptotic gene products that are involved in the regulation or execution of programmed cell death. Expression of anti-apoptotic genes, such as Bcl2 or Bcl-x_L, inhibits apoptotic cell death induced by various stimuli. On the other hand, expression of pro-apoptotic genes, such as Bax or Bad, leads to programmed cell death (Adams et al. *Science*, 281:1322-1326 (1998)). The execution of programmed cell death is mediated by caspase -1 related proteinases, including caspase-3, caspase- 7, caspase-8 and caspase-9 etc (Thornberry et al. *Science*, 281:1312-1316 (1998)).

The phosphatidylinositol 3'-OH kinase (PI3K)/Akt/PKB pathway appears important for regulating cell survival/cell death (Kulik et al. *Mol.Cell.Biol.* 17:1595-1606 (1997);

Franke et al, *Cell*, 88:435-437 (1997); Kauffmann-Zeh et al. *Nature* 385:544-548 (1997) Hemmings *Science*, 275:628-630 (1997); Dudek et al., *Science*, 275:661-665 (1997)). Survival factors, such as platelet derived growth factor (PDGF), nerve growth factor (NGF) and insulin-like growth factor-1 (IGF-I), promote cell survival under various
5 conditions by inducing the activity of PI3K (Kulik et al. 1997, Hemmings 1997). Activated PI3K leads to the production of phosphatidylinositol (3,4,5)-triphosphate (PtdIns (3,4,5)-P3), which in turn binds to, and promotes the activation of, the serine/threonine kinase Akt, which contains a pleckstrin homology (PH)-domain (Franke et al *Cell*, 81:727-736 (1995); Hemmings *Science*, 277:534 (1997); Downward, *Curr. Opin. Cell Biol.* 10:262-267
10 (1998), Alessi et al., *EMBO J.* 15: 6541-6551 (1996)). Specific inhibitors of PI3K or dominant negative Akt/PKB mutants abolish survival-promoting activities of these growth factors or cytokines. It has been previously disclosed that inhibitors of PI3K (LY294002 or wortmannin) blocked the activation of Akt/PKB by upstream kinases. In addition, introduction of constitutively active PI3K or Akt/PKB mutants promotes cell survival under
15 conditions in which cells normally undergo apoptotic cell death (Kulik et al. 1997, Dudek et al. 1997).

Analysis of Akt levels in human tumors showed that Akt2 is overexpressed in a significant number of ovarian (J. Q. Cheung et al. *Proc. Natl. Acad. Sci. U.S.A.* 89:9267-
20 9271(1992)) and pancreatic cancers (J. Q. Cheung et al. *Proc. Natl. Acad. Sci. U.S.A.* 93:3636-3641 (1996)). Similarly, Akt3 was found to be overexpressed in breast and prostate cancer cell lines (Nakatani et al. *J. Biol.Chem.* 274:21528-21532 (1999). It was demonstrated that Akt-2 was over-expressed in 12% of ovarian carcinomas and that amplification of Akt was especially frequent in 50% of undifferentiated tumors, suggestion
25 that Akt may also be associated with tumor aggressiveness (Bellacosa, et al., *Int. J. Cancer*, 64, pp. 280-285, 1995). Increased Akt1 kinase activity has been reported in breast, ovarian and prostate cancers (Sun et al. *Am. J. Pathol.* 159: 431-7 (2001)).

The tumor suppressor PTEN, a protein and lipid phosphatase that specifically
30 removes the 3' phosphate of PtdIns(3,4,5)-P3, is a negative regulator of the PI3K/Akt pathway (Li et al. *Science* 275:1943-1947 (1997), Stambolic et al. *Cell* 95:29-39 (1998), Sun et al. *Proc. Natl. Acad. Sci. U.S.A.* 96:6199-6204 (1999)). Germline mutations of PTEN are responsible for human cancer syndromes such as Cowden disease (Liaw et al. *Nature Genetics* 16:64-67 (1997)). PTEN is deleted in a large percentage of human
35 tumors and tumor cell lines without functional PTEN show elevated levels of activated Akt

(Li et al. supra, Guldberg et al. *Cancer Research* 57:3660-3663 (1997), Risinger et al. *Cancer Research* 57:4736-4738 (1997)).

These observations demonstrate that the PI3K/Akt pathway plays important roles
5 for regulating cell survival or apoptosis in tumorigenesis and/or cancer.

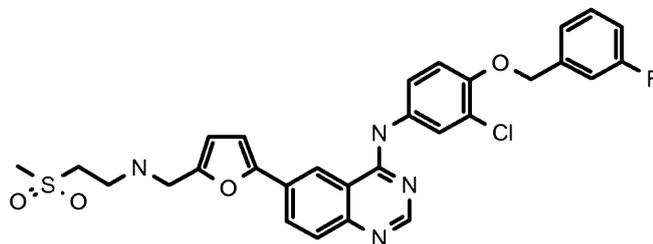
It would be useful to provide a novel therapy which provides more effective
and/or enhanced treatment of an individual suffering the effects of cancer.

10

SUMMARY OF THE INVENTION

One embodiment of this invention provides a combination comprising:

(i) a compound of Structure (I):

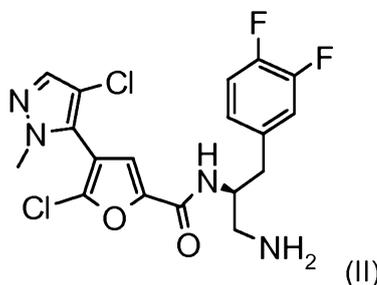


15

(I)

or a pharmaceutically acceptable hydrate and/or salt thereof; and

(ii) a compound of Structure (II):



20

(II)

or a pharmaceutically acceptable salt thereof.

One embodiment of this invention provides a method of treating cancer in a
human in need thereof which comprises the in vivo administration of a therapeutically
25 effective amount of a combination of N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-

(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine, or a pharmaceutically acceptable hydrate and/or salt thereof, suitably the ditosylate monohydrate salt, thereof, and *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide, or a pharmaceutically acceptable salt thereof, to
5 such human.

One embodiment of this invention provides a method of treating cancer in a human in need thereof which comprises the *in vivo* administration of a therapeutically effective amount of a combination of *N*-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine, or a pharmaceutically acceptable hydrate and/or salt thereof, suitably the ditosylate monohydrate salt, thereof,
10 and *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide, or a pharmaceutically acceptable salt thereof, to such human,
15 wherein the combination is administered within a specified period, and wherein the combination is administered for a duration of time.

One embodiment of this invention provides a method of treating cancer in a human in need thereof which comprises the *in vivo* administration of a therapeutically effective amount of a combination of *N*-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine, or a pharmaceutically acceptable hydrate and/or salt thereof, suitably the ditosylate monohydrate salt, thereof,
20 and *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide, or a pharmaceutically acceptable salt thereof, to
25 such human,
wherein the compounds of the combination are administered sequentially.

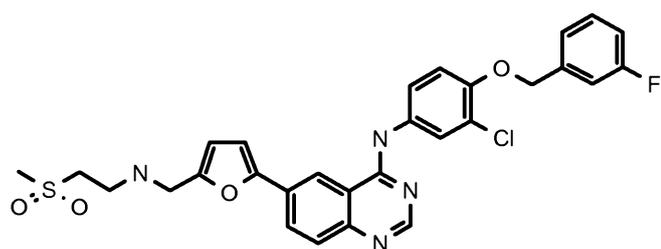
BRIEF DESCRIPTION OF THE DRAWINGS

30 Figure - 1 Figure 1 depicts representative dose response curves of cell growth inhibition by Compound A, Compound B or a combination of Compound A and Compound B on the growth of ten HER2+ breast tumor lines, UACC893, KPL-4, MDA-MB-361, HCC202, HCC1419, BT474, SK-BR-3, BT474-J4, SK-BR-3-W13 and JIMT-1.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to combinations that exhibit antiproliferative activity. Suitably, the method relates to methods of treating cancer by the co-administration of N-
 5 {3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine, or a pharmaceutically acceptable hydrate and/or salt thereof, suitably the ditosylate monohydrate salt, thereof, (hereinafter Compound A, or a pharmaceutically acceptable hydrate and/or salt, suitably the ditosylate monohydrate salt, thereof,

10 which compound is represented by Structure I:

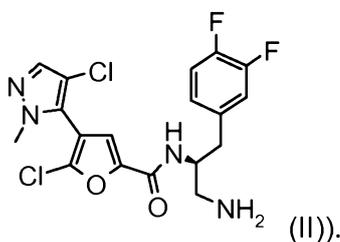


(I));

and N-((1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide or a pharmaceutically acceptable salt thereof, (hereinafter Compound B or a pharmaceutically acceptable salt thereof,

15

which compound is represented by Structure II:



(II)).

20

Compound A is disclosed and claimed, along with pharmaceutically acceptable solvates and salts thereof, as being useful as an inhibitor of EGF-R/erbB-2 activity, particularly in treatment of cancer, in International Application No. PCT/EP99/00048, having an International filing date of January 8, 1999, International Publication Number WO 99/35146 and an International Publication date of July 15, 1999, the entire disclosure
 25 of which is hereby incorporated by reference, Compound A is the compound of Example

29. Compound A can be prepared as described in International Application No. PCT/EP99/00048.

Suitably, Compound A is in the form of a ditosylate monohydrate salt. This salt
5 form can be prepared by one of skill in the art from the description in International Application No. PCT/US01/20706, having an International filing date of June 28, 2001, International Publication Number WO 02/02552 and an International Publication date of January 10, 2002, the entire disclosure of which is hereby incorporated by reference, see particularly Example 10.

10

Suitable pharmaceutical compositions containing Compound A as a single active
ingredient are prepared as described in International Application No. PCT/US2006/014447, having an International filing date of April 18, 2006, International
15 Publication Number WO 06/113649 and an International Publication date of October 26, 2006, the entire disclosure of which is hereby incorporated by reference, see particularly the formulation in Table 3.

Compound A is sold commercially as the ditosylate monohydrate salt and is
known by the generic name lapatinib and trade names Tykerb® and Tyverb®.

20

Compound B is disclosed and claimed, along with pharmaceutically acceptable
salts thereof, as being useful as an inhibitor of AKT activity, particularly in treatment of
cancer, in International Application No. PCT/US2008/053269, having an International
filing date of February 7, 2008; International Publication Number WO 2008/098104 and
25 an International Publication date of August 14, 2008, the entire disclosure of which is hereby incorporated by reference, Compound B is the compound of example 224. Compound B can be prepared as described in International Application No. PCT/US2008/053269.

30

The administration of a therapeutically effective amount of the combinations of the
invention are advantageous over the individual component compounds in that the
combinations will provide one or more of the following improved properties when
compared to the individual administration of a therapeutically effective amount of a
component compound: i) a greater anticancer effect than the most active single agent, ii)
35 synergistic or highly synergistic anticancer activity, iii) a dosing protocol that provides

enhanced anticancer activity with reduced side effect profile, iv) a reduction in the toxic effect profile, v) an increase in the therapeutic window, or vi) an increase in the bioavailability of one or both of the component compounds.

5 The compounds of the invention may contain one or more chiral atoms, or may otherwise be capable of existing as two 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 pharmaceutically acceptable hydrates and/or salts thereof, and Compound B, and pharmaceutically acceptable salts thereof.

15 The compounds of the invention may form a solvate which is understood to be a complex of variable stoichiometry formed by a solute (in this invention, Compound A or a salt thereof and/or Compound B 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 sulfoxide, ethanol and acetic acid. Suitably the solvent used is a pharmaceutically acceptable solvent. Suitably the solvent used is water.

20

 The pharmaceutically acceptable salts of the compounds of the invention are readily prepared by those of skill in the art.

25 Also, contemplated herein is a method of treating cancer using a combination of the invention where Compound A, or a pharmaceutically acceptable hydrate and/or salt thereof, and/or Compound B or a pharmaceutically acceptable salt thereof are administered as pro-drugs. Pharmaceutically acceptable pro-drugs of the compounds of the invention are readily prepared by those of skill in the art.

30 When referring to a dosing protocol, the term "day", "per day" and the like, refer to a time within one calendar day which begins at midnight and ends at the following midnight.

35 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 or

prevent the condition of 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 treatment thereof, or (4) to slow the progression of the condition or one or more of the biological manifestations of the condition. Prophylactic therapy is also contemplated thereby. The skilled artisan will appreciate that "prevention" is not an absolute term. In medicine, "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. 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.

By the term "combination" and derivatives thereof, as used herein is meant either, simultaneous administration or any manner of separate sequential administration of a therapeutically effective amount of Compound A, or a pharmaceutically acceptable hydrate and/or salt thereof, and Compound B or a pharmaceutically acceptable salt thereof. Preferably, if the administration is not simultaneous, the compounds are administered in a close time proximity to each other. 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.

By the term "combination kit" as used herein is meant the pharmaceutical composition or compositions that are used to administer Compound A, or a

pharmaceutically acceptable hydrate and/or salt thereof, and Compound B, or a pharmaceutically acceptable salt thereof, according to the invention. When both compounds are administered simultaneously, the combination kit can contain Compound A, or a pharmaceutically acceptable hydrate and/or salt thereof, and Compound B, or a pharmaceutically acceptable salt thereof, in a single pharmaceutical composition, such as a tablet, or in separate pharmaceutical compositions. When the compounds are not administered simultaneously, the combination kit will contain Compound A, or a pharmaceutically acceptable hydrate and/or salt thereof, and Compound B, or a pharmaceutically acceptable salt thereof, in separate pharmaceutical compositions. The combination kit can comprise Compound A, or a pharmaceutically acceptable hydrate and/or salt thereof, and Compound B, or a pharmaceutically acceptable salt thereof, in separate pharmaceutical compositions in a single package or in separate pharmaceutical compositions in separate packages.

In one aspect there is provided a combination kit comprising the components:

Compound A, or a pharmaceutically acceptable hydrate and/or salt thereof, in association with a pharmaceutically acceptable carrier; and

Compound B, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

In one embodiment of the invention the combination kit comprises the following components:

Compound A, or a pharmaceutically acceptable hydrate and/or salt thereof, in association with a pharmaceutically acceptable carrier; and

Compound B, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier,

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

In one embodiment the combination kit comprises:

a first container comprising Compound A, or a pharmaceutically acceptable hydrate and/or salt thereof, in association with a pharmaceutically acceptable carrier; and

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

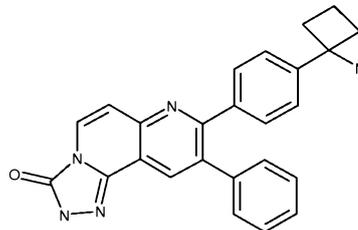
The "combination kit" can also be provided by instruction, such as dosage and administration instructions. Such dosage and administration instructions can be of the

kind that is provided to a doctor, for example by a drug product label, or they can be of the kind that is provided by a doctor, such as instructions to a patient.

As used herein the term "Compound A²" means ---Compound A, or a
5 pharmaceutically acceptable hydrate and/or salt thereof---

As used herein the term "Compound B²" means ---Compound B, or a
pharmaceutically acceptable salt thereof---

10 In one embodiment of the present invention Compound B is replaced by:
8-[4-(1-aminocyclobutyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-
3(2H)-one; which has the following structure (depicted as the chloride salt):



Cl⁻;

15 provided that when said compound is administered on a day 1, day 3, and day 5
of a dosing protocol the compound is not administered at a dose selected from: 30mg,
45mg or 60mg.

In one embodiment of the present invention Compound B² is replaced by the
20 compound:

8-[4-(1-aminocyclobutyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-
3(2H)-one or a pharmaceutically acceptable salt thereof;

provided that when said compound is administered on a day 1, day 3, and day 5
of a dosing protocol the compound is not administered at a dose selected from: 30mg,
25 45mg or 60mg.

The compound 8-[4-(1-aminocyclobutyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3(2H)-one is disclosed and claimed, along with pharmaceutically acceptable salts thereof, as being useful as an inhibitor of AKT activity, particularly in treatment of cancer, in United States Patent 7,576,209 which issued on August 18, 2009. 8-[4-(1-aminocyclobutyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3(2H)-one can be prepared as described in United States Patent 7,576,209.

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

10

By the term “specified period” and derivatives thereof, as used herein is meant the interval of time between the administration of one of Compound A² and Compound B² and the other of Compound A² and Compound B². 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 timing of the administration of Compound A² and Compound B² 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.

20

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

25

30

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 –
5 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 A² and Compound B² in less than about 45 minutes apart is considered
10 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”.

15 By the term “duration of time” and derivatives thereof, as used herein is meant that both compounds of the invention are administered within a “specified period” for an indicated number of consecutive days, optionally followed by a number of consecutive days where only one of the component compounds is administered. Unless otherwise defined, the “duration of time” and in all dosing protocols described herein, do not have to
20 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, occur at some point during the course of treatment.

25

Regarding “specified period” administration:

Suitably, during the course of treatment, both compounds will be administered within a specified period for at least 1 day – in this case, the duration of time will be at least 1 day; suitably, during the course of treatment, both compounds will be administered
30 within a specified period for at least 2 consecutive days – in this case, the duration of time will be at least 2 days; suitably, during the course of 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 of treatment, both compounds will be administered within a specified period for at least 5 consecutive days
35 – in this case, the duration of time will be at least 5 days; suitably, during the course of

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 of 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 of 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. When, during the course of treatment, both compounds are administered within a specified period for over 30 days, the treatment is considered chronic treatment and will continue until an altering event, such as a reassessment in cancer status or a change in the condition of the patient, warrants a modification to the protocol.

Further regarding “specified period” administration:

Suitably, during the course of treatment, both compounds will be administered within a specified period for at least 1 day, followed by the administration of Compound A² alone for at least 1 day – in this case, the duration of time will be at least 2 days; suitably, during the course of treatment, both compounds will be administered within a specified period for at least 1 day, followed by administration of Compound A² alone for at least 2 days – in this case, the duration of time will be at least 3 days; suitably, during the course of treatment, both compounds will be administered within a specified period for at least 1 day, followed by administration of Compound A² alone for at least 3 days – in this case, the duration of time will be at least 4 days; suitably, during the course of treatment, both compounds will be administered within a specified period for at least 1 day, followed by administration of Compound A² alone for at least 4 days – in this case, the duration of time will be at least 5 days; suitably, during the course of treatment, both compounds will be administered within a specified period for at least 1 day, followed by administration of Compound A² alone for at least 5 days – in this case, the duration of time will be at least 6 days; suitably, during the course of treatment, both compounds will be administered within a specified period for at least 1 day, followed by administration of Compound A² alone for at least 6 days – in this case, the duration of time will be at least 7 days; suitably, during the course of treatment, both compounds will be administered within a specified period for at least 1 day, followed by administration of Compound A² alone for at least 7 days – in this case, the duration of time will be at least 8 days; suitably, during the

course of treatment, both compounds will be administered within a specified period for at least 2 consecutive days, followed by administration of Compound A² alone for at least 1 day – in this case, the duration of time will be at least 3 days; suitably, during the course of treatment, both compounds will be administered within a specified period for at least 2 consecutive days, followed by administration of Compound A² alone for at least 2 consecutive days – in this case, the duration of time will be at least 4 days; suitably, during the course of treatment, both compounds will be administered within a specified period for at least 2 consecutive days, followed by administration of Compound A² alone for at least 3 consecutive days – in this case, the duration of time will be at least 5 days; suitably, during the course of treatment, both compounds will be administered within a specified period for at least 2 consecutive days, followed by administration of Compound A² alone for at least 4 consecutive days – in this case, the duration of time will be at least 6 days; suitably, during the course of treatment, both compounds will be administered within a specified period for at least 2 consecutive days, followed by administration of Compound A² alone for at least 5 consecutive days – in this case, the duration of time will be at least 7 days; suitably, during the course of treatment, both compounds will be administered within a specified period for at least 2 consecutive days, followed by administration of Compound A² alone for at least 6 consecutive days – in this case, the duration of time will be at least 8 days; suitably, during the course of treatment, both compounds will be administered within a specified period for at least 2 consecutive days, followed by administration of Compound A² alone for at least 7 consecutive days – in this case, the duration of time will be at least 9 days; suitably, during the course of treatment, both compounds will be administered within a specified period for at least 3 consecutive days, followed by administration of Compound A² alone for at least 1 day – in this case, the duration of time will be at least 4 days; suitably, during the course of treatment, both compounds will be administered within a specified period for at least 3 consecutive days, followed by administration of Compound A² alone for at least 2 consecutive days – in this case, the duration of time will be at least 5 days; suitably, during the course of treatment, both compounds will be administered within a specified period for at least 3 consecutive days, followed by administration of Compound A² alone for at least 3 consecutive days – in this case, the duration of time will be at least 6 days; suitably, during the course of treatment, both compounds will be administered within a specified period for at least 3

consecutive days, followed by administration of Compound A² alone for at least 4 consecutive days – in this case, the duration of time will be at least 7 days; suitably, during the course of treatment, both compounds will be administered within a specified period for at least 3 consecutive days, followed by administration of Compound A² alone

5 for at least 5 consecutive days – in this case, the duration of time will be at least 8 days; suitably, during the course of treatment, both compounds will be administered within a specified period for at least 3 consecutive days, followed by administration of Compound A² alone for at least 6 consecutive days – in this case, the duration of time will be at least 9 days; suitably, during the course of treatment, both compounds will be administered

10 within a specified period for at least 3 consecutive days, followed by administration of Compound A² alone for at least 7 consecutive days – in this case, the duration of time will be at least 10 days; suitably, during the course of treatment, both compounds will be administered within a specified period for at least 4 consecutive days, followed by administration of Compound A² alone for at least 1 day – in this case, the duration of time

15 will be at least 5 consecutive days; suitably, during the course of treatment, both compounds will be administered within a specified period for at least 4 consecutive days, followed by administration of Compound A² alone for at least 2 consecutive days – in this case, the duration of time will be at least 6 consecutive days; suitably, during the course of treatment, both compounds will be administered within a specified period for at least 4

20 consecutive days, followed by administration of Compound A² alone for at least 3 consecutive days – in this case, the duration of time will be at least 7 consecutive days; suitably, during the course of treatment, both compounds will be administered within a specified period for at least 4 consecutive days, followed by administration of Compound A² alone for at least 4 consecutive days – in this case, the duration of time will be at least

25 8 consecutive days; suitably, during the course of treatment, both compounds will be administered within a specified period for at least 4 consecutive days, followed by administration of Compound A² alone for at least 7 consecutive days – in this case, the duration of time will be at least 11 consecutive days; suitably, during the course of treatment, both compounds will be administered within a specified period for at least 5

30 consecutive days, followed by administration of Compound A² alone for at least 1 day – in this case, the duration of time will be at least 6 consecutive days; suitably, during the course of treatment, both compounds will be administered within a specified period for at

least 5 consecutive days, followed by administration of Compound A² alone for at least 2 consecutive days – in this case, the duration of time will be at least 7 consecutive days; suitably, during the course of treatment, both compounds will be administered within a specified period for at least 5 consecutive days, followed by administration of Compound A² alone for at least 3 consecutive days – in this case, the duration of time will be at least 8 consecutive days; suitably, during the course of treatment, both compounds will be administered within a specified period for at least 5 consecutive days, followed by administration of Compound A² alone for at least 4 consecutive days – in this case, the duration of time will be at least 9 consecutive days; suitably, during the course of treatment, both compounds will be administered within a specified period for at least 5 consecutive days, followed by administration of Compound A² alone for at least 5 consecutive days – in this case, the duration of time will be at least 10 consecutive days; suitably, during the course of treatment, both compounds will be administered within a specified period for at least 7 consecutive days, followed by administration of Compound A² alone for at least 2 consecutive days – in this case, the duration of time will be at least 9 consecutive days; suitably, during the course of treatment, both compounds will be administered within a specified period for at least 14 consecutive days, followed by administration of Compound A² alone for at least 7 consecutive days – in this case, the duration of time will be at least 21 consecutive days; suitably, during the course of treatment, both compounds will be administered within a specified period for at least 30 consecutive days, followed by administration of Compound A² alone for at least 7 consecutive days – in this case, the duration of time will be at least 37 consecutive days. Suitably, during the course of treatment, both compounds will be administered within a specified period for from 1 to 3 consecutive days, followed by administration of Compound A² alone for from 3 to 7 consecutive days. Suitably, during the course of treatment, both compounds will be administered within a specified period for from 3 to 6 consecutive days, followed by administration of Compound A² alone for from 1 to 4 consecutive days. Suitably, during the course of treatment, both compounds will be administered within a specified period for 5 consecutive days, followed by administration of Compound A² alone for 2 consecutive days. Suitably, during the course of treatment, both compounds will be administered within a specified period for 2 consecutive days, followed by administration of Compound A² alone for from 3 to 7 consecutive days.

Suitably, during the course of treatment, both compounds will be administered within a specified period for from 1 to 3 days over a 7 day period, and during the other days of the 7 day period Compound A² will be administered alone. Suitably, during the course of treatment, both compounds will be administered within a specified period for 2 days over
5 a 7 day period, and during the other days of the 7 day period Compound A² will be administered alone.

Suitably, if the compounds are not administered during a "specified period", they are administered sequentially. By the term "sequential administration", and derivatives
10 thereof, as used herein is meant that one of Compound A² and Compound B² is administered for 1 or more consecutive days and the other of Compound A² and Compound B² is subsequently administered for 1 or more consecutive days. Unless otherwise defined, the "sequential administration" and in all dosing protocols described herein, do not have to commence with the start of treatment and terminate with the end of
15 treatment, it is only required that the administration of one of Compound A² and Compound B² followed by the administration of the other of Compound A² and Compound B², or the indicated dosing protocol, occur at some point during the course of treatment. Also, contemplated herein is a drug holiday utilized between the sequential administration of one of Compound A² and Compound B² and the other of Compound A²
20 and Compound B². As used herein, a drug holiday is a period of days after the sequential administration of one of Compound A² and Compound B² and before the administration of the other of Compound A² and Compound B² where neither Compound A² nor Compound B² 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
25 days, 11 days, 12 days, 13 days and 14 days.

Regarding sequential administration:

Suitably, one of Compound A² and Compound B² is administered for from 1 to 30 consecutive days, followed by an optional drug holiday, followed by administration of the
30 other of Compound A² and Compound B² for from 1 to 30 consecutive days. Suitably, one of Compound A² and Compound B² is administered for from 1 to 21 consecutive

days, followed by an optional drug holiday, followed by administration of the other of Compound A² and Compound B² for from 1 to 21 consecutive days. Suitably, one of Compound A² and Compound B² is administered for from 1 to 14 consecutive days, followed by a drug holiday of from 1 to 14 days, followed by administration of the other of
5 Compound A² and Compound B² for from 1 to 14 consecutive days. Suitably, one of Compound A² and Compound B² is administered for from 2 to 7 consecutive days, followed by a drug holiday of from 2 to 10 days, followed by administration of the other of Compound A² and Compound B² for from 2 to 7 consecutive days.

10 Suitably, Compound B² will be administered first in the sequence, followed by an optional drug holiday, followed by administration of Compound A². Suitably, Compound B² is administered for from 1 to 21 consecutive days, followed by an optional drug holiday, followed by administration of Compound A² for from 1 to 21 consecutive days. Suitably, Compound B² is administered for from 3 to 21 consecutive days, followed by a
15 drug holiday of from 1 to 14 days, followed by administration of Compound A² for from 3 to 21 consecutive days. Suitably, Compound B² 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 A² for from 3 to 21 consecutive days. Suitably, Compound B² is administered for 21 consecutive days, followed by an optional drug holiday, followed
20 by administration of Compound A² for 14 consecutive days. Suitably, Compound B² is administered for 14 consecutive days, followed by a drug holiday of from 1 to 14 days, followed by administration of Compound A² for 14 consecutive days. Suitably, Compound B² is administered for 7 consecutive days, followed by a drug holiday of from 3 to 10 days, followed by administration of Compound A² for 7 consecutive days.
25 Suitably, Compound B² is administered for 3 consecutive days, followed by a drug holiday of from 3 to 14 days, followed by administration of Compound A² for 7 consecutive days. Suitably, Compound B² is administered for 3 consecutive days, followed by a drug holiday of from 3 to 10 days, followed by administration of Compound A² for 3 consecutive days.

Suitably, Compound A² will be administered first in the sequence, followed by an optional drug holiday, followed by administration of Compound B². Suitably, Compound A² is administered for from 1 to 21 consecutive days, followed by an optional drug holiday, followed by administration of Compound B² for from 1 to 21 consecutive days. Suitably, Compound A² 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 B² for from 3 to 21 consecutive days. Suitably, Compound A² 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 B² for from 3 to 21 consecutive days. Suitably, Compound A² is administered for 21 consecutive days, followed by an optional drug holiday, followed by administration of Compound B² for 14 consecutive days. Suitably, Compound A² is administered for 14 consecutive days, followed by a drug holiday of from 1 to 14 days, followed by administration of Compound B² for 14 consecutive days. Suitably, Compound A² is administered for 7 consecutive days, followed by a drug holiday of from 3 to 10 days, followed by administration of Compound B² for 7 consecutive days. Suitably, Compound A² is administered for 3 consecutive days, followed by a drug holiday of from 3 to 14 days, followed by administration of Compound B² for 7 consecutive days. Suitably, Compound A² is administered for 3 consecutive days, followed by a drug holiday of from 3 to 10 days, followed by administration of Compound B² for 3 consecutive days. Suitably, Compound A² is administered for 7 consecutive days, followed by administration of Compound B² for 1 day. Suitably, Compound A² is administered for 6 consecutive days, followed by administration of Compound B² for 1 day. Suitably, Compound B² is administered for 1 day, followed by administration of Compound A² for 7 consecutive days. Suitably, Compound B² is administered for 1 day, followed by administration of Compound A² for 6 consecutive days.

It is understood that a "specified period" administration and a "sequential" administration can be followed by one or more cycles of 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 A² administered as part of the combination according to the present invention will be an amount selected from about 250mg to about 1,500mg; suitably, the amount will be selected from about 500mg to about 1,250mg; suitably, the amount will be selected from about 750mg to about 1,250mg; suitably, the amount will be selected from about 1,000mg to about 1,250mg; suitably, the amount will be 250mg, suitably, the amount will be 500mg, suitably, the amount will be 750mg, suitably, the amount will be 1,000mg, suitably, the amount will be 1,250mg; suitably, the amount will be 1,500mg. Accordingly, the amount of Compound A² administered as part of the combination according to the present invention will be an amount selected from about 250mg to about 1,500 mg. For example, the amount of Compound A² administered as part of the combination according to the present invention is suitably selected from 250mg, 500mg, 750mg, 1,000mg, 1,250mg and 1,500mg. Suitably, the selected amount of Compound A² is administered from 1 to 4 times a day, in one or more tablets. Suitably, the selected amount of Compound A² is administered twice a day, in one or more tablets. Suitably, the selected amount of Compound A² is administered once a day, in one or more tablets.

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Suitably, the amount of Compound B² administered as part of the combination according to the present invention will be an amount selected from about 5mg to about 500mg; suitably, the amount will be selected from about 25mg to about 400mg; suitably, the amount will be selected from about 30mg to about 375mg; suitably, the amount will be selected from about 35mg to about 350mg; suitably, the amount will be selected from about 40mg to about 300mg; suitably, the amount will be selected from about 45mg to about 275mg; suitably, the amount will be selected from about 50mg to about 250mg; suitably, the amount will be selected from about 55mg to about 225mg; suitably, the amount will be selected from about 60mg to about 200mg; suitably, the amount will be selected from about 65mg to about 175mg; suitably, the amount will be selected from about 70mg to about 150mg; suitably, the amount will be selected from about 50mg to about 300mg; suitably, the amount will be selected from about 75mg to about 150mg; suitably, the amount will be about 100mg. Accordingly, the amount of Compound B²

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administered as part of the combination according to the present invention will be an amount selected from about 5mg to about 500mg. For example, the amount of Compound B² administered as part of the combination according to the present invention can be 5mg, 10mg, 15mg, 20mg, 25mg, 30mg, 35mg, 40mg, 45mg, 50mg, 55mg, 60mg, 5 65mg, 70mg, 75mg, 80mg, 85mg, 90mg, 95mg, 100mg, 105mg, 110mg, 115mg, 120mg, 125mg, 130mg, 135mg, 140mg, 145mg, 150mg, 175mg, 200mg, 225mg, 250mg, 275mg, 300mg, 325mg, 350mg, 375mg, 400mg, 425mg, 450mg, 475mg or 500mg. Suitably, the selected amount of Compound B² is administered twice a day. Suitably, the selected amount of Compound B² is administered once a day.

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As used herein, all amounts specified for Compound A² and Compound B² are indicated as the administered amount of free or unsalted and unsolvated compound per dose.

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The method of the present invention may also be employed with other therapeutic methods of cancer treatment.

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While it is possible that, for use in therapy, therapeutically effective amounts of the combinations of the present invention may be administered as the raw chemical, it is preferable to present the combinations as a pharmaceutical composition or compositions. Accordingly, the invention further provides pharmaceutical compositions, which include Compound A² and/or Compound B², and one or more pharmaceutically acceptable carriers. The combinations of the present invention are as described above. The carrier(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 formulation including admixing Compound A² and/or Compound B² with one or more pharmaceutically acceptable carriers. As indicated above, such elements of the pharmaceutical combination utilized 25 30 may be presented in separate pharmaceutical compositions or formulated together in one pharmaceutical formulation.

Pharmaceutical formulations 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 formulations are those containing a daily dose or sub-dose, or an appropriate fraction thereof, of an active ingredient. Furthermore, such pharmaceutical
5 formulations may be prepared by any of the methods well known in the pharmacy art.

Compound A² and Compound B² may be administered by any appropriate route. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal, and parenteral (including subcutaneous, intramuscular, intravenous, intradermal,
10 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 Compound A² and Compound B² may be compounded together in a pharmaceutical composition/formulation. Suitably, Compound A² and
15 Compound B² are administered in separate pharmaceutical compositions.

The compounds or combinations of the current invention are incorporated into convenient dosage forms such as capsules, tablets, or injectable preparations. Solid or liquid pharmaceutical carriers are employed. Solid carriers include, starch, lactose,
20 calcium sulfate dihydrate, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Liquid carriers include syrup, peanut oil, olive oil, saline, and water. Similarly, the carrier may include a prolonged release material, such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies widely but, suitably, may be from about 25 mg to about 1 g per dosage unit.
25 When a liquid carrier is used, the preparation will suitably be in the form of a syrup, elixir, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampoule, or an aqueous or nonaqueous liquid suspension.

For instance, for oral administration in the form of a tablet or capsule, the active
30 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.

It should be understood that in addition to the ingredients mentioned above, the formulations 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
5 flavoring agents.

As indicated, therapeutically effective amounts of the combinations of the invention (Compound A² in combination with Compound B²) are administered to a human. Typically, the therapeutically effective amount of the administered agents of the
10 present invention will depend upon a number of factors including, for example, the age and weight of the subject, 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 attending physician.

15 The combinations of the invention are tested for efficacy, advantageous and synergistic properties generally according to known procedures.

Methods:

20 Cell lines and growth conditions

Human tumor cell lines from breast, BT474, BT474-J4, JIMT-1, MDA-MB-361, SK-BR-3, HCC1419, UACC893 and HCC202 in RPMI 1640 containing 10 % FBS media; SK-BR-3-W13 and BT474-J4 in RPMI 1640 containing 10% FBS and 1 μ M Compound A (in
25 this assay, Compound A, was used in the form of the ditosylate monohydrate salt) media were kept in a humidified incubator at 37°C in 95% air and 5% CO₂. JIMT-1 is a line derived from a patient clinically resistant to trastuzumab (Herceptin®). SK-BR-3-W13 is a single cell clone isolated by a cloning cylinder after a single treatment of SK-BR-3 cells with 0.5 μ M Compound A. BT474-J4 is a single cell clone derived from BT474 cells that
30 were selected to grow in Compound A to a concentration of 3 μ M.

Cell growth inhibition assay and combination data analysis.

All cells were cultured without Compound A for a minimum of 72 hours prior to cell
35 plating. Cells were assayed in a 96-well tissue culture plate (NUNC 136102) of RPMI

containing 10% FBS at 2,000 cells/well. Approximately 24 hours after plating, cells were exposed to ten, two-fold or three-fold serial dilutions of Compound A or the combination of the two agents at a constant molar to molar ratio of 10:1 Compound A to Compound B (in this assay, Compound B refers to *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide and was used as the free or unsalted compound) in RPMI media containing 10% FBS. Cells were incubated in the presence of compounds for 3 days. ATP levels were determined by adding Cell Titer Glo® (Promega) according to the manufacturer's protocol. Briefly, Cell Titer Glo® was added each plate, incubated for 20 minutes then luminescent signal was read on the SpectraMax L plate reader with a 0.5 sec integration time.

Inhibition of cell growth was estimated after treatment with Compound A or the combination of Compound A and Compound B for three days and comparing the signal to cells treated with vehicle (DMSO). Cell growth was calculated relative to vehicle (DMSO) treated control wells. Concentration of compound that inhibits 50% of control cell growth (IC_{50}) was interpolated using nonlinear regression with the equation, $y=(A+(B-A)/(1+(C/x)^D))$, where A is the minimum response (y_{min}), B is the maximum response (y_{max}), C is the inflection point of the curve (EC_{50}) and D is the Hill coefficient.

20

Combination effects on potency were evaluated using Combination Index (CI) which was calculated with the back-interpolated IC_{50} values and the mutually non-exclusive equation derived by Chou and Talalay (Chou TC, Talalay P. *Adv Enzyme Regul*; 22:27-55,1984):

$$CI = Da/IC_{50}(a) + Db/IC_{50}(b) + (Da \times Db)/(IC_{50}(a) \times IC_{50}(b))$$

where $IC_{50}(a)$ is the IC_{50} of Compound A; $IC_{50}(b)$ is the IC_{50} for Compound B; Da is the concentration of Compound A in combination with Compound B that inhibited 50 % of cell growth; and Db is the concentration of Compound B in combination with Compound A that inhibited 50% of cell growth. In general, a CI value <0.9, between 0.9 and 1.1, or >1.1 indicates synergy, additivity and antagonism, respectively. In general, the smaller the CI number, the greater is the strength of synergy.

The combination effects on the response scale were quantified by Excess Over Highest Single Agent (EOHSA). EOHSA values are defined as increases in improvement (here, in 'percentage points' (ppts) difference) produced by the combination over the best single drug at its component dose level. More specifically, suppose we have a

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combination composed of drug 1 at dose d1 and drug 2 at dose d2. If the effect of the combination of drugs 1 and 2 at doses d1 and d2 is better than either drug 1 (alone) at dose d1 or drug 2 (alone) at dose d2, then the combination is said to have a positive EOHSA and beneficial for that combination. For a combination drug experiment (involving drug 1 at dose d1 and drug 2 at dose d2), a drug combination (at total dose d1+d2) is said to have a statistically significant EOHSA if the mean response at the combination is significantly better than the mean responses for either drug 1 (alone) at dose d1 or drug 2 (alone) at dose d2. EOHSA is a common approach for evaluating drug combinations, and is an FDA criterion (21 CFR 300.50) for combination drug approval. See Borisy et al. (Borisy AA, et al. Proc Natl Acad Sci;100(13):7977-82, 2003) or Hung et al. (Hung HM, Chi GY, Lipicky RJ. Biometrics 49(1):85-94,1993) for examples and discussion. The EOHSA analysis was conducted as follows. Since dose response curves were fit to the experimental data (for both of the single drug regimens and also for the combination drug at a fixed-dose-ratio ray), comparisons needed for making EOHSA statistical inferences could be done by interpolation using the fitted regression models. At specified total dose levels of IC_{50} along the dose response curve of a fixed-dose-ratio ray, the dose combination (corresponding to IC_{50}) was determined for making EOHSA statistical inferences. Here, the mean response at a given combination, IC_{50} for example, was compared to the mean response at the component dose levels for drugs 1 and 2 on their dose response curves. More specifically, suppose that the IC_{50} for the combination drug (along the fixed-dose-ratio ray) corresponds to a total dose of d1+d2. We then compare the mean response for the combination (d1+d2) to drug 1 at d1 and drug 2 at d2 using the respective fitted dose response curves corresponding to the fixed -dose-ratio combination curve and the dose response curves for drugs 1 and 2 alone.

25

Cell growth inhibition by Compound A, Compound B and the combination of Compound A with Compound B.

The effects of cell growth inhibition by Compound A, Compound B and their combination were determined in ten HER2+ breast tumor lines, UACC893, KPL-4, MDA-MB-361, HCC202, HCC1419, BT474, SK-BR-3, BT474-J4, SK-BR-3-W13 and JIMT-1. The mean IC_{50} s (at least two independent experiments) and the combination effects at IC_{50} s are summarized in Table 1. Representative dose response curves are provided in Figure 1.

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HCC1419, BT474 and SK-BR-3 HER2+ lines are highly sensitive to Compound A with IC_{50} values of less than 0.2 μ M, and less sensitive to Compound B with $IC_{50} > 0.5$ μ M. The combination of Compound A and Compound B showed additive or similar to the most active single agent effects in these cells.

5 UACC893 and KPL-4 HER2+ lines with an H1047R PIK3CA mutation are sensitive to both Compound A and Compound B single agents. The combination of Compound A and Compound B showed synergistic effects as demonstrated by the combination index values (CI, 0.38 and 0.73 respectively) and greater than the most active single agent by EOHSA analysis (29 and 24 ppt respectively). MDA-MB-361 and
10 HCC202 HER2+ lines with an E545K PIK3CA mutation are less sensitive to Compound A or Compound B as single agents. The combination of Compound A and Compound B is beneficial as indicated by the CI of 0.72 in HCC202 and EOHSA values of >12 ppt in both MDA-MB-361 and HCC202 cell lines.

Both BT474-J4 and SK-BR-3-W13 lines are HER2+, Compound A acquired
15 resistant clones developed from BT474 and Sk-Br-3 cells respectively. JIMT-1 is a line derived from a patient who was resistant to trastuzumab therapy (Tanner et al, Mol Cancer Ther 2004;3:1585–92). BT474-J4 line is sensitive to cell growth inhibition by Compound B. The combination of Compound A and Compound B is synergistic in BT474-J4 cells. Both SK-BR-3-W13 and JIMT1 are not sensitive to Compound A ($IC_{50}>5$
20 μ M) or Compound B ($IC_{50}>1$ μ M). The combination of Compound A and Compound B showed a greater effect than the most active single agent (EOHSA >10 ppt).

Table 1. Cell growth inhibition by Compound A, Compound B and their combination in tumor cell lines.

Cell Line	PIK3CA Status	Single agent (IC ₅₀ , μM)		Combination (Compound A:Compound B=10:1)			
		Compound A	Compound B	Compound A (IC ₅₀ , μM)	Compound B (IC ₅₀ , μM)	CI Mut non Ex	EOHSA (ppts)
HCC1419	WT	0.084 ± 0.034	0.573 ± 0.154	0.078 ± 0.016	0.008 ± 0.002	0.99 ± 0.20	0.55 ± 2.73
BT474	K111N	0.171 ± 0.034	>1	0.182 ± 0.052	0.018 ± 0.005	N/A	-0.52 ± 0.93
SK-BR-3	WT	0.196 ± 0.070	>1	0.199 ± 0.079	0.020 ± 0.008	N/A	-0.35 ± 3.22
UACC893	H1047R	0.492 ± 0.498	0.030 ± 0.027	0.069 ± 0.069	0.007 ± 0.007	0.38 ± 0.04	29.12 ± 3.65
KPL4	H1047R	0.430 ± 0.159	0.019 ± 0.004	0.078 ± 0.012	0.008 ± 0.001	0.73 ± 0.32	23.58 ± 0.91
MDA-MB-361	E545K	>10	0.151 ± 0.022	0.751 ± 0.008	0.075 ± 0.001	N/A	20.69 ± 6.71
HCC202	E545K	2.408 ± 0.022	0.919 ± 0.356	1.229 ± 0.244	0.123 ± 0.024	0.72 ± 0.08	12.49 ± 0.34
BT474-J4*	K111N	5.175 ± 2.199	0.142 ± 0.047	0.377 ± 0.054	0.038 ± 0.005	0.38 ± 0.09	17.51 ± 2.63
SK-BR3-W13*	ND	5.605 ± 1.049	>1	4.775 ± 0.552	0.478 ± 0.055	N/A	10.99 ± 2.29
JIMT1*	C420R	7.782 ± 1.267	>1	3.642 ± 0.697	0.364 ± 0.070	N/A	19.82 ± 3.06

*lines resistant to Compound A and trastuzumab; ND: not determined; NA: not applicable;

5 Combination index:CI.

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

10

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

15 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, 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,

20 Lymphoblastic T cell leukemia, Chronic myelogenous leukemia, Chronic lymphocytic leukemia, Hairy-cell leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, 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,

5 malignant lymphoma, hodgkins lymphoma, non-hodgkins lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma, follicular lymphoma,

10 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.

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, 15 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.

20 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 Ras/Raf and either wild type or mutant for PIK3CA/PTEN. This includes patients who are wild type for both Ras/Raf and PIK3CA/PTEN, mutant for both Ras/Raf and PIK3CA/PTEN, mutant for Ras/Raf and wild type for PIK3CA/PTEN and wild type for Ras/Raf and mutant for PIK3CA/PTEN. The 25 present invention also relates to a method of treating or lessening the severity of a cancer that has activated AKT, e.g., by mutation or amplification of AKT1, AKT2 or AKT3 genes. The present invention also relates to a method of treating or lessening the severity of a cancer that has activated EGFR or ErbB-2, e.g., by mutation, amplification of the gene or overexpression of the protein.

30 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 35 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.

5

Cancers that are either wild type or mutant for Ras/Raf, PIK3CA/PTEN, AKT, EGFR or ErbB-2 or have amplification of PIK3CA, AKT, EGFR or ErbB-2 genes or have overexpression of EGFR or ErbB2 protein are identified by known methods.

10

For example, wild type or mutant Ras/Raf, PIK3CA/PTEN, AKT EGFR or ErbB-2 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 or in-situ hybridization. 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.

15

This invention provides a combination comprising N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine, or a pharmaceutically acceptable hydrate and/or salt thereof, suitably the ditosylate monohydrate salt thereof, and N-[(1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl]-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide, or a pharmaceutically acceptable salt thereof.

20

25

This invention also provides for a combination comprising N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine, or a pharmaceutically acceptable hydrate and/or salt thereof, suitably the ditosylate monohydrate salt, thereof, and N-[(1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl]-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide, or a pharmaceutically acceptable salt thereof, for use in therapy.

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35

This invention also provides for a combination comprising N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine, or a pharmaceutically acceptable hydrate and/or salt thereof, suitably the ditosylate monohydrate salt, thereof, and N-[(1S)-2-amino-1-[(3,4-

difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide, or a pharmaceutically acceptable salt thereof, for use in treating cancer.

5 This invention also provides a pharmaceutical composition comprising a combination of N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine, or a pharmaceutically acceptable hydrate and/or salt thereof, suitably the ditosylate monohydrate salt, thereof, and N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-10 1*H*-pyrazol-5-yl)-2-furancarboxamide, or a pharmaceutically acceptable salt thereof.

 This invention also provides a combination kit comprising N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine, or a pharmaceutically acceptable hydrate and/or salt thereof, suitably the ditosylate monohydrate salt, thereof, and N-{(1*S*)-2-amino-1-[(3,4-15 difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide, or a pharmaceutically acceptable salt thereof.

 This invention also provides for the use of a combination comprising N-{3-20 Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine, or a pharmaceutically acceptable hydrate and/or salt thereof, suitably the ditosylate monohydrate salt, thereof, and N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide, or a pharmaceutically acceptable salt thereof, in the manufacture of a25 medicament.

 This invention also provides for the use of a combination comprising N-{3-30 Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine, or a pharmaceutically acceptable hydrate and/or salt thereof, suitably the ditosylate monohydrate salt, thereof, and N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide, or a pharmaceutically acceptable 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 N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine, or a pharmaceutically acceptable hydrate and/or salt thereof, suitably the ditosylate monohydrate salt, thereof,
 5 and N-((1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide, or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

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

Experimental Details

Example 1 - Capsule Composition

15

An oral dosage form for administering a combination of the present invention is produced by filing a standard two piece hard gelatin capsule with the ingredients in the proportions shown in Table I, below.

20

Table I

<u>INGREDIENTS</u>	<u>AMOUNTS</u>
N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine ditosylate monohydrate (the ditosylate monohydrate salt of Compound A)	250mg
N-((1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide (Compound B)	75mg
Mannitol	250 mg
Talc	125 mg
Magnesium Stearate	8 mg

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Example 2 - Capsule Composition

An oral dosage form for administering one of the compounds of the present invention is produced by filing a standard two piece hard gelatin capsule with the ingredients in the proportions shown in Table II, below.

Table II

<u>INGREDIENTS</u>	<u>AMOUNTS</u>
N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine ditosylate monohydrate (the ditosylate monohydrate salt of Compound A)	250mg
Mannitol	55 mg
Talc	16 mg
Magnesium Stearate	4 mg

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Example 3 - Capsule Composition

An oral dosage form for administering one of the compounds of the present invention is produced by filing a standard two piece hard gelatin capsule with the ingredients in the proportions shown in Table III, below.

Table III

<u>INGREDIENTS</u>	<u>AMOUNTS</u>
<i>N</i> -{(1 <i>S</i>)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1 <i>H</i> -pyrazol-5-yl)-2-furancarboxamide (Compound B)	75mg
Mannitol	250mg
Talc	125mg
Magnesium Stearate	8mg

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Example 4 - Tablet Composition

The sucrose, microcrystalline cellulose and the compounds of the invented combination, as shown in Table IV below, are mixed and granulated in the proportions shown with a 10% gelatin solution. The wet granules are screened, dried, mixed with the starch, talc and stearic acid, then screened and compressed into a tablet.

25

Table IV

<u>INGREDIENTS</u>	<u>AMOUNTS</u>
N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine ditosylate monohydrate (the ditosylate monohydrate salt of Compound A)	250mg
N-[(1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl]-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide (Compound B)	75mg
Microcrystalline cellulose	300mg
sucrose	10mg
starch	40mg
talc	20mg
stearic acid	5mg

5

Example 5 - Tablet Composition

The sucrose, microcrystalline cellulose and one of the compounds of the invented combination, as shown in Table V below, are mixed and granulated in the proportions shown with a 10% gelatin solution. The wet granules are screened, dried, mixed with the starch, talc and stearic acid, then screened and compressed into a tablet.

10

Table V

<u>INGREDIENTS</u>	<u>AMOUNTS</u>
N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine ditosylate monohydrate (the ditosylate monohydrate salt of Compound A)	250mg
Microcrystalline cellulose	30mg
sucrose	4mg
starch	2mg
talc	1mg
stearic acid	0.5mg

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Example 6 - Tablet Composition

The sucrose, microcrystalline cellulose and one of the compounds of the invented combination, as shown in Table VI below, are mixed and granulated in the proportions shown with a 10% gelatin solution. The wet granules are screened, dried, mixed with the starch, talc and stearic acid, then screened and compressed into a tablet.

Table VI

<u>INGREDIENTS</u>	<u>AMOUNTS</u>
<i>N</i> -{(1 <i>S</i>)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1 <i>H</i> -pyrazol-5-yl)-2-furancarboxamide (Compound B)	75mg
Microcrystalline cellulose	300mg
sucrose	40mg
starch	20mg
talc	10mg
stearic acid	5mg

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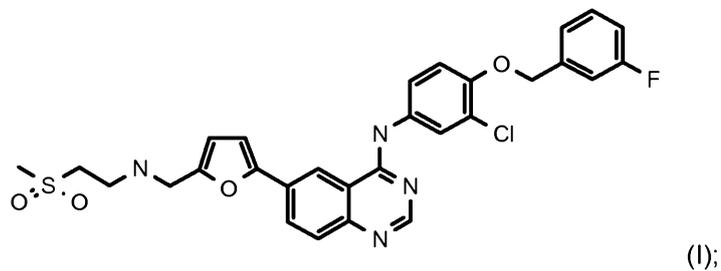
While the preferred embodiments of the invention are illustrated by the above, it is to be understood that the invention is not limited to the precise instructions herein disclosed and that the right to all modifications coming within the scope of the following claims is reserved.

15

We claim:

1. A combination comprising:

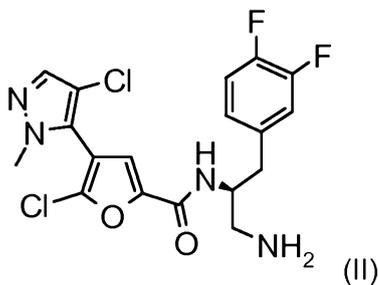
5 (i) a compound of Structure (I):



or a pharmaceutically acceptable hydrate and/or salt thereof; and

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(ii) a compound of Structure (II):



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or a pharmaceutically acceptable salt thereof.

2. A combination according to claim 1 where the compound of Structure (I) is in the form of a ditosylate monohydrate salt.

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3. A combination kit comprising a combination according to claim 1 or claim 2 together with a pharmaceutically acceptable carrier or carriers.

25

4. A combination according to any one of claims 1 to 3 where the amount of the compound of Structure (I) is an amount selected from 750mg to 1,250mg, and that amount is administered once per day in one or more tablets, and the amount of the compound of Structure (II) is an amount selected from 50mg to 300mg, and that amount is administered once per day.

5

5. Use of a combination according to any of claims 1 to 4 in the manufacture of a medicament or medicaments for the treatment of cancer.

10

6. A method of treating cancer in a human in need thereof which comprises the in vivo administration of a therapeutically effective amount of a combination of N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({2-(methanesulphonyl)ethyl}amino)methyl]-2-furyl]-4-quinazolinamine, or a pharmaceutically acceptable hydrate and/or salt thereof, and *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide, or a pharmaceutically acceptable salt thereof, to such human,

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wherein the combination is administered within a specified period, and

20

wherein the combination is administered for a duration of time.

7. A method according to claim 6 wherein the amount of N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({2-(methanesulphonyl)ethyl}amino)methyl]-2-furyl]-4-quinazolinamine, or a pharmaceutically acceptable hydrate and/or salt thereof, is selected from about 750mg to about 1,250mg, and that amount is administered once per day in one or more tablets, and the amount of *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide, or a pharmaceutically acceptable salt thereof, is selected from about 50mg to about 300mg, and that amount is administered once per day.

25

30

8. A method according to claim 7 wherein the amount of N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({2-(methanesulphonyl)ethyl}amino)methyl]-2-furyl]-4-quinazolinamine, or a pharmaceutically acceptable hydrate and/or salt thereof, is selected

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from about 750mg to about 1,250mg, and that amount is administered once per day in one or more tablets, and the amount of *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide, or a pharmaceutically acceptable salt thereof, is selected from about
5 60mg to about 300mg, and that amount is administered once per day.

9. A method according to claim 8 wherein *N*-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-
10 quinazolinamine ditosylate monohydrate and *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide, or a pharmaceutically acceptable salt thereof, are administered within 12 hours of each other for from 1 to 3 consecutive days followed by administration of *N*-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-
15 (methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine ditosylate monohydrate for from 3 to 7 consecutive days, optionally followed by one or more cycles of repeat dosing.

20 10. A method treating a cancer selected from: brain (gliomas), glioblastomas, 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,
25 Lymphoblastic T cell leukemia, Chronic myelogenous leukemia, Chronic lymphocytic leukemia, Hairy-cell leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, Chronic neutrophilic leukemia, Acute lymphoblastic T cell leukemia, Plasmacytoma, Immunoblastic large cell leukemia, Mantle cell leukemia, Multiple myeloma Megakaryoblastic leukemia, multiple myeloma, acute megakaryocytic
30 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,
35 salivary gland cancer, hepatocellular cancer, gastric cancer, nasopharangeal cancer,

buccal cancer, cancer of the mouth, GIST (gastrointestinal stromal tumor) and testicular cancer;

in a human in need thereof which comprises the *in vivo* administration of a therapeutically effective amount of a combination of N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine, or a pharmaceutically acceptable hydrate and/or salt thereof, and N-
5 { (1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide, or a pharmaceutically acceptable salt thereof, to such human,

10 wherein the combination is administered within a specified period, and
 wherein the combination is administered for a duration of time.

11. A method according to claim 10 wherein the amount of N-{3-Chloro-4-[(3-
15 fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine, or a pharmaceutically acceptable hydrate and/or salt thereof, is selected from about 750mg to about 1,250mg, and that amount is administered once per day in one or more tablets, and the amount of N-
20 { (1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide, or a pharmaceutically acceptable salt thereof, is selected from about 50mg to about 300mg, and that amount is administered once per day.

12. A method according to claim 11 wherein the amount of N-{3-Chloro-4-[(3-
25 fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine, or a pharmaceutically acceptable hydrate and/or salt thereof, is selected from about 750mg to about 1,250mg, and that amount is administered once per day in one or more tablets, and the amount of N-
30 { (1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide, or a pharmaceutically acceptable salt thereof, is selected from about 60mg to about 300mg, and that amount is administered once per day.

13. A method according to claim 12 wherein N-{3-Chloro-4-[(3-
35 fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-

quinazolinamine ditosylate monohydrate and *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide, or a pharmaceutically acceptable salt thereof, are administered within 12 hours of each other for from 1 to 3 consecutive days followed by administration of *N*-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({2-(methanesulphonyl)ethyl}amino)methyl]-2-furyl]-4-quinazolinamine ditosylate monohydrate for from 3 to 7 consecutive days, optionally followed by one or more cycles of repeat dosing.

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14. A method according to claim 10 wherein the cancer selected from ovarian, breast, pancreatic and prostate.

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15. A method according to claim 11 wherein the cancer selected from ovarian, breast, pancreatic and prostate.

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16. A method according to claim 12 wherein the cancer selected from ovarian, breast, pancreatic and prostate.

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17. A method according to claim 13 wherein the cancer selected from ovarian, breast, pancreatic and prostate.

18. A method of treating a cancer that is either wild type or mutant for Ras/Raf, PIK3CA/PTEN, AKT, EGFR or ErbB-2 or have amplification of PIK3CA, AKT, EGFR or ErbB-2 genes or have overexpression of EGFR or ErbB2 protein, in a human in need thereof which comprises the in vivo administration of a therapeutically effective amount of a combination of *N*-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({2-(methanesulphonyl)ethyl}amino)methyl]-2-furyl]-4-quinazolinamine, or a pharmaceutically acceptable hydrate and/or salt thereof, and *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide, or a pharmaceutically acceptable salt thereof, to such human,

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22. A method according to claim 18 wherein the cancer selected from ovarian, breast, pancreatic and prostate.

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23. A method according to claim 19 wherein the cancer selected from ovarian, breast, pancreatic and prostate.

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24. A method according to claim 20 wherein the cancer selected from ovarian, breast, pancreatic and prostate.

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25. A method according to claim 21 wherein the cancer selected from ovarian, breast, pancreatic and prostate.

20

26. A method treating a cancer selected from: brain (gliomas), glioblastomas, 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,

25

Lymphoblastic T cell leukemia, Chronic myelogenous leukemia, Chronic lymphocytic leukemia, Hairy-cell leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, 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,

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malignant lymphoma, hodgkins lymphoma, non-hodgkins lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma, follicular lymphoma,

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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;

in a human in need thereof which comprises the *in vivo* administration of a therapeutically effective amount of a combination of N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino)methyl]-2-furyl]-4-quinazolinamine, or a pharmaceutically acceptable hydrate and/or salt thereof, and N-
5 {(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide, or a pharmaceutically acceptable salt thereof, to such human,

wherein the compounds of the combination are administered sequentially.

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27. A method according to claim 26 wherein the amount of N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino)methyl]-2-furyl]-4-quinazolinamine, or a pharmaceutically acceptable hydrate and/or salt thereof, is selected from about 750mg to about 1,250mg, and that amount is administered once per day in
15 one or more tablets, and the amount of N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide, or a pharmaceutically acceptable salt thereof, is selected from about 50mg to about 300mg, and that amount is administered once per day.

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28. A method according to claim 27 wherein the amount of N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino)methyl]-2-furyl]-4-quinazolinamine, or a pharmaceutically acceptable hydrate and/or salt thereof, is selected from about 750mg to about 1,250mg, and that amount is administered once per day in
25 one or more tablets, and the amount of N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide, or a pharmaceutically acceptable salt thereof, is selected from about 60mg to about 300mg, and that amount is administered once per day.

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29. A method according to claim 28 wherein N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino)methyl]-2-furyl]-4-quinazolinamine ditosylate monohydrate is administered for from 1 to 30 consecutive days, followed by an optional drug holiday of from 1 to 14 days, followed by
35 administration of N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-

chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide, or a pharmaceutically acceptable salt thereof, for from 1 to 30 days, optionally followed by one or more cycles of repeat dosing.

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30. A method according to claim 26 wherein the cancer selected from ovarian, breast, pancreatic and prostate.

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31. A method according to claim 27 wherein the cancer selected from ovarian, breast, pancreatic and prostate.

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31. A method according to claim 28 wherein the cancer selected from ovarian, breast, pancreatic and prostate.

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33. A method according to claim 29 wherein the cancer selected from ovarian, breast, pancreatic and prostate.

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34. A method of treating a cancer that is either wild type or mutant for Ras/Raf, PIK3CA/PTEN, AKT, EGFR or ErbB-2 or have amplification of PIK3CA, AKT, EGFR or ErbB-2 genes or have overexpression of EGFR or ErbB2 protein, in a human in need thereof which comprises the in vivo administration of a therapeutically effective amount of a combination of N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine, or a pharmaceutically acceptable hydrate and/or salt thereof, and N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-

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furancarboxamide, or a pharmaceutically acceptable salt thereof, to such human, wherein the compounds of the combination are administered sequentially.

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35. A method according to claim 34 wherein the amount of N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-

quinazolinamine, or a pharmaceutically acceptable hydrate and/or salt thereof, is selected from about 750mg to about 1,250mg, and that amount is administered once per day in one or more tablets, and the amount of *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-

5 furancarboxamide, or a pharmaceutically acceptable salt thereof, is selected from about 50mg to about 300mg, and that amount is administered once per day.

36. A method according to claim 35 wherein the amount of *N*-{3-Chloro-4-[(3-
10 fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-
quinazolinamine, or a pharmaceutically acceptable hydrate and/or salt thereof, is selected from about 750mg to about 1,250mg, and that amount is administered once per day in one or more tablets, and the amount of *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-
15 furancarboxamide, or a pharmaceutically acceptable salt thereof, is selected from about 60mg to about 300mg, and that amount is administered once per day.

37. A method according to claim 36 wherein *N*-{3-Chloro-4-[(3-
20 fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-
quinazolinamine ditosylate monohydrate is administered for from 1 to 7 consecutive days, followed by an optional drug holiday of from 1 to 14 days, followed by administration of *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide, or a pharmaceutically acceptable salt thereof, for 1
25 day, optionally followed by one or more cycles of repeat dosing.

38. A method according to claim 34 wherein the cancer selected from ovarian,
breast, pancreatic and prostate.
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39. A method according to claim 35 wherein the cancer selected from ovarian,
breast, pancreatic and prostate.

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40. A method according to claim 36 wherein the cancer selected from ovarian, breast, pancreatic and prostate.

5 41. A method according to claim 37 wherein the cancer selected from ovarian, breast, pancreatic and prostate.

10 42. A method according to claim 36 wherein *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide, or a pharmaceutically acceptable salt thereof, is administered for from 1 to 3 consecutive days, followed by an optional drug holiday, followed by administration of *N*-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-{{2-(methanesulphonyl)ethyl}amino}methyl)-2-furyl]-4-quinazolinamine ditosylate
15 monohydrate, for from 3 to 7 days, optionally followed by one or more cycles of repeat dosing.

20 43. A method according to claim 42 wherein the cancer selected from ovarian, breast, pancreatic and prostate.

25 44. A method according to claim 29 wherein *N*-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-{{2-(methanesulphonyl)ethyl}amino}methyl)-2-furyl]-4-quinazolinamine ditosylate monohydrate is administered for from 1 to 21 consecutive days, followed by a drug holiday of from 3 to 10 days, followed by administration of *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide, or a pharmaceutically acceptable salt thereof, from 1 to 21 days, optionally followed by one or more cycles of repeat dosing.

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45. A method according to claim 44 wherein the cancer selected from ovarian, breast, pancreatic and prostate.

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46. A method according to claim 9 wherein N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine ditosylate monohydrate and N-((1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl)-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide, or a pharmaceutically acceptable salt thereof, are administered within 12 hours of each other for 2 consecutive days followed by administration of N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine ditosylate monohydrate for from 4 to 6 consecutive days, optionally followed by one or more cycles of repeat dosing.

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47. A method according to claim 8 wherein N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine ditosylate monohydrate and N-((1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl)-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide, or a pharmaceutically acceptable salt thereof, are administered within 12 hours of each other for 2 days over a 7 day period, and during the other days of the 7 day period N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine ditosylate monohydrate is administered alone, optionally followed by one or more cycles of repeat dosing.

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48. A method according to claim 13 wherein N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine ditosylate monohydrate and N-((1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl)-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide, or a pharmaceutically acceptable salt thereof, are administered within 12 hours of each other for 2 consecutive days followed by administration of N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine ditosylate monohydrate for from 4 to 6 consecutive days, optionally followed by one or more cycles of repeat dosing.

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49. A method according to claim 12 wherein N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-([2-(methanesulphonyl)ethyl]amino)methyl]-2-furyl]-4-quinazolinamine ditosylate monohydrate and N-[(1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl]-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide, or a pharmaceutically acceptable salt thereof, are administered within 12 hours of each other for 2 days over a 7 day period, and during the other days of the 7 day period N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-([2-(methanesulphonyl)ethyl]amino)methyl]-2-furyl]-4-quinazolinamine ditosylate monohydrate is administered alone, optionally followed by one or more cycles of repeat dosing.

50. A method according to claim 21 wherein N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-([2-(methanesulphonyl)ethyl]amino)methyl]-2-furyl]-4-quinazolinamine ditosylate monohydrate and N-[(1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl]-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide, or a pharmaceutically acceptable salt thereof, are administered within 12 hours of each other for 2 consecutive days followed by administration of N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-([2-(methanesulphonyl)ethyl]amino)methyl]-2-furyl]-4-quinazolinamine ditosylate monohydrate for from 4 to 6 consecutive days, optionally followed by one or more cycles of repeat dosing.

51. A method according to claim 20 wherein N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-([2-(methanesulphonyl)ethyl]amino)methyl]-2-furyl]-4-quinazolinamine ditosylate monohydrate and N-[(1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl]-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide, or a pharmaceutically acceptable salt thereof, are administered within 12 hours of each other for 2 days over a 7 day period, and during the other days of the 7 day period N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-([2-(methanesulphonyl)ethyl]amino)methyl]-2-furyl]-4-quinazolinamine ditosylate monohydrate is administered alone, optionally followed by one or more cycles of repeat dosing.

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52. A method according to claim 8 wherein N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine ditosylate monohydrate and N-((1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl)-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide, or a pharmaceutically acceptable salt thereof, are administered within 12 hours of each other for 5 consecutive days followed by administration of N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine ditosylate monohydrate for 2 consecutive days, optionally followed by one or more cycles of repeat dosing.

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53. A method according to claim 12 wherein N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine ditosylate monohydrate and N-((1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl)-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide, or a pharmaceutically acceptable salt thereof, are administered within 12 hours of each other for 5 consecutive days followed by administration of N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine ditosylate monohydrate for 2 consecutive days, optionally followed by one or more cycles of repeat dosing.

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54. A method according to claim 20 wherein N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine ditosylate monohydrate and N-((1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl)-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide, or a pharmaceutically acceptable salt thereof, are administered within 12 hours of each other for 5 consecutive days followed by administration of N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methanesulphonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine ditosylate monohydrate for 2 consecutive days, optionally followed by one or more cycles of repeat dosing.

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55. A combination according to claim 4 wherein the compound of Structure (I) and the compound of Structure (II) are administered within 12 hours of each other for at least 5 consecutive days.

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56. A combination according to claim 4 wherein the compound of Structure (I) and the compound of Structure (II) are administered within 12 hours of each other for at least 7 consecutive days.

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57. A combination according to claim 4 wherein the compound of Structure (I) and the compound of Structure (II) are administered within 12 hours of each other for at least 14 consecutive days.

Figure 1

