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COMBINATION OF PI3KINASE INHIBITORS AND SPLEEN TYROSINE KINASE INHIBITORS

CROSS REFERENCE TO RELATED APPLICATIONS

[001] This application claims the benefit under 35 U.S.C. § 119, of United States Application No. 62/195,522 filed on July 22, 2015 and United States Application No. 62/221,839 filed on September 22, 2015. The entire contents of each of the aforesaid applications are incorporated by reference herein in their entirety.

FIELD

[002] This disclosure provides new combination therapies for treating cancers. In particular, this disclosure provides methods for treating a cancer, comprising administering to a subject having a cancer a therapeutically effective amount of a combination of a PI3K-kinase α (PI3K α) inhibitor and a spleen tyrosine kinase (SYK) inhibitor.

BACKGROUND

[003] Cancer is characterized by uncontrolled cell reproduction. Uncontrolled cell reproduction results from the deregulation of the normal processes that control cell division, differentiation and apoptotic cell death.

[004] The phosphoinositide 3-kinases (PI3Ks) signaling pathway is one of the most highly mutated systems in human cancers. PI3K signaling is involved in many other disease states including rheumatoid arthritis, osteoarthritis, inflammatory diseases, inflammation mediated angiogenesis, inflammatory bowel diseases, chronic obstructive pulmonary disorder, psoriasis, multiple sclerosis, asthma, disorders related to diabetic complications, and inflammatory complications of the cardiovascular system such as acute coronary syndrome, allergic reactions, rheumatoid arthritis, autoimmune diseases such as lupus, asthma, emphysema and other respiratory diseases.

[005] The alpha (α) isoform of PI3K (PI3K α) has been implicated, for example, in a variety of human cancers. Angiogenesis has been shown to selectively require the α isoform of PI3K in the control of endothelial cell migration. (Graupera et al, Nature 2008; 453:662-6). Mutations in the gene coding for PI3K α or mutations which lead to upregulation of PI3K α are believed to occur in many human cancers such as lung, stomach, endometrial, ovarian, bladder, breast, gastric, colon, brain and skin cancers. Often, mutations in the gene coding for PI3K α are point mutations clustered within several hotspots in helical and kinase domains, such as E542K, E545K, and H1047R. Many of these mutations have been shown to be oncogenic gain-of-function mutations. Because of the high rate of PI3K mutations, targeting of this pathway may provide valuable therapeutic opportunities. While other PI3K isoforms such as PI3K γ or PI3K δ are expressed primarily in hematopoietic cells, PI3K α , along with PI3K β , is expressed constitutively.

[006] Spleen tyrosine kinase (SYK) is a 72 kDa non-receptor cytoplasmic tyrosine kinase. SYK has a primary amino acid sequence similar to that of zeta-associated protein-70 (ZAP-70) and is involved in receptor-mediated signal transduction. The N-terminal domain of SYK contains two Src-homology 2 (SH2) domains, which bind to diphosphorylated immunoreceptor tyrosine-based activation motifs (ITAMs) found in the cytoplasmic signaling domains of many immunoreceptor complexes. The C-terminus contains the catalytic domain, and includes several catalytic loop autophosphorylation sites that are responsible for receptor-induced SYK activation and subsequent downstream signal propagation. SYK is expressed in many cell types involved in adaptive and innate immunity, including lymphocytes (B cells, T cells, and NK cells), granulocytes (basophils, neutrophils, and eosinophils), monocytes, macrophages, dendritic cells, and mast cells. SYK is expressed in other cell types, including airway epithelium and fibroblasts in the upper respiratory system. See, e.g., Martin Turner et al., *Immunology Today* (2000) 21(3):148-54; and Michael P. Sanderson et al., *Inflammation & Allergy--Drug Targets* (2009) 8:87-95.

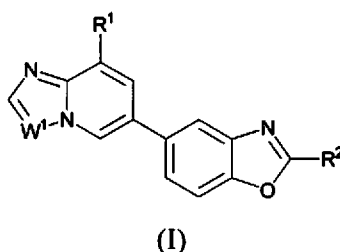
[007] SYK's role in ITAM-dependent signaling and its expression in many cell types suggest that compounds which inhibit SYK activity may be useful for treating hematological malignancies, such as acute myeloid leukemia, B-cell chronic lymphocytic leukemia, B-cell lymphoma (e.g., mantle cell lymphoma), and T-cell lymphoma (e.g., peripheral T-cell lymphoma); as well as epithelial cancers, such as lung cancer, pancreatic cancer, and colon cancer. See, e.g., Cynthia K. Hahn et al., *Cancer Cell* (2009) 16:281-294; D. H. Chu et al., *Immunol. Rev.* (1998) 165:167-180; A. L. Feldman et al., *Leukemia* (2008) 22:1139-43; A. Rinaldi et al., *Br. J. Haematol.* (2006) 132:303-316; B. Streubel et al., *Leukemia* (2006) 20:313-18; Maïke Buchner et al., *Cancer Research* (2009) 69(13):5424-32; A. D. Baudot et al., *Oncogene* (2009) 28:3261-73; and Anurag Singh et al., *Cancer Cell* (2009) 15:489-500.

[008] It would be beneficial if more effective cancer treatment regimens could be developed. Combinations of cancer treatments that could both treat cancer, and overcome resistance to anticancer agents would be especially helpful. Thus, there is a need for new cancer treatment regimens, including combination therapies of PI3K inhibitors in combination with SYK inhibitors.

BRIEF SUMMARY

[009] In certain embodiments, the invention relates to a method of treating a cancer comprising administering to a subject having a cancer a therapeutically effective amount of a combination of a PI3K α inhibitor and an SYK inhibitor.

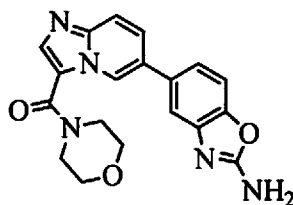
[010] In certain such embodiments, the PI3K α inhibitor is a compound of formula I:



or a pharmaceutically acceptable salt thereof, wherein R^1 is hydrogen; R^2 is amino; W^1 is CR^3 ; and R^3 is amido.

[011] In certain such embodiments, R^3 is $-C(O)N(R)_2$ wherein the two R groups taken together with the nitrogen to which they are attached form a 4-, 5-, 6- or 7-membered ring, optionally including one or two nonadjacent heteroatoms selected from N, O or S. In certain such embodiments, R^3 is $-C(O)N(R)_2$ wherein the two R groups taken together with the nitrogen to which they are attached form a morpholinyl ring. In certain embodiments, R^2 is NH_2 .

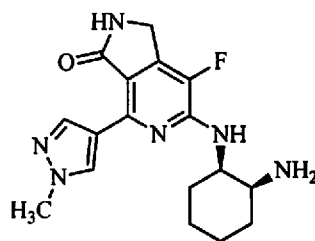
[012] In certain embodiments, the PI3K α inhibitor is a compound of formula II:



(II)

or a pharmaceutically acceptable salt thereof.

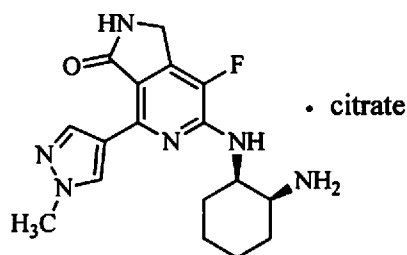
[013] In certain embodiments, the SYK inhibitor is a compound of formula III:



(III)

or a pharmaceutically acceptable salt thereof.

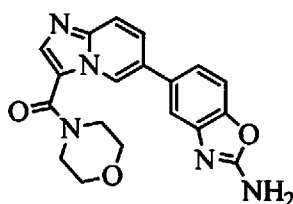
[014] In certain embodiments, the SYK inhibitor is a compound of formula IV:



(IV)

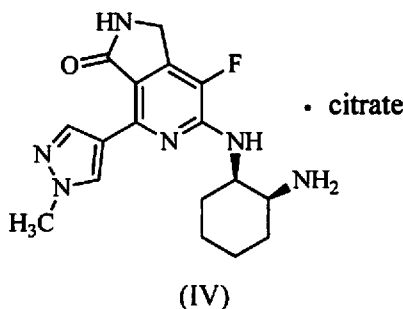
or a crystalline form thereof.

[015] In certain embodiments, the invention relates to a method of treating a cancer comprising administering to a subject having a cancer a therapeutically effective amount of a combination of a PI3K α inhibitor and a SYK inhibitor, wherein the PI3K α inhibitor is a compound of formula II:



(II)

or a pharmaceutically acceptable salt thereof; and
the SYK inhibitor is a compound of formula IV:



or a crystalline form thereof.

[016] In certain embodiments, the cancer is selected from lung cancer, head and neck squamous cell cancer, pancreatic cancer, breast cancer, ovarian cancer, renal cell carcinoma, prostate cancer, neuroendocrine cancer, gastrointestinal cancer, bladder cancer, colon cancer, cervical cancer and endometrial cancer.

[017] In certain embodiments, the cancer is gastrointestinal cancer. In certain such embodiments, the cancer is selected from gastric cancer and gastroesophageal adenocarcinoma. In certain embodiments, the cancer is gastric cancer. In certain embodiments, the cancer is gastroesophageal adenocarcinoma.

[018] In certain embodiments, the PI3K α inhibitor is administered for 3 consecutive days followed by an intermission of 4 consecutive days for at least one 7-day cycle. In certain embodiments, the PI3K α inhibitor is administered 3 days on and 4 days off for a 4 week cycle. In certain embodiments, the PI3K α inhibitor is administered once a day (QD) in each of the days that the PI3K α inhibitor is administered to the subject. In certain embodiments, the PI3K α inhibitor is administered twice a day (BID) in each of the days that the PI3K α inhibitor is administered to the subject.

[019] In certain embodiments, the SYK inhibitor is administered once daily (QD).

[020] In certain embodiments, the PI3K α inhibitor is administered once-daily on a 28-day cycle in which the PI3K α inhibitor is administered on days 1, 2, 3, 8, 9, 10, 15, 16, 17, 22, 23, and 24 of a 28-day cycle.

[021] In certain embodiments, a daily dose of the PI3K α inhibitor is about 300 to about 1200 mg. In certain embodiments, a daily dose of the PI3K α inhibitor is about 300 mg. In certain embodiments, a daily dose of the PI3K α inhibitor is about 600 mg. In certain embodiments, a daily dose of the PI3K α inhibitor is about 900 mg. In certain embodiments, a daily dose of the PI3K α inhibitor is about 1200 mg.

[022] In certain embodiments, a daily dose of the SYK inhibitor is about 20 mg to about 150 mg per day. In certain embodiments, a daily dose of the SYK inhibitor is about 60 mg given once daily. In certain embodiments, a daily dose of the SYK inhibitor is about 80 mg given once daily. In certain embodiments, a daily dose of the SYK inhibitor is about 100 mg given once daily.

[023] In certain embodiments, the PI3K α inhibitor and the SYK inhibitor are both administered orally.

[024] In certain embodiments, the PI3K α inhibitor and the SYK inhibitor are administered simultaneously. In certain embodiments, the PI3K α inhibitor and the SYK inhibitor are administered sequentially.

BRIEF DESCRIPTION OF THE DRAWINGS

[025] Figure 1 shows the mean tumor volume (MTV) over time for various treatment groups.

[026] Figure 2 shows mean percent body the mean percent body weight change for various treatment groups.

[027] Figure 3 shows the antitumor activity of Compound A and Compound B alone or in combination against PHTXM-30Ga xenografts.

[028] Figure 4 shows the changes in animal body weight following the administration of Compound A and Compound B alone or in combination.

DETAILED DESCRIPTION

[029] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this disclosure belongs. All patents and publications referred to herein are incorporated by reference in their entirety.

[030] The term “phosphoinositide 3-kinase (PI3K)” as used herein refers to any kinase family capable of phosphorylating the 3-position hydroxyl group of the inositol ring of phosphatidylinositol. The PI3Ks are involved in cellular functions such as cell growth, proliferation, differentiation, motility, survival and intracellular trafficking. Examples of the PI3Ks include, but are not limited to, PI3K α , PI3K β , PI3K δ and PI3K γ . In certain embodiments, the PI3K is PI3K α .

[031] The term “PI3K inhibitor” or “PI3K antagonist” as used herein refers a compound having the ability to interact with a phosphoinositide 3-kinases (PI3K), whether by inhibiting, reducing or expression of PI3K activity. Inhibiting or reducing PI3K activity means reducing the ability of a PI3K to phosphorylate a substrate peptide or protein. In certain embodiments, such reduction of PI3K activity is at least about 50%, at least about 75%, at least about 90%, at least about 95%, or at least about 99%. In certain embodiments, the PI3K inhibitor is a selective PI3K α inhibitor. In certain embodiments, the PI3K inhibitor is a PI3K β , δ or γ selective inhibitor.

[032] The term “Spleen tyrosine kinase” used herein refers to any member of the Syk family of tyrosine kinases. SYK is a 72 kDa non-receptor cytoplasmic tyrosine kinase.

[033] The term “Spleen tyrosine kinase inhibitor” or “SYK inhibitor” used herein refers to a compound having the ability to interact with Spleen tyrosine kinase and inhibiting its enzymatic activity.

[034] As used herein, the terms “treatment,” “treat,” and “treating” are meant to include the full spectrum of intervention for the cancer from which the subject is suffering, such as administration of the combination to alleviate, slow, stop, or reverse one or more symptoms of the cancer or to delay the progression of the cancer even if the cancer is not actually eliminated. Treatment can include, for example, a decrease in the severity of a symptom, the number of symptoms, or frequency of relapse, e.g., the inhibition of tumor growth, the arrest of tumor growth, or the regression of already existing tumors.

[035] The term “subject”, as used herein, means a mammal, and “mammal” includes, but is not limited to, a human. In certain embodiments, the subject has been treated with an agent, e.g., a PI3K inhibitor and/or an SYK inhibitor, prior to initiation of treatment according to the method of the disclosure. In certain embodiments, the subject is at risk of developing or experiencing a recurrence of a cancer.

[036] The term “anti-cancer agent”, “anti-tumor agent” or “chemotherapeutic agent” refers to any agent useful in the treatment of a neoplastic condition. One class of anti-cancer agents comprises chemotherapeutic agents.

[037] The term “effective amount” or “therapeutically effective amount” refers to that the amount of a compound, or combination of one or more compounds when administered (either sequentially or simultaneously) that elicits the desired biological or medicinal response, e.g., either destroys the target cancer cells or slows or arrests the progression of the cancer in a subject. The therapeutically effective amount may vary depending upon the intended application (in vitro or in vivo), or the subject and disease condition being treated, e.g., the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one skilled in the art. The term also applies to a dose that will induce a particular response in target cells, e.g., reduction of platelet adhesion and/or cell migration. For example, the “therapeutically effective amount” as used herein refers to the amount of a PI3K inhibitor and the amount of an SYK inhibitor that, when administered in combination have a beneficial effect. In certain embodiments, the combined effect is additive. In certain embodiments, the combined effect is synergistic. Further, it will be recognized by one skilled in the art that in the case of combination therapy, the amount of the PI3K inhibitors and/or the amount of the SYK inhibitor may be used in a “sub-therapeutic amount”, i.e., less than the therapeutically effective amount of the PI3K or SYK inhibitor alone.

[038] The term “about” refers to approximately, in the region of, roughly, or around. When the term “about” is used in conjunction with a number or a numerical range, it means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range may vary from, for example, between 1% and 15% of the stated number or numerical range. In general, the term “about” is used herein to modify a numerical value above and below the stated value by a variance of $\pm 10\%$.

[039] The term “neoplastic disorder” refers to disorders, diseases, and conditions generally related to the presence of cells possessing abnormal growth characteristics, such as uncontrolled proliferation, immortality, metastatic potential, rapid growth and proliferation rate, perturbed oncogenic signaling, and certain characteristic morphological features. This includes, but is not limited to the growth of: (1) benign or malignant cells (e.g., tumor cells) that correlates with overexpression of a tyrosine or serine/threonine kinase; (2) benign or malignant cells (e.g., tumor cells) that correlates with abnormally high level of tyrosine or serine/threonine kinase activity or lipid kinase activity. Exemplary tyrosine kinases implicated in a neoplastic condition include but are not limited to receptor tyrosine kinases such as epidermal growth factor receptors (EGF receptor), platelet derived growth factor (PDGF) receptors, and

cytosolic tyrosine kinases such as *src* and *abl* kinase. Non-limiting serine/threonine kinases implicated in neoplastic condition include but are not limited to *raf*, *mek*, *mTor*, and *akt*. Exemplary lipid kinases include but are not limited to PI3 kinases such as PI3K α , PI3K β , PI3K γ and PI3K δ .

[040] The term “combination administration,” or “administered in combination” refers to administering of more than one pharmaceutically active ingredients (including but not limited to a PI3K inhibitor and an SYK inhibitor as disclosed herein) to a subject. Combination administration may refer to simultaneous administration or may refer to sequential administration of the PI3K inhibitor and the SYK inhibitor as disclosed herein.

[041] The terms “simultaneous” and “simultaneously” refer to the administration of the PI3K inhibitor and the SYK inhibitor as disclosed herein, to a subject at the same time, or at two different time points that are separated by no more than 2 hours.

[042] The terms “sequential” and “sequentially” refer to the administration of the PI3K inhibitor and the SYK inhibitor as disclosed herein, to a subject at two different time points that are separated by more than 2 hours, e.g., about 3 hours, 4 hours, 5 hours, about 8 hours, 12 hours, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days or even longer.

[043] The term “intermission” refers to a period that is that subsequent to the administration of one or more particular pharmaceutically active ingredients to a subject in an intermittent regimen. Intermission refers to a rest period wherein a particular pharmaceutically active ingredient is not administered for at least one day.

[044] The term “synergistic effect” refers to a situation where the combination of two or more agents produces a greater effect than the sum of the effects of each of the individual agents. The term encompasses not only a reduction in symptoms of the disorder to be treated, but also an improved side effect profile, improved tolerability, improved patient compliance, improved efficacy, or any other improved clinical outcome.

[045] The term a “sub-therapeutic amount” of an agent or therapy is an amount less than the effective amount for that agent or therapy as a single agent, but when combined with an effective or sub-therapeutic amount of another agent or therapy can produce a result desired by the physician, due to, for example, synergy in the resulting efficacious effects, or reduced side effects.

[046] The terms “a week” or “7-day cycle”, as used herein, are used interchangeably. These terms refer to a continuous period of time covering the duration of seven consecutive days. For example, a week can start on Monday and end on the following Sunday, or a 7-day cycle can start on Wednesday and end on the next Tuesday.

[047] The term “pharmaceutically acceptable salt” refers to salts derived from a variety of organic and inorganic counter ions well known in the art. Pharmaceutically acceptable acid addition salts may be formed with inorganic acids and organic acids. For reviews of suitable salts, see, e.g., Berge et al, J. Pharm. Sci. 66:1-19 (1977) and Remington: The Science and Practice of Pharmacy, 20th Ed., ed. A. Gennaro, Lippincott Williams & Wilkins, 2000. Non-limiting examples of suitable acid salts includes: hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, acetic acid, propionic

acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, lactate acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Non-limiting examples of suitable base salts includes: sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, specifically such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine.

[048] The term “pharmaceutically acceptable carrier” or “pharmaceutically acceptable excipient” includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions of the disclosure is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

[049] The terms “carrier”, “adjuvant”, or “vehicle” are used interchangeably herein, and include any and all solvents, diluents, and other liquid vehicles, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. *Remington: The Science and Practice of Pharmacy, 20th Ed.*, ed. A. Gennaro, Lippincott Williams & Wilkins, 2000 discloses various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds of the disclosure, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this disclosure.

[050] Unless otherwise stated, compounds described herein include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structure except for the replacement of a hydrogen atom by a deuterium or tritium, or the replacement of a carbon atom by a ^{13}C - or ^{14}C -enriched carbon are within the scope of the disclosure.

[051] Unless otherwise stated, compounds described herein include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the disclosure. In the compounds described herein where relative stereochemistry is defined, the diastereomeric purity of such a compound may be at least 80%, at least 90%, at least 95%, or at least 99%. As used herein, the term “diastereomeric purity” refers to the amount of a compound having the depicted relative stereochemistry, expressed as a percentage of the total amount of all diastereomers present.

[052] The term “solvate or solvated” means a physical association of a compound of this invention with one or more solvent molecules. This physical association includes hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are

incorporated in the crystal lattice of the crystalline solid. "Solvate" or "solvated" encompasses both solution-phase and isolable solvates. Representative solvates include, but are not limited to, hydrates, ethanolates, and methanolates. Unless otherwise stated, compounds described herein include the solvated and hydrated forms.

[053] The term "amino" or "amine" refers to a $-N(R^a)_2$ group, where each R^a is independently selected from hydrogen, alkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl. In certain embodiments, the two R^a groups may be combined with the nitrogen atom to which they are attached to form a 4-, 5-, 6-, or 7-membered ring.

[054] The term "amido" or "amide" refers to a chemical moiety with formula $-C(O)N(R)_2$ or $-NHC(O)R$, where each R is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl and heteroalicyclic; or wherein the two R groups taken together with the nitrogen to which they are attached may form a 4-10 membered ring optionally containing one or two nonadjacent heteroatoms selected from N, O, or S. Unless otherwise stated, an amido group is optionally substituted independently by one or more of the substituents as described herein for alkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl.

[055] The term "aryl" refers to a carbocyclic aromatic moiety with six to ten ring atoms (e.g., C_6 - C_{10} aryl). Examples of aryl rings include, but are not limited to benzene and naphthalene. As used, a numerical range refers to each integer in the given range; e.g., "6 to 10 ring atoms" is meant to include aryl groups that have 6 ring atoms, 7 ring atoms, etc., up to and including 10 ring atoms. The term includes monocyclic, bicyclic, tricyclic and tetracyclic ring systems.

[056] The term "heteroaryl" refers to a 5- to 18-membered aromatic moiety (e.g., C_5 - C_{13} heteroaryl) that includes one or more ring heteroatoms selected from nitrogen, oxygen and sulfur. The term heteroaryl includes monocyclic, bicyclic, tricyclic and tetracyclic ring systems. As used, a numerical range refers to each integer in the given range; e.g., "6 to 10 ring atoms" is meant to include aryl groups that have 6 ring atoms, 7 ring atoms, etc., up to and including 10 ring atoms. The heteroatom(s) in the heteroaryl radical is optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. Examples of heteroaryl groups include, but are not limited to, benzoxazole, benzofuran, benzothiophene, pyrrole, furan, thiophene, pyrazole, imidazole, pyridine, pyridazine, pyrimidine, pyrazine, indole, indazole, purine, quinoline, isoquinoline, and quinazoline.

[057] The terms "arylalkyl" and "aralkyl" as used herein refer to a group wherein an aryl group is linked to the rest of the molecule through an alkylene moiety. Examples of aralkyl groups include, but are not limited to, benzyl, phenethyl, phenpropyl and phenbutyl.

[058] The terms "heteroarylalkyl" as used herein refer wherein a heteroaryl group is linked to the rest of the molecule through an alkylene moiety, for example 3-furylmethyl.

[059] The terms "heterocycloalkyl" or "heterocyclyl" refers to a stable 3- to 18-membered non-aromatic (fully or partially saturated) ring moiety comprising one to six heteroatoms selected from nitrogen, oxygen and sulfur. In certain embodiments, the term heterocycloalkyl as used herein refers to a C_5 - C_{10} heterocycloalkyl, a C_4 - C_{10} heterocycloalkyl, or a C_3 - C_{10} heterocycloalkyl. The term

heterocycloalkyl includes monocyclic, bicyclic, tricyclic and tetracyclic ring systems. The heteroatoms in the heterocycloalkyl radical may be optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. Examples of such heterocycloalkyl groups include, but are not limited to pyrrolidine, piperidine, piperazine, morpholine, tetrahydrofuran, and tetrahydropyran.

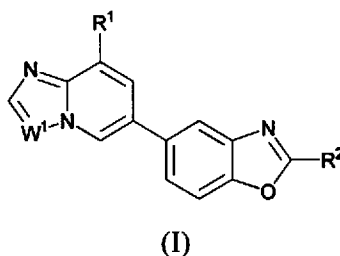
[060] The term “alkoxy” as used herein refers to the group -O-alkyl. Examples include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy and the like.

[061] The term “sulfonamido” refers to a $-S(=O)_2-NR'R'$ radical, where each R' is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl.

[062] Unless otherwise stated, each of the alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, aryl, heteroaryl, heteroarylalkyl, heterocycloalkyl and alkoxy groups are optionally substituted, when it is chemically possible and stable, by one or more substituents which are independently selected from alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilyl, $-OR^b$, SR^b , $-OC(O)-R^b$, $-N(R^b)_2$, $-C(O)R^b$, $-C(O)OR^b$, $-OC(O)N(R^b)_2$, $-C(O)N(R^b)_2$, $-N(R^b)C(O)OR^b$, $-N(R^b)C(O)R^b$, $-N(R^b)C(O)N(R^b)_2$, $-N(R^b)C(NR^b)N(R^b)_2$, $-N(R^b)S(O)_tR^b$ (where t is 1 or 2), $-S(O)_tOR^b$ (where t is 1 or 2), $-S(O)_tN(R^b)_2$ (where t is 1 or 2), and $PO_3(R^b)_2$ where each R^b is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

PI3K kinase inhibitors

[063] In certain embodiments described herein, the PI3K α inhibitor is a compound of formula I:



or a pharmaceutically acceptable salt thereof, wherein

W^1 is CR^3 ;

R^1 is hydrogen;

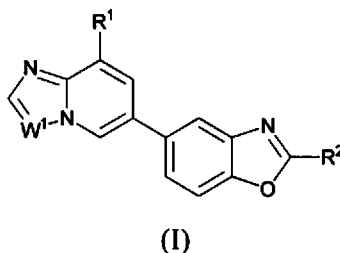
R^2 is hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocycloalkyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, or carbonate; and

R^3 is $-C(O)N(R)_2$ or $-NHC(O)R$, wherein R is hydrogen, alkyl, cycloalkyl, aryl, heteroaryl and heteroalicyclic; or wherein the two R groups taken together with the nitrogen to which they are attached form a 4-10 membered ring optionally contains one or two nonadjacent heteroatoms selected from N, O, or S.

[064] In certain embodiments, R^2 is amino. In certain such embodiments, R^2 is NH_2 .

[065] In certain embodiments, R^3 is $-C(O)N(R)_2$ wherein the two R groups taken together with the nitrogen to which they are attached form a 4-10 membered heterocyclic ring.

[066] In certain embodiments, the PI3K kinase inhibitor is a compound of formula I:



or a pharmaceutically acceptable salt thereof, wherein

R^1 is hydrogen;

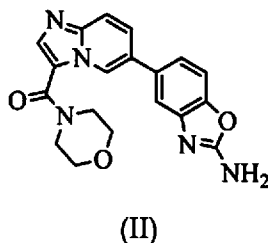
R^2 is NH_2 ;

W^1 is CR^3 ; and

R^3 is $-C(O)N(R)_2$, wherein the two R groups taken together with the nitrogen to which they are attached form a 4-10 membered heterocyclic ring.

[067] In certain embodiments, R^3 is $-C(O)N(R)_2$ wherein the two R groups taken together with the nitrogen to which they are attached form a 4-, 5-, 6-, or 7-membered heterocyclic ring. In certain such embodiments, R^3 is $-C(O)N(R)_2$ wherein the two R groups taken together with the nitrogen to which they are attached form a 6-membered heterocyclic ring. In certain such embodiments, R^3 is $-C(O)N(R)_2$ wherein the two R groups taken together with the nitrogen to which they are attached form a morpholino ring.

[068] In certain embodiments, PI3K α inhibitor is a compound of formula II:



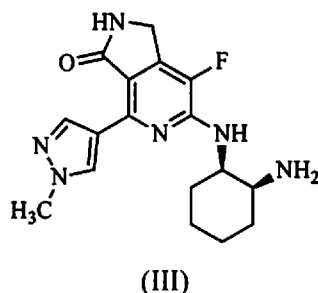
or a pharmaceutically acceptable salt thereof.

[069] In certain embodiments, the PI3K α inhibitor is a compound of formula II, or (6-(2-aminobenzo[d]oxazol-5-yl)imidazo[1,2-a]pyridin-3-yl)(morpholino)methanone. This compound may also be referred to as Compound A.

[070] PI3K α inhibitors as disclosed herein are described in, for example, in WO 2011/022439 A1 and US 9,085,560. They may be prepared by methods known to one skilled in the art and/or according to the methods described in WO2011/022439 and US 9,085,560, each of which is hereby incorporated by reference in their entirety.

SYK inhibitors

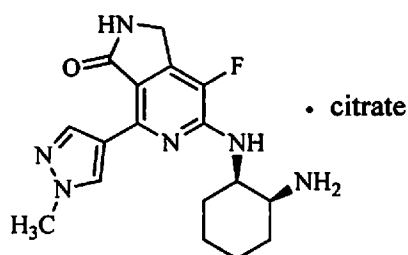
[071] In certain embodiments, the SYK inhibitor is a compound of formula III, or 6-((1R,2S)-2-aminocyclohexylamino)-7-fluoro-4-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[3,4-c]pyridine-3(2H)-one:



(III)

or a pharmaceutically acceptable salt thereof.

[072] In certain embodiments, the SYK inhibitor is a compound of formula IV, or 6-((1R,2S)-2-aminocyclohexylamino)-7-fluoro-4-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[3,4-c]pyridine-3(2H)-one citrate:



(IV)

or a crystalline form thereof. This compound may also be referred to as Compound B.

[073] The compounds of formula III or formula IV are described in WO 2011079051, US 8,440,689, and US 62/093564. They may be prepared by methods known to one skilled in the art and/or according to the methods described in WO 2011/022439, US 8,440,689, and US 62/093564, each of which is hereby incorporated by reference in its entirety.

Methods of treatments and/or medical uses

[074] There is growing evidence that SYK is a component of the cellular signaling cascade associated with EBV latency and transformation. EBV-positive tumors may express latent membrane protein 2A (LMP2A), which contains an immunoreceptor tyrosine-based activation motif (ITAM) domain. ITAM-mediated SYK activation has been shown to be essential to the LMP2A-induced tumorigenicity in EBV driven tumor models for both EBV associated lymphomas such as Burkitt's lymphoma, and EBV associated solid tumors such as nasopharyngeal carcinoma. Recently, this subtype (approximately 9%) of gastric cancer has been identified as positive for EBV with a high frequency of PIK3CA mutations, suggesting a role of SYK and PI3K α in the pathogenesis of EBV-positive gastric cancer. Accordingly, in certain embodiments, the invention relates to a method of treating a neoplastic condition comprising administering to a subject having a neoplastic condition a therapeutically effective amount of a combination of a PI3K α inhibitor and a SYK inhibitor.

[075] In certain embodiments, the invention relates to a method of treating a neoplastic condition, such as a cancer, comprising administering to a subject having a neoplastic condition a therapeutically effective amount of a combination of a PI3K α inhibitor and a SYK inhibitor. In certain such embodiments, the PI3K α inhibitor is a compound of formula I or II. In certain such embodiments, the SYK inhibitor is a compound of formula III or IV. In certain embodiments, the neoplastic condition

(e.g., cancer) is a PI3-kinase mediated cancer. Such PI3-kinase mediated cancers include, but are not limited to, lung cancer, head and neck squamous cell carcinoma, pancreatic cancer, breast cancer, ovarian cancer, renal cell carcinoma, prostate cancer, neuroendocrine cancer, gastrointestinal cancer, bladder cancer, colon cancer, cervical cancer and endometrial cancer. In certain embodiments, the neoplastic condition (e.g., cancer) is an EBV-positive cancer. In certain embodiments, the subject has a PIK3CA mutation and/or amplification.

[076] In certain embodiments the invention relates to a method for treating a cancer selected from non-small cell lung cancer (NSCLC), small cell lung cancer, head and neck squamous cell carcinoma, pancreatic cancer, breast cancer, ovarian cancer, renal cell carcinoma, prostate cancer, neuroendocrine cancer, gastrointestinal cancer, bladder cancer, colon cancer, cervical cancer and endometrial cancer, comprising administering to a subject having a cancer selected from non-small cell lung cancer (NSCLC), small cell lung cancer, head and neck squamous cell carcinoma, pancreatic cancer, breast cancer, ovarian cancer, renal cell carcinoma, prostate cancer, neuroendocrine cancer, gastrointestinal cancer, bladder cancer, colon cancer, cervical cancer and endometrial cancer a therapeutically effective amount of a combination of a PI3K α inhibitor and a SYK inhibitor. In certain such embodiments, the PI3K α inhibitor is a compound of formula I or II. In certain such embodiments, the SYK inhibitor is a compound of formula III or IV.

[077] In certain embodiments, the cancer condition is lung cancer. In certain embodiments, the cancer is non-small cell lung cancer. In certain such embodiments, the non-small cell lung cancer is squamous non-small cell lung cancer. In certain embodiments, the non-small cell lung cancer is non-squamous non-small cell lung cancer. In certain embodiments, the cancer is small cell lung cancer. Thus, in certain embodiments, the invention relates to a method for treating lung cancer (e.g., non-small cell lung cancer or small cell lung cancer) comprising administering to a subject having lung cancer a therapeutically effective amount of a combination of a therapeutically effective amount of a combination of a PI3K α inhibitor and a SYK inhibitor. In certain such embodiments, the PI3K α inhibitor is a compound of formula I or II. In certain such embodiments, the SYK inhibitor is a compound of formula III or IV.

[078] In certain embodiments, the cancer is gastrointestinal cancer. In certain embodiments, the gastrointestinal cancer is selected from esophageal cancer, stomach cancer (also known as gastric cancer or gastric carcinoma), gastroesophageal cancer (e.g., gastroesophageal adenocarcinoma), biliary system cancer, pancreatic cancer, intestinal cancer (e.g., small or large intestinal cancer), rectal cancer, and anal cancer. In certain embodiments, the cancer is gastric cancer or gastroesophageal adenocarcinoma. In certain embodiments, the cancer is gastric cancer. In certain embodiments, the cancer is gastroesophageal adenocarcinoma. Thus, in certain embodiments, the invention relates to a method for treating a gastrointestinal cancer (e.g., gastric cancer or gastroesophageal adenocarcinoma), comprising administering to a subject having a gastrointestinal cancer a therapeutically effective amount of a combination of a PI3K α inhibitor and a SYK inhibitor. In certain such embodiments, the PI3K α inhibitor

is a compound of formula I or II. In certain such embodiments, the SYK inhibitor is a compound of formula III or IV.

[079] In certain embodiments, the invention relates to a method of suppressing tumor regrowth comprising administering to a subject having a tumor a therapeutically effective amount of a combination of a PI3K α inhibitor and a SYK inhibitor. In certain such embodiments, the PI3K α inhibitor is a compound of formula I or II. In certain such embodiments, the SYK inhibitor is a compound of formula III or IV.

[080] In certain embodiments, the present disclosure provides a method of suppressing tumor regrowth in a subject in need thereof administering to the subject simultaneously or sequentially a therapeutically effective amount of a PI3K α inhibitor of formula I or II and a SYK inhibitor of formula III or IV. In certain embodiments, the growth of cells contacted with a PI3K inhibitor and a SYK inhibitor is retarded by at least about 50% as compared to growth of non-contacted cells. In certain embodiments, cell proliferation of contacted cells is inhibited by at least about 75%, at least about 90%, or at least about 95% as compared to non-contacted cells. In certain embodiments, the phrase “inhibiting cell proliferation” includes a reduction in the number of contacted cells, as compare to non-contacted cells. Thus, a PI3K inhibitor and an inhibitor of SYK that inhibits cell proliferation in a contacted cell may induce the contacted cell to undergo growth retardation, to undergo growth arrest, to undergo programmed cell death (i.e., apoptosis), or to undergo necrotic cell death.

[081] In certain embodiments, the PI3K α inhibitor and SYK inhibitor are administered such that they provide a synergistic effect in the treatment of a neoplastic disease. In certain such embodiments, the PI3K α inhibitor and/or the SYK inhibitor may be administered in a sub-therapeutic amount. In certain embodiments, the PI3K α inhibitor and SYK inhibitor are administered such that they provide an additive effect in the treatment of a neoplastic disease.

[082] In certain embodiments, the PI3K α inhibitor and the SYK inhibitor are administered simultaneously, wherein simultaneous administration may comprise the two agents in a single formulation or may comprise the two agents in separate. In certain embodiments, the PI3K α inhibitor and the SYK inhibitor are administered sequentially. In certain such embodiments, the the PI3K α inhibitor is administered prior to the SYK inhibitor. In certain such embodiments, the SYK inhibitor is administered prior to the PI3K α inhibitor.

[083] In certain embodiments, the PI3K α inhibitor and the SYK inhibitor as disclosed herein are administered orally. In certain embodiments the PI3K α inhibitor of formula I or II and the SYK inhibitor of formula III or IV are both administered orally.

[084] The therapeutically effective amount of the subject combination of compounds may vary depending upon the intended application (*in vitro* or *in vivo*), or the subject and disease condition being treated, e.g., the weight and age of the subject, the severity of the disease condition, the manner of administration and the like. The term also applies to a dose that will induce a particular response in target cells, e.g., reduction of proliferation or downregulation of activity of a target protein. The specific dose will vary depending on the particular compounds chosen, the dosing regimen to be followed,

whether it is administered in combination with other compounds, timing of administration, the tissue to which it is administered, and the physical delivery system in which it is carried.

[085] The amounts or suitable doses of the methods of this disclosure depends upon a number of factors, including the nature of the severity of the condition to be treated, the particular inhibitor, the route of administration and the age, weight, general health, and response of the individual subject. In certain embodiments, the suitable dose level is one that achieves a therapeutic response as measured by tumor regression, or other standard measures of disease progression, progression free survival or overall survival. In certain embodiments, the suitable dose level is one that achieves this therapeutic response and also minimizes any side effects associated with the administration of the therapeutic agent. The suitable dose levels may be ones that prolong the therapeutic response and/or prolong life.

[086] It will be understood that a suitable dose of the PI3K α inhibitor and the SYK inhibitor may be taken at any time of the day or night. In certain embodiments, a suitable dose of each inhibitor is taken in the morning. In some other embodiments, a suitable dose of each inhibitor is taken in the evening. In certain embodiments, a suitable dose of each of the inhibitors is taken both in the morning and the evening. It will be understood that a suitable dose of each inhibitor may be taken with or without food. In certain embodiments a suitable dose of an inhibitor is taken with a meal. In certain embodiments a suitable dose of an inhibitor is taken while fasting.

[087] In certain embodiments, the PI3K α inhibitor is administered on consecutive days in a 7-day cycle followed by an intermission. In certain such embodiments, the PI3K α inhibitor is administered for 3 consecutive days followed by an intermission of 4 consecutive days for at least one 7-day cycle. In certain embodiments, the PI3K α inhibitor is administered for 3 consecutive days followed by an intermission of at least one day per 7-day cycle. In certain embodiments, the PI3K α inhibitor is administered for 3 consecutive days followed by an intermission of 4 consecutive days per 7-day cycle. In yet other embodiments, the PI3K α inhibitor is administered for 4 consecutive days followed by an intermission of 3 consecutive days for at least one 7-day cycle. In yet other embodiments, the PI3K α inhibitor is administered for 5 consecutive days followed by an intermission of 2 consecutive days for at least one 7-day cycle. In yet other embodiments, the PI3K α inhibitor is administered for 6 consecutive days followed by an intermission of 1 day for at least one 7-day cycle.

[088] In certain embodiments, the PI3K α inhibitor is administered every other day (i.e., 7 dosing days in 2 weeks). In certain embodiments, the PI3K α inhibitor is administered for three non-consecutive days within a 7-day cycle. In certain embodiments, the PI3K α inhibitor is administered on alternate days in a 7-day cycle. In certain embodiments, the PI3K α inhibitor is administered on alternate days in a 7-day cycle followed by an intermission. For example, the PI3K α inhibitor is administered at least 2 times on alternate days within a 7-day cycle. In certain embodiments, the PI3K α inhibitor is administered at least 3 times on alternate days within a 7-day cycle. In certain embodiments, the PI3K α inhibitor is administered at least 4 times on alternate days within a 7-day cycle.

[089] In certain embodiments, the PI3K α inhibitor is administered at least once a day (QD) in each of the days that the PI3K α inhibitor is administered to the subject. In certain embodiments, the PI3K α

inhibitor is administered once a day (QD) in each of the days that the PI3K α inhibitor is administered to the subject. In certain embodiments, the PI3K α inhibitor is administered twice a day (BID) in each of the days that the PI3K α inhibitor is administered to the subject.

[090] In certain embodiments, a daily dose of the PI3K α inhibitor is about 100 to about 1200 mg. In certain embodiments, a daily dose of the PI3K α inhibitor is about 100 to about 2100 mg. In certain embodiments, a daily dose of the PI3K α inhibitor is about 300 to about 1200 mg. In certain embodiments, a daily dose of the PI3K α inhibitor is about 300 to about 2100 mg. In certain embodiments a daily dose of the PI3K α inhibitor is about 100 mg, about 300 mg, about 600 mg, or about 900 mg. In certain embodiments a daily dose of the PI3K α inhibitor is about 300 mg, about 600 mg, or about 900 mg. In certain embodiments a daily dose of the PI3K α inhibitor is about 100 mg, about 300 mg, about 600 mg, about 900 mg, about 1200 mg, about 1500 mg, about 1800 mg or about 2100 mg. In certain embodiments, a daily dose of the PI3K α inhibitor is about 300 mg, about 600 mg, about 900 mg, about 1200 mg, about 1500 mg, about 1800 mg or about 2100 mg. In certain embodiments, a daily dose of the PI3K α inhibitor is about 100 mg. In certain embodiments, a daily dose of the PI3K α inhibitor is about 300 mg. In certain embodiments, a daily dose of the PI3K α inhibitor is about 600 mg. In certain embodiments, a daily dose of the PI3K α inhibitor is about 900 mg. In certain embodiments, a daily dose of the PI3K α inhibitor is about 1200 mg. In certain embodiments, a daily dose of the PI3K α inhibitor is about 1500 mg. In certain embodiments, a daily dose of the PI3K α inhibitor is about 1800 mg. In certain embodiments, a daily dose of the PI3K α inhibitor is about 2100 mg.

[091] The amounts or suitable doses of the selective inhibitor of SYK depends upon a number of factors, including the nature of the severity of the condition to be treated, the particular inhibitor, the route of administration and the age, weight, general health, and response of the individual subject. In certain embodiments, the suitable dose level is one that achieves an effective exposure as measured by increased skin mitotic index, or decreased chromosome alignment and spindle bipolarity in tumor mitotic cells, or other standard measures of effective exposure in cancer patients. In certain embodiments, the suitable dose level is one that achieves a therapeutic response as measured by tumor regression, or other standard measures of disease progression, progression free survival or overall survival. In certain embodiments, the suitable dose level is one that achieves this therapeutic response and also minimizes any side effects associated with the administration of the therapeutic agent.

[092] Suitable daily dosages of a SYK inhibitor of formula III or IV can generally range, in single or divided or multiple doses, from about 20 mg to about 150 mg per day or about 40 mg to about 120 mg. In certain embodiments, suitable daily doses are about 20 mg, 30 mg, about 30 mg, about 40 mg, 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, or about 140 mg or about 150 mg per day. In some embodiments, the suitable dose may be given once daily or may be divided such that the compound is given twice or three times daily. In certain embodiments, the daily dose of the SYK inhibitor is about 20 mg. In certain embodiments, the daily dose of the SYK inhibitor is about 30 mg. In certain embodiments, the daily dose of the SYK inhibitor is about 40 mg. In certain embodiments, the daily dose of the SYK inhibitor is about 60 mg. In certain

embodiments, the daily dose of the SYK inhibitor is about 80 mg. In certain embodiments, the daily dose of the SYK inhibitor is about 100 mg. In certain embodiments, the daily dose of the SYK inhibitor is about 120 mg. In certain embodiments, the daily dose of the SYK inhibitor is about 150 mg. In certain embodiments, the SYK inhibitor is administered once daily.

[093] In certain embodiments, the PI3K α inhibitor is administered 3 days on and 4 days off for a 4 week cycle (i.e., 28-days). In certain embodiments, the PI3K α inhibitor is administered on a 28-day cycle in which the PI3K α inhibitor is administered on days 1, 2, 3, 8, 9, 10, 15, 16, 17, 22, 23, and 24 of a 28-day cycle. In certain embodiments, the PI3K α inhibitor is administered once-daily on a 28-day cycle in which the PI3K α inhibitor is administered on days 1, 2, 3, 8, 9, 10, 15, 16, 17, 22, 23, and 24 of a 28-day cycle.

Pharmaceutical Compositions

[094] In certain embodiments, the SYK inhibitor and the PI3K α inhibitor are both administered orally such as in a solid dosage form or a liquid dosage form. In certain embodiments, the PI3K α inhibitor is administered as a solid dosage form. In certain embodiments, the PI3K α inhibitor is administered as a liquid dosage form. In certain embodiments, the SYK inhibitor is administered as a solid dosage form. In certain embodiments, the SYK inhibitor is administered as a liquid dosage form.

[095] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar--agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents such as phosphates or carbonates.

[096] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules may be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that may be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[097] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, cyclodextrins, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Medical kits

[098] The present disclosure also provides medical kits. The kits include a PI3K α inhibitor and an SYK inhibitor as described herein, in suitable packaging, and written material that can include instructions for use, discussion of clinical studies, listing of side effects, and the like. Such kits may also include information, such as scientific literature references, package insert materials, clinical trial results, and/or summaries of these and the like, which indicate or establish the activities and/or advantages of the composition, and/or which describe dosing, administration, side effects, drug interactions, or other information useful to the health care provider. Such information may be based on the results of various studies, for example, studies using experimental animals involving in vivo models and studies based on human clinical trials. The kit may further contain another agent. In some embodiments, the inhibitors of the present disclosure and the agent are provided as separate compositions in separate containers within the kit. In some embodiments, the inhibitors of the present disclosure and the agent are provided as a single composition within a container in the kit. Suitable packaging and additional articles for use (e.g., measuring cup for liquid preparations, foil wrapping to minimize exposure to air, and the like) are known in the art and may be included in the kit. Kits described herein can be provided, marketed and/or promoted to health providers, including physicians, nurses, pharmacists, formulary officials, and the like. Kits may also, in some embodiments, be marketed directly to the consumer.

Further Combination therapies

[099] The present invention also provides methods for further combination therapies in which, in addition to a PI3K α inhibitor and an SYK inhibitor, one or more agents known to modulate other pathways, or the same pathway, may be used. In some embodiments, such therapy includes but is not limited to the combination of the composition comprising at least one PI3K α inhibitor and at least one SYK inhibitor, as described herein, with one or more additional therapeutic agents such as anticancer agents, chemotherapeutic agents, therapeutic antibodies, and radiation treatment, to provide, where desired, a synergistic or additive therapeutic effect. Pathways that may be targeted by administering another agent include, but are not limited to, spleen tyrosine kinase (SYK), MAP kinase, Raf kinases, Akt, NF κ B, WNT, RAS/RAF/MEK/ERK, JNK/SAPK, p38 MAPK, Src Family Kinases, JAK/STAT and/or PKC signaling pathways. Other agents may target one or more members of one or more signaling pathways. Representative members of the nuclear factor-kappaB (NF κ B) pathway include but are not

limited to RelA (p65), RelB, c-Rel, p50/p105 (NF- κ B 1), p52/p 100 (NF- κ B2), I κ B, and I κ B kinase. Non-limiting examples of receptor tyrosine kinases that are members of the phosphatidylinositol 3-kinase (PI3K)/AKT pathway that may be targeted by one or more agents include FLT3 LIGAND, EGFR, IGF-1R, HER2/neu, VEGFR, and PDGFR. Downstream members of the PI3K/AKT pathway that may be targeted by agents according to the methods of the invention include, but are not limited to, forkhead box O transcription factors, Bad, GSK-3 β , I- κ B, mTOR, MDM-2, and S6 ribosomal subunit.

Examples

Example 1: Non-clinical data: Evaluation of the Combination of Compound A and Compound B in PHTXM-32Ga and PHTXM-30Ga primary gastric models in vivo

[0100] There is growing evidence that SYK is a component of the cellular signaling cascade associated with EBV latency and transformation. EBV-positive tumors may express latent membrane protein 2A (LMP2A), which contains an immunoreceptor tyrosine-based activation motif (ITAM) domain. ITAM-mediated SYK activation has been shown to be essential to the LMP2A-induced tumorigenicity in EBV driven tumor models for both EBV associated lymphomas such as Burkitt's lymphoma, and EBV associated solid tumors such as nasopharyngeal carcinoma. Recently, this subtype (approximately 9%) of gastric cancer has been identified as positive for EBV with a high frequency of PIK3CA mutations, suggesting a role of SYK and PI3K α in the pathogenesis of EBV-positive gastric cancer.

Experimental Design

[0101] Female 7 week old female nude mice received PHTXM-32Ga human gastric xenograft fragments (1 x 1 – 2 x 2 mm per implant) implanted subcutaneously (SC) to the right flank via trocar for tumor development. Body weight and the tumor growth were monitored twice weekly. Tumor size was measured to the nearest 0.1 mm using a vernier caliper. The tumor volume (TV) was calculated using the formula $V = (W^2 \times L) \div 2$. When mean tumor volume (MTV) reached approximately 170 mm³ the mice were randomly assigned to treatment groups, with 8 mice per group and started treatment with their assigned test materials.

[0102] Animals in the vehicle treatment group were given 0.5% CMC plus 0.05% Tween 80 (PO, QD x 3) described as Vehicle I and 0.5% methylcellulose (PO, QD) described as Vehicle II. Compound A was administered PO at 140 mg/kg QD x 3 for three weeks. Compound B was dosed PO at 60 mg/kg QD for 21 days. In addition to each treatment, mice also received doses of the alternate vehicle.

[0103] The first day of treatment was designated as Day 1, and dosing continued up to Day 21. Tumor size and body weights were measured twice weekly beginning on the day of animal grouping (e.g., Day 0) and obtained up to Day 31. Data up to Day 21 are presented herein.

[0104] The maximum mean body weight loss (BWL) was determined for each group using the mean BWL data from the treatment period, and the mean percent body weight (BW) change was calculated on the basis of predose body weights. Percent TGI and body weight change were calculated on Day 21. Inhibition of tumor growth was determined by calculating the percent TGI using the following equation:

Percent TGI = (MTV of the control group – MTV of a treated group) ÷ MTV of the control group × 100

[0105] Antitumor activity was determined by statistical comparisons of tumor growth between treatment groups and vehicle, conducted using a linear mixed effects regression analysis on the Δ AUC.

Statistical Analysis

[0106] Change in Area Under the Curve: the differences in the tumor growth trends over time between the vehicle control and treatment groups were assessed using linear mixed effects regression models. These models take into account that each animal was measured at multiple time points. A model was fit for the comparison, and the areas under the tumor volume-versus-time curve (AUCs) for control and treatment groups were calculated using the values predicted from the model. A statistically significant p value suggests that the trends over time for the 2 groups (vehicle and treatment) were different. A p-value < 0.05 was considered statistically significant.

[0107] All tumor values (tumor volumes or photon flux) had a value of 1 added to them before log₁₀ transformation. These values were compared across treatment groups to assess whether the differences in the trends over time were statistically significant. To compare pairs of treatment groups, the following mixed-effects linear regression model was fit to the data using the maximum likelihood method:

$$Y_{ijk} - Y_{i0k} = Y_{i0k} + treat_i + day_j + day_j^2 + (treat * day)_{ij} + (treat * day^2)_{ij} + \epsilon_{ijk}$$

[0108] where Y_{ijk} is the log₁₀ tumor value at the j^{th} time point of the k^{th} animal in the i^{th} treatment, Y_{i0k} is the day 0 (baseline) log₁₀ tumor value in the k^{th} animal in the i^{th} treatment, day_j was the median-centered time point and (along with day_j^2) was treated as a continuous variable, and ϵ_{ijk} is the residual error. A spatial power law covariance matrix was used to account for the repeated measurements on the same animal over time. Interaction terms as well as day_j^2 terms were removed if they were not statistically significant.

[0109] A likelihood ratio test was used to assess whether a given pair of treatment groups exhibited differences which were statistically significant. The -2 log likelihood of the full model was compared to one without any treatment terms (reduced model) and the difference in the values was tested using a Chi-squared test. The degrees of freedom of the test were calculated as the difference between the degrees of freedom of the full model and that of the reduced model.

[0110] The predicted differences in the log tumor values ($Y_{ijk} - Y_{i0k}$, which can be interpreted as log₁₀(fold change from day 0)) were taken from the above models to calculate mean AUC values for each treatment group. A dAUC value was then calculated as:

$$dAUC = \frac{mean(AUC_{ctl}) - mean(AUC_{trt})}{mean(AUC_{ctl})} * 100$$

[0111] This assumes AUC_{ctl} was positive. In instances where AUC_{ctl} was negative, the above formula was multiplied by -1.

Synergy Analysis

[0112] A combination score calculation was used to address the question of whether the effects of the combination treatments were synergistic, additive, sub-additive, or antagonistic relative to the individual

treatments. The effect was considered synergistic if the synergy score was less than 0, and additive if the synergy score was not statistically different from 0. If the synergy score was greater than 0, but the mean AUC for the combination was lower than the lowest mean AUC among the two single agent treatments, then the combination was sub-additive. If the synergy score was greater than the mean AUC for at least one of the single agent treatments, then the combination was antagonistic.

[0113] The observed differences in the log tumor values were used to calculate AUC values for each animal. In instances when an animal in a treatment group was removed from the study, the last observed tumor value was carried forward through all subsequent time points. The AUC for the control, or vehicle, group was calculated using the predicted values from the pairwise models described above. To address the question of whether the effects of the combination treatments were synergistic, additive, sub-additive, or antagonistic relative to the individual treatments, the following statistics were calculated:

$$\begin{aligned} \text{Frac}_{A_k} &= \frac{AUC_{ctl} - AUC_{A_k}}{AUC_{ctl}} \\ \text{Frac}_{B_k} &= \frac{AUC_{ctl} - AUC_{B_k}}{AUC_{ctl}} \\ \text{Frac}_{AB_k} &= \frac{AUC_{ctl} - AUC_{AB_k}}{AUC_{ctl}} \end{aligned}$$

$$\text{Synergy Score} = (\text{mean}(\text{Frac}_A) + \text{mean}(\text{Frac}_B) - \text{mean}(\text{Frac}_{AB})) * 100$$

[0114] where A_k and B_k are the k^{th} animal in the individual treatment groups and AB_k is the k^{th} animal in combination treatment group. AUC_{ctl} is the model-predicted AUC for the control group and was treated as a constant with no variability. The standard error of the synergy score was calculated as the square root of the sum of squared standard errors across groups A, B, and AB. The degrees of freedom were estimated using the Welch-Satterthwaite equation. A hypothesis test was performed to determine if the synergy score differed from 0. P values were calculated by dividing the synergy score by its standard error and tested against a t-distribution (two-tailed) with the above-calculated degrees of freedom. The effect of the combination treatment was considered synergistic if the synergy score was less than 0 and additive if the synergy score wasn't statistically different from 0. If the synergy score was greater than zero, but the mean AUC for the combination was lower than the lowest mean AUC among the two single agent treatments, then the combination was sub-additive. If the synergy score was greater than zero, and the mean AUC for the combination was greater than the mean AUC for at least one of the single agent treatments, then the combination was antagonistic.

[0115] Interval analysis involved a specified treatment group and time interval compared with another treatment group and time interval. For a given treatment group, time interval, and animal, the tumor growth rate per day was estimated by

$$\text{Rate} = 100 * (10^{\Delta Y / \Delta t} - 1)$$

where ΔY is the difference in the $\log_{10}$ tumor volume over the interval of interest, and Δt is the length of the time interval. If one or both of the time points were missing, then the animal was ignored (but not

removed from further analysis). The mean rates across the animals were then compared using a two-sided unpaired t-test with unequal variances.

[0116] Given the exploratory nature of this study, there were no adjustments pre-specified for the multiple comparisons and endpoints examined in the pairwise comparisons or combination analyses. All P values < 0.05 in these analyses were called statistically significant.

Results and Discussion

[0117] In the PHTXM-32Ga model, PO administration of Compound A alone at 140 mg/kg on a QD x 3 schedule for three weeks resulted in a TGI of 47.2% and the anti-tumor activity that was statistically significant (Δ AUC, $p < 0.001$) when compared to vehicle. Compound B as a single agent at 60 mg/kg on a QD schedule also showed significant antitumor activity compared to vehicle (Δ AUC, $p < 0.001$), with Day 21 TGI value of 52.2% (Figure 1).

[0118] The combination of both agents resulted in greater TGI. Combination treatment of Compound A at 140 mg/kg (QDx3) with Compound B at 60 mg/kg (QD) demonstrated statistically significant antitumor activity as compared to the vehicle treatment (Δ AUC, $p < 0.001$) and a TGI value of 66.8% on Day 21. The synergy analysis of this combination effect was additive. (Table 1).

[0119] The antitumor activity of Compound A and Compound B alone or in combination against PHTXM-32Ga xenografts is summarized in Table 2 and graphically presented in Figure 1. Changes in animal body weight following the administration of Compound A and Compound B alone or in combination are summarized in Figure 2. The results of combination analysis are summarized in Table 1.

Table 1

Comparison	Score	SEM	P Value	Assessment
Compound B (60 mg/kg, PO, QD) + Compound A (140 mg/kg, PO, QD x 3)	12.5	9.2	0.190	Additive
PO = orally; QD = daily; QD x 3 = once daily for 3 days followed by 4 days off; SEM = standard error of the mean.				
Note: Synergistic analysis: $p > 0.05$ = additive; $p < 0.05$ and score < 0 = synergistic; $p < 0.05$, score > 0 , and the combination growth rate is lower than both the single agent growth rates = subadditive; $p < 0.05$, score > 0 , and the combination growth rate is higher than at least one of the single agent growth rates = antagonistic. Assessment was made on the basis of whether synergy score was significantly ($p < 0.05$) different from 0. P values < 0.05 were considered statistically significant.				

[0120] All treatments were well tolerated and the greatest maximum mean BWL (4.7%) was observed on Day 21 in animals dosed with Compound B alone at 60 mg/kg (QD). These results suggest that Compound A and Compound B can be combined in mice without significantly increasing toxicity, as evidenced by acceptable changes in body weight.

[0121] The mean percent body weight change for each group are shown graphically in Figure 2. No animals were removed from the study and all mice were included in the analysis.

[0122] This study demonstrated that Compound A and Compound B as single agents resulted in statistically significant antitumor activity. Combination of Compound A with Compound B was well tolerated and resulted in statistically significant antitumor activity compared to control mice bearing PHTXM-32Ga primary human gastric xenografts. The combination effect of Compound A in combination with Compound B was determined to be additive in this model.

[0123] Female 8 week old female nude mice received PHTXM-30Ga human gastric xenograft fragments (1 x 1 – 2 x 2 mm per implant) implanted subcutaneously (SC) to the right flank via trocar for tumor development. Body weight and tumor growth were monitored twice weekly. Tumor size was measured to the nearest 0.1 mm using a vernier caliper. The tumor volume (TV) was calculated using the formula $V = (W^2 \times L) \div 2$. When mean tumor volume (MTV) reached approximately 190 mm³ the mice were randomly assigned to treatment groups, with 8 mice per group and started treatment with their assigned test materials. Mice bearing the proper size xenograft were randomly assigned into one of the four groups shown in Table 2 were treated with their assigned test materials, either vehicles (0.5% CMC plus 0.05% Tween 80 and 0.5% Methylcellulose), Compound A (at 140 mg/kg), Compound B (at 60 mg/kg), or Compound A in combination with Compound B. In addition to each treatment, mice also received doses of the alternate vehicle.

[0124] The antitumor activity of Compound A and Compound B alone or in combination against PHTXM-30Ga xenografts is summarized in Table 2 and graphically presented in Figure 3. Changes in animal body weight following the administration of Compound A and Compound B alone or in combination are summarized in Figure 4. The results of combination analysis are summarized in Table 3.

[0125] In the PHTXM-30Ga model, PO administration of Compound A alone at 140 mg/kg on a QD x 3 schedule and Compound B alone at 60 mg/kg on a QD schedule showed minimal antitumor activity compared to vehicle treatment with Day 21 TGI values of 12.4% and 27%, respectively.

[0126] The combination of both agents resulted in greater TGI. Combination treatment of Compound A at 140 mg/kg (QDx3) with Compound B at 60 mg/kg (QD) demonstrated statistically significant antitumor activity as compared to the vehicle treatment (ΔAUC , $p < 0.001$) and a TGI value of 52.2%. The synergy analysis of this combination effect was additive. (Table 3).

[0127] All treatments were well tolerated and the greatest maximum mean BWL (10.8%) was observed on Day 21 in animals dosed with Compound B alone at 60 mg/kg (QD). These results suggest that Compound A and Compound B can be combined in mice without notable increase in toxicity, as evidenced by acceptable changes in body weight. The maximal mean percent body weight change for each group shown in Table 2. No animals were removed from the study and all mice were included in the analysis.

[0128] This study demonstrated that combination of Compound A with Compound B was well tolerated and resulted in statistically significant antitumor activity compared to control mice bearing

PHTXM-30Ga primary human gastric xenografts. The combination effect of Compound A in combination with Compound B was determined to be additive in this gastric model.

Table 2 Study Design and Noteworthy Findings for Compound B and Compound A in PHTXM-30Ga gastric model

Treatment Group	Dose ^a (mg/kg)	Method of Administration/ Frequency	Sex/Number Per Group	Species/ Strain	Endpoints	Noteworthy Findings
Vehicle I	NA	PO / QD x 3	Female/8	Mouse	TGI ^b	N/A
+		Days 1-3, 8-10, 15-17		(<i>Mus musculus</i>)		
Vehicle II	NA	PO / QD x 21		Balb/c Nude		
		Days 1-21			Maximum Mean %BWL ^c	4.3% (Day 21)
Compound B	60	PO / QD x 21	Female/8	Mouse	TGI ^b	27.0%
+		Days 1-21		(<i>Mus musculus</i>)		
Vehicle I	NA	PO / QD x 3		Balb/c Nude	Δ AUC ^d	15.7 (p = 0.025)
		Days 1-3, 8-10, 15-17			Maximum Mean %BWL	10.8% (Day 21)
Compound A	140	PO / QD x 3	Female/8	Mouse	TGI	12.4%
+		Days 1-3, 8-10, 15-17		(<i>Mus musculus</i>)		
Vehicle II	NA	PO / QD x 21		Balb/c Nude	Δ AUC	11.2 (p = 0.574)
		Days 1-21			Maximum Mean %BWL	1.8% (Day 21)
Compound B	60	PO / QD x 21	Female/8	Mouse	TGI	52.2%
+		Days 1-21		(<i>Mus musculus</i>)	Δ AUC	41.2 (p < 0.001)
Compound A	140	PO / QD x 3		Balb/c Nude	Synergy analysis ^e	Additive
		Days 1-3, 8-10, 15-17			Maximum Mean %BWL	9.2% (Day 17)

Δ AUC = change in areas under the tumor volume-versus-time curves; BWL = body weight loss; NA = not applicable; PO = orally; QD = daily; TGI = tumor growth inhibition; Vehicle I = 0.5% CMC + 0.05% Tween 80; Vehicle II = 0.5% Methylcellulose;

^a Dose volume for Vehicle I and Compound A was 5 mL/kg body weight. Dose volume for Vehicle II and Compound B was 10 mL/kg body weight.

^b TGI values were calculated on Day 21 post treatment initiation.

^c Maximum mean percent BWL between Day 0 to Day 21

^d Δ AUC = Statistical analysis was performed with a linear mixed effects regression model. A p value of < 0.05 was considered significant

^e Synergistic analysis: p > 0.05 = additive; p < 0.05 and score < 0 = synergistic; p < 0.05, score > 0, and the combination growth rate is lower than both the single agent growth rates = subadditive; p < 0.05, score > 0, and the combination growth rate is higher than at least one of the single agent growth rates = antagonistic..P values < 0.05 were considered statistically significant. Calculated on Day 21 post treatment initiation.

Table 1 Combination Comparisons (Log-Transformed) for Compound B and Compound A in PHTXM-30Ga model

Comparison	Score	SEM	P-Value	Assess
Compound B (60 mg/kg, PO, QD) + Compound A (140 mg/kg, PO, QD x 3)	-16.2	14.6	0.281	Additive

PO = orally; QD = daily; QD x 3 = once daily for 3 days followed by 4 days off; SEM = standard error of the mean. Note: Synergistic analysis: $p > 0.05$ = additive; $p < 0.05$ and score < 0 = synergistic; $p < 0.05$, score > 0 , and the combination growth rate is lower than both the single agent growth rates = subadditive; $p < 0.05$, score > 0 , and the combination growth rate is higher than at least one of the single agent growth rates = antagonistic. Assessment was made on the basis of whether synergy score was significantly ($p < 0.05$) different from 0. P values < 0.05 were considered statistically significant.

Example 2: Gastric Study Design

[0129] This is an open-label, multicenter, phase 1b study of Compound A in combination with Compound B, alisertib (MLN8237), paclitaxel, or docetaxel in adult patients with locally advanced and metastatic gastric or gastroesophageal adenocarcinoma. The study consists of a dose escalation phase (Part 1) and a dose expansion phase (Part 2). The statistical design for the dose expansion consists of equal randomization and adaptive randomization phases.

[0130] The primary objective in Part 1 (dose escalation) is to determine dose-limiting toxicity (DLT) and the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) for Compound A when administered with each of the combination partners.

[0131] The primary objective in Part 2 (dose expansion) is to evaluate the overall response rate (ORR) as the primary efficacy measure of Compound A in combination with each of the combination partners in patients with gastric or gastroesophageal adenocarcinoma.

[0132] The secondary objectives are to evaluate the safety and tolerability of Compound A in combination with each of the combination partners, to evaluate additional efficacy measures, such as progression-free survival (PFS), disease control rate, response duration, time to progression (TTP), and overall survival (OS) of Compound A in combination with each of the combination partners in patients with gastric or gastroesophageal adenocarcinoma, and to evaluate the pharmacokinetics (PK) of Compound A when dosed in combination with alisertib, Compound B, docetaxel, or paclitaxel, and to evaluate the PK of alisertib and Compound B when these agents are dosed in combination with Compound A.

[0133] Inclusion criteria: Male and female patients aged 18 years or older at the time of consent. In Part 1 (dose escalation), patients must have a histologically confirmed diagnosis of advanced solid tumor, including but not limited to gastric or gastroesophageal adenocarcinoma, and are refractory to or relapsed after prior line(s) of therapy with no effective therapeutic options available. In Part 2 (dose expansion), patients must have a histologically confirmed diagnosis of metastatic or locally advanced adenocarcinoma of the stomach or gastroesophageal junction (Stage IIb or IV), with measurable lesions per modified RECIST, Version 1.1 by radiographic techniques (CT or MRI), and have received 1 prior systemic chemotherapy regimen for advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction with documented progressive disease.

[0134] Exclusion criteria: Patients who have received prior systemic anticancer therapies, or other investigational agents or radiotherapy within 2 weeks before first dose of study drug; are receiving treatment with P-glycoprotein (P gp) inhibitors/inducers (Compound A + Compound B arm only); have received strong cytochrome P 450 (CYP) 3A4 inducers/inhibitors or proton pump inhibitors (PPIs) within 7 days before the first administration of study drug or have conditions that require the concomitant use of CYP3A4 inducers/inhibitors or PPIs during the course of the study; have poorly controlled diabetes mellitus; have signs of peripheral neuropathy $\geq$ NCI CTCAE Grade 2; have symptomatic brain metastases or brain metastases with a stable neurologic status for <2 weeks after completion of the definitive therapy and steroids. In Part 2 (dose expansion), prior treatment with any of the following: Aurora A-targeted agent (excluding the Compound A + Compound B arm); taxane-containing regimen (excluding the Compound A + Compound B arm); spleen tyrosine kinase (SYK) inhibitor (Compound A + Compound B arm only); or phosphoinositide 3-kinase (PI3K) or serine/threonine kinase, also known as protein kinase B or PKB (AKT) inhibitor

[0135] Part 1 (Dose Escalation)

[0136] During Part 1, the dose of Compound A will be escalated (planned doses of 300 mg, 600 mg, and 900 mg) according to a 3+3 dose escalation scheme, while Compound B, alisertib, paclitaxel, and docetaxel will be administered at a fixed dose and regimen until the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) is determined.

[0137] Part 2 (Dose Expansion)

[0138] All patients who enter Part 2 of the study will be screened to determine whether or not their tumor tissue is positive for Epstein-Barr virus (EBV) (approximately 9% of patients with gastric cancer). An estimated 28 patients who are EBV-positive will be assigned to treatment with Compound B in combination with Compound A (Cohort A). Patients who are EBV-negative, initially will be randomized equally to 1 of the other treatment cohorts, Compound A + alisertib (Cohort B), Compound A + paclitaxel (Cohort C), or Compound A + docetaxel (Cohort D).

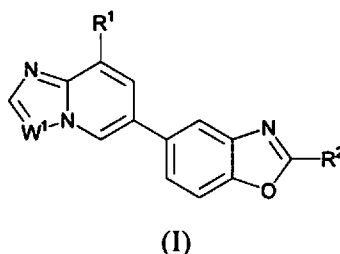
[0139] Compound A will be administered PO once daily (QD) for 3 days on (i.e., Days 1, 2, 3; 8, 9, 10; 15, 16, 17; 22, 23, and 24) and 4 days off per week in each 28-day cycle. The recommended phase 2 dose (RP2D) of Compound A when administered in combination with Compound B as determined in Part 1 will be used in Part 2. Compound B will be administered PO at the RP2D in a continuous QD dosing schedule in each 28-day cycle.

	28-Day Cycle, All Cycles																											
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Compound A	x	x	x					x	x	x					x	x	x					x	x	x				
Compound B	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

CLAIMS

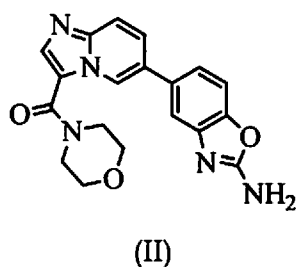
We claim:

1. A method of treating a cancer comprising administering to a subject having a cancer a therapeutically effective amount of a combination of a PI3K α inhibitor and a SYK inhibitor.
2. The method of claim 1, wherein the PI3K α inhibitor is a compound of formula I:



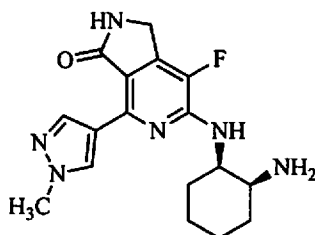
or a pharmaceutically acceptable salt thereof, wherein R¹ is hydrogen; R² is amino; W¹ is CR³; and R³ is amido.

3. The method of claim 2, wherein R³ is -C(O)N(R)₂ wherein the two R groups taken together with the nitrogen to which they are attached form a 4-, 5-, 6- or 7-membered ring, optionally including one or two nonadjacent heteroatoms selected from N, O or S.
4. The method of claim 2, wherein, R³ is -C(O)N(R)₂ wherein the two R groups taken together with the nitrogen to which they are attached form a morpholinyl ring.
5. The method of claim 2, wherein R² is NH₂.
6. The method of claim 2, wherein the PI3K α inhibitor is a compound of formula II:



or a pharmaceutically acceptable salt thereof.

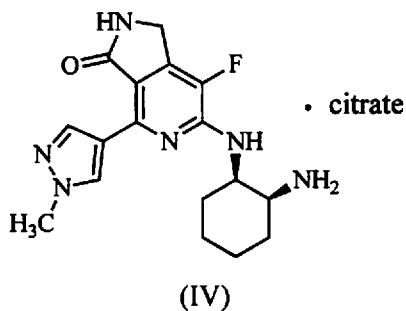
7. The method of any one of claims 1 to 6, wherein the SYK inhibitor is a compound of formula III:



(III)

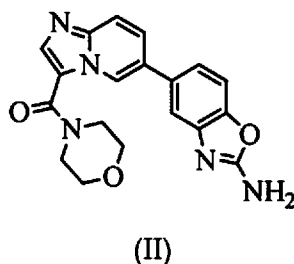
or a pharmaceutically acceptable salt thereof.

8. The method of any one of claims 1 to 6, wherein the SYK inhibitor is a compound of formula IV:



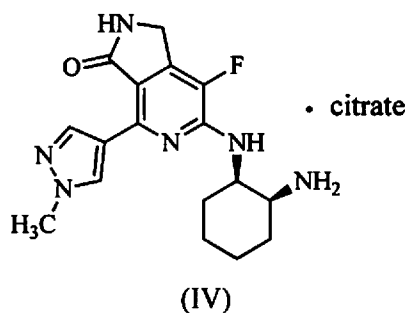
or a crystalline form thereof.

9. A method of treating a cancer comprising administering to a subject having a cancer a therapeutically effective amount of a combination of a PI3K α inhibitor and a SYK inhibitor, wherein the PI3K α inhibitor is a compound of formula II:



or a pharmaceutically acceptable salt thereof; and

the SYK inhibitor is a compound of formula IV:



or a crystalline form thereof.

10. The method of any one of claims 1 to 9, wherein the cancer is selected from lung cancer, head and neck squamous cell cancer, pancreatic cancer, breast cancer, ovarian cancer, renal cell carcinoma, prostate cancer, neuroendocrine cancer, gastrointestinal cancer, bladder cancer, colon cancer, cervical cancer and endometrial cancer.

11. The method of any one of claims 1 to 9, wherein the cancer is gastrointestinal cancer.

12. The method of any one of claims 1 to 9, wherein the cancer is selected from gastric cancer and gastroesophageal adenocarcinoma.
13. The method of any one of claims 1 to 9, wherein the cancer is gastric cancer.
14. The method of any one of claims 1 to 9, wherein the cancer is gastroesophageal adenocarcinoma.
15. The method of any one of claims 1 to 14, wherein the PI3K α inhibitor is administered for 3 consecutive days followed by an intermission of 4 consecutive days for at least one 7-day cycle.
16. The method of any one of claims 1 to 14, wherein the PI3K α inhibitor is administered 3 days on and 4 days off for a 4 week cycle.
17. The method of claim 15 or 16, wherein the PI3K α inhibitor is administered once a day (QD) in each of the days that the PI3K α inhibitor is administered to the subject.
18. The method of claim 15 or 16, wherein the PI3K α inhibitor is administered twice a day (BID) in each of the days that the PI3K α inhibitor is administered to the subject.
19. The method of any one of claims 1 to 18, wherein the SYK inhibitor is administered once daily (QD).
20. The method of any one of claims 1 to 19, wherein the PI3K α inhibitor is administered once-daily on a 28-day cycle in which the PI3K α inhibitor is administered on days 1, 2, 3, 8, 9, 10, 15, 16, 17, 22, 23, and 24 of a 28-day cycle.
21. The method any one of claims 1 to 20, wherein a daily dose of the PI3K α inhibitor is about 300 to about 1200 mg.
22. The method of claim 21, wherein a daily dose of the PI3K α inhibitor is about 300 mg.
23. The method of claim 21, wherein a daily dose of the PI3K α inhibitor is about 600 mg.
24. The method of claim 21, wherein a daily dose of the PI3K α inhibitor is about 900 mg.
25. The method of claim 21, wherein a daily dose of the PI3K α inhibitor is about 1200 mg.

26. The method any one of claims 1 to 25, wherein a daily dose of the SYK inhibitor is about 20 mg to about 150 mg per day.
27. The method of claim 26, wherein a daily dose of the SYK inhibitor is about 60 mg given once daily.
28. The method of claim 26, wherein a daily dose of the SYK inhibitor is about 80 mg given once daily.
29. The method of claim 28, wherein a daily dose of the SYK inhibitor is about 100 mg given once daily.
30. The method of any one of claims 1 to 29, wherein the PI3K α inhibitor and the SYK inhibitor are both administered orally.
31. The method of any one of claims 1 to 30, wherein the PI3K α inhibitor and the SYK inhibitor are administered simultaneously.
32. The method of any one of claims 1 to 30, wherein the PI3K α inhibitor and the SYK inhibitor are administered sequentially.

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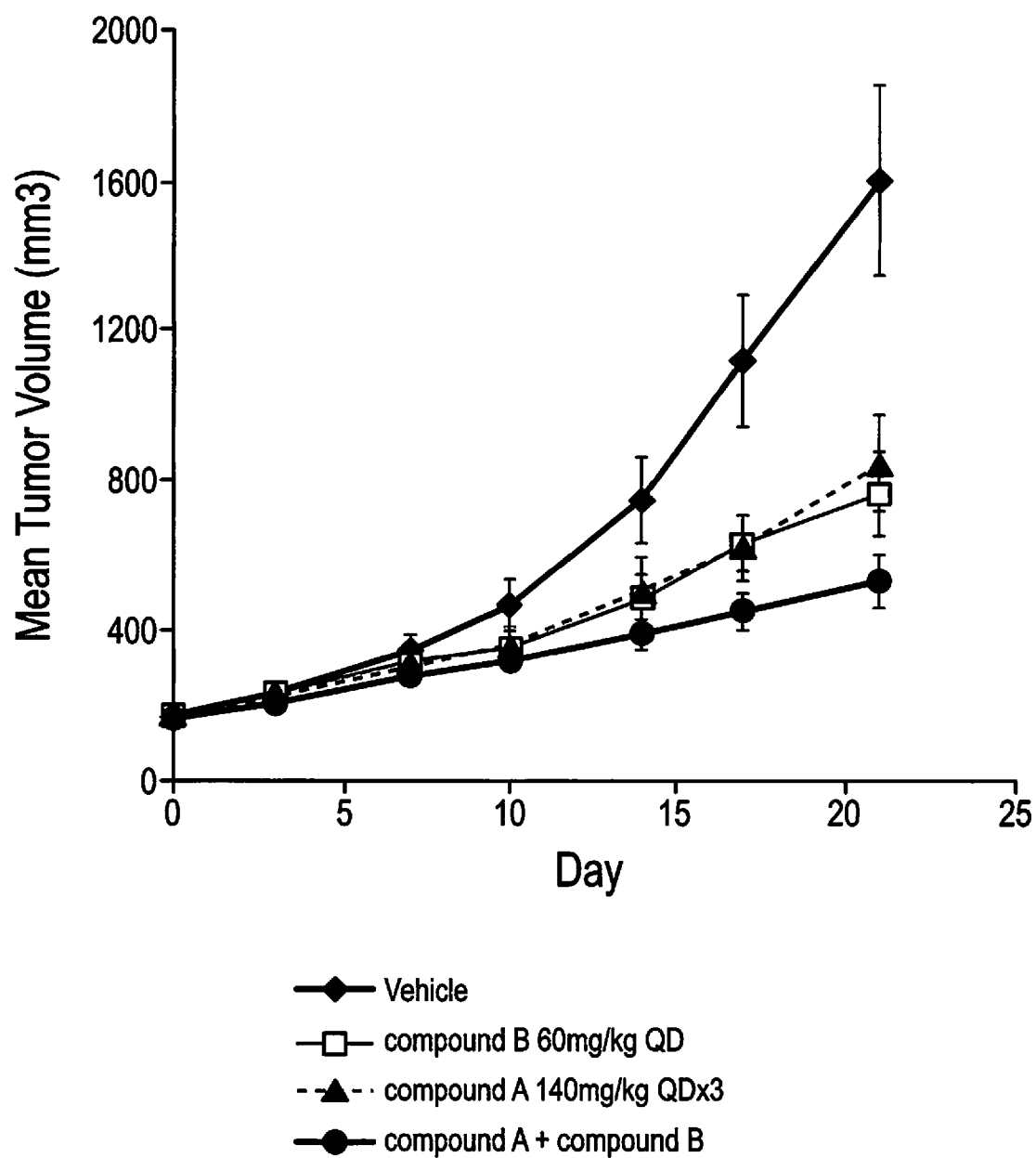
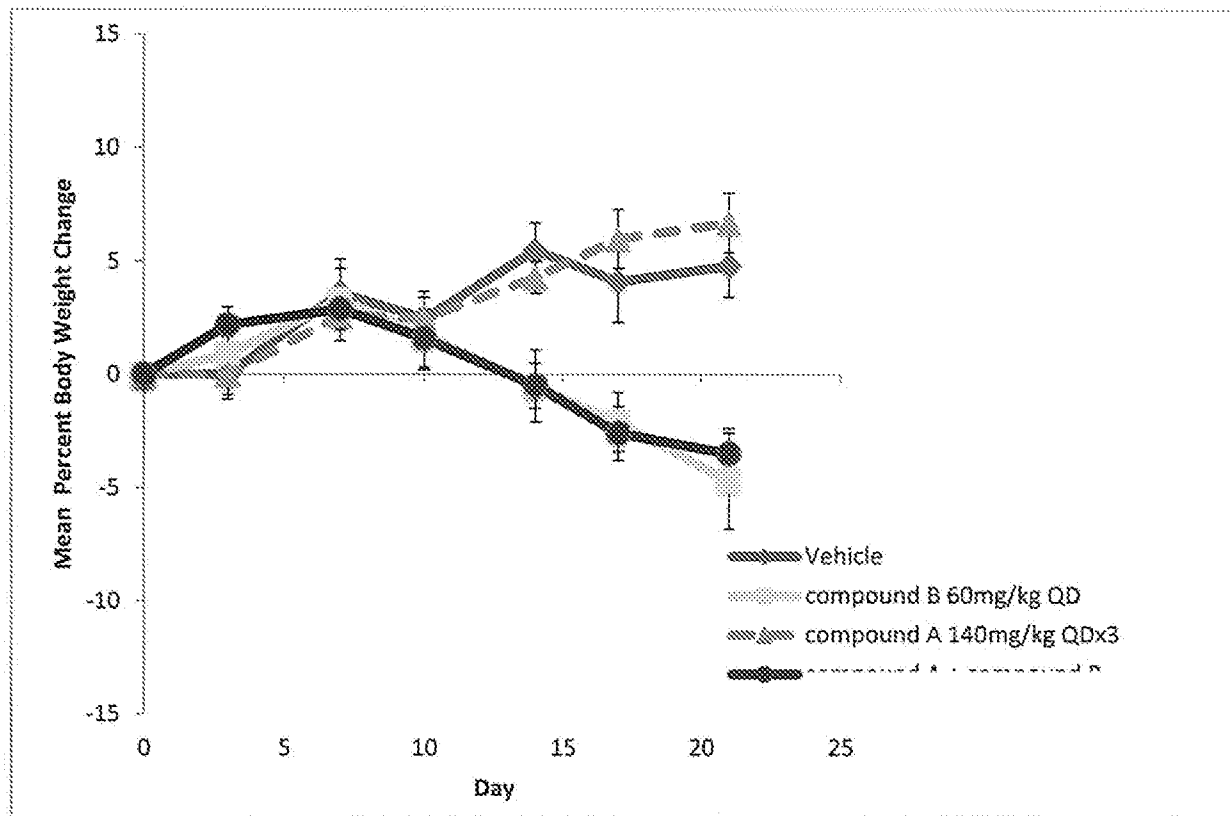


FIG. 1

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FIG. 2



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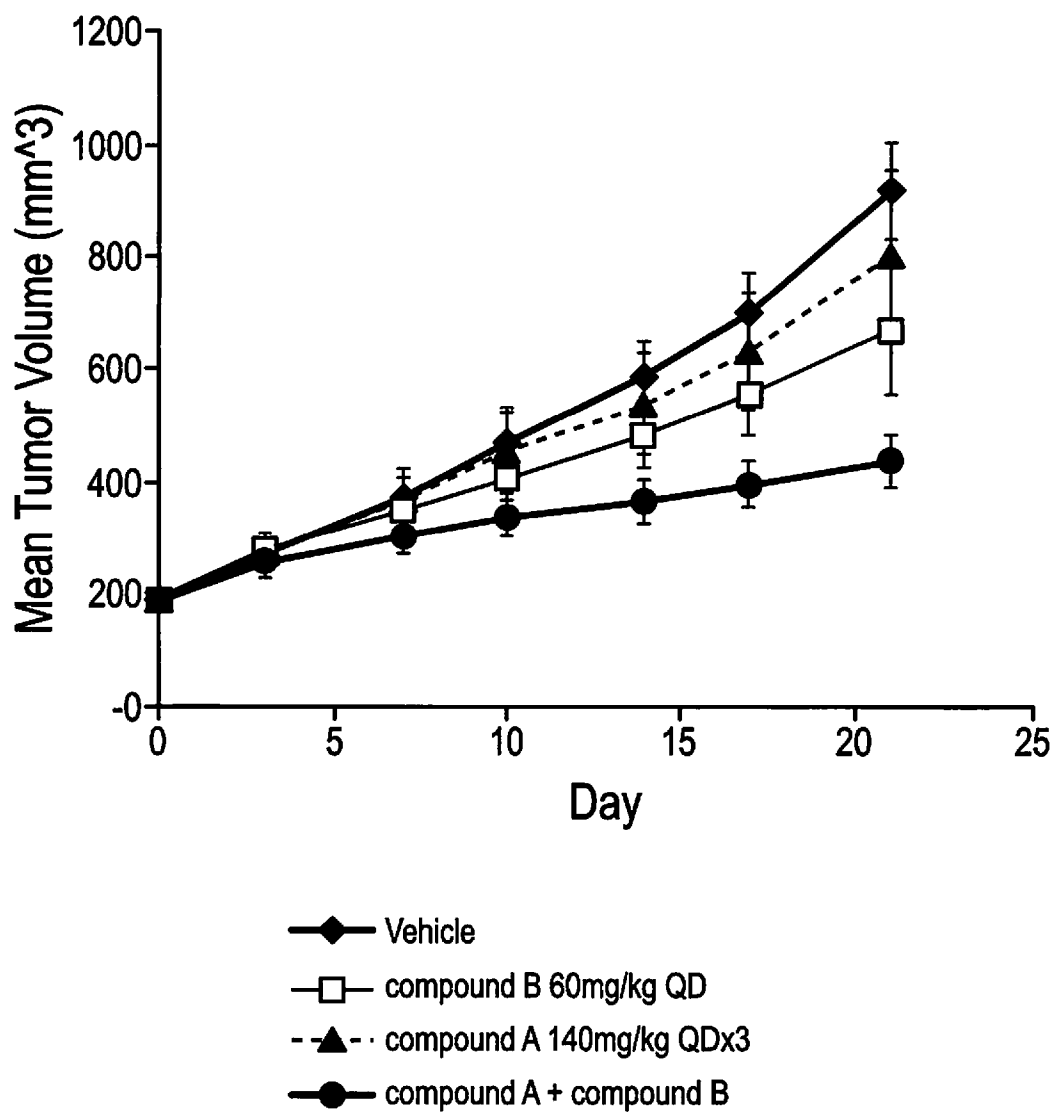


FIG. 3

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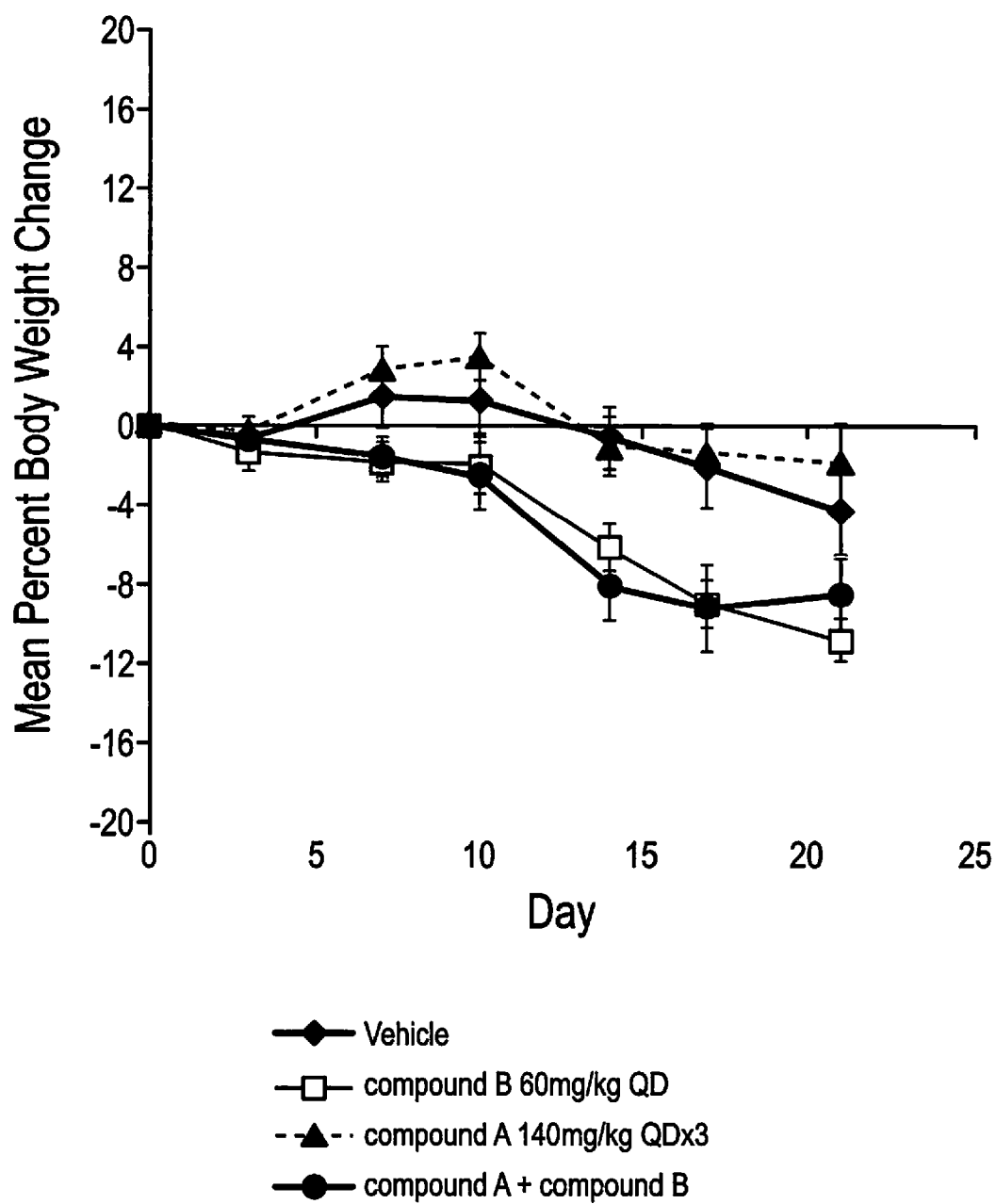


FIG. 4

PATENT COOPERATION TREATY

PCT

DECLARATION OF NON-ESTABLISHMENT OF INTERNATIONAL SEARCH REPORT
(PCT Article 17(2)(a), Rules 13ter.1(c) and (d) and 39)

Applicant's or agent's file reference 223266-396994	IMPORTANT DECLARATION	Date of mailing (<i>day/month/year</i>) 20 October 2016 (20.10.2016)
International application No. PCT/US2016/043286	International filing date (<i>day/month/year</i>) 21 July 2016 (21.07.2016)	(Earliest) Priority date (<i>day/month/year</i>) 22 July 2015 (22.07.2015)
International Patent Classification (IPC) or both national classification and IPC A61K 31/437(2006.01)i, A61K 31/423(2006.01)i, A61K 31/5377(2006.01)i, A61K 31/4155(2006.01)i		
Applicant MILLENNIUM PHARMACEUTICALS, INC.		

This International Searching Authority hereby declares, according to Article 17(2)(a), that **no international search report will be established** on the international application for the reasons indicated below.

1. ☒ The subject matter of the international application relates to:
 - a. ☐ scientific theories
 - b. ☐ mathematical theories
 - c. ☐ plant varieties
 - d. ☐ animal varieties
 - e. ☐ essentially biological processes for the production of plants and animals, other than microbiological processes and the products of such processes
 - f. ☐ schemes, rules or methods of doing business
 - g. ☐ schemes, rules or methods of performing purely mental acts
 - h. ☐ schemes, rules or methods of playing games
 - i. ☒ methods for treatment of the human body by surgery or therapy
 - j. ☐ methods for treatment of the animal body by surgery or therapy
 - k. ☐ diagnostic methods practised on the human or animal body
 - l. ☐ mere presentation of information
 - m. ☐ computer programs for which this International Searching Authority is not equipped to search prior art
2. ☒ The failure of the following parts of the international application to comply with prescribed requirements prevents a meaningful search from being carried out:

☐ the description
 ☒ the claims
 ☐ the drawings
3. ☐ A meaningful search could not be carried out without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in a form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).
4. Further comments:

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