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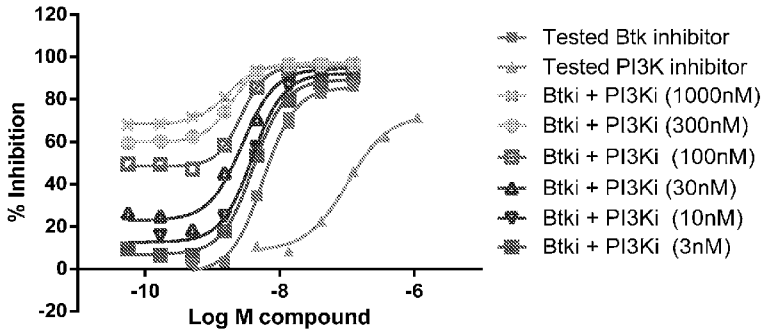


FIG. 1

(57) Abstract: Therapeutic compositions and methods of using the compositions, including combinations of a Bruton's tyrosine kinase (BTK) inhibitor, a phosphoinositide 3-kinase (PI3K) inhibitor, including PI3K inhibitors selective for the γ- and δ-isoforms and selective for both γ- and δ-isoforms (PI3K-γ,δ, PI3K-γ, and PI3K-δ, a programmed death 1 (PD-1) or programmed death ligand 1 (PD-L1) inhibitor, and/or a Janus kinase-2 (JAK- 2) inhibitor are described. In certain embodiments, the invention includes therapeutic methods of using a PD-1 monoclonal antibody and a BTK inhibitor. In other embodiments, the invention includes therapeutic methods of using a PD-L1 monoclonal antibody and a BTK inhibitor. In other embodiments, the invention includes therapeutic methods of using a PD-1 inhibitor, a BTK inhibitor, and a PI3K-δ inhibitor. In other embodiments, the invention includes therapeutic methods of using a PD-L1 inhibitor, a BTK inhibitor, and a PI3K-δ inhibitor.

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# THERAPEUTIC COMBINATIONS OF A BTK INHIBITOR, A PI3K INHIBITOR, A JAK-2 INHIBITOR, A PD-1 INHIBITOR, AND/OR A PD-L1 INHIBITOR

## CROSS-REFERENCE TO RELATED APPLICATIONS

**[001]** This application claims the benefit of U.S. Provisional Application No. 62/035,812 filed on August 11, 2014; U.S. Provisional Application No. 62/088,357 filed on December 5, 2014; U.S. Provisional Application No. 62/115,489 filed on February 12, 2015; and U.S. Provisional Application No. 62/181,164 filed on June 17, 2015, all of which are herein incorporated by reference in their entireties.

## FIELD OF THE INVENTION

**[002]** In some embodiments, therapeutic combinations of a programmed death 1 (PD-1) inhibitor or PD-1 ligand (PD-L1 or PD-L2) inhibitor, a Bruton's tyrosine kinase (BTK) inhibitor, a Janus kinase 2 (JAK-2) inhibitor, and/or a phosphoinositide 3-kinase (PI3K) inhibitor, and methods of using the therapeutic combinations are disclosed herein.

## BACKGROUND OF THE INVENTION

**[003]** Bruton's tyrosine kinase (BTK) is a Tec family non-receptor protein kinase expressed in B cells and myeloid cells. BTK is composed of the pleckstrin homology (PH), Tec homology (TH), Src homology 3 (SH3), Src homology 2 (SH2), and tyrosine kinase or Src homology 1 (TK or SH1) domains. The function of BTK in signaling pathways activated by the engagement of the B cell receptor (BCR) in mature B cells and FCER1 on mast cells is well established. Functional mutations in BTK in humans result in a primary immunodeficiency disease (X-linked agammaglobuinaemia) characterized by a defect in B cell development with a block between pro- and pre-B cell stages. The result is an almost complete absence of B lymphocytes, causing a pronounced reduction of serum immunoglobulin of all classes. These findings support a key role for BTK in the regulation of the production of auto-antibodies in autoimmune diseases.

**[004]** BTK is expressed in numerous B cell lymphomas and leukemias. Other diseases with an important role for dysfunctional B cells are B cell malignancies, as described in Hendriks, *et al., Nat. Rev. Cancer,* **2014,** *14,* 219-231. The reported role for BTK in the regulation of proliferation and apoptosis of B cells indicates the potential for

BTK inhibitors in the treatment of B cell lymphomas. BTK inhibitors have thus been developed as potential therapies for many of these malignancies, as described in D'Cruz, *et al.*, *OncoTargets and Therapy* **2013,** *6,* 161-176.

**[005]** Programmed death 1 (PD-1) is a 288-amino acid transmembrane immunocheckpoint receptor protein expressed by T cells, B cells, natural killer (NK) T cells, activated monocytes, and dendritic cells. PD-1, which is also known as CD279, is an immunoreceptor belonging to the CD28 family and in humans is encoded by the *Pdcd1* gene on chromosome 2. PD-1 consists of one immunoglobulin (Ig) superfamily domain, a transmembrane region, and an intracellular domain containing an immunoreceptor tyrosine-based inhibitory motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). PD-1 and its ligands (PD-L1 and PD-L2) play a key role in immune tolerance, as described in Keir, *et al.*, *Annu. Rev. Immunol.* **2008,** *26,* 677-704. PD-1 provides inhibitory signals that negatively regulate T cell immune responses. PD-L1 (also known as B7-H1 or CD274) and PD-L2 (also known as B7-DC or CD273) are expressed on tumor cells and stromal cells, which may be encountered by activated T cells expressing PD-1, leading to immunosuppression of the T cells. PD-L1 is a 290 amino acid transmembrane protein encoded by the *Cd274* gene on human chromosome 9. Blocking the interaction between PD-1 and its ligands PD-L1 and PD-L2 by use of a PD-1 inhibitor, a PD-L1 inhibitor, and/or a PD-L2 inhibitor can overcome immune resistance, as demonstrated in recent clinical studies, such as that described in Topalian, *et al.*, *N. Eng. J. Med.* **2012,** *366,* 2443. PD-L1 is expressed on many tumor cell lines, while PD-L2 is expressed is expressed mostly on dendritic cells and a few tumor lines. In addition to T cells (which inducibly express PD-1 after activation), PD-1 is also expressed on B cells, natural killer cells, macrophages, activated monocytes, and dendritic cells.

**[006]** In many solid tumors, the supportive microenvironment (which may make up the majority of the tumor mass) is a dynamic force that enables tumor survival. The tumor microenvironment is generally defined as a complex mixture of "cells, soluble factors, signaling molecules, extracellular matrices, and mechanical cues that promote neoplastic transformation, support tumor growth and invasion, protect the tumor from host immunity, foster therapeutic resistance, and provide niches for dominant metastases

to thrive," as described in Swartz, *et al.*, *Cancer Res.*, **2012,** *72,* 2473. Although tumors express antigens that should be recognized by T cells, tumor clearance by the immune system is rare because of immune suppression by the microenvironment. Addressing the tumor cells themselves with e.g. chemotherapy has also proven to be insufficient to overcome the protective effects of the microenvironment. New approaches are thus urgently needed for more effective treatment of solid tumors that take into account the role of the microenvironment. The supportive microenvironment also plays a critical role in many B cell cancers such as acute leukemias, myelodysplastic syndromes, chronic lymphocytic leukemia (CLL) and small lymphocytic leukemia (SLL), mucosa-associated lymphoid tissue (MALT) lymphomas, and multiple myeloma (MM). Burger, *et al.*, *Blood*, **2009,** *114,* 3367-75. For example, CLL and SLL cells rapidly accumulate and are resistant to apoptosis in vivo, but are known to die rapidly in vitro. Buchner, *et al.*, *Blood* **2010,** *115,* 4497-506. One cause of this effect is from nonmalignant accessory cells in the tumor microenvironment, such as stromal cell contact mediated cell survival. Stromal cells in the bone marrow and lymph nodes are known to have an antiapoptotic and protective effect on CLL cells, protecting them from both chemotherapeutic and spontaneous apoptosis. Mudry, *et al.*, *Blood* **2000,** *96,* 1926-32. The chemokine SDF1α (CXCL12) directs homing of CLL cells towards protective niches. Burger, *et al.*, *Blood* **2005,** *106,* 1824-30. Existing drugs that target the BCR pathway in B cell malignancies can lead to some lymphocytosis (lymphocyte egress from nodal compartments), through disruption of CXCR4-SDF1α signaling and other adhesion factors in bone marrow and the resulting mobilization of cells. However, existing therapies may not eradicate residual malignant B cell populations in the microenvironment of the bone marrow and lymph nodes, where protective stromal cells prevent apoptosis. There is thus an urgent need for treatments that reduce or overcome the protective effect of the microenvironment on CLL cells to enable superior clinical responses in patients.

**[007]** PI3K inhibitors are members of a unique and conserved family of intracellular lipid kinases that phosphorylate the 3'-OH group on phosphatidylinositols or phosphoinositides. PI3K inhibitors are key signaling enzymes that relay signals from cell surface receptors to downstream effectors. The PI3K family comprises 15 kinases with distinct substrate specificities, expression patterns, and modes of regulation. The class I

PI3K inhibitors (p110α, p110β, p110δ, and p110γ) are typically activated by tyrosine kinases or G-protein coupled receptors to generate PIP3, which engages downstream effectors such as those in the Akt/PDK1 pathway, mTOR, the Tec family kinases, and the Rho family GTPases.

**[008]** The PI3K signaling pathway is known to be one of the most highly mutated in human cancers. PI3K signaling is also a key factor in disease states including hematologic malignancies, non-Hodgkin's lymphoma (such as diffuse large B-cell lymphoma), allergic contact dermatitis, rheumatoid arthritis, osteoarthritis, 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. The role of PI3K in cancer has been discussed, for example, in Engleman, *Nat. Rev. Cancer* **2009,** *9,* 550-562. The PI3K-δ and PI3K-γ isoforms are preferentially expressed in normal and malignant leukocytes.

**[009]** The delta (δ) isoform of class I PI3K (PI3K-δ) is involved in mammalian immune system functions such as T-cell function, B-cell activation, mast cell activation, dendritic cell function, and neutrophil activity. Due to its role in immune system function, PI3K-δ is also involved in a number of diseases related to undesirable immune response such as allergic reactions, inflammatory diseases, inflammation mediated angiogenesis, rheumatoid arthritis, auto-immune diseases such as lupus, asthma, emphysema and other respiratory diseases. The gamma (γ) isoform of class I PI3K (PI3K-γ) is also involved in immune system functions and plays a role in leukocyte signaling and has been implicated in inflammation, rheumatoid arthritis, and autoimmune diseases such as lupus.

**[0010]** Downstream mediators of the PI3K signal transduction pathway include Akt and mammalian target of rapamycin (mTOR). One important function of Akt is to augment the activity of mTOR, through phosphorylation of TSC2 and other mechanisms. mTOR is a serine-threonine kinase related to the lipid kinases of the PI3K family and has been implicated in a wide range of biological processes including cell growth, cell proliferation, cell motility and survival. Disregulation of the mTOR pathway has been

reported in various types of cancer.

**[0011]** In view of the above, PI3K inhibitors are prime targets for drug development, as described in Kurt, *et al.*, *Anticancer Res.* **2012,** *32,* 2463-70. Several PI3K inhibitors are known, including those that are PI3K-δ inhibitors, PI3K-γ inhibitors and those that are PI3K-δ,γ inhibitors.

**[0012]** The present invention includes the unexpected discovery that combinations of a BTK inhibitor, a PD-1 inhibitor, and/or a PI3K inhibitor exhibit surprising and synergistic effectiveness in the treatment of any of several types of cancers such as solid tumor cancers and hematological cancers, as well as other disorders. The present invention also includes the unexpected discovery that the combination of a PD-1 inhibitor and a BTK inhibitor is effective and synergistic in the treatment of any of several types of cancers such as solid tumor cancers. The present invention further includes the unexpected discovery that the combination of a PD-1 inhibitor and a PI3K inhibitor is effective and synergistic in the treatment of any of several types of cancers such as solid tumor cancers. The present invention additionally includes the unexpected discovery that combinations of a BTK inhibitor, a PD-1 inhibitor (such as an anti-PD-1 antibody) and/or a PD-L1 inhibitor (such as an anti-PD-L1 antibody), and/or a PI3K inhibitor exhibit surprising synergy in the suppression of the supportive solid tumor microenvironment.

## SUMMARY OF THE INVENTION

**[0013]** In an embodiment, the invention provides a method of treating a hyperproliferative disease in a subject, comprising co-administering to a mammal in need thereof a therapeutically effective amount of a PD-1 inhibitor and/or a PD-L1 inhibitor and a BTK inhibitor.

**[0014]** In an embodiment, the invention provides a method of treating leukemia, lymphoma or a solid tumor cancer in a subject, comprising co-administering to a mammal in need thereof a therapeutically effective amount of a PD-1 inhibitor and/or a PD-L1 inhibitor and a BTK inhibitor.

**[0015]** In an embodiment, the invention provides a method of treating leukemia, lymphoma or a solid tumor cancer in a subject, comprising co-administering to a

mammal in need thereof a therapeutically effective amount of a PI3K inhibitor, a PD-1 inhibitor and/or a PD-L1 inhibitor, and a BTK inhibitor.

**[0016]** In an embodiment, the invention provides a method of treating leukemia, lymphoma or a solid tumor cancer in a subject, comprising co-administering to a mammal in need thereof a therapeutically effective amount of a PI3K-γ inhibitor, a PD-1 inhibitor and/or a PD-L1 inhibitor, and a BTK inhibitor.

**[0017]** In an embodiment, the invention provides a method of treating leukemia, lymphoma or a solid tumor cancer in a subject, comprising co-administering to a mammal in need thereof a therapeutically effective amount of a PI3K-δ inhibitor, a PD-1 inhibitor and/or a PD-L1 inhibitor, and a BTK inhibitor.

**[0018]** In an embodiment, the invention provides a method of treating leukemia, lymphoma or a solid tumor cancer in a subject, comprising co-administering to a mammal in need thereof a therapeutically effective amount of a PI3K-γ,δ inhibitor, a PD-1 inhibitor and/or a PD-L1 inhibitor, and a BTK inhibitor.

**[0019]** In an embodiment, the invention provides a method of treating leukemia, lymphoma, or a solid tumor cancer in a subject, comprising co-administering to a mammal in need thereof a therapeutically effective amount of a PD-1 inhibitor and/or a PD-L1 inhibitor and a BTK inhibitor, and further comprises the step of administering a therapeutically effective dose of an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, $^{131}$I-tositumomab, ibritumomab, $^{90}$Y-ibritumomab, $^{111}$In-ibritumomab, ibritumomab tiuxetan, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof.

**[0020]** In an embodiment, the invention provides a method of treating leukemia, lymphoma, or a solid tumor cancer in a subject, comprising co-administering to a mammal in need thereof a therapeutically effective amount of a PI3K inhibitor, a PD-1 inhibitor and/or a PD-L1 inhibitor, and a BTK inhibitor, and further comprises the step of administering a therapeutically effective dose of an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, $^{131}$I-tositumomab, ibritumomab, $^{90}$Y-ibritumomab, $^{111}$In-ibritumomab,

ibritumomab tiuxetan, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof.

**[0021]** In an embodiment, the invention provides a composition comprising (1) a PD-1 inhibitor and/or a PD-L1 inhibitor or an antigen-binding fragment, variant, or conjugate thereof; and (2) a BTK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.

**[0022]** In an embodiment, the invention provides a composition comprising (1) a PD-1 inhibitor and/or a PD-L1 inhibitor or an antigen-binding fragment, variant, or conjugate thereof; (2) a BTK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) a PI3K inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.

**[0023]** In an embodiment, the invention provides a composition comprising (1) a PD-1 inhibitor and/or a PD-L1 inhibitor or an antigen-binding fragment, variant, or conjugate thereof; (2) a BTK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.

**[0024]** In an embodiment, the invention provides a composition comprising (1) a PD-1 inhibitor and/or a PD-L1 inhibitor or an antigen-binding fragment, variant, or conjugate thereof; (2) a BTK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) an anti-coagulant or antiplatelet active pharmaceutical ingredient. This composition is typically a pharmaceutical composition.

**[0025]** In an embodiment, the invention provides a composition comprising (1) a PD-1 inhibitor and/or a PD-L1 inhibitor or an antigen-binding fragment, variant, or conjugate thereof; (2) a BTK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) a PI3K inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) an anti-coagulant or

antiplatelet active pharmaceutical ingredient. This composition is typically a pharmaceutical composition.

**[0026]** In an embodiment, the invention provides a composition comprising (1) a PD-1 inhibitor and/or a PD-L1 inhibitor or an antigen-binding fragment, variant, or conjugate thereof; (2) a BTK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) an anti-coagulant or antiplatelet active pharmaceutical ingredient. This composition is typically a pharmaceutical composition.

**[0027]** The anti-coagulant or the anti-platelet active pharmaceutical ingredient in some specific embodiments is a compound selected from the group consisting of acenocoumarol, anagrelide, anagrelide hydrochloride, abciximab, aloxiprin, antithrombin, apixaban, argatroban, aspirin, aspirin with extended-release dipyridamole, beraprost, betrixaban, bivalirudin, carbasalate calcium, cilostazol, clopidogrel, clopidogrel bisulfate, cloricromen, dabigatran etexilate, darexaban, dalteparin, dalteparin sodium, defibrotide, dicumarol, diphenadione, dipyridamole, ditazole, desirudin, edoxaban, enoxaparin, enoxaparin sodium, eptifibatide, fondaparinux, fondaparinux sodium, heparin, heparin sodium, heparin calcium, idraparinux, idraparinux sodium, iloprost, indobufen, lepirudin, low molecular weight heparin, melagatran, nadroparin, otamixaban, parnaparin, phenindione, phenprocoumon, prasugrel, picotamide, prostacyclin, ramatroban, reviparin, rivaroxaban, sulodexide, terutroban, terutroban sodium, ticagrelor, ticlopidine, ticlopidine hydrochloride, tinzaparin, tinzaparin sodium, tirofiban, tirofiban hydrochloride, treprostinil, treprostinil sodium, triflusal, vorapaxar, warfarin, warfarin sodium, ximelagatran, salts thereof, solvates thereof, hydrates thereof, and combinations thereof.

**[0028]** In an embodiment, the invention provides a kit comprising (1) a PD-1 inhibitor and/or a PD-L1 inhibitor or an antigen-binding fragment, variant, or conjugate thereof; and (2) a composition comprising a BTK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. These compositions are typically pharmaceutical compositions. The kit is for co-administration of a PD-1 and/or PD-L1 inhibitor and a BTK inhibitor, either simultaneously or separately.

**[0029]** In an embodiment, the invention provides a composition comprising (1) a PD-1 inhibitor and/or a PD-L1 inhibitor or an antigen-binding fragment, variant, or conjugate thereof; (2) a composition comprising a BTK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) a composition comprising a PI3K inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. These compositions are typically pharmaceutical compositions. The kit is for co-administration of PD-1 and/or PD-L1 inhibitor, a BTK inhibitor, and a PI3K inhibitor, either simultaneously or separately.

**[0030]** In an embodiment, the invention provides a composition comprising (1) a PD-1 inhibitor and/or a PD-L1 inhibitor or an antigen-binding fragment, variant, or conjugate thereof; (2) a composition comprising a BTK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) a composition comprising a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. These compositions are typically pharmaceutical compositions. The kit is for co-administration of a PD-1 and/or a PD-L1 inhibitor, a BTK inhibitor, and an anti-coagulant or antiplatelet active pharmaceutical ingredient, either simultaneously or separately.

**[0031]** In an embodiment, the invention provides a composition comprising (1) a PD-1 inhibitor and/or a PD-L1 inhibitor or an antigen-binding fragment, variant, or conjugate thereof; (2) a composition comprising a BTK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) an anti-coagulant or antiplatelet active pharmaceutical ingredient. These compositions are typically pharmaceutical compositions. The kit is for co-administration of a PD-1 and/or a PD-L1 inhibitor, a BTK inhibitor, and an anti-coagulant or antiplatelet active pharmaceutical ingredient, either simultaneously or separately.

**[0032]** In an embodiment, the invention provides a composition comprising (1) a composition comprising a PD-1 inhibitor and/or a PD-L1 inhibitor or an antigen-binding fragment, variant, or conjugate thereof; (2) a composition comprising a BTK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) a composition comprising a PI3K inhibitor or a pharmaceutically acceptable salt, solvate,

hydrate, cocrystal, or prodrug thereof; and (4) an anti-coagulant or antiplatelet active pharmaceutical ingredient. These compositions are typically pharmaceutical compositions. The kit is for co-administration of a PI3K-δ inhibitor and an anti-coagulant or antiplatelet active pharmaceutical ingredient, either simultaneously or separately.

**[0033]** In an embodiment, the invention provides a composition comprising (1) a composition comprising a PD-1 inhibitor and/or a PD-L1 inhibitor or an antigen-binding fragment, variant, or conjugate thereof; (2) a composition comprising a BTK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) a composition comprising a PI3K-δ inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (4) an anti-coagulant or antiplatelet active pharmaceutical ingredient. These compositions are typically pharmaceutical compositions. The kit is for co-administration of a PD-1 and/or a PD-L1 inhibitor, a BTK inhibitor, a PI3K-δ inhibitor, and an anti-coagulant or antiplatelet active pharmaceutical ingredient, either simultaneously or separately.

**[0034]** In some embodiments, the compositions and the kits disclosed herein are for use in treating cancer. In some specific embodiments, the compositions and the kits disclosed herein are for use in treating cancer selected from the group consisting of a B cell hematological malignancy selected from the hematological malignancy is selected from the group consisting of chronic lymphocytic leukemia (CLL), small lymphocytic leukemia (SLL), non-Hodgkin's lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Hodgkin's lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Burkitt's lymphoma, Waldenström's macroglobulinemia (WM), Burkitt's lymphoma, multiple myeloma (MM), or myelofibrosis.

**[0035]** In some embodiments, the compositions and the kits disclosed herein are for use in treating a cancer selected from the group consisting of bladder cancer, squamous cell carcinoma including head and neck cancer, pancreatic ductal adenocarcinoma (PDA), pancreatic cancer, colon carcinoma, mammary carcinoma, breast cancer, fibrosarcoma, mesothelioma, renal cell carcinoma, lung carcinoma, thyoma, prostate cancer, colorectal

cancer, ovarian cancer, acute myeloid leukemia, thymus cancer, brain cancer, squamous cell cancer, skin cancer, eye cancer, retinoblastoma, melanoma, intraocular melanoma, oral cavity and oropharyngeal cancers, gastric cancer, stomach cancer, cervical cancer, head, neck, renal cancer, kidney cancer, liver cancer, ovarian cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, acquired immune deficiency syndrome (AIDS)-related cancers (e.g., lymphoma and Kaposi's sarcoma), viral-induced cancer, glioblastoma, glioma, esophageal tumors, hematological neoplasms, non-small-cell lung cancer, chronic myelocytic leukemia, diffuse large B-cell lymphoma, esophagus tumor, follicle center lymphoma, head and neck tumor, hepatitis C virus infection, hepatocellular carcinoma, Hodgkin's disease, metastatic colon cancer, multiple myeloma, non-Hodgkin's lymphoma, indolent non-Hodgkin's lymphoma, ovary tumor, pancreas tumor, renal cell carcinoma, small-cell lung cancer, stage IV melanoma, chronic lymphocytic leukemia, B-cell acute lymphoblastic leukemia (ALL), mature B-cell ALL, follicular lymphoma, mantle cell lymphoma, and Burkitt's lymphoma.

**[0036]** In other embodiments, the compositions and the kits disclosed herein are for use in treating a solid tumor cancer selected from the group consisting of bladder cancer, non-small cell lung cancer, cervical cancer, anal cancer, pancreatic cancer, squamous cell carcinoma including head and neck cancer, renal cell carcinoma, melanoma, ovarian cancer, small cell lung cancer, glioblastoma, glioma, gastrointestinal stromal tumor, breast cancer, lung cancer, colorectal cancer, thyroid cancer, bone sarcoma, stomach cancer, oral cavity cancer, oropharyngeal cancer, gastric cancer, kidney cancer, liver cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, colon cancer, and brain cancer.

**[0037]** In some embodiments, the compositions and the kits disclosed herein are for use in treating a solid tumor cancer, wherein the compositions are in a dosage that is effective in inhibiting signaling between the cells of the solid tumor cancer and at least one tumor microenvironment selected from the group consisting of macrophages, monocytes, mast cells, helper T cells, cytotoxic T cells, regulatory T cells, natural killer cells, myeloid-derived suppressor cells, regulatory B cells, neutrophils, dendritic cells, and fibroblasts.

[0038] In some embodiments, the compositions and the kits disclosed herein are for use in treating a solid tumor cancer, wherein the compositions are in a dosage that is effective in increasing immune system recognition and rejection of the solid tumor by the human body receiving the treatment.

[0039] In some embodiments, the compositions and the kits disclosed herein are for use in treating cancer, wherein the PD-1 and/or PD-L1 inhibitor is administered before administration of the BTK inhibitor.

[0040] In some embodiments, the compositions and the kits disclosed herein are for use in treating cancer, wherein the PD-1 and/or PD-L1 inhibitor is administered concurrently with the administration of the BTK inhibitor.

[0041] In some embodiments, the compositions and the kits disclosed herein are for use in treating cancer, wherein the PD-1 and/or PD-L1 inhibitor is administered to the subject after administration of the BTK inhibitor.

## BRIEF DESCRIPTION OF THE DRAWINGS

[0042] The foregoing summary, as well as the following detailed description of the invention, will be better understood when read in conjunction with the appended drawings.

[0043] FIG. 1 illustrates the sensitivity of the TMD8 diffuse large B cell lymphoma (DLBCL) cell line to individual treatment with the BTK inhibitor of Formula XVIII ("Tested Btk Inhibitor") and the PI3K inhibitor of Formula IX ("Tested PI3K Inhibitor") and combined treatment with Formula XVIII and Formula IX ("Btki + PI3Ki") at different concentrations. The concentration of the first active pharmaceutical ingredient in the combination (the BTK inhibitor) and the concentration of the individual active pharmaceutical ingredients is given on the x-axis, and the concentration of the added PI3K inhibitor in combination with the BTK inhibitor is given in the legend.

[0044] FIG. 2 illustrates the sensitivity of the MINO mantle cell lymphoma cell to individual treatment with the BTK inhibitor of Formula XVIII ("Tested Btk Inhibitor") and the PI3K inhibitor of Formula IX ("Tested PI3K Inhibitor") and combined treatment with Formula XVIII and Formula IX ("Btki + PI3Ki") at different concentrations. The

concentration of the first active pharmaceutical ingredient in the combination (the BTK inhibitor) and the concentration of the individual active pharmaceutical ingredients is given on the x-axis, and the concentration of the added PI3K inhibitor in combination with the BTK inhibitor is given in the legend.

**[0045]** FIG. 3 illustrates the proproliferative activity in primary mantle cell lymphoma cells of Formula XVIII ("Tested Btki") and Formula IX ("Tested PI3Ki"). The percentage viability of cells ("% viability", y-axis) is plotted versus the concentration of the active pharmaceutical ingredient or active pharmaceutical ingredients. Single-active pharmaceutical ingredient BTK ("Tested Btki") and PI3K inhibitors ("Tested PI3Ki") are compared to four combinations of Formula XVIII and Formula IX ("(10 μM) Tested PI3Ki", "1.0 μM Tested PI3Ki," "0.1 μM Tested PI3Ki," "0.01 μM Tested PI3Ki").

**[0046]** FIG. 4 illustrates the interaction index of the combination of the BTK inhibitor of Formula XVIII and the PI3K inhibitor of Formula IX in primary mantle cell lymphoma cells from different patients (MCL-1 to MCL-5). Each symbol represents a concentration from 10 uM to 0.0001 uM.

**[0047]** FIG. 5 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula XVIII and the PI3K-δ inhibitor of Formula IX are combined. The tested cell lines include Maver-1 (B cell lymphoma, mantle), Jeko (B cell lymphoma, mantle), CCRF (B lymphoblast, acute lymphoblastic leukemia), and SUP-B15 (B lymphoblast, acute lymphoblastic leukemia). The dose-effect curves for these cell lines are given in FIG. 6, FIG. 7, FIG. 8, and FIG. 9. ED25, ED50, ED75, and ED90 refer to the effective doses causing 25%, 50%, 75%, and 90% of the maximum biological effect (proliferation).

**[0048]** FIG. 6 illustrates the dose-effect curves obtained for the tested Maver-1 cell line (B cell lymphoma, mantle) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the PI3K-δ inhibitor of Formula IX ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0049]** FIG. 7 illustrates the dose-effect curves obtained for the tested Jeko cell line (B cell lymphoma, mantle) using combined dosing of the BTK inhibitor of Formula XVIII

("Inh.1") and the PI3K-δ inhibitor of Formula IX ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0050]** FIG. 8 illustrates the dose-effect curves obtained for the tested CCRF cell line (B lymphoblast, acute lymphoblastic leukemia) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the PI3K-δ inhibitor of Formula IX ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0051]** FIG. 9 illustrates the dose-effect curves obtained for the tested SUP-B15 cell line (B lymphoblast, acute lymphoblastic leukemia) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the PI3K-δ inhibitor of Formula IX ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0052]** FIG. 10 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula XVIII and the PI3K-δ inhibitor of Formula IX are combined. The tested cell lines include Jeko (B cell lymphoma, mantle) and SU-DHL-4 (diffuse large B cell lymphoma, ABC). The dose-effect curves for these cell lines are given in FIG. 11 and FIG. 12.

**[0053]** FIG. 11 illustrates the dose-effect curves obtained for the tested Jeko cell line (B cell lymphoma, mantle) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the PI3K-δ inhibitor of Formula IX ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0054]** FIG. 12 illustrates the dose-effect curves obtained for the tested SU-DHL-4 cell line (diffuse large B cell lymphoma, ABC) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the PI3K-δ inhibitor of Formula IX ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0055]** FIG. 13 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula XVIII and the PI3K-δ inhibitor of Formula IX are combined. The tested cell lines include CCRF (B lymphoblast, acute lymphoblastic leukemia), SUP-B15 (B lymphoblast, acute lymphoblastic leukemia), JVM-2 (prolymphocytic leukemia), Ramos (Burkitt's lymphoma), and Mino (mantle cell lymphoma). The dose-effect curves for these cell lines are given in FIG. 14, FIG. 15, FIG. 16, and FIG. 17. No dose-effect curve is given for Ramos (Burkitt's lymphoma) because of negative slope.

**[0056]** FIG. 14 illustrates the dose-effect curves obtained for the tested CCRF cell line (B lymphoblast, acute lymphoblastic leukemia) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the PI3K-δ inhibitor of Formula IX ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0057]** FIG. 15 illustrates the dose-effect curves obtained for the tested SUP-B15 cell line (B lymphoblast, acute lymphoblastic leukemia) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the PI3K-δ inhibitor of Formula IX ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0058]** FIG. 16 illustrates the dose-effect curves obtained for the tested JVM-2 cell line (prolymphocytic leukemia) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the PI3K-δ inhibitor of Formula IX ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0059]** FIG. 17 illustrates the dose-effect curves obtained for the tested Mino cell line (mantle cell lymphoma) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the PI3K-δ inhibitor of Formula IX ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0060]** FIG. 18 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula XVIII and the PI3K-δ inhibitor of Formula IX are combined. The tested cell lines include Raji (B lymphocyte, Burkitt's lymphoma), SU-DHL-1 (DLBCL-

ABC), and Pfeiffer (follicular lymphoma). The dose-effect curves for these cell lines are given in FIG. 19, FIG. 20, and FIG. 21.

**[0061]** FIG. 19 illustrates the dose-effect curves obtained for the tested Raji cell line (B lymphocyte, Burkitt's lymphoma) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the PI3K-δ inhibitor of Formula IX ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0062]** FIG. 20 illustrates the dose-effect curves obtained for the tested SU-DHL-1 cell line (Activated B-cell like diffuse large B-cell lymphoma, DLBCL-ABC) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the PI3K-δ inhibitor of Formula IX ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0063]** FIG. 21 illustrates the dose-effect curves obtained for the tested Pfeiffer cell line (follicular lymphoma) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the PI3K-δ inhibitor of Formula IX ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0064]** FIG. 22 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula XVIII and the PI3K-δ inhibitor of Formula IX are combined. The tested cell lines include Ly1 (Germinal center B-cell like diffuse large B-cell lymphoma, DLBCL-GCB), Ly7 (DLBCL-GCB), Ly19 (DLBCL-GCB), SU-DHL-2 (Activated B-cell like diffuse large B-cell lymphoma, DLBCL-ABC), and DOHH2 (follicular lymophoma, FL). The dose-effect curves for these cell lines are given in FIG. 23, FIG. 24, FIG. 25, and FIG. 26, except for the Ly19 cell line, which is not graphed because of a negative slope.

**[0065]** FIG. 23 illustrates the dose-effect curves obtained for the tested Ly1 cell line (DLBCL-GCB) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the PI3K-δ inhibitor of Formula IX ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0066]** FIG. 24 illustrates the dose-effect curves obtained for the tested Ly7 cell line (DLBCL-GCB) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the PI3K-δ inhibitor of Formula IX ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0067]** FIG. 25 illustrates the dose-effect curves obtained for the tested DOHH2 cell line (FL) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the PI3K-δ inhibitor of Formula IX ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0068]** FIG. 26 illustrates the dose-effect curves obtained for the tested SU-DHL-2 cell line (DLBCL-ABC) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the PI3K-δ inhibitor of Formula IX ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0069]** FIG. 27 illustrates the synergy observed in certain cell lines when Formula XVIII and Formula IX are combined. The tested cell lines include U937 (histiocytic lymphoma and/or myeloid), K562 (leukemia, myeloid, and/or chronic myelogenous leukemia), Daudi (human Burkitt's lymphoma), and SU-DHL-6 (DLBCL-GCB and/or peripheral T-cell lymphoma, PTCL). The dose-effect curves for these cell lines are given in FIG. 28, FIG. 29, FIG. 30, and FIG. 31.

**[0070]** FIG. 28 illustrates the dose-effect curves obtained for the tested U937 cell line (histiocytic lymphoma and/or myeloid) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the PI3K-δ inhibitor of Formula IX ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0071]** FIG. 29 illustrates the dose-effect curves obtained for the tested K562 cell line (leukemia, myeloid, and/or chronic myelogenous leukemia) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the PI3K-δ inhibitor of Formula IX ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0072]** FIG. 30 illustrates the dose-effect curves obtained for the tested Daudi cell line (human Burkitt's lymphoma) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the PI3K-δ inhibitor of Formula IX ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0073]** FIG. 31 illustrates the dose-effect curves obtained for the tested SU-DHL-6 cell line (DLBCL-GCB and/or PTCL) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the PI3K-δ inhibitor of Formula IX ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0074]** FIG. 32 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula XVIII and the PI3K-δ inhibitor of Formula IX are combined. The tested cell lines include SU-DHL-6 (DLBCL-GCB or PTCL), TMD-8 (DLBCL-ABC), HBL-1 (DLBCL-ABC), and Rec-1 (follicular lymphoma). The dose-effect curves for these cell lines are given in FIG. 34, FIG. 35, FIG. 36, and FIG. 37.

**[0075]** FIG. 33 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula XVIII and the PI3K-δ inhibitor of Formula IX are combined. The tested cell lines include SU-DHL-6 (DLBCL-GCB or PTCL), TMD-8 (DLBCL-ABC), HBL-1 (DLBCL-ABC), and Rec-1 (follicular lymphoma). All corresponding CIs are shown for each of the combinations tested as listed on the x axis.

**[0076]** FIG. 34 illustrates the dose-effect curves obtained for the tested SU-DHL-6 cell line (DLBCL-GCB or PTCL) cell line using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the PI3K-δ inhibitor of Formula IX ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0077]** FIG. 35 illustrates the dose-effect curves obtained for the tested TMD-8 cell line (DLBCL-ABC) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the PI3K-δ inhibitor of Formula IX ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0078]** FIG. 36 illustrates the dose-effect curves obtained for the tested HBL-1 cell line (DLBCL-ABC) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the PI3K-δ inhibitor of Formula IX ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0079]** FIG. 37 illustrates the dose-effect curves obtained for the tested Rec-1 cell line (follicular lymphoma) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the PI3K-δ inhibitor of Formula IX ("Inh.3"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0080]** FIG. 38 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula XVIII and the JAK-2 inhibitor of Formula XXX (ruxolitinib) are combined. The tested cell lines included Maver-1 (B cell lymphoma, mantle), Jeko (B cell lymphoma, mantle), SUP-B15 (B lymphoblast, acute lymphoblastic leukemia), and CCRF (B lymphoblast, acute lymphoblastic leukemia). The dose-effect curves for these cell lines are given in FIG. 39, FIG. 40, FIG. 41, and FIG. 42.

**[0081]** FIG. 39 illustrates the dose-effect curves obtained for the tested Maver-1 cell line (B cell lymphoma, mantle) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the JAK-2 inhibitor of Formula XXX ("Inh.2") (ruxolitinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0082]** FIG. 40 illustrates the dose-effect curves obtained for the tested Jeko cell line (B cell lymphoma, mantle) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the JAK-2 inhibitor of Formula XXX ("Inh.2") (ruxolitinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0083]** FIG. 41 illustrates the dose-effect curves obtained for the tested SUP-B15 cell line (B lymphoblast, acute lymphoblastic leukemia) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the JAK-2 inhibitor of Formula XXX ("Inh.2") (ruxolitinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0084]** FIG. 42 illustrates the dose-effect curves obtained for the tested CCRF cell line (B lymphoblast, acute lymphoblastic leukemia) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the JAK-2 inhibitor of Formula XXX ("Inh.2") (ruxolitinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0085]** FIG. 43 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula XVIII and the JAK-2 inhibitor of Formula XXX (ruxolitinib) are combined. Repeat experiments for two of the cell lines previously shown in FIG. 38 are shown, including SUP-B15 (B lymphoblast, acute lymphoblastic leukemia) and CCRF (B lymphoblast, acute lymphoblastic leukemia).

**[0086]** FIG. 44 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula XVIII and the JAK-2 inhibitor of Formula XXX (ruxolitinib) are combined. The tested cell lines included JVM-2 (prolymphocytic leukemia), Raji (B lymphocyte, Burkitt's lymphoma), Ramos (B lymphocyte, Burkitt's lymphoma), and Mino (mantle cell lymphoma). The dose-effect curves for these cell lines are given in FIG. 45, FIG. 46, FIG. 47, and FIG. 48.

**[0087]** FIG. 45 illustrates the dose-effect curves obtained for the tested JVM-2 cell line (prolymphocytic leukemia) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the JAK-2 inhibitor of Formula XXX ("Inh.2") (ruxolitinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0088]** FIG. 46 illustrates the dose-effect curves obtained for the tested Raji cell line (B lymphocyte, Burkitt's lymphoma) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the JAK-2 inhibitor of Formula XXX ("Inh.2") (ruxolitinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0089]** FIG. 47 illustrates the dose-effect curves obtained for the tested Ramos cell line (B lymphocyte, Burkitt's lymphoma) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the JAK-2 inhibitor of Formula XXX ("Inh.2")

(ruxolitinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0090]** FIG. 48 illustrates the dose-effect curves obtained for the tested Mino cell line (mantle cell lymphoma) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the JAK-2 inhibitor of Formula XXX ("Inh.2") (ruxolitinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0091]** FIG. 49 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula XVIII and the JAK-2 inhibitor of Formula XXX (ruxolitinib) are combined. The tested cell lines included Pfeiffer (follicular lymphoma) and SU-DHL-1 (DLBCL-ABC). The dose-effect curves for these cell lines are given in FIG. 50 and FIG. 51.

**[0092]** FIG. 50 illustrates the dose-effect curves obtained for the tested Pfeiffer cell line (follicular lymphoma) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the JAK-2 inhibitor of Formula XXX ("Inh.2") (ruxolitinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0093]** FIG. 51 illustrates the dose-effect curves obtained for the tested SU-DHL-1 cell line (follicular lymphoma) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the JAK-2 inhibitor of Formula XXX ("Inh.2") (ruxolitinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0094]** FIG. 52 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula XVIII and the JAK-2 inhibitor of Formula XXX (ruxolitinib) are combined. The tested cell lines included DOHH2 (follicular lymphoma), SU-DHL-1 (DLBCL-ABC), Ly1 (DLBCL-GCB), Ly7 (DLBCL-GCB), and Ly19 (DLBCL-GCB). The dose-effect curves for these cell lines are given in FIG. 53, FIG. 54, FIG. 55, and FIG. 56, except for the Ly19 cell line, which is not graphed because of a negative slope.

**[0095]** FIG. 53 illustrates the dose-effect curves obtained for the tested DOHH2 cell line (follicular lymphoma) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the JAK-2 inhibitor of Formula XXX ("Inh.2") (ruxolitinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0096]** FIG. 54 illustrates the dose-effect curves obtained for the tested SU-DHL-1 cell line (DLBCL-ABC) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the JAK-2 inhibitor of Formula XXX ("Inh.2") (ruxolitinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0097]** FIG. 55 illustrates the dose-effect curves obtained for the tested Ly1 cell line (DLBCL-GCB) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the JAK-2 inhibitor of Formula XXX ("Inh.2") (ruxolitinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0098]** FIG. 56 illustrates the dose-effect curves obtained for the tested Ly7 cell line (DLBCL-GCB) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the JAK-2 inhibitor of Formula XXX ("Inh.2") (ruxolitinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[0099]** FIG. 57 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula XVIII and the JAK-2 inhibitor of Formula XXX (ruxolitinib) are combined. The tested cell lines included U937 (histiocytic lymphoma), Daudi (human Burkitt's lymphoma), and K562 (leukemia, myeloid, and/or chronic myelogenous leukemia). The dose-effect curves for these cell lines are given in FIG. 58, FIG. 59, and FIG. 60.

**[00100]** FIG. 58 illustrates the dose-effect curves obtained for the tested U937 cell line (histiocytic lymphoma) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the JAK-2 inhibitor of Formula XXX ("Inh.2") (ruxolitinib). The y-axis

("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[00101]** FIG. 59 illustrates the dose-effect curves obtained for the tested Daudi cell line (human Burkitt's lymphoma) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the JAK-2 inhibitor of Formula XXX ("Inh.2") (ruxolitinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[00102]** FIG. 60 illustrates the dose-effect curves obtained for the tested K562 cell line (leukemia, myeloid, and/or chronic myelogenous leukemia) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the JAK-2 inhibitor of Formula XXX ("Inh.2") (ruxolitinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[00103]** FIG. 61 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula XVIII and the JAK-2 inhibitor of Formula XXX (ruxolitinib) are combined. The tested cell lines include SU-DHL-6 (DLBCL-GCB or PTCL), TMD-8 (DLBCL-ABC), HBL-1 (DLBCL-ABC), and Rec-1 (follicular lymphoma). The dose-effect curves for these cell lines are given in FIG. 62, FIG. 63, FIG. 64, and FIG. 65.

**[00104]** FIG. 62 illustrates the dose-effect curves obtained for the tested SU-DHL-6 cell line (DLBCL-GCB or PTCL) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the JAK-2 inhibitor of Formula XXX ("Inh.2") (ruxolitinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[00105]** FIG. 63 illustrates the dose-effect curves obtained for the tested TMD-8 cell line (DLBCL-ABC) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the JAK-2 inhibitor of Formula XXX ("Inh.2") (ruxolitinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[00106]** FIG. 64 illustrates the dose-effect curves obtained for the tested HBL-1 cell line (DLBCL-ABC) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1")

and the JAK-2 inhibitor of Formula XXX ("Inh.2") (ruxolitinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[00107]** FIG. 65 illustrates the dose-effect curves obtained for the tested Rec-1 cell line (follicular lymphoma) using combined dosing of the BTK inhibitor of Formula XVIII ("Inh.1") and the JAK-2 inhibitor of Formula XXX ("Inh.2") (ruxolitinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[00108]** FIG. 66 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula (XVIII) and the JAK-2 inhibitor of Formula LIV (pacritinib) are combined. The tested cell lines include Mino (mantle cell lymphoma), Maver-1 (B cell lymphoma, mantle cell lymophoma), Raji (B lymphocyte, Burkitt's lymphoma), JVM-2 (prolymphocytic leukemia), Daudi (Human Burkitt's lymphoma), Rec-1 (follicular lymphoma), SUP-B15 (B lymphoblast, acute lymphoblastic leukemia), CCRF (B lymphoblast, acute lymphoblastic leukemia), and SU-DHL-4 (DLBCL-ABC). The dose-effect curves for these cell lines are given in FIG. 67, FIG. 68, FIG. 69, FIG. 70, FIG. 71, FIG. 72, FIG. 73, FIG. 74, and FIG. 75.

**[00109]** FIG. 67 illustrates the dose-effect curves obtained for the tested Mino cell line (mantle cell lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the JAK-2 inhibitor of Formula LIV ("Inh.4") (pacritinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[00110]** FIG. 68 illustrates the dose-effect curves obtained for the tested Maver-1 cell line (B cell lymphoma, mantle cell lymophoma) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the JAK-2 inhibitor of Formula LIV ("Inh.4") (pacritinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[00111]** FIG. 69 illustrates the dose-effect curves obtained for the tested Raji cell line (B lymphocyte, Burkitt's lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the JAK-2 inhibitor of Formula LIV ("Inh.4") (pacritinib).

The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[00112]** FIG. 70 illustrates the dose-effect curves obtained for the tested JVM-2 cell line (prolymphocytic leukemia) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the JAK-2 inhibitor of Formula LIV ("Inh.4") (pacritinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[00113]** FIG. 71 illustrates the dose-effect curves obtained for the tested Daudi cell line (human Burkitt's lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the JAK-2 inhibitor of Formula LIV ("Inh.4") (pacritinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[00114]** FIG. 72 illustrates the dose-effect curves obtained for the tested Rec-1 cell line (follicular lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the JAK-2 inhibitor of Formula LIV ("Inh.4") (pacritinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[00115]** FIG. 73 illustrates the dose-effect curves obtained for the tested SUP-B15 cell line (B lymphoblast, acute lymphoblastic leukemia) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the JAK-2 inhibitor of Formula LIV ("Inh.4") (pacritinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[00116]** FIG. 74 illustrates the dose-effect curves obtained for the tested CCRF cell line (B lymphoblast, acute lymphoblastic leukemia) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the JAK-2 inhibitor of Formula LIV ("Inh.4") (pacritinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[00117]** FIG. 75 illustrates the dose-effect curves obtained for the tested SU-DHL-4 cell line (DLBCL-ABC) using combined dosing of the BTK inhibitor of Formula (XVIII)

("Inh.1") and the JAK-2 inhibitor of Formula LIV ("Inh.4") (pacritinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[00118]** FIG. 76 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula (XVIII) and the JAK-2 inhibitor of Formula LIV (pacritinib) are combined. The tested cell lines include EB3 (B lymphocyte, Burkitt's lymphoma), CA46 (B lymphocyte, Burkitt's lymphoma), DB (B cell lymphoma, mantle cell lymphoma), Pfeiffer (follicular lymphoma), DOHH2 (follicular lymphoma), Namalwa (B lymphocyte, Burkitt's lymphoma), JVM-13 (B cell lymphoma, mantle cell lymphoma), SU-DHL-1 (DLBCL-ABC), and SU-DHL-2 (DLBCL-ABC). The dose-effect curves for these cell lines are given in FIG. 77, FIG. 78, FIG. 79, FIG. 80, FIG. 81, FIG. 82, FIG. 83, FIG. 84, and FIG. 85.

**[00119]** FIG. 77 illustrates the dose-effect curves obtained for the tested EB3 cell line (B lymphocyte, Burkitt's lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the JAK-2 inhibitor of Formula LIV ("Inh.4") (pacritinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[00120]** FIG. 78 illustrates the dose-effect curves obtained for the tested CA46 cell line (B lymphocyte, Burkitt's lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the JAK-2 inhibitor of Formula LIV ("Inh.4") (pacritinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[00121]** FIG. 79 illustrates the dose-effect curves obtained for the tested DB cell line (B cell lymphoma, mantle cell lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the JAK-2 inhibitor of Formula LIV ("Inh.4") (pacritinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[00122]** FIG. 80 illustrates the dose-effect curves obtained for the tested Pfeiffer cell line (follicular lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the JAK-2 inhibitor of Formula LIV ("Inh.4") (pacritinib). The y-axis

("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[00123]** FIG. 81 illustrates the dose-effect curves obtained for the tested DOHH2 cell line (follicular lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the JAK-2 inhibitor of Formula LIV ("Inh.4") (pacritinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[00124]** FIG. 82 illustrates the dose-effect curves obtained for the tested Namalwa cell line (B lymphocyte, Burkitt's lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the JAK-2 inhibitor of Formula LIV ("Inh.4") (pacritinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[00125]** FIG. 83 illustrates the dose-effect curves obtained for the tested JVM-13 cell line (B cell lymphoma, mantle cell lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the JAK-2 inhibitor of Formula LIV ("Inh.4") (pacritinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[00126]** FIG. 84 illustrates the dose-effect curves obtained for the tested SU-DHL-1 cell line (DLBCL-ABC) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the JAK-2 inhibitor of Formula LIV ("Inh.4") (pacritinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[00127]** FIG. 85 illustrates the dose-effect curves obtained for the tested SU-DHL-2 cell line (DLBCL-ABC) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the JAK-2 inhibitor of Formula LIV ("Inh.4") (pacritinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[00128]** FIG. 86 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula (XVIII) and the JAK-2 inhibitor of Formula LIV (pacritinib) are

combined. The tested cell lines include Jeko (B cell lymphoma, mantle cell lymphoma), TMD-8 (DLBCL-ABC), SU-DHL6 (DLBCL-GCB), Ramos (human Burkitt's lymphoma), HBL-1 (DLBCL-ABC), SU-DHL-10 (DLBCL-GCB), OCI-Ly7 (DLBCL-ABC), and OCI-Ly3 (DLBCL-ABC). The dose-effect curves for these cell lines are given in FIG. 87, FIG. 88, FIG. 89, FIG. 90, FIG. 91, FIG. 92, FIG. 93, and FIG. 94.

**[00129]** FIG. 87 illustrates the dose-effect curves obtained for the tested Jeko cell line (B cell lymphoma, mantle cell lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the JAK-2 inhibitor of Formula LIV ("Inh.4") (pacritinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[00130]** FIG. 88 illustrates the dose-effect curves obtained for the tested TMD-8 cell line (DLBCL-ABC) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the JAK-2 inhibitor of Formula LIV ("Inh.4") (pacritinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[00131]** FIG. 89 illustrates the dose-effect curves obtained for the tested SU-DHL6 cell line (DLBCL-GCB) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the JAK-2 inhibitor of Formula LIV ("Inh.4") (pacritinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[00132]** FIG. 90 illustrates the dose-effect curves obtained for the tested Ramos cell line (human Burkitt's lymphoma) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the JAK-2 inhibitor of Formula LIV ("Inh.4") (pacritinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[00133]** FIG. 91 illustrates the dose-effect curves obtained for the tested HBL-1 cell line (DLBCL-ABC) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the JAK-2 inhibitor of Formula LIV ("Inh.4") (pacritinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[00134]** FIG. 92 illustrates the dose-effect curves obtained for the tested SU-DHL-10 cell line (DLBCL-GCB) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the JAK-2 inhibitor of Formula LIV ("Inh.4") (pacritinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[00135]** FIG. 93 illustrates the dose-effect curves obtained for the tested OCI-Ly7 cell line (DLBCL-ABC) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the JAK-2 inhibitor of Formula LIV ("Inh.4") (pacritinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[00136]** FIG. 94 illustrates the dose-effect curves obtained for the tested OCI-Ly3 cell line (DLBCL-ABC) using combined dosing of the BTK inhibitor of Formula (XVIII) ("Inh.1") and the JAK-2 inhibitor of Formula LIV ("Inh.4") (pacritinib). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[00137]** FIG. 95 illustrates the dosing schema used for the α-PD-L1 inhibitor (BioXcell InVivoMAb anti-m-PD-L1, Clone 10F.9G2) in combination with the BTK inhibitor of Formula (XVIII) in a syngeneic CT26 colon cancer model in the Balb/c strain of mice.

**[00138]** FIG. 96 illustrates the effect of vehicle on tumor volume in a study of the combined effect of an α-PD-L1 inhibitor and a BTK inhibitor in a syngeneic CT26 colon cancer model in mice.

**[00139]** FIG. 97 illustrates the effect of α-PD-L1 inhibitor (BioXcell InVivoMAb anti-m-PD-L1, Clone 10F.9G2) on tumor volume in a study of the combined effect of an α-PD-L1 inhibitor and a BTK inhibitor in a syngeneic CT26 colon cancer model in mice.

**[00140]** FIG. 98 illustrates the effect of α-PD-L1 inhibitor (BioXcell InVivoMAb anti-m-PD-L1, Clone 10F.9G2) in combination with the BTK inhibitor of Formula (XVIII) on tumor volume in a study of the combined effect of an α-PD-L1 inhibitor and a BTK inhibitor in a syngeneic CT26 colon cancer model in mice.

**[00141]** FIG. 99 illustrates the synergistic effect of α-PD-L1 inhibitor (BioXcell

InVivoMAb anti-m-PD-L1, clone 10F.9G2) in combination with the BTK inhibitor of Formula (XVIII) as measured through modulation of circulating immature myeloid cells (myeloid-derived suppressor cells, or MDSCs) in a syngeneic CT26 colon cancer model in mice.

**[00142]** FIG. 100 illustrates the effects of vehicle on flux at two timepoints, as a control for comparison with FIG. 101, in the ID8 syngeneic orthotropic ovarian cancer model.

**[00143]** FIG. 101 illustrates the effects of the BTK inhibitor of Formula (XVIII) on flux at two timepoints, for comparison with FIG. 100, in the ID8 syngeneic orthotropic ovarian cancer model.

**[00144]** FIG. 102 illustrates tumor response to treatment with the BTK inhibitor of Formula (XVIII) correlates with a significant reduction in immunosuppressive tumor associated lymphocytes in tumor-bearing mice, in comparison to a control (vehicle).

**[00145]** FIG. 103 illustrates that treatment with the BTK inhibitor of Formula (XVIII) impairs ID8 ovarian cancer growth in the syngeneic murine model in comparison to a control (vehicle).

**[00146]** FIG. 104 illustrates that treatment with the BTK inhibitor of Formula (XVIII) induces a tumor response that correlates with a significant reduction in total B cells in tumor-bearing mice.

**[00147]** FIG. 105 illustrates that treatment with the BTK inhibitor of Formula (XVIII) induces a tumor response that correlates with a significant reduction in B regulatory cells (Bregs) in tumor-bearing mice.

**[00148]** FIG. 106 illustrates that treatment with the BTK inhibitor of Formula (XVIII) induces a tumor response that correlates with a significant reduction in immunosuppressive tumor associated Tregs.

**[00149]** FIG. 107 illustrates that treatment with the BTK inhibitor of Formula (XVIII) induces a tumor response that correlates with an increase in $CD8^+$ T cells.

**[00150]** FIG. 108 illustrates bioluminescence images from mice in the different treatment arms of the ID8 ovarian cancer model study.

**[00151]** FIG. 109 illustrates bioluminescence imaging results 2 weeks after start of dosing in the ID8 ovarian cancer model study.

**[00152]** FIG. 110 illustrates tumor growth suppression in an orthotopic pancreatic cancer model. Mice were dosed orally with 15 mg/kg of the BTK inhibitor of Formula (XVIII), 15 mg/kg of the PI3K inhibitor of Formula (IX), or a combination of both drugs. The statistical p-value (presumption against null hypothesis) is shown for each tested single active pharmaceutical ingredient and for the combination against the vehicle.

**[00153]** FIG. 111 illustrates the effects of oral dosing with 15 mg/kg of the BTK inhibitor of Formula (XVIII), 15 mg/kg of the PI3K inhibitor of Formula (IX), or a combination of both inhibitors on myeloid tumor-associated macrophages (TAMs) in pancreatic tumor-bearing mice.

**[00154]** FIG. 112 illustrates the effects of oral dosing with 15 mg/kg of the BTK inhibitor of Formula (XVIII), 15 mg/kg of the PI3K inhibitor of Formula (IX), or a combination of both inhibitors on myeloid-derived suppressor cells (MDSCs) in pancreatic tumor-bearing mice.

**[00155]** FIG. 113 illustrates the effects of oral dosing with 15 mg/kg of the BTK inhibitor of Formula (XVIII), 15 mg/kg of the PI3K inhibitor of Formula (IX), or a combination of both inhibitors on regulatory T cells (Tregs) in pancreatic tumor-bearing mice.

**[00156]** FIG. 114 illustrates the effects on tumor volume of vehicle (measured in $mm^3$) of the BTK inhibitor of Formula (XVIII), a combination of the BTK inhibitor of Formula (XVIII) and gemcitabine ("Gem"), and gemcitabine alone.

**[00157]** FIG. 115 illustrates the effects on the amount of $CD8^+$ T cells, given as a percentage of cells expressing the T cell receptor (CD3), of the BTK inhibitor of Formula (XVIII), a combination of the BTK inhibitor of Formula (XVIII) and gemcitabine ("Gem"), and gemcitabine alone.

**[00158]** FIG. 116 illustrates the effects on the percentage of $CD4^+$, $CD25^+$, and $FoxP3^+$ T regulatory cells ("Tregs"), given as a percentage of cells expressing the T cell receptor (CD3), of the BTK inhibitor of Formula (XVIII), a combination of the BTK inhibitor of

Formula (XVIII) and gemcitabine ("Gem"), and gemcitabine alone.

**[00159]** FIG. 117 illustrates the effects on the percentage of $CD11b^{+}$, $LY6C^{low}$, $F4/80^{+}$, and $Csf1r^{+}$ tumor-associated macrophages ("TAMs"), given as a percentage of cells expressing the T cell receptor (CD3), of the BTK inhibitor of Formula (XVIII), a combination of the BTK inhibitor of Formula (XVIII) and gemcitabine ("Gem"), and gemcitabine alone.

**[00160]** FIG. 118 illustrates the effects on the percentage of $Gr1^{+}$ and $LY6C^{hi}$, $F4/80^{+}$, and $Csf1r^{+}$ myeloid-derived suppressor cells ("MDSCs"), given as a percentage of cells expressing the T cell receptor (CD3), of the BTK inhibitor of Formula (XVIII), a combination of the BTK inhibitor of Formula (XVIII) and gemcitabine ("Gem"), and gemcitabine alone.

**[00161]** FIG. 119 illustrates the effects of treatment with single-active pharmaceutical ingredient Formula (XVIII) on tumor volumes in the KPC pancreatic cancer model.

**[00162]** FIG. 120 illustrates the results of analysis of tumor tissues showing that immunosuppressive TAMs ($CD11b^{+}Ly6ClowF4/80^{+}Csf1r^{+}$) were significantly reduced with Formula (XVIII) treatment in the KPC pancreatic cancer model.

**[00163]** FIG. 121 illustrates the results of analysis of tumor tissues showing that immunosuppressive MDSCs ($Gr1^{+}Ly6CHi$) were significantly reduced with Formula (XVIII) treatment in the KPC pancreatic cancer model.

**[00164]** FIG. 122 illustrates the results of analysis of tumor tissues showing that immunosuppressive Tregs ($CD4^{+}CD25^{+}FoxP3^{+}$) were significantly reduced with Formula (XVIII) treatment in the KPC pancreatic cancer model.

**[00165]** FIG. 123 illustrates that the decrease in immunosuppressive TAMs, MDSCs, and Tregs in the KPC pancreatic cancer model correlated with a significant increase in $CD8^{+}$ cells (FIG. 123).

**[00166]** FIG. 124 illustrates representative photomicrographs and comparison of maximal thrombus size in laser injured arterioles of VWF HA1 mutant mice infused with human platelets in the absence or presence of various BTK inhibitors. Representative photomicrographs are given as a comparison of maximal thrombus size in laser-injured

arterioles (1 μM concentrations shown).

**[00167]** FIG. 125 illustrates a quantitative comparison obtained by *in vivo* analysis of early thrombus dynamics in a humanized mouse laser injury model using three BTK inhibitors at a concentration 1 μM.

**[00168]** FIG. 126 illustrates the effect of the tested BTK inhibitors on thrombus formation. The conditions used were N=4, 3 mice per drug; anti-clotting active pharmaceutical ingredients < 2000 $\mu M^2$. In studies with ibrutinib, 48% MCL bleeding events were observed with 560 mg QD and 63% CLL bleeding events were observed with 420 mg QD, where bleeding event is defined as subdural hematoma, ecchymoses, GI bleeding, or hematuria.

**[00169]** FIG. 127 illustrates the effect of the concentration of the tested BTK inhibitors on thrombus formation.

**[00170]** FIG. 128 illustrates the results of GPVI platelet aggregation studies of Formula XVIII (IC50 = 1.15 μM) and Formula (XX-A) (ibrutinib, IC50 = 0.13 μM).

**[00171]** FIG. 129 illustrates the results of GPVI platelet aggregation studies of Formula XVIII and Formula (XX-A) (ibrutinib).

**[00172]** FIG. 130 shows *in vitro* analysis of antibody-dependent NK cell–mediated INF-γ release with BTK inhibitors. To evaluate NK cell function, purified NK cells were isolated from healthy peripheral blood mononuclear cells and cultured with 0.1 or 1 μM of ibrutinib or 1 μM of Formula (XVIII) for 4 hours together with rituximab-coated (10 μg/mL) lymphoma cells, DHL4, or trastuzumab-coated (10 μg/mL) HER2+ breast cancer cells, HER18, and supernatant was harvested and analyzed by enzyme-linked immunosorbent assay for interferon-γ (IFN-γ). All *in vitro* experiments were performed in triplicate. Labels are defined as follows: *p = 0.018, **p = 0.002, ***p = 0.001.

**[00173]** FIG. 131 shows *in vitro* analysis of antibody-dependent NK cell–mediated degranulation with BTK inhibitors. To evaluate NK cell function, purified NK cells were isolated from healthy peripheral blood mononuclear cells and cultured with 0.1 or 1 μM of ibrutinib or 1 μM of Formula (XVIII) for 4 hours together with rituximab-coated (10 μg/mL) lymphoma cells, DHL4, or trastuzumab-coated (10 μg/mL) HER2+ breast cancer

cells, HER18, and NK cells isolated and analyzed for degranulation by flow cytometry for CD107a mobilization. All *in vitro* experiments were performed in triplicate. Labels are defined as follows: *p = 0.01, **p = 0.002, ***p = 0.003, ****p = 0.0005.

**[00174]** FIG. 132 shows that ibrutinib antagonizes antibody-dependent NK cell–mediated cytotoxicity using the Raji cell line. NK cell cytotoxicity as percent lysis of tumor cells was analyzed in chromium release assays with purified NK cells incubated with chromium-labeled Raji cells for 4 hours at variable rituximab concentrations at a constant effector:target ratio of 25:1 and ibrutinib (1 μM), Formula (II) (1 μM), or other ITK sparing BTK inhibitors CGI-1746, inhibA (1 μM) and BGB-3111 ("inhib B," 1 μM). All *in vitro* experiments were performed in triplicate. Labels are defined as follows: *p = 0.001.

**[00175]** FIG. 133 shows a summary of the results given in FIG. 132 at the highest concentration of rituximab ("Ab") (10 μg/mL).

**[00176]** FIG. 134 shows that ibrutinib antagonizes antibody-dependent NK cell–mediated cytotoxicity in primary CLL cells, as with Raji cells in FIG. 132.

**[00177]** FIG. 135 illustrates the treatment schema used for the α-PD-L1 inhibitor (BioXcell InVivoMAb anti-m-PD-L1, Clone 10F.9G2) in combination with the BTK inhibitor of Formula (XVIII), the PI3K inhibitor of Formula (IX), and the BTK inhibitor ibrutinib in a 4T1 orthotopic breast cancer model.

**[00178]** FIG. 136 illustrates tumor volumes observed in each of the ten treatment arms in the 4T1 orthotopic breast cancer model study: (1) IgG only; (2) the BTK inhibitor of Formula (XVIII) at 15 mg/kg, BID, on days 6 to 20; (3) the PI3K-δ inhibitor of Formula (IX) at 15 mg/kg, BID, on days 6 to 20; (4) the BTK inhibitor of Formula (XVIII) and the PI3K inhibitor of Formula (IX) each at 15 mg/kg, BID, on days 6 to 20; (5) the BTK inhibitor ibrutinib at 6 mg/kg, QD, on days 6 to 20; (6) α-PD-L1 antibody at 150 μg, on days 6, 9, 12, 15, and 18; (7) the BTK inhibitor of Formula (XVIII) at 15 mg/kg, BID, on days 6 to 20, combined with α-PD-L1 antibody at 150 μg, on days 6, 9, 12, 15, and 18; (8) the PI3K-δ inhibitor of Formula (IX) at 15 mg/kg, BID, on days 6 to 20, combined with α-PD-L1 antibody at 150 μg, on days 6, 9, 12, 15, and 18; (9) the PI3K-δ inhibitor ibrutinib at 6 mg/kg, QD, on days 6 to 20, combined with α-PD-L1 antibody at 150 μg,

on days 6, 9, 12, 15, and 18; and (10) the BTK inhibitor of Formula (XVIII) and the PI3K inhibitor of Formula (IX) each at 15 mg/kg, BID, on days 6 to 20, further combined with α-PD-L1 antibody at 150 μg, on days 6, 9, 12, 15, and 18.

**[00179]** FIG. 137 illustrates changes in tumor infiltrating lymphocytes ("TILs") observed in each of the ten treatment arms in the 4T1 orthotopic breast cancer model study.

**[00180]** FIG. 138 illustrates the treatment schema used for the α-PD-L1 inhibitor (BioXcell InVivoMAb anti-m-PD-L1, Clone 10F.9G2) in combination with the BTK inhibitor of Formula (XVIII), the PI3K inhibitor of Formula (IX), and the BTK inhibitor ibrutinib in an A20 orthotopic lymphoma model.

**[00181]** FIG. 139 illustrates tumor volumes observed in each of the ten treatment arms in the A20 orthotopic lymphoma model study: (1) IgG only; (2) the BTK inhibitor of Formula (XVIII) at 15 mg/kg, BID, on days 6 to 20; (3) the PI3K-δ inhibitor of Formula (IX) at 15 mg/kg, BID, on days 6 to 20; (4) the BTK inhibitor of Formula (XVIII) and the PI3K inhibitor of Formula (IX) each at 15 mg/kg, BID, on days 6 to 20; (5) the BTK inhibitor ibrutinib at 6 mg/kg, QD, on days 6 to 20; (6) α-PD-L1 antibody at 150 μg, on days 6, 9, 12, 15, and 18; (7) the BTK inhibitor of Formula (XVIII) at 15 mg/kg, BID, on days 6 to 20, combined with α-PD-L1 antibody at 150 μg, on days 6, 9, 12, 15, and 18; (8) the PI3K-δ inhibitor of Formula (IX) at 15 mg/kg, BID, on days 6 to 20, combined with α-PD-L1 antibody at 150 μg, on days 6, 9, 12, 15, and 18; (9) the PI3K-δ inhibitor ibrutinib at 6 mg/kg, QD, on days 6 to 20, combined with α-PD-L1 antibody at 150 μg, on days 6, 9, 12, 15, and 18; and (10) the BTK inhibitor of Formula (XVIII) and the PI3K inhibitor of Formula (IX) each at 15 mg/kg, BID, on days 6 to 20, further combined with α-PD-L1 antibody at 150 μg, on days 6, 9, 12, 15, and 18.

**[00182]** FIG. 140 illustrates changes in tumor infiltrating lymphocytes ("TILs") observed in each of the ten treatment arms in the A20 orthotopic lymphoma model study.

**[00183]** FIG. 141 illustrates *in vivo* potency of Formula (XVIII) (labeled "BTK inhibitor") and ibrutinib. Mice were gavaged at increasing drug concentration and sacrificed at one time point (3 h post-dose). BCR is stimulated with IgM and the expression of activation markers CD69 and CD86 are monitored by flow cytometry to

determine $EC_{50}$'s. The results show that Formula (XVIII) is more potent at inhibiting expression of activation makers than ibrutinib.

**[00184]** FIG. 142 illustrates the results of the clinical study of Formula (XVIII) (labeled "BTK inhibitor") in CLL, which are shown in comparison to the results reported for ibrutinib in Figure 1A of Byrd, *et al.*, *N. Engl. J. Med.* **2013,** *369,* 32-42. The results show that the BTK inhibitor of Formula (XVIII) causes a much smaller relative increase and much faster decrease in absolute lymphocyte count (ALC) relative to the BTK inhibitor ibrutinib. The sum of the product of greatest diameters (SPD) also decreases more rapidly during treatment with the BTK inhibitor than with the BTK inhibitor ibrutinib.

**[00185]** FIG. 143 shows overall response data shown by SPD of enlarged lymph nodes in CLL patients as a function of dose of the BTK inhibitor of Formula (XVIII).

**[00186]** FIG. 144 shows a comparison of progression-free survival (PFS) in CLL patients treated with the BTK inhibitor ibrutinib or the BTK inhibitor of Formula (XVIII). The ibrutinib data is taken from Byrd, *et al.*, *N. Engl. J. Med.* **2013,** *369,* 32-42. CLL patients treated with Formula (XVIII) for at least 8 days are included.

**[00187]** FIG. 145 shows a comparison of number of patients at risk in CLL patients treated with the BTK inhibitor ibrutinib or the BTK inhibitor of Formula (XVIII). CLL patients treated with Formula (XVIII) for at least 8 days are included.

**[00188]** FIG. 146 shows a comparison of progression-free survival (PFS) in CLL patients exhibiting the 17p deletion and treated with the BTK inhibitor ibrutinib or the BTK inhibitor of Formula (XVIII). The ibrutinib data is taken from Byrd, *et al.*, *N. Engl. J. Med.* **2013,** *369,* 32-42.

**[00189]** FIG. 147 shows a comparison of number of patients at risk in CLL patients exhibiting the 17p deletion and treated with the BTK inhibitor ibrutinib or the BTK inhibitor of Formula (XVIII). The ibrutinib data is taken from Byrd, *et al.*, *N. Engl. J. Med.* **2013,** *369,* 32-42. CLL patients treated with Formula (XVIII) for at least 8 days are included.

**[00190]** FIG. 148 shows improved BTK target occupancy of Formula (XVIII) at lower dosage versus ibrutinib in relapsed/refractory CLL patients.

**[00191]** FIG. 149 shows the % change in myeloid-derived suppressor cell (MDSC) (monocytic) level over 28 days versus % ALC change at Cycle 1, day 28 (C1D28) with trendlines.

**[00192]** FIG. 150 shows the % change in MDSC (monocytic) level over 28 days versus % ALC change at Cycle 2, day 28 (C2D28) with trendlines.

**[00193]** FIG. 151 shows the % change in natural killer (NK) cell level over 28 days versus % ALC change at Cycle 1, day 28 (C2D28) with trendlines.

**[00194]** FIG. 152 shows the % change in NK cell level over 28 days versus % ALC change at Cycle 2, day 28 (C2D28) with trendlines.

**[00195]** FIG. 153 compares the % change in MDSC (monocytic) level and % change in NK cell level over 28 days versus % ALC change with the % change in level of $CD4^+$ T cells, $CD8^+$ T cells, $CD4^+/CD8^+$ T cell ratio, NK-T cells, PD-$1^+$ $CD4^+$ T cells, and PD-$1^+$ $CD8^+$ T cells, also versus % ALC change, at Cycle 1 day 28 (C1D28). Trendlines are shown for % change in MDSC (monocytic) level and % change in NK cell level.

**[00196]** FIG. 154 compares the % change in MDSC (monocytic) level and % change in NK cell level over 28 days versus % ALC change with the % change in level of $CD4^+$ T cells, $CD8^+$ T cells, $CD4^+/CD8^+$ T cell ratio, NK-T cells, PD-$1^+$ $CD4^+$ T cells, and PD-$1^+$ $CD8^+$ T cells, also versus % ALC change, at Cycle 2 day 28 (C2D28). Trendlines are shown for % change in MDSC (monocytic) level and % change in NK cell level.

**[00197]** FIG. 155 shows additional clinical data related to that presented in FIG. 142.

**[00198]** FIG. 156 shows additional clinical data related to that presented in FIG. 148, and includes BID dosing results.

**[00199]** FIG. 157 illustrates PFS for patients with 17p deletion.

**[00200]** FIG. 158 illustrates PFS across relapsed/refractory patients with 17p deletion and with 11q deletion and no 17p deletion.

**[00201]** FIG. 159 illustrates PFS for patients with 11q deletion and no 17p deletion.

**[00202]** FIG. 160 illustrates shows additional clinical SPD results from the clinical study of Formula (XVIII) in relapsed/refractory CLL patients.

**[00203]** FIG. 161 illustrates that treatment of CLL patients with Formula (XVIII) resulted in increased apoptosis.

**[00204]** FIG. 162 illustrates a decrease in CXCL12 levels observed in patients treated with Formula (XVIII).

**[00205]** FIG. 163 illustrates a decrease in CCL2 levels observed in patients treated with Formula (XVIII).

**[00206]** FIG. 164 illustrates BTK inhibitory effects on MDSCs.

**[00207]** FIG. 165 illustrates the dosing schema used with the KrasLA2 non-small cell lung cancer (NSCLC) model.

**[00208]** FIG. 166 illustrates tumor volume variation from baseline as assessed by microcomputerized tomography (microCT) in the KrasL2 NSCLC model.

**[00209]** FIG. 167 illustrates TAMs in the KrasL2 NSCLC model, and indicates that Formula (XVIII) induces a tumor response that correlates with a significant reduction in immunosuppressive tumor associated TAMs.

**[00210]** FIG. 168 illustrates MDSCs in the KrasL2 NSCLC model, and indicates that Formula (XVIII) induces a tumor response that correlates with a significant reduction in immunosuppressive tumor associated MDSCs.

**[00211]** FIG. 169 illustrates Tregs in the KrasL2 NSCLC model, and indicates that Formula (XVIII) induces a tumor response that correlates with a significant reduction in immunosuppressive tumor associated Tregs.

**[00212]** FIG. 170 illustrates $CD8^+$ T cells in the KrasL2 NSCLC model.

**[00213]** FIG. 171 illustrates *in vitro* potency in whole blood of Formula (XVIII), ibrutinib and CC-292 in inhibition of signals through the B cell receptor.

**[00214]** FIG. 172 illustrates EGF receptor phosphorylation *in vitro* for Formula (XVIII) and ibrutinib.

**[00215]** FIG. 173 shows NK cell degranulation results. The percentage of $CD56^+/CD107a^+$ NK cells observed in whole blood after pretreatment for 1 hour with the BTK inhibitors and stimulation with MEC-1 cells opsonised with obinutuzumab at 1 μg/mL for 4 hours (n = 3) is shown.

**[00216]** FIG. 174 shows the effects of BTK inhibition on generalized NK cell mediated cytotoxicity.

**[00217]** FIG. 175 shows that Formula (XVIII) has no adverse effect on T helper 17 (Th17) cells, which are a subset of T helper cells that produce interleukin 17 (IL-17), while ibrutinib strongly inhibits Th17 cells.

**[00218]** FIG. 176 shows that Formula (XVIII) has no effect on regulatory T cell (Treg) development, while ibrutinib strongly increases Treg development.

**[00219]** FIG. 177 shows that Formula (XVIII) has no effect on $CD8^+$ T cell viability, development, while ibrutinib strongly affects $CD8^+$ T cell viability at higher doses.

**[00220]** FIG. 178 illustrates the results of the cytotoxicity assay for $CD8^+$ T cell function. Formula (XX-A) (ibrutinib) affects $CD8^+$ T cell function as measured by % cytotoxicity, while Formula (XVIII) has no effect on $CD8^+$ T cell function as measured by % cytotoxicity relative to vehicle.

**[00221]** FIG. 179 illustrates the results of IFN-γ level measurements for $CD8^+$ T cell function. Formula (XX-A) (ibrutinib) affects $CD8^+$ T cell function as measured by IFN-γ level, while Formula (XVIII) has no effect on $CD8^+$ T cell function as measured by IFN-γ level relative to vehicle.

**[00222]** FIG. 180 shows the results of the brain penetration study, demonstrating the surprising result that Formula (XVIII) crosses the blood-brain barrier.

**[00223]** FIG. 181 shows the effect on tumor volumes in the ID8 ovarian cancer mouse

model of treatment with vehicle, Formula (XVIII), a murine anti-PD-1 monoclonal antibody, and a combination of Formula (XVIII) and a murine anti-PD-1 monoclonal antibody.

**[00224]** FIG. 182 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula (XXVIII-R) (ONO-4059) and the PI3K-δ inhibitor of Formula (XVI) (idelalisib) are combined. The tested cell lines include TMD-8 (DLBCL-ABC), Mino (MCL), RI-1 (NHL), DOHH-2 (follicular lymphoma), and SU-DHL-6 (DLBCL-GCB). The dose-effect curves for these cell lines are given in FIG. 183, FIG. 184, FIG. 185, FIG. 186, and FIG. 187.

**[00225]** FIG. 183 illustrates the dose-effect curves obtained for the tested TMD-8 cell line (DLBCL-ABC) using combined dosing of the BTK inhibitor of Formula (XXVIII-R) (ONO-4059) ("Inh.6") and the PI3K-δ inhibitor of Formula (XVI) (idelalisib) ("Inh.7"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[00226]** FIG. 184 illustrates the dose-effect curves obtained for the tested Mino cell line (MCL) using combined dosing of the BTK inhibitor of Formula (XXVIII-R) (ONO-4059) ("Inh.6") and the PI3K-δ inhibitor of Formula (XVI) (idelalisib) ("Inh.7"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[00227]** FIG. 185 illustrates the dose-effect curves obtained for the tested RI-1 cell line (NHL) using combined dosing of the BTK inhibitor of Formula (XXVIII-R) (ONO-4059) ("Inh.6") and the PI3K-δ inhibitor of Formula (XVI) (idelalisib) ("Inh.7"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[00228]** FIG. 186 illustrates the dose-effect curves obtained for the tested DOHH-2 cell line (follicular lymphoma) using combined dosing of the BTK inhibitor of Formula (XXVIII-R) (ONO-4059) ("Inh.6") and the PI3K-δ inhibitor of Formula (XVI) (idelalisib) ("Inh.7"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

**[00229]** FIG. 187 illustrates the dose-effect curves obtained for the tested SU-DHL-6 cell line (DLBCL-GCB) using combined dosing of the BTK inhibitor of Formula (XXVIII-R) (ONO-4059) ("Inh.6") and the PI3K-δ inhibitor of Formula (XVI) (idelalisib) ("Inh.7"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

## BRIEF DESCRIPTION OF THE SEQUENCE LISTING

**[00230]** SEQ ID NO:1 is the heavy chain amino acid sequence of the PD-1 inhibitor nivolumab (corresponding to SEQ ID NO:17 in International Patent Publication No. WO 2014/055648 A1).

**[00231]** SEQ ID NO:2 is the light chain amino acid sequence of the PD-1 inhibitor nivolumab (corresponding to SEQ ID NO:18 in International Patent Publication No. WO 2014/055648 A1).

**[00232]** SEQ ID NO:3 is the heavy chain variable region ($V_H$) amino acid sequence of the PD-1 inhibitor nivolumab (corresponding to SEQ ID NO:4 in WO 2006/121168 and SEQ ID NO:19 in WO 2014/055648 A1).

**[00233]** SEQ ID NO:4 is the light chain variable region ($V_L$) amino acid sequence of the PD-1 inhibitor nivolumab (corresponding to SEQ ID NO:11 in WO 2006/121168 and SEQ ID NO:21 in WO 2014/055648 A1).

**[00234]** SEQ ID NO:5 is the heavy chain CDR1 amino acid sequence of the PD-1 inhibitor nivolumab (corresponding to SEQ ID NO:18 in WO 2006/121168 and SEQ ID NO:23 in WO 2014/055648 A1).

**[00235]** SEQ ID NO:6 is the heavy chain CDR2 amino acid sequence of the PD-1 inhibitor nivolumab (corresponding to SEQ ID NO:25 in WO 2006/121168 and SEQ ID NO:24 in WO 2014/055648 A1).

**[00236]** SEQ ID NO:7 is the heavy chain CDR3 amino acid sequence of the PD-1 inhibitor nivolumab (corresponding to SEQ ID NO:32 in WO 2006/121168 and SEQ ID NO:25 in WO 2014/055648 A1)

**[00237]** SEQ ID NO:8 is the light chain CDR1 amino acid sequence of the PD-1 inhibitor nivolumab (corresponding to SEQ ID NO:39 from WO 2006/121168 and SEQ

ID NO:26 in WO 2014/055648 A1).

**[00238]** SEQ ID NO:9 is the light chain CDR2 amino acid sequence of the PD-1 inhibitor nivolumab (corresponding to SEQ ID NO:46 in WO 2006/121168 and SEQ ID NO:27 in WO 2014/055648 A1).

**[00239]** SEQ ID NO:10 is the light chain CDR3 amino acid sequence of the PD-1 inhibitor nivolumab (corresponding to SEQ ID NO:53 in WO 2006/121168 and SEQ ID NO:28 in WO 2014/055648 A1).

**[00240]** SEQ ID NO:11 is the 409A-H heavy chain full length sequence of the PD-1 inhibitor pembrolizumab (corresponding to SEQ ID NO:31 in U.S. Patent No. 8,354,509 B2).

**[00241]** SEQ ID NO:12 is amino acids 20 to 466 of the heavy chain full length sequence of the PD-1 inhibitor pembrolizumab.

**[00242]** SEQ ID NO:13 is the K09A-L-11 light chain variable region sequence of the PD-1 inhibitor pembrolizumab (corresponding to SEQ ID NO:32 in U.S. Patent No. 8,354,509 B2).

**[00243]** SEQ ID NO:14 is the K09A-L-11 light chain full length sequence of the PD-1 inhibitor pembrolizumab (corresponding to SEQ ID NO:36 in U.S. Patent No. 8,354,509 B2).

**[00244]** SEQ ID NO:15 is the hPD-1.09A light chain CDR1 sequence of the PD-1 inhibitor pembrolizumab (corresponding to SEQ ID NO:15 in U.S. Patent No. 8,354,509 B2).

**[00245]** SEQ ID NO:16 is the hPD-1.09A light chain CDR2 sequence of the PD-1 inhibitor pembrolizumab (corresponding to SEQ ID NO:16 in U.S. Patent No. 8,354,509 B2).

**[00246]** SEQ ID NO:17 is the hPD-1.09A light chain CDR3 sequence of the PD-1 inhibitor pembrolizumab (corresponding to SEQ ID NO:17 in U.S. Patent No. 8,354,509 B2).

**[00247]** SEQ ID NO:18 is the hPD-1.09A heavy chain CDR1 sequence of the PD-1

inhibitor pembrolizumab (corresponding to SEQ ID NO:18 in U.S. Patent No. 8,354,509 B2).

**[00248]** SEQ ID NO:19 is the hPD-1.09A heavy chain CDR2 sequence of the PD-1 inhibitor pembrolizumab (corresponding to SEQ ID NO:19 in U.S. Patent No. 8,354,509 B2).

**[00249]** SEQ ID NO:20 is the hPD-1.09A heavy chain CDR3 sequence of the PD-1 inhibitor pembrolizumab (corresponding to SEQ ID NO:20 in U.S. Patent No. 8,354,509 B2).

**[00250]** SEQ ID NO:21 is heavy chain amino acid sequence of the PD-1 inhibitor pidilizumab.

**[00251]** SEQ ID NO:22 is light chain amino acid sequence of the PD-1 inhibitor pidilizumab.

**[00252]** SEQ ID NO:23 is the variable heavy chain region of the PD-1 inhibitor pidilizumab (corresponding to SEQ ID NO:5 in U.S. Patent No. 8,686,119 B2).

**[00253]** SEQ ID NO:24 is the variable light chain region of the PD-1 inhibitor pidilizumab (corresponding to SEQ ID NO:1 in U.S. Patent No. 8,686,119 B2).

**[00254]** SEQ ID NO:25 is the amino acid sequence of a peptide derivative PD-1 inhibitor.

**[00255]** SEQ ID NO:26 is the amino acid sequence of a peptide derivative PD-1 inhibitor, with a branched group given by SEQ ID NO:25.

**[00256]** SEQ ID NO:27 is the amino acid sequence of a peptide derivative PD-1 inhibitor, with a branched group given by SEQ ID NO:25.

**[00257]** SEQ ID NO:28 is the amino acid sequence of a peptide derivative PD-1 inhibitor, with a branched group given by SEQ ID NO:25.

**[00258]** SEQ ID NO:29 is the amino acid sequence of a peptide derivative PD-1 inhibitor, with a branched group given by SEQ ID NO:25.

**[00259]** SEQ ID NO:30 is the heavy chain of the anti-PD-L1 antibody durvalumab (MEDI4736).

**[00260]** SEQ ID NO:31 is the light chain of the anti-PD-L1 antibody durvalumab (MEDI4736).

**[00261]** SEQ ID NO:32 is the durvalumab (MEDI4736) anti-PD-L1 antibody heavy chain variable region (corresponding to SEQ ID NO:72 in U.S. Patent Application Publication No. US 2013/0034559 A1).

**[00262]** SEQ ID NO:33 is the durvalumab (MEDI4736) anti-PD-L1 antibody light chain variable region (corresponding to SEQ ID NO:77 in U.S. Patent Application Publication No. US 2013/0034559 A1).

**[00263]** SEQ ID NO:34 is the durvalumab (MEDI4736) anti-PD-L1 antibody heavy chain variable region CDR1 (corresponding to SEQ ID NO:3 in U.S. Patent Application Publication No. US 2013/0034559 A1).

**[00264]** SEQ ID NO:35 is the durvalumab (MEDI4736) anti-PD-L1 antibody heavy chain variable region CDR2 (corresponding to SEQ ID NO:4 in U.S. Patent Application Publication No. US 2013/0034559 A1).

**[00265]** SEQ ID NO:36 is the durvalumab (MEDI4736) anti-PD-L1 antibody heavy chain variable region CDR3 (corresponding to SEQ ID NO:5 in U.S. Patent Application Publication No. US 2013/0034559 A1).

**[00266]** SEQ ID NO:37 is the durvalumab (MEDI4736) anti-PD-L1 antibody light chain variable region CDR1 (corresponding to SEQ ID NO:8 in U.S. Patent Application Publication No. US 2013/0034559 A1).

**[00267]** SEQ ID NO:38 is the durvalumab (MEDI4736) anti-PD-L1 antibody light chain variable region CDR2 (corresponding to SEQ ID NO:9 in U.S. Patent Application Publication No. US 2013/0034559 A1).

**[00268]** SEQ ID NO:39 is the durvalumab (MEDI4736) anti-PD-L1 antibody light chain variable region CDR3 (corresponding to SEQ ID NO:10 in U.S. Patent Application Publication No. US 2013/0034559 A1).

**[00269]** SEQ ID NO:40 is an alternative durvalumab (MEDI4736) anti-PD-L1 antibody heavy chain variable region CDR1 (corresponding to SEQ ID NO:23 in U.S. Patent Application Publication No. US 2013/0034559 A1).

**[00270]** SEQ ID NO:41 is an alternative durvalumab (MEDI4736) anti-PD-L1 antibody heavy chain variable region CDR2 (corresponding to SEQ ID NO:24 in U.S. Patent Application Publication No. US 2013/0034559 A1).

**[00271]** SEQ ID NO:42 is an alternative durvalumab (MEDI4736) anti-PD-L1 antibody heavy chain variable region CDR3 (corresponding to SEQ ID NO:25 in U.S. Patent Application Publication No. US 2013/0034559 A1).

**[00272]** SEQ ID NO:43 is an alternative durvalumab (MEDI4736) anti-PD-L1 antibody light chain variable region CDR1 (corresponding to SEQ ID NO:28 in U.S. Patent Application Publication No. US 2013/0034559 A1).

**[00273]** SEQ ID NO:44 is an alternative durvalumab (MEDI4736) anti-PD-L1 antibody light chain variable region CDR2 (corresponding to SEQ ID NO:29 in U.S. Patent Application Publication No. US 2013/0034559 A1).

**[00274]** SEQ ID NO:45 is an alternative durvalumab (MEDI4736) anti-PD-L1 antibody light chain variable region CDR3 (corresponding to SEQ ID NO:30 in U.S. Patent Application Publication No. US 2013/0034559 A1).

**[00275]** SEQ ID NO:46 is an alternative durvalumab (MEDI4736) anti-PD-L1 antibody heavy chain variable region CDR1 (corresponding to SEQ ID NO:13 in U.S. Patent Application Publication No. US 2013/0034559 A1).

**[00276]** SEQ ID NO:47 is an alternative durvalumab (MEDI4736) anti-PD-L1 antibody heavy chain variable region CDR2 (corresponding to SEQ ID NO:14 in U.S. Patent Application Publication No. US 2013/0034559 A1).

**[00277]** SEQ ID NO:48 is an alternative durvalumab (MEDI4736) anti-PD-L1 antibody heavy chain variable region CDR3 (corresponding to SEQ ID NO:15 in U.S. Patent Application Publication No. US 2013/0034559 A1).

**[00278]** SEQ ID NO:49 is an alternative durvalumab (MEDI4736) anti-PD-L1 antibody light chain variable region CDR1 (corresponding to SEQ ID NO:18 in U.S. Patent Application Publication No. US 2013/0034559 A1).

**[00279]** SEQ ID NO:50 is an alternative durvalumab (MEDI4736) anti-PD-L1 antibody light chain variable region CDR2 (corresponding to SEQ ID NO:19 in U.S. Patent

Application Publication No. US 2013/0034559A1).

**[00280]** SEQ ID NO:51 is an alternative durvalumab (MEDI4736) anti-PD-L1 antibody light chain variable region CDR3 (corresponding to SEQ ID NO:20 in U.S. Patent Application Publication No. US 2013/0034559A1).

**[00281]** SEQ ID NO:52 is an alternative durvalumab (MEDI4736) anti-PD-L1 antibody heavy chain variable region CDR1 (corresponding to SEQ ID NO:63 in U.S. Patent Application Publication No. US 2013/0034559A1).

**[00282]** SEQ ID NO:53 is an alternative durvalumab (MEDI4736) anti-PD-L1 antibody heavy chain variable region CDR2 (corresponding to SEQ ID NO:64 in U.S. Patent Application Publication No. US 2013/0034559A1).

**[00283]** SEQ ID NO:54 is an alternative durvalumab (MEDI4736) anti-PD-L1 antibody heavy chain variable region CDR3 (corresponding to SEQ ID NO:65 in U.S. Patent Application Publication No. US 2013/0034559A1).

**[00284]** SEQ ID NO:55 is an alternative durvalumab (MEDI4736) anti-PD-L1 antibody light chain variable region CDR1 (corresponding to SEQ ID NO:68 in U.S. Patent Application Publication No. US 2013/0034559A1).

**[00285]** SEQ ID NO:56 is an alternative durvalumab (MEDI4736) anti-PD-L1 antibody light chain variable region CDR2 (corresponding to SEQ ID NO:69 in U.S. Patent Application Publication No. US 2013/0034559A1).

**[00286]** SEQ ID NO:57 is an alternative durvalumab (MEDI4736) anti-PD-L1 antibody light chain variable region CDR3 (corresponding to SEQ ID NO:70 in U.S. Patent Application Publication No. US 2013/0034559A1).

**[00287]** SEQ ID NO:58 is an alternative durvalumab (MEDI4736) anti-PD-L1 antibody heavy chain variable region CDR1 (corresponding to SEQ ID NO:73 in U.S. Patent Application Publication No. US 2013/0034559A1).

**[00288]** SEQ ID NO:59 is an alternative durvalumab (MEDI4736) anti-PD-L1 antibody heavy chain variable region CDR2 (corresponding to SEQ ID NO:74 in U.S. Patent Application Publication No. US 2013/0034559 A1).

**[00289]** SEQ ID NO:60 is an alternative durvalumab (MEDI4736) anti-PD-L1 antibody heavy chain variable region CDR3 (corresponding to SEQ ID NO:75 in U.S. Patent Application Publication No. US 2013/0034559 A1).

**[00290]** SEQ ID NO:61 is an alternative durvalumab (MEDI4736) anti-PD-L1 antibody light chain variable region CDR1 (corresponding to SEQ ID NO:78 in U.S. Patent Application Publication No. US 2013/0034559 A1).

**[00291]** SEQ ID NO:62 is an alternative durvalumab (MEDI4736) anti-PD-L1 antibody light chain variable region CDR2 (corresponding to SEQ ID NO:79 in U.S. Patent Application Publication No. US 2013/0034559 A1).

**[00292]** SEQ ID NO:63 is an alternative durvalumab (MEDI4736) anti-PD-L1 antibody light chain variable region CDR3 (corresponding to SEQ ID NO:80 in U.S. Patent Application Publication No. US 2013/0034559 A1).

**[00293]** SEQ ID NO:64 is the heavy chain of the anti-PD-L1 antibody atezolizumab (MPDL3280A).

**[00294]** SEQ ID NO:65 is the light chain of the anti-PD-L1 antibody atezolizumab (MPDL3280A).

**[00295]** SEQ ID NO:66 is the $V_H$ region of the anti-PD-L1 antibody atezolizumab (MPDL3280A) (corresponding to SEQ ID NO:20 in U.S. Patent No. 8,217,149).

**[00296]** SEQ ID NO:67 is the $V_L$ region of the anti-PD-L1 antibody atezolizumab (MPDL3280A) (corresponding to SEQ ID NO:21 in U.S. Patent No. 8,217,149).

**[00297]** SEQ ID NO:68 is the HVR-H1 region of the anti-PD-L1 antibody atezolizumab (MPDL3280A) (corresponding to SEQ ID NO:1 in U.S. Patent No. 8,217,149).

**[00298]** SEQ ID NO:69 is the HVR-H2 region of the anti-PD-L1 antibody atezolizumab (MPDL3280A) (corresponding to SEQ ID NO:2 in U.S. Patent No. 8,217,149).

**[00299]** SEQ ID NO:70 is the HVR-H3 region of the anti-PD-L1 antibody atezolizumab (MPDL3280A) (corresponding to SEQ ID NO:3 in U.S. Patent No. 8,217,149).

**[00300]** SEQ ID NO:71 is the HVR-L1 region of the anti-PD-L1 antibody atezolizumab (MPDL3280A) (corresponding to SEQ ID NO:8 in U.S. Patent No. 8,217,149).

**[00301]** SEQ ID NO:72 is the HVR-L2 region of the anti-PD-L1 antibody atezolizumab (MPDL3280A) (corresponding to SEQ ID NO:9 in U.S. Patent No. 8,217,149).

**[00302]** SEQ ID NO:73 is the HVR-L3 region of the anti-PD-L1 antibody atezolizumab (MPDL3280A) (corresponding to SEQ ID NO:10 in U.S. Patent No. 8,217,149).

**[00303]** SEQ ID NO:74 is the heavy chain of the anti-PD-L1 antibody avelumab (MSB0010718C).

**[00304]** SEQ ID NO:75 is the light chain of the anti-PD-L1 antibody avelumab (MSB0010718C).

**[00305]** SEQ ID NO:76 is the $V_H$ region of the anti-PD-L1 antibody avelumab (MSB0010718C) (corresponding to SEQ ID NO:24 in U.S. Patent Application Publication No. US 2014/0341917 A1).

**[00306]** SEQ ID NO:77 is the $V_L$ region of the anti-PD-L1 antibody avelumab (MSB0010718C) (corresponding to SEQ ID NO:25 in U.S. Patent Application Publication No. US 2014/0341917 A1).

**[00307]** SEQ ID NO:78 is the HVR-H1 region of the anti-PD-L1 antibody avelumab (MSB0010718C) (corresponding to SEQ ID NO:15 in U.S. Patent Application Publication No. US 2014/0341917 A1).

**[00308]** SEQ ID NO:79 is the HVR-H2 region of the anti-PD-L1 antibody avelumab (MSB0010718C) (corresponding to SEQ ID NO:16 in U.S. Patent Application Publication No. US 2014/0341917 A1).

**[00309]** SEQ ID NO:80 is the HVR-H3 region of the anti-PD-L1 antibody avelumab (MSB0010718C) (corresponding to SEQ ID NO:17 in U.S. Patent Application Publication No. US 2014/0341917 A1).

**[00310]** SEQ ID NO:81 is the HVR-L1 region of the anti-PD-L1 antibody avelumab (MSB0010718C) (corresponding to SEQ ID NO:18 in U.S. Patent Application Publication No. US 2014/0341917 A1).

**[00311]** SEQ ID NO:82 is the HVR-L2 region of the anti-PD-L1 antibody avelumab (MSB0010718C) (corresponding to SEQ ID NO:19 in U.S. Patent Application

Publication No. US 2014/0341917 A1).

**[00312]** SEQ ID NO:83 is the HVR-L3 region of the anti-PD-L1 antibody avelumab (MSB0010718C) (corresponding to SEQ ID NO:20 in U.S. Patent Application Publication No. US 2014/0341917 A1).

**[00313]** SEQ ID NO:84 is the heavy chain amino acid sequence of the anti-CD20 monoclonal antibody rituximab.

**[00314]** SEQ ID NO:85 is the light chain amino acid sequence of the anti-CD20 monoclonal antibody rituximab.

**[00315]** SEQ ID NO:86 is the heavy chain amino acid sequence of the anti-CD20 monoclonal antibody obinutuzumab.

**[00316]** SEQ ID NO:87 is the light chain amino acid sequence of the anti-CD20 monoclonal antibody obinutuzumab.

**[00317]** SEQ ID NO:88 is the variable heavy chain amino acid sequence of the anti-CD20 monoclonal antibody ofatumumab.

**[00318]** SEQ ID NO:89 is the variable light chain amino acid sequence of the anti-CD20 monoclonal antibody ofatumumab.

**[00319]** SEQ ID NO:90 is the Fab fragment heavy chain amino acid sequence of the anti-CD20 monoclonal antibody ofatumumab.

**[00320]** SEQ ID NO:91 is the Fab fragment light chain amino acid sequence of the anti-CD20 monoclonal antibody ofatumumab.

**[00321]** SEQ ID NO:92 is the heavy chain amino acid sequence of the anti-CD20 monoclonal antibody veltuzumab.

**[00322]** SEQ ID NO:93 is the light chain amino acid sequence of the anti-CD20 monoclonal antibody veltuzumab.

**[00323]** SEQ ID NO:94 is the heavy chain amino acid sequence of the anti-CD20 monoclonal antibody tositumomab.

**[00324]** SEQ ID NO:95 is the light chain amino acid sequence of the anti-CD20

monoclonal antibody tositumomab.

**[00325]** SEQ ID NO:96 is the heavy chain amino acid sequence of the anti-CD20 monoclonal antibody ibritumomab.

**[00326]** SEQ ID NO:97 is the light chain amino acid sequence of the anti-CD20 monoclonal antibody ibritumomab.

## DETAILED DESCRIPTION OF THE INVENTION

**[00327]** 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 invention belongs. All patents and publications referred to herein are incorporated by reference in their entireties.

**[00328]** The terms "co-administration," "co-administering," "administered in combination with," and "administering in combination with" as used herein, encompass administration of two or more active pharmaceutical ingredients to a subject so that both active pharmaceutical ingredients and/or their metabolites are present in the subject at the same time. Co-administration includes simultaneous administration in separate compositions, administration at different times in separate compositions, or administration in a composition in which two or more active pharmaceutical ingredients are present. Simultaneous administration in separate compositions and administration in a composition in which two or more active pharmaceutical ingredients are present is preferred.

**[00329]** The term "effective amount" or "therapeutically effective amount" refers to that amount of a compound or combination of compounds as described herein that is sufficient to effect the intended application including, but not limited to, disease treatment. A 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, age and gender of the subject), the severity of the disease condition, the manner of administration, *etc.* which can readily be determined by one of ordinary skill in the art. The term also applies to a dose that will induce a particular response in target cells, (*e.g.*, the reduction of platelet adhesion and/or cell migration). The specific dose

will vary depending on the particular compounds chosen, the dosing regimen to be followed, whether the compound is administered in combination with other compounds, timing of administration, the tissue to which it is administered, and the physical delivery system in which the compound is carried.

**[00330]** A "therapeutic effect" as that term is used herein, encompasses a therapeutic benefit and/or a prophylactic benefit as described herein. A prophylactic effect includes delaying or eliminating the appearance of a disease or condition, delaying or eliminating the onset of symptoms of a disease or condition, slowing, halting, or reversing the progression of a disease or condition, or any combination thereof.

**[00331]** The term "pharmaceutically acceptable salt" refers to salts derived from a variety of organic and inorganic counter ions known in the art. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid and salicylic acid. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese and aluminum. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins. Specific examples include isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. In some embodiments, the pharmaceutically acceptable base addition salt is chosen from ammonium, potassium, sodium, calcium, and magnesium salts. The term "cocrystal" refers to a molecular complex derived from a number of cocrystal formers known in the art. Unlike a salt, a cocrystal typically does not involve hydrogen transfer between the cocrystal and the drug, and instead involves intermolecular interactions, such as hydrogen bonding, aromatic ring stacking, or dispersive forces, between the cocrystal former and

the drug in the crystal structure.

**[00332]** "Pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and inert ingredients. The use of such pharmaceutically acceptable carriers or pharmaceutically acceptable excipients for active pharmaceutical ingredients is well known in the art. Except insofar as any conventional pharmaceutically acceptable carrier or pharmaceutically acceptable excipient is incompatible with the active pharmaceutical ingredient, its use in the therapeutic compositions of the invention is contemplated. Additional active pharmaceutical ingredients, such as other drugs, can also be incorporated into the described compositions and methods.

**[00333]** "Prodrug" is intended to describe a compound that may be converted under physiological conditions or by solvolysis to a biologically active compound described herein. Thus, the term "prodrug" refers to a precursor of a biologically active compound that is pharmaceutically acceptable. A prodrug may be inactive when administered to a subject, but is converted *in vivo* to an active compound, for example, by hydrolysis. The prodrug compound often offers the advantages of solubility, tissue compatibility or delayed release in a mammalian organism (see, *e.g.*, Bundgaard, H., Design of Prodrugs (1985) (Elsevier, Amsterdam). The term "prodrug" is also intended to include any covalently bonded carriers, which release the active compound *in vivo* when administered to a subject. Prodrugs of an active compound, as described herein, may be prepared by modifying functional groups present in the active compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to yield the active parent compound. Prodrugs include, for example, compounds wherein a hydroxy, amino or mercapto group is bonded to any group that, when the prodrug of the active compound is administered to a mammalian subject, cleaves to form a free hydroxy, free amino or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetates, formates and benzoate derivatives of an alcohol, various ester derivatives of a carboxylic acid, or acetamide, formamide and benzamide derivatives of an amine functional group in the active compound.

**[00334]** The terms "QD," "qd," or "q.d." mean *quaque die*, once a day, or once daily. The terms "BID," "bid," or "b.i.d." mean *bis in die*, twice a day, or twice daily. The terms "TID," "tid," or "t.i.d." mean *ter in die*, three times a day, or three times daily. The terms "QID," "qid," or "q.i.d." mean *quater in die*, four times a day, or four times daily.

**[00335]** The term "*in vivo*" refers to an event that takes place in a subject's body.

**[00336]** The term "*in vitro*" refers to an event that takes places outside of a subject's body. *In vitro* assays encompass cell-based assays in which cells alive or dead are employed and may also encompass a cell-free assay in which no intact cells are employed.

**[00337]** Unless otherwise stated, the chemical structures depicted herein are intended to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds where one or more hydrogen atoms is replaced by deuterium or tritium, or wherein one or more carbon atoms is replaced by $^{13}C$- or $^{14}C$-enriched carbons, are within the scope of this invention.

**[00338]** When ranges are used herein to describe, for example, physical or chemical properties such as molecular weight or chemical formulae, all combinations and subcombinations of ranges and specific embodiments therein are intended to be included. Use of the term "about" when referring to a number or a numerical range 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. The variation is typically from 0% to 15%, preferably from 0% to 10%, more preferably from 0% to 5% of the stated number or numerical range. The term "comprising" (and related terms such as "comprise" or "comprises" or "having" or "including") includes those embodiments such as, for example, an embodiment of any composition of matter, method or process that "consist of" or "consist essentially of" the described features.

**[00339]** "Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to ten carbon atoms (*e.g.*, $(C_{1-10})$alkyl or $C_{1-10}$ alkyl). Whenever it appears herein, a numerical range such as "1 to 10" refers to each integer in the given range - *e.g.*, "1 to 10 carbon

atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 10 carbon atoms, although the definition is also intended to cover the occurrence of the term "alkyl" where no numerical range is specifically designated. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *iso*-butyl, *sec*-butyl isobutyl, *tert*-butyl, pentyl, isopentyl, neopentyl, hexyl, septyl, octyl, nonyl and decyl. The alkyl moiety may be attached to the rest of the molecule by a single bond, such as for example, methyl (Me), ethyl (Et), *n*-propyl (Pr), 1-methylethyl (*iso*-propyl), *n*-butyl, *n*-pentyl, 1,1-dimethylethyl (*tert*-butyl) and 3-methylhexyl. Unless stated otherwise specifically in the specification, an alkyl group is optionally substituted by one or more of substituents which are independently heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$ where each $R^a$ is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

**[00340]** "Alkylaryl" refers to an -(alkyl)aryl radical where aryl and alkyl are as disclosed herein, having from one to ten carbon atoms, and which are optionally substituted by one or more of the substituents described as suitable substituents for aryl and alkyl respectively.

**[00341]** "Alkylhetaryl" refers to an -(alkyl)hetaryl radical where hetaryl and alkyl are as disclosed herein, having from one to ten carbon atoms, and which are optionally substituted by one or more of the substituents described as suitable substituents for aryl and alkyl respectively.

**[00342]** "Alkylheterocycloalkyl" refers to an -(alkyl) heterocycyl radical where alkyl and heterocycloalkyl are as disclosed herein, having from one to ten carbon atoms, and which are optionally substituted by one or more of the substituents described as suitable substituents for heterocycloalkyl and alkyl respectively.

**[00343]** An "alkene" moiety refers to a group consisting of at least two carbon atoms and at least one carbon-carbon double bond, and an "alkyne" moiety refers to a group consisting of at least two carbon atoms and at least one carbon-carbon triple bond. The alkyl moiety, whether saturated or unsaturated, may be branched, straight chain, or cyclic.

**[00344]** "Alkenyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one double bond, and having from two to ten carbon atoms (*i.e.*, ($C_{2-10}$)alkenyl or $C_{2-10}$ alkenyl). Whenever it appears herein, a numerical range such as "2 to 10" refers to each integer in the given range - *e.g.*, "2 to 10 carbon atoms" means that the alkenyl group may consist of 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 10 carbon atoms. The alkenyl moiety may be attached to the rest of the molecule by a single bond, such as for example, ethenyl (*i.e.*, vinyl), prop-1-enyl (*i.e.*, allyl), but-1-enyl, pent-1-enyl and penta-1,4-dienyl. Unless stated otherwise specifically in the specification, an alkenyl group is optionally substituted by one or more substituents which are independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each $R^a$ is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

**[00345]** "Alkenyl-cycloalkyl" refers to an -(alkenyl)cycloalkyl radical where alkenyl and cyclo alkyl are as disclosed herein, having from two to ten carbon atoms, and which are optionally substituted by one or more of the substituents described as suitable substituents for alkenyl and cycloalkyl respectively.

**[00346]** "Alkynyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one triple bond, having from two to ten carbon atoms (i.e., ($C_{2-10}$)alkynyl or $C_{2-10}$ alkynyl). Whenever it

appears herein, a numerical range such as "2 to 10" refers to each integer in the given range - *e.g.*, "2 to 10 carbon atoms" means that the alkynyl group may consist of 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 10 carbon atoms. The alkynyl may be attached to the rest of the molecule by a single bond, for example, ethynyl, propynyl, butynyl, pentynyl and hexynyl. Unless stated otherwise specifically in the specification, an alkynyl group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each $R^a$ is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

**[00347]** "Alkynyl-cycloalkyl" refers to an -(alkynyl)cycloalkyl radical where alkynyl and cycloalkyl are as disclosed herein, having from two to ten carbon atoms, and which are optionally substituted by one or more of the substituents described as suitable substituents for alkynyl and cycloalkyl respectively.

**[00348]** "Carboxaldehyde" refers to a -(C=O)H radical.

**[00349]** "Carboxyl" refers to a -(C=O)OH radical.

**[00350]** "Cyano" refers to a -CN radical.

**[00351]** "Cycloalkyl" refers to a monocyclic or polycyclic radical that contains only carbon and hydrogen, and may be saturated, or partially unsaturated. Cycloalkyl groups include groups having from 3 to 10 ring atoms (i.e. $(C_{3-10})$cycloalkyl or $C_{3-10}$ cycloalkyl). Whenever it appears herein, a numerical range such as "3 to 10" refers to each integer in the given range - *e.g.*, "3 to 10 carbon atoms" means that the cycloalkyl group may consist of 3 carbon atoms, *etc.*, up to and including 10 carbon atoms. Illustrative examples of cycloalkyl groups include, but are not limited to the following moieties: cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, norbornyl, and the like. Unless stated

otherwise specifically in the specification, a cycloalkyl group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each $R^a$ is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

**[00352]** "Cycloalkyl-alkenyl" refers to a -(cycloalkyl)alkenyl radical where cycloalkyl and alkenyl are as disclosed herein, having from three to ten carbon atoms, and which are optionally substituted by one or more of the substituents described as suitable substituents for cycloalkyl and alkenyl, respectively.

**[00353]** "Cycloalkyl-heterocycloalkyl" refers to a -(cycloalkyl)heterocycloalkyl radical where cycloalkyl and heterocycloalkyl are as disclosed herein, having from three to ten carbon atoms, and which are optionally substituted by one or more of the substituents described as suitable substituents for cycloalkyl and heterocycloalkyl, respectively.

**[00354]** "Cycloalkyl-heteroaryl" refers to a -(cycloalkyl)heteroaryl radical where cycloalkyl and heteroaryl are as disclosed herein, having from three to ten carbon atoms, and which are optionally substituted by one or more of the substituents described as suitable substituents for cycloalkyl and heteroaryl, respectively.

**[00355]** The term "alkoxy" refers to the group -O-alkyl, including from 1 to 8 carbon atoms of a straight, branched, cyclic configuration and combinations thereof attached to the parent structure through an oxygen. Examples include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy and cyclohexyloxy. "Lower alkoxy" refers to alkoxy groups containing one to six carbons.

**[00356]** The term "substituted alkoxy" refers to alkoxy wherein the alkyl constituent is substituted (*i.e.*, -O-(substituted alkyl)). Unless stated otherwise specifically in the specification, the alkyl moiety of an alkoxy group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl,

cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, -$OR^a$, -$SR^a$, -$OC(O)$-$R^a$, -$N(R^a)_2$, -$C(O)R^a$, -$C(O)OR^a$, -$OC(O)N(R^a)_2$, -$C(O)N(R^a)_2$, -$N(R^a)C(O)OR^a$, -$N(R^a)C(O)R^a$, -$N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, -$N(R^a)S(O)_tR^a$ (where t is 1 or 2), -$S(O)_tOR^a$ (where t is 1 or 2), -$S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each $R^a$ is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

**[00357]** The term "alkoxycarbonyl" refers to a group of the formula (alkoxy)(C=O)- attached through the carbonyl carbon wherein the alkoxy group has the indicated number of carbon atoms. Thus a $(C_1$-$_6)$alkoxycarbonyl group is an alkoxy group having from 1 to 6 carbon atoms attached through its oxygen to a carbonyl linker. "Lower alkoxycarbonyl" refers to an alkoxycarbonyl group wherein the alkoxy group is a lower alkoxy group.

**[00358]** The term "substituted alkoxycarbonyl" refers to the group (substituted alkyl)-O-C(O)- wherein the group is attached to the parent structure through the carbonyl functionality, and wherein the alkoxy group has the indicated number of carbon atoms. Unless stated otherwise specifically in the specification, the alkyl moiety of an alkoxycarbonyl group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, -$OR^a$, -$SR^a$, -$OC(O)$-$R^a$, -$N(R^a)_2$, -$C(O)R^a$, -$C(O)OR^a$, -$OC(O)N(R^a)_2$, -$C(O)N(R^a)_2$, -$N(R^a)C(O)OR^a$, -$N(R^a)C(O)R^a$, -$N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, -$N(R^a)S(O)_tR^a$ (where t is 1 or 2), -$S(O)_tOR^a$ (where t is 1 or 2), -$S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each $R^a$ is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

**[00359]** "Acyl" refers to the groups (alkyl)-C(O)-, (aryl)-C(O)-, (heteroaryl)-C(O)-, (heteroalkyl)-C(O)- and (heterocycloalkyl)-C(O)-, having from one to ten carbon atoms, wherein the group is attached to the parent structure through the carbonyl functionality. If the R radical is heteroaryl or heterocycloalkyl, the hetero ring or chain atoms contribute to the total number of chain or ring atoms. Unless stated otherwise specifically

in the specification, the alkyl, aryl or heteroaryl moiety of the acyl group is optionally substituted by one or more substituents which are independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each $R^a$ is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

**[00360]** "Acyloxy" refers to a R(C=O)O- radical wherein "R" is alkyl, aryl, heteroaryl, heteroalkyl or heterocycloalkyl, which are as described herein. If the R radical is heteroaryl or heterocycloalkyl, the hetero ring or chain atoms contribute to the total number of chain or ring atoms. Unless stated otherwise specifically in the specification, the "R" of an acyloxy group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each $R^a$ is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

**[00361]** "Amino" or "amine" refers to a $-N(R^a)_2$ radical group, where each $R^a$ is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, unless stated otherwise specifically in the specification. When a $-N(R^a)_2$ group has two $R^a$ substituents other than hydrogen, they can be combined with the nitrogen atom to form a 4-, 5-, 6- or 7-membered ring. For example, $-N(R^a)_2$ is intended to include, but is not limited to, 1-pyrrolidinyl and 4-morpholinyl. Unless stated otherwise specifically in the specification, an amino group is optionally substituted by one or more substituents which independently

are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, -$OR^a$, -$SR^a$, -$OC(O)$-$R^a$, -$N(R^a)_2$, -$C(O)R^a$, -$C(O)OR^a$, -$OC(O)N(R^a)_2$, -$C(O)N(R^a)_2$, -$N(R^a)C(O)OR^a$, -$N(R^a)C(O)R^a$, -$N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, -$N(R^a)S(O)_tR^a$ (where t is 1 or 2), -$S(O)_tOR^a$ (where t is 1 or 2), -$S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each $R^a$ is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

**[00362]** The term "substituted amino" also refers to N-oxides of the groups -$NHR^d$, and $NR^dR^d$ each as described above. N-oxides can be prepared by treatment of the corresponding amino group with, for example, hydrogen peroxide or m-chloroperoxybenzoic acid.

**[00363]** "Amide" or "amido" refers to a chemical moiety with formula -$C(O)N(R)_2$ or -$NHC(O)R$, where R is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon), each of which moiety may itself be optionally substituted. The $R_2$ of -$N(R)_2$ of the amide may optionally be taken together with the nitrogen to which it is attached to form a 4-, 5-, 6- or 7-membered ring. Unless stated otherwise specifically in the specification, an amido group is optionally substituted independently by one or more of the substituents as described herein for alkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl. An amide may be an amino acid or a peptide molecule attached to a compound disclosed herein, thereby forming a prodrug. The procedures and specific groups to make such amides are known to those of skill in the art and can readily be found in seminal sources such as Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, N.Y., 1999, which is incorporated herein by reference in its entirety.

**[00364]** "Aromatic" or "aryl" or "Ar" refers to an aromatic radical with six to ten ring atoms (*e.g.*, $C_6$-$C_{10}$ aromatic or $C_6$-$C_{10}$ aryl) which has at least one ring having a conjugated pi electron system which is carbocyclic (*e.g.*, phenyl, fluorenyl, and naphthyl). Bivalent radicals formed from substituted benzene derivatives and having the

free valences at ring atoms are named as substituted phenylene radicals. Bivalent radicals derived from univalent polycyclic hydrocarbon radicals whose names end in "-yl" by removal of one hydrogen atom from the carbon atom with the free valence are named by adding "-idene" to the name of the corresponding univalent radical, *e.g.*, a naphthyl group with two points of attachment is termed naphthylidene. Whenever it appears herein, a numerical range such as "6 to 10" refers to each integer in the given range; *e.g.*, "6 to 10 ring atoms" means that the aryl group may consist of 6 ring atoms, 7 ring atoms, *etc.*, up to and including 10 ring atoms. The term includes monocyclic or fused-ring polycyclic (*i.e.*, rings which share adjacent pairs of ring atoms) groups. Unless stated otherwise specifically in the specification, an aryl moiety is optionally substituted by one or more substituents which are independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each $R^a$ is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

**[00365]** "Aralkyl" or "arylalkyl" refers to an (aryl)alkyl-radical where aryl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for aryl and alkyl respectively.

**[00366]** "Ester" refers to a chemical radical of formula -COOR, where R is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon). The procedures and specific groups to make esters are known to those of skill in the art and can readily be found in seminal sources such as Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, N.Y., 1999, which is incorporated herein by reference in its entirety. Unless stated otherwise specifically in the specification, an ester group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy,

nitro, trimethylsilanyl, -$OR^a$, -$SR^a$, -$OC(O)$-$R^a$, -$N(R^a)_2$, -$C(O)R^a$, -$C(O)OR^a$, -$OC(O)N(R^a)_2$, -$C(O)N(R^a)_2$, -$N(R^a)C(O)OR^a$, -$N(R^a)C(O)R^a$, -$N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, -$N(R^a)S(O)_tR^a$ (where t is 1 or 2), -$S(O)_tOR^a$ (where t is 1 or 2), -$S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each $R^a$ is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

**[00367]** "Fluoroalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more fluoro radicals, as defined above, for example, trifluoromethyl, difluoromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like. The alkyl part of the fluoroalkyl radical may be optionally substituted as defined above for an alkyl group.

**[00368]** "Halo", "halide", or, alternatively, "halogen" is intended to mean fluoro, chloro, bromo or iodo. The terms "haloalkyl," "haloalkenyl," "haloalkynyl" and "haloalkoxy" include alkyl, alkenyl, alkynyl and alkoxy structures that are substituted with one or more halo groups or with combinations thereof. For example, the terms "fluoroalkyl" and "fluoroalkoxy" include haloalkyl and haloalkoxy groups, respectively, in which the halo is fluorine.

**[00369]** "Heteroalkyl", "heteroalkenyl" and "heteroalkynyl" include optionally substituted alkyl, alkenyl and alkynyl radicals and which have one or more skeletal chain atoms selected from an atom other than carbon, e.g., oxygen, nitrogen, sulfur, phosphorus or combinations thereof. A numerical range may be given - *e.g.*, $C_1$-$C_4$ heteroalkyl which refers to the chain length in total, which in this example is 4 atoms long. A heteroalkyl group may be substituted with one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, nitro, oxo, thioxo, trimethylsilanyl, -$OR^a$, -$SR^a$, -$OC(O)$-$R^a$, -$N(R^a)_2$, -$C(O)R^a$, -$C(O)OR^a$, -$OC(O)N(R^a)_2$, -$C(O)N(R^a)_2$, -$N(R^a)C(O)OR^a$, -$N(R^a)C(O)R^a$, -$N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, -$N(R^a)S(O)_tR^a$ (where t is 1 or 2), -$S(O)_tOR^a$ (where t is 1 or 2), -$S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each $R^a$ is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

**[00370]** "Heteroalkylaryl" refers to an -(heteroalkyl)aryl radical where heteroalkyl and aryl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and aryl, respectively.

**[00371]** "Heteroalkylheteroaryl" refers to an -(heteroalkyl)heteroaryl radical where heteroalkyl and heteroaryl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and heteroaryl, respectively.

**[00372]** "Heteroalkylheterocycloalkyl" refers to an -(heteroalkyl)heterocycloalkyl radical where heteroalkyl and heterocycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and heterocycloalkyl, respectively.

**[00373]** "Heteroalkylcycloalkyl" refers to an -(heteroalkyl)cycloalkyl radical where heteroalkyl and cycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and cycloalkyl, respectively.

**[00374]** "Heteroaryl" or "heteroaromatic" or "HetAr" refers to a 5- to 18-membered aromatic radical (*e.g.*, $C_5$-$C_{13}$ heteroaryl) that includes one or more ring heteroatoms selected from nitrogen, oxygen and sulfur, and which may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system. Whenever it appears herein, a numerical range such as "5 to 18" refers to each integer in the given range - *e.g.*, "5 to 18 ring atoms" means that the heteroaryl group may consist of 5 ring atoms, 6 ring atoms, etc., up to and including 18 ring atoms. Bivalent radicals derived from univalent heteroaryl radicals whose names end in "-yl" by removal of one hydrogen atom from the atom with the free valence are named by adding "-idene" to the name of the corresponding univalent radical - *e.g.*, a pyridyl group with two points of attachment is a pyridylidene. A N-containing "heteroaromatic" or "heteroaryl" moiety refers to an aromatic group in which at least one of the skeletal atoms of the ring is a nitrogen atom. The polycyclic heteroaryl group may be fused or non-fused. The heteroatom(s) in the heteroaryl radical are optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heteroaryl may be attached to the rest of the molecule through any atom of the ring(s).

Examples of heteroaryls include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzindolyl, 1,3-benzodioxolyl, benzofuranyl, benzooxazolyl, benzo[*d*]thiazolyl, benzothiadiazolyl, benzo[*b*][1,4]dioxepinyl, benzo[*b*][1,4]oxazinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzoxazolyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzofurazanyl, benzothiazolyl, benzothienyl(benzothiophenyl), benzothieno[3,2-*d*]pyrimidinyl, benzotriazolyl, benzo[4,6]imidazo[1,2-*a*]pyridinyl, carbazolyl, cinnolinyl, cyclopenta[*d*]pyrimidinyl, 6,7-dihydro-5*H*-cyclopenta[4,5]thieno[2,3-*d*]pyrimidinyl, 5,6-dihydrobenzo[*h*]quinazolinyl, 5,6-dihydrobenzo[*h*]cinnolinyl, 6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-*c*]pyridazinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furazanyl, furanonyl, furo[3,2-*c*]pyridinyl, 5,6,7,8,9,10-hexahydrocycloocta[*d*]pyrimidinyl, 5,6,7,8,9,10-hexahydrocycloocta[*d*]pyridazinyl, 5,6,7,8,9,10-hexahydrocycloocta[*d*]pyridinyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, 5,8-methano-5,6,7,8-tetrahydroquinazolinyl, naphthyridinyl, 1,6-naphthyridinonyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 5,6,6a,7,8,9,10,10a-octahydrobenzo[*h*]quinazolinyl, 1-phenyl-1*H*-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyranyl, pyrrolyl, pyrazolyl, pyrazolo[3,4-*d*]pyrimidinyl, pyridinyl, pyrido[3,2-*d*]pyrimidinyl, pyrido[3,4-*d*]pyrimidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, 5,6,7,8-tetrahydroquinazolinyl, 5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidinyl, 6,7,8,9-tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidinyl, 5,6,7,8-tetrahydropyrido[4,5-*c*]pyridazinyl, thiazolyl, thiadiazolyl, thiapyranyl, triazolyl, tetrazolyl, triazinyl, thieno[2,3-*d*]pyrimidinyl, thieno[3,2-*d*]pyrimidinyl, thieno[2,3-*c*]pyridinyl, and thiophenyl (*i.e.* thienyl). Unless stated otherwise specifically in the specification, a heteroaryl moiety is optionally substituted by one or more substituents which are independently: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, nitro, oxo, thioxo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2),

$-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each $R^a$ is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

**[00375]** Substituted heteroaryl also includes ring systems substituted with one or more oxide (-O-) substituents, such as, for example, pyridinyl *N*-oxides.

**[00376]** "Heteroarylalkyl" refers to a moiety having an aryl moiety, as described herein, connected to an alkylene moiety, as described herein, wherein the connection to the remainder of the molecule is through the alkylene group.

**[00377]** "Heterocycloalkyl" refers to a stable 3- to 18-membered non-aromatic ring radical that comprises two to twelve carbon atoms and from one to six heteroatoms selected from nitrogen, oxygen and sulfur. Whenever it appears herein, a numerical range such as "3 to 18" refers to each integer in the given range - *e.g.*, "3 to 18 ring atoms" means that the heterocycloalkyl group may consist of 3 ring atoms, 4 ring atoms, *etc.*, up to and including 18 ring atoms. Unless stated otherwise specifically in the specification, the heterocycloalkyl radical is a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems. The heteroatoms in the heterocycloalkyl radical may be optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heterocycloalkyl radical is partially or fully saturated. The heterocycloalkyl may be attached to the rest of the molecule through any atom of the ring(s). Examples of such heterocycloalkyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl. Unless stated otherwise specifically in the specification, a heterocycloalkyl moiety is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, nitro, oxo, thioxo,

trimethylsilanyl, -$OR^a$, -$SR^a$, -$OC(O)$-$R^a$, -$N(R^a)_2$, -$C(O)R^a$, -$C(O)OR^a$, -$OC(O)N(R^a)_2$, -$C(O)N(R^a)_2$, -$N(R^a)C(O)OR^a$, -$N(R^a)C(O)R^a$, -$N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, -$N(R^a)S(O)_tR^a$ (where t is 1 or 2), -$S(O)_tOR^a$ (where t is 1 or 2), -$S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each $R^a$ is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

**[00378]** "Heterocycloalkyl" also includes bicyclic ring systems wherein one non-aromatic ring, usually with 3 to 7 ring atoms, contains at least 2 carbon atoms in addition to 1-3 heteroatoms independently selected from oxygen, sulfur, and nitrogen, as well as combinations comprising at least one of the foregoing heteroatoms; and the other ring, usually with 3 to 7 ring atoms, optionally contains 1-3 heteroatoms independently selected from oxygen, sulfur, and nitrogen and is not aromatic.

**[00379]** "Nitro" refers to the -$NO_2$ radical.

**[00380]** "Oxa" refers to the -O- radical.

**[00381]** "Oxo" refers to the =O radical.

**[00382]** "Sulfanyl" refers to groups that include -S-(optionally substituted alkyl), -S-(optionally substituted aryl), -S-(optionally substituted heteroaryl) and -S-(optionally substituted heterocycloalkyl).

**[00383]** "Sulfinyl" refers to groups that include -S(O)-H, -S(O)-(optionally substituted alkyl), -S(O)-(optionally substituted amino), -S(O)-(optionally substituted aryl), -S(O)-(optionally substituted heteroaryl) and -S(O)-(optionally substituted heterocycloalkyl).

**[00384]** "Sulfonyl" refers to groups that include -$S(O_2)$-H, -$S(O_2)$-(optionally substituted alkyl), -$S(O_2)$-(optionally substituted amino), -$S(O_2)$-(optionally substituted aryl), -$S(O_2)$-(optionally substituted heteroaryl), and -$S(O_2)$-(optionally substituted heterocycloalkyl).

**[00385]** "Sulfonamidyl" or "sulfonamido" refers to a -$S(=O)_2$-NRR radical, where each R is selected independently from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon). The R groups in -NRR of the -$S(=O)_2$-NRR radical may be taken together with the nitrogen to which it is attached to form a 4-, 5-, 6- or 7-membered ring. A

sulfonamido group is optionally substituted by one or more of the substituents described for alkyl, cycloalkyl, aryl, heteroaryl, respectively.

**[00386]** "Sulfoxyl" refers to a $-S(=O)_2OH$ radical.

**[00387]** "Sulfonate" refers to a $-S(=O)_2-OR$ radical, where R is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon). A sulfonate group is optionally substituted on R by one or more of the substituents described for alkyl, cycloalkyl, aryl, heteroaryl, respectively. "Isomers" are different compounds that have the same molecular formula. "Stereoisomers" are isomers that differ only in the way the atoms are arranged in space - *i.e.*, having a different stereochemical configuration. "Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic" mixture. The term "(±)" is used to designate a racemic mixture where appropriate. "Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry is specified according to the Cahn-Ingold-Prelog R-S system. When a compound is a pure enantiomer the stereochemistry at each chiral carbon can be specified by either *(R)* or *(S)*. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain of the compounds described herein contain one or more asymmetric centers and can thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that can be defined, in terms of absolute stereochemistry, as *(R)* or *(S)*. The present chemical entities, pharmaceutical compositions and methods are meant to include all such possible isomers, including racemic mixtures, optically pure forms and intermediate mixtures. Optically active *(R)*- and *(S)*-isomers can be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both *E* and *Z* geometric isomers.

**[00388]** "Enantiomeric purity" as used herein refers to the relative amounts, expressed

as a percentage, of the presence of a specific enantiomer relative to the other enantiomer. For example, if a compound, which may potentially have an (*R*)- or an (*S*)-isomeric configuration, is present as a racemic mixture, the enantiomeric purity is about 50% with respect to either the (*R*)- or (*S*)-isomer. If that compound has one isomeric form predominant over the other, for example, 80% (*S*)-isomer and 20% (*R*)-isomer, the enantiomeric purity of the compound with respect to the (S)-isomeric form is 80%. The enantiomeric purity of a compound can be determined in a number of ways known in the art, including but not limited to chromatography using a chiral support, polarimetric measurement of the rotation of polarized light, nuclear magnetic resonance spectroscopy using chiral shift reagents which include but are not limited to lanthanide containing chiral complexes or Pirkle's reagents, or derivatization of a compounds using a chiral compound such as Mosher's acid followed by chromatography or nuclear magnetic resonance spectroscopy.

**[00389]** In preferred embodiments, the enantiomerically enriched composition has a higher potency with respect to therapeutic utility per unit mass than does the racemic mixture of that composition. Enantiomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred enantiomers can be prepared by asymmetric syntheses. See, for example, Jacques, *et al.*, Enantiomers, Racemates and Resolutions (Wiley Interscience, New York, 1981); Eliel, Stereochemistry of Carbon Compounds (McGraw-Hill, NY, 1962); and Eliel and Wilen, Stereochemistry of Organic Compounds (Wiley-Interscience, New York, 1994).

**[00390]** The terms "enantiomerically enriched" and "non-racemic," as used herein, refer to compositions in which the percent by weight of one enantiomer is greater than the amount of that one enantiomer in a control mixture of the racemic composition (e.g., greater than 1:1 by weight). For example, an enantiomerically enriched preparation of the (*S*)-enantiomer, means a preparation of the compound having greater than 50% by weight of the (*S*)-enantiomer relative to the (*R*)-enantiomer, such as at least 75% by weight, or such as at least 80% by weight. In some embodiments, the enrichment can be significantly greater than 80% by weight, providing a "substantially enantiomerically enriched" or a "substantially non-racemic" preparation, which refers to preparations of

compositions which have at least 85% by weight of one enantiomer relative to other enantiomer, such as at least 90% by weight, or such as at least 95% by weight. The terms "enantiomerically pure" or "substantially enantiomerically pure" refers to a composition that comprises at least 98% of a single enantiomer and less than 2% of the opposite enantiomer.

**[00391]** "Moiety" refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

**[00392]** "Tautomers" are structurally distinct isomers that interconvert by tautomerization. "Tautomerization" is a form of isomerization and includes prototropic or proton-shift tautomerization, which is considered a subset of acid-base chemistry. "Prototropic tautomerization" or "proton-shift tautomerization" involves the migration of a proton accompanied by changes in bond order, often the interchange of a single bond with an adjacent double bond. Where tautomerization is possible (e.g. in solution), a chemical equilibrium of tautomers can be reached. An example of tautomerization is keto-enol tautomerization. A specific example of keto-enol tautomerization is the interconversion of pentane-2,4-dione and 4-hydroxypent-3-en-2-one tautomers. Another example of tautomerization is phenol-keto tautomerization. A specific example of phenol-keto tautomerization is the interconversion of pyridin-4-ol and pyridin-4(1*H*)-one tautomers.

**[00393]** A "leaving group or atom" is any group or atom that will, under selected reaction conditions, cleave from the starting material, thus promoting reaction at a specified site. Examples of such groups, unless otherwise specified, include halogen atoms and mesyloxy, p-nitrobenzensulphonyloxy and tosyloxy groups.

**[00394]** "Protecting group" is intended to mean a group that selectively blocks one or more reactive sites in a multifunctional compound such that a chemical reaction can be carried out selectively on another unprotected reactive site and the group can then be readily removed after the selective reaction is complete. A variety of protecting groups are disclosed, for example, in T. H. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, Third Edition, John Wiley & Sons, New York (1999).

**[00395]** "Solvate" refers to a compound in physical association with one or more molecules of a pharmaceutically acceptable solvent.

**[00396]** "Substituted" means that the referenced group may have attached one or more additional groups, radicals or moieties individually and independently selected from, for example, acyl, alkyl, alkylaryl, cycloalkyl, aralkyl, aryl, carbohydrate, carbonate, heteroaryl, heterocycloalkyl, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, halo, carbonyl, ester, thiocarbonyl, isocyanato, thiocyanato, isothiocyanato, nitro, oxo, perhaloalkyl, perfluoroalkyl, phosphate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, and amino, including mono- and di-substituted amino groups, and protected derivatives thereof. The substituents themselves may be substituted, for example, a cycloalkyl substituent may itself have a halide substituent at one or more of its ring carbons. The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

**[00397]** As used herein, the term "warhead" or "warhead group" refers to a functional group present on a compound of the present invention wherein that functional group is capable of covalently binding to an amino acid residue (such as cysteine, lysine, histidine, or other residues capable of being covalently modified) present in the binding pocket of the target protein, thereby irreversibly inhibiting the protein.

**[00398]** Compounds of the invention also include crystalline and amorphous forms of those compounds, including, for example, polymorphs, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrates), conformational polymorphs, and amorphous forms of the compounds, as well as mixtures thereof. "Crystalline form" and "polymorph" are intended to include all crystalline and amorphous forms of the compound, including, for example, polymorphs, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrates), conformational polymorphs, and amorphous forms, as well as mixtures thereof, unless a particular crystalline or amorphous form is referred to.

**[00399]** Compounds of the invention also include antibodies. The terms "antibody" and its plural form "antibodies" refer to whole immunoglobulins and any antigen-binding fragment ("antigen-binding portion") or single chains thereof. An "antibody" further

refers to a glycoprotein comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds, or an antigen-binding portion thereof. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as $V_H$) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as $V_L$) and a light chain constant region. The light chain constant region is comprised of one domain, $C_L$. The $V_H$ and $V_L$ regions of an antibody may be further subdivided into regions of hypervariability, which are referred to as complementarity determining regions (CDR) or hypervariable regions (HVR), and which can be interspersed with regions that are more conserved, termed framework regions (FR). Each $V_H$ and $V_L$ is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen epitope or epitopes. The constant regions of the antibodies may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (e.g., effector cells) and the first component (Clq) of the classical complement system.

**[00400]** The terms "monoclonal antibody," "mAb," "monoclonal antibody composition," or their plural forms refer to a preparation of antibody molecules of single molecular composition. A monoclonal antibody composition displays a single binding specificity and affinity for a particular epitope. Monoclonal antibodies specific to e.g. PD-1, PD-L1, or PD-L2 can be made using knowledge and skill in the art of injecting test subjects with PD-1, PD-L1, or PD-L2 antigen and then isolating hybridomas expressing antibodies having the desired sequence or functional characteristics. DNA encoding the monoclonal antibodies is readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the monoclonal antibodies). The hybridoma cells serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as E. coli cells, simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the

recombinant host cells. Recombinant production of antibodies will be described in more detail below.

**[00401]** The terms "antigen-binding portion" or "antigen-binding fragment" of an antibody (or simply "antibody portion"), as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to an antigen (e.g., PD-1, PD-L1, or PD-L2). It has been shown that the antigen-binding function of an antibody can be performed by fragments of a full-length antibody. Examples of binding fragments encompassed within the term "antigen-binding portion" of an antibody include (i) a Fab fragment, a monovalent fragment consisting of the $V_L$, $V_H$, $C_L$ and CH1 domains; (ii) a F(ab')2 fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the $V_H$ and CH1 domains; (iv) a Fv fragment consisting of the $V_L$ and $V_H$ domains of a single arm of an antibody, (v) a domain antibody (dAb) fragment (Ward *et al.*, *Nature*, **1989**, *341*, 544-546), which may consist of a $V_H$ or a $V_L$ domain; and (vi) an isolated complementarity determining region (CDR). Furthermore, although the two domains of the Fv fragment, $V_L$ and $V_H$, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the $V_L$ and $V_H$ regions pair to form monovalent molecules known as single chain Fv (scFv); see e.g., Bird *et al.*, *Science* **1988**, *242*, 423-426; and Huston *et al.*, *Proc. Natl. Acad. Sci. USA* **1988**, *85*, 5879-5883). Such scFv chain antibodies are also intended to be encompassed within the terms "antigen-binding portion" or "antigen-binding fragment" of an antibody. These antibody fragments are obtained using conventional techniques known to those with skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies.

**[00402]** The term "human antibody," as used herein, is intended to include antibodies having variable regions in which both the framework and CDR regions are derived from human germline immunoglobulin sequences. Furthermore, if the antibody contains a constant region, the constant region also is derived from human germline immunoglobulin sequences. The human antibodies of the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic

mutation *in vivo*). The term "human antibody", as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

**[00403]** The term "human monoclonal antibody" refers to antibodies displaying a single binding specificity which have variable regions in which both the framework and CDR regions are derived from human germline immunoglobulin sequences. In one embodiment, the human monoclonal antibodies are produced by a hybridoma which includes a B cell obtained from a transgenic nonhuman animal, e.g., a transgenic mouse, having a genome comprising a human heavy chain transgene and a light chain transgene fused to an immortalized cell.

**[00404]** The term "recombinant human antibody", as used herein, includes all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as (a) antibodies isolated from an animal (e.g., a mouse) that is transgenic or transchromosomal for human immunoglobulin genes or a hybridoma prepared therefrom (described further below), (b) antibodies isolated from a host cell transformed to express the human antibody, e.g., from a transfectoma, (c) antibodies isolated from a recombinant, combinatorial human antibody library, and (d) antibodies prepared, expressed, created or isolated by any other means that involve splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies have variable regions in which the framework and CDR regions are derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies can be subjected to *in vitro* mutagenesis (or, when an animal transgenic for human Ig sequences is used, *in vivo* somatic mutagenesis) and thus the amino acid sequences of the $V_H$ and $V_L$ regions of the recombinant antibodies are sequences that, while derived from and related to human germline $V_H$ and $V_L$ sequences, may not naturally exist within the human antibody germline repertoire *in vivo*.

**[00405]** As used herein, "isotype" refers to the antibody class (e.g., IgM or IgG1) that is encoded by the heavy chain constant region genes.

**[00406]** The phrases "an antibody recognizing an antigen" and "an antibody specific for an antigen" are used interchangeably herein with the term "an antibody which binds

specifically to an antigen."

**[00407]** The term "human antibody derivatives" refers to any modified form of the human antibody, e.g., a conjugate of the antibody and another active pharmaceutical ingredient or antibody. The term "conjugate" or "immunoconjugate" refers to an antibody, or a fragment thereof, conjugated to a therapeutic moiety, such as a bacterial toxin, a cytotoxic drug or a radionuclide-containing toxin. Toxic moieties can be conjugated to antibodies of the invention using methods available in the art.

**[00408]** The terms "humanized antibody," "humanized antibodies," and "humanized" are intended to refer to antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences. Additional framework region modifications may be made within the human framework sequences. Humanized forms of non-human (for example, murine) antibodies are chimeric antibodies that contain minimal sequence derived from non-human immunoglobulin. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a hypervariable region of the recipient are replaced by residues from a 15 hypervariable region of a non-human species (donor antibody) such as mouse, rat, rabbit or nonhuman primate having the desired specificity, affinity, and capacity. In some instances, Fv framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may comprise residues that are not found in the recipient antibody or in the donor antibody. These modifications are made to further refine antibody performance. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin sequence. The humanized antibody optionally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see Jones *et al.*, *Nature* **1986,** *321,* 522-525; Riechmann *et al.*, *Nature* **1988,** *332,* 323-329; and Presta, *Curr. Op. Struct. Biol.* **1992,** *2,* 593-596.

**[00409]** The term "chimeric antibody" is intended to refer to antibodies in which the variable region sequences are derived from one species and the constant region sequences are derived from another species, such as an antibody in which the variable region sequences are derived from a mouse antibody and the constant region sequences are derived from a human antibody.

**[00410]** A "diabody" is a small antibody fragment with two antigen-binding sites. The fragments comprises a heavy chain variable domain ($V_H$) connected to a light chain variable domain ($V_L$) in the same polypeptide chain ($V_H$-$V_L$ or $V_L$-$V_H$). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, *e.g.*, European Patent No. EP 404,097, International Patent Publication No. WO 93/11161; and Bolliger *et al.*, *Proc. Natl. Acad. Sci. USA* **1993,** *90,* 6444-6448.

**[00411]** The term "glycosylation" refers to a modified derivative of an antibody. An aglycoslated antibody lacks glycosylation. Glycosylation can be altered to, for example, increase the affinity of the antibody for antigen. Such carbohydrate modifications can be accomplished by, for example, altering one or more sites of glycosylation within the antibody sequence. For example, one or more amino acid substitutions can be made that result in elimination of one or more variable region framework glycosylation sites to thereby eliminate glycosylation at that site. Aglycosylation may increase the affinity of the antibody for antigen, as described in U.S. Patent Nos. 5,714,350 and 6,350,861. Additionally or alternatively, an antibody can be made that has an altered type of glycosylation, such as a hypofucosylated antibody having reduced amounts of fucosyl residues or an antibody having increased bisecting GlcNac structures. Such altered glycosylation patterns have been demonstrated to increase the ability of antibodies. Such carbohydrate modifications can be accomplished by, for example, expressing the antibody in a host cell with altered glycosylation machinery. Cells with altered glycosylation machinery have been described in the art and can be used as host cells in which to express recombinant antibodies of the invention to thereby produce an antibody with altered glycosylation. For example, the cell lines Ms704, Ms705, and Ms709 lack the fucosyltransferase gene, FUT8 (alpha (1,6) fucosyltransferase), such that antibodies

expressed in the Ms704, Ms705, and Ms709 cell lines lack fucose on their carbohydrates. The Ms704, Ms705, and Ms709 FUT8−/− cell lines were created by the targeted disruption of the FUT8 gene in CHO/DG44 cells using two replacement vectors (see e.g. U.S. Patent Publication No. 2004/0110704 or Yamane-Ohnuki, *et al. Biotechnol. Bioeng.*, **2004,** *87,* 614-622). As another example, European Patent No. EP 1,176,195 describes a cell line with a functionally disrupted FUT8 gene, which encodes a fucosyl transferase, such that antibodies expressed in such a cell line exhibit hypofucosylation by reducing or eliminating the alpha 1,6 bond-related enzyme, and also describes cell lines which have a low enzyme activity for adding fucose to the N-acetylglucosamine that binds to the Fc region of the antibody or does not have the enzyme activity, for example the rat myeloma cell line YB2/0 (ATCC CRL 1662). International Patent Publication WO 03/035835 describes a variant CHO cell line, Lec 13 cells, with reduced ability to attach fucose to Asn(297)-linked carbohydrates, also resulting in hypofucosylation of antibodies expressed in that host cell (see also Shields, *et al., J. Biol. Chem.* **2002,** *277,* 26733-26740. International Patent Publication WO 99/54342 describes cell lines engineered to express glycoprotein-modifying glycosyl transferases (e.g., beta(1,4)-N-acetylglucosaminyltransferase III (GnTIII)) such that antibodies expressed in the engineered cell lines exhibit increased bisecting GlcNac structures which results in increased ADCC activity of the antibodies (see also Umana, *et al., Nat. Biotech.* **1999,** *17,* 176-180). Alternatively, the fucose residues of the antibody may be cleaved off using a fucosidase enzyme. For example, the fucosidase alpha-L-fucosidase removes fucosyl residues from antibodies as described in Tarentino, *et al., Biochem.* **1975,** *14,* 5516-5523.

**[00412]** "Pegylation" refers to a modified antibody, or a fragment thereof, that typically is reacted with polyethylene glycol (PEG), such as a reactive ester or aldehyde derivative of PEG, under conditions in which one or more PEG groups become attached to the antibody or antibody fragment. Pegylation may, for example, increase the biological (e.g., serum) half life of the antibody. Preferably, the pegylation is carried out via an acylation reaction or an alkylation reaction with a reactive PEG molecule (or an analogous reactive water-soluble polymer). As used herein, the term "polyethylene glycol" is intended to encompass any of the forms of PEG that have been used to derivatize other proteins, such as mono ($C_1$-$C_{10}$) alkoxy- or aryloxy-polyethylene glycol

or polyethylene glycol-maleimide. The antibody to be pegylated may be an aglycosylated antibody. Methods for pegylation are known in the art and can be applied to the antibodies of the invention, as described for example in European Patent Nos. EP 0154316 and EP 0401384.

**[00413]** As used herein, an antibody that "specifically binds to human PD-1" is intended to refer to an antibody that binds to human PD-1 with a $K_D$ of $1\times10^{-7}$ M or less, more preferably $5\times10^{-8}$ M or less, more preferably $1\times10^{-8}$ M or less, more preferably $5\times10^{-9}$ M or less.

**[00414]** As used herein, an antibody that "specifically binds to human PD-L1" is intended to refer to an antibody that binds to human PD-L1 with a $K_D$ of $1\times10^{-7}$ M or less, more preferably $5\times10^{-8}$ M or less, more preferably $1\times10^{-8}$ M or less, more preferably $5\times10^{-9}$ M or less.

**[00415]** As used herein, an antibody that "specifically binds to human PD-L2" is intended to refer to an antibody that binds to human PD-L2 with a $K_D$ of $1\times10^{-7}$ M or less, more preferably $5\times10^{-8}$ M or less, more preferably $1\times10^{-8}$ M or less, more preferably $5\times10^{-9}$ M or less.

**[00416]** As used herein, an antibody that "specifically binds to human CD20" is intended to refer to an antibody that binds to human CD20 with a $K_D$ of $1\times10^{-7}$ M or less, more preferably $5\times10^{-8}$ M or less, more preferably $1\times10^{-8}$ M or less, more preferably $5\times10^{-9}$ M or less.

**[00417]** The term "radioisotope-labeled complex" refers to both non-covalent and covalent attachment of a radioactive isotope, such as $^{90}Y$, $^{111}In$, or $^{131}I$, to an antibody, including conjugates.

**[00418]** The term "biosimilar" means a biological product that is highly similar to a U.S. licensed reference biological product notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product. Furthermore, a similar biological or "biosimilar" medicine is a biological medicine that is similar to another biological medicine that has already been

authorized for use by the European Medicines Agency. The term "biosimilar" is also used synonymously by other national and regional regulatory agencies. Biological products or biological medicines are medicines that are made by or derived from a biological source, such as a bacterium or yeast. They can consist of relatively small molecules such as human insulin or erythropoietin, or complex molecules such as monoclonal antibodies. For example, if the reference anti-CD20 monoclonal antibody is rituximab, an anti-CD20 biosimilar monoclonal antibody approved by drug regulatory authorities with reference to rituximab is a "biosimilar to" rituximab or is a "biosimilar thereof" rituximab. If the reference anti-PD-1 monoclonal antibody is pembrolizumab, an anti-PD-1 biosimilar monoclonal antibody approved by drug regulatory authorities with reference to pembrolizumab is a "biosimilar to" pembrolizumabor is a "biosimilar thereof" pembrolizumab.

**[00419]** The term "hematological malignancy" refers to mammalian cancers and tumors of the hematopoietic and lymphoid tissues, including but not limited to tissues of the blood, bone marrow, lymph nodes, and lymphatic system. Hematological malignancies are also referred to as "liquid tumors." Hematological malignancies include, but are not limited to, ALL, CLL, SLL, acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), acute monocytic leukemia (AMoL), Hodgkin's lymphoma, and non-Hodgkin's lymphomas. The term "B cell hematological malignancy" refers to hematological malignancies that affect B cells.

**[00420]** The term "solid tumor" refers to an abnormal mass of tissue that usually does not contain cysts or liquid areas. Solid tumors may be benign or malignant. The term "solid tumor cancer" refers to malignant, neoplastic, or cancerous solid tumors. Solid tumor cancers include, but are not limited to, sarcomas, carcinomas, and lymphomas, such as cancers of the lung, breast, prostate, colon, rectum, and bladder. The tissue structure of solid tumors includes interdependent tissue compartments including the parenchyma (cancer cells) and the supporting stromal cells in which the cancer cells are dispersed and which may provide a supporting microenvironment.

**[00421]** The term "microenvironment," as used herein, may refer to the tumor microenvironment as a whole or to an individual subset of cells within the

microenvironment.

**[00422]** For the avoidance of doubt, it is intended herein that particular features (for example integers, characteristics, values, uses, diseases, formulae, compounds or groups) described in conjunction with a particular aspect, embodiment or example of the invention are to be understood as applicable to any other aspect, embodiment or example described herein unless incompatible therewith. Thus such features may be used where appropriate in conjunction with any of the definition, claims or embodiments defined herein. All of the features disclosed in this specification (including any accompanying claims, abstract and drawings), and/or all of the steps of any method or process so disclosed, may be combined in any combination, except combinations where at least some of the features and/or steps are mutually exclusive. The invention is not restricted to any details of any disclosed embodiments. The invention extends to any novel one, or novel combination, of the features disclosed in this specification (including any accompanying claims, abstract and drawings), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.

Co-administration of compounds

**[00423]** An aspect of the invention is a composition, such as a pharmaceutical composition, comprising a combination of a PI3K inhibitor, a BTK inhibitor, a JAK-2 inhibitor, a PD-1 inhibitor, and/or a PD-L1 or PD-L2 inhibitor. Another aspect of the invention is a method of treating leukemia, lymphoma or a solid tumor cancer in a subject, comprising co-administering to the subject in need thereof a therapeutically effective amount of a combination of a PI3K inhibitor, a BTK inhibitor, and/or a PD-1 inhbitor.

**[00424]** In an embodiment, the PI3K inhibitor is a PI3K-γ inhibitor.

**[00425]** In an embodiment, the PI3K inhibitor is a PI3K-δ inhibitor.

**[00426]** In an embodiment, the PI3K inhibitor is a PI3K-γ,δ inhibitor.

**[00427]** In an embodiment, the PI3K inhibitor is a selective PI3K inhibitor.

**[00428]** In an embodiment, the combination of the PI3K inhibitor, PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor with the BTK inhibitor is administered by oral,

intravenous, intramuscular, intraperitoneal, subcutaneous or transdermal means.

**[00429]** In an embodiment, the PI3K inhibitor, PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor is in the form of a pharmaceutically acceptable salt, solvate, hydrate, complex, derivative, prodrug (such as an ester or phosphate ester), or cocrystal.

**[00430]** In an embodiment, the BTK inhibitor is in the form of a pharmaceutically acceptable salt, solvate, hydrate, complex, derivative, prodrug (such as an ester or phosphate ester), or cocrystal.

**[00431]** In an embodiment, the PI3K inhibitor, PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor is administered to the subject before administration of the BTK inhibitor.

**[00432]** In an embodiment, the PI3K inhibitor, PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor is administered concurrently with the administration of the BTK inhibitor.

**[00433]** In an embodiment, the PI3K inhibitor, PI3K-γ inhibitor, PI3K-δ inhibitor, PI3K-γ,δ inhibitor is administered to the subject after administration of the BTK inhibitor.

**[00434]** In an embodiment, the PD-1 inhibitor is administered to the subject before administration of the BTK inhibitor.

**[00435]** In an embodiment, the PD-1 inhibitor is administered concurrently with the administration of the BTK inhibitor.

**[00436]** In an embodiment, the PD-1 inhibitor is administered to the subject after administration of the BTK inhibitor.

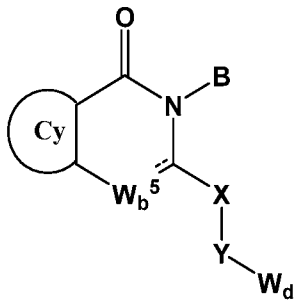
**[00437]** In an embodiment, the BTK inhibitor, PD-1 inhibitor, JAK-2 inhibitor, and PI3K inhibitor are administered concurrently.

**[00438]** In an embodiment, the subject is a mammal. In an embodiment, the subject is a human. In an embodiment, the subject is a companion animal, such as a canine, feline, or equine.

PI3K Inhibitors

**[00439]** The PI3K inhibitor may be any PI3K inhibitor known in the art. In particular, it is one of the PI3K inhibitors described in more detail in the following paragraphs. Preferably, it is a PI3K inhibitor selected from the group consisting of a PI3K-γ inhibitor, a PI3K-δ inhibitor, and a PI3K-γ,δ inhibitor. In one specific embodiment, it is a PI3K-δ inhibitor. For avoidance of doubt, references herein to a PI3K inhibitor may refer to a compound or a pharmaceutically acceptable salt, ester, solvate, hydrate, cocrystal, or prodrug thereof.

**[00440]** In an embodiment, the PI3K inhibitor, which is preferably selected from the group consisting of a PI3K-γ inhibitor, a PI3K-δ inhibitor, and a PI3K-γ,δ inhibitor, is a compound selected from the structures disclosed in U.S. Patent Nos. 8,193,182 and 8,569,323, and U.S. Patent Application Publication Nos. 2012/0184568 A1, 2013/0344061 A1, and 2013/0267521 A1, the disclosures of which are incorporated by reference herein. In an embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound of Formula (I):




Formula (I)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal or prodrug thereof, wherein:

Cy is aryl or heteroaryl substituted by 0 or 1 occurrences of $R^3$ and 0, 1, 2, or 3 occurrences of $R^5$;

$W_b^5$ is $CR^8$, $CHR^8$, or N;

$R^8$ is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl or nitro;

B is hydrogen, alkyl, amino, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is substituted with 0, 1, 2, 3, or 4 occurrences of $R^2$;

each $R^2$ is independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl,

aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, or carbonate;

X is $-(CH(R^9))_z-$;

Y is $-N(R^9)-C(=O)-$, $-C(=O)-N(R^9)-$, $-C(=O)-N(R^9)-(CHR^9)-$, $-N(R^9)-S(=O)-$, $-S(=O)-N(R^9)-$, $S(=O)_2-N(R^9)-$, $-N(R^9)-C(=O)-N(R^9)$ or $-N(R^9)S(=O)_2-$;

z is an integer of 1, 2, 3, or 4;

$R^3$ is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, fluoroalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfinyl, sulfonyl, sulfoxide, sulfone, sulfonamido, halo, cyano, aryl, heteroaryl, hydroxyl, or nitro;

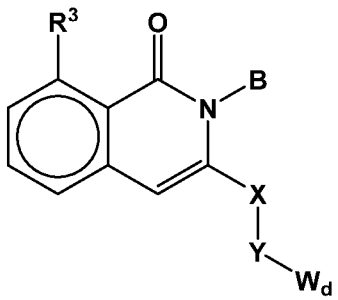
each $R^5$ is independently alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxyl, or nitro;

each $R^9$ is independently hydrogen, alkyl, cycloalkyl, heterocyclyl, or heteroalkyl; or two adjacent occurrences of $R^9$ together with the atoms to which they are attached form a 4- to 7-membered ring;

$W_d$ is heterocyclyl, aryl, cycloalkyl, or heteroaryl, each of which is substituted with one or more $R^{10}$, $R^{11}$, $R^{12}$ or $R^{13}$, and

$R^{10}$, $R^{11}$, $R^{12}$ and $R^{13}$ are each independently hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbonate or NR'R" wherein R' and R" are taken together with nitrogen to form a cyclic moiety.

**[00441]** In an embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound of Formula (I-1):

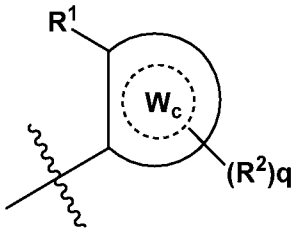



Formula (II)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof,

wherein:

B is a moiety of Formula (II-A):




Formula (II-A) ;

$W_c$ is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl;

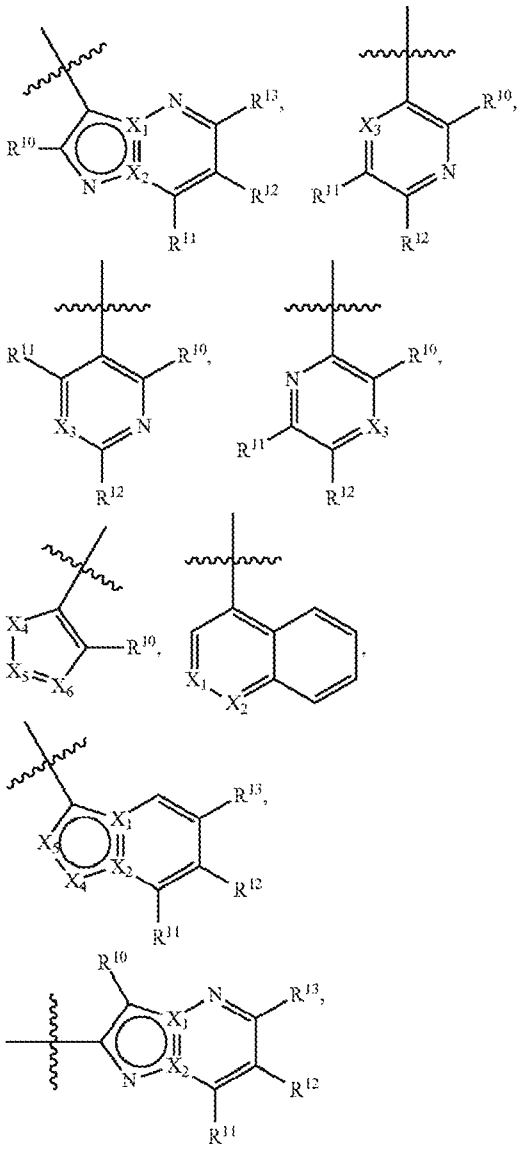
q is an integer of 0, 1, 2, 3, or 4;

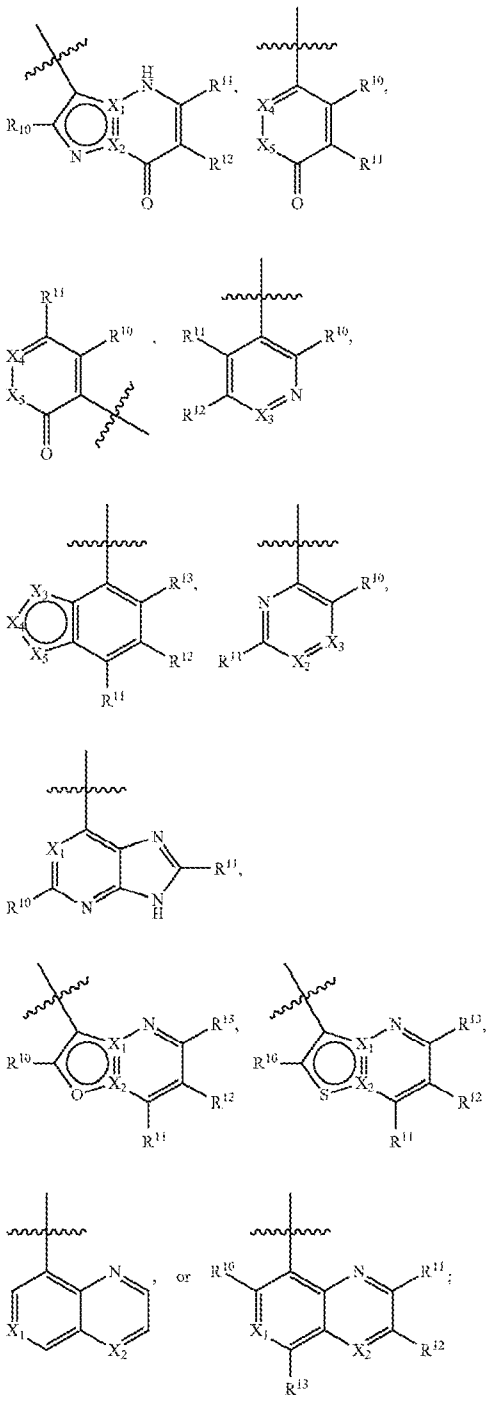
X is a bond or $-(CH(R^9))_z-$, and z is an integer of 1, 2, 3 or 4;

Y is a bond, $-N(R^9)-$, -O-, -S-, $-S(=O)-$, $-S(=O)_2$, $-C(=O)-$, $-C(=O)(CHR^9)_z-$, $-N(R^9)-C(=O)-$, $-N(R^9)-C(=O)NH-$ or $-N(R^9)C(R^9)_2-$;

z is an integer of 1, 2, 3, or 4;

$W_d$ is:





$X_1$, $X_2$ and $X_3$ are each independently C, $CR^{13}$ or N; and $X_4$, $X_5$ and $X_6$ are each independently N, NH, $CR^{13}$, S or O;

$R^1$ is hydrogen, alkyl, alkenyl, alkynyl, alkoxy, amido, alkoxycarbonyl, sulfonamido, halo, cyano, or nitro;

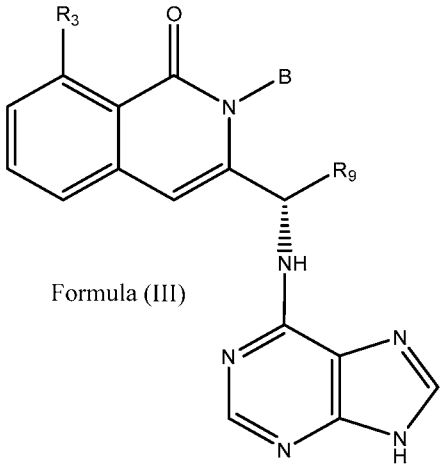
$R^2$ is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl,

heteroarylalkyl, alkoxy, amino, halo, cyano, hydroxy or nitro;

$R^3$ is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkoxy, amido, amino, alkoxycarbonyl sulfonamido, halo, cyano, hydroxy or nitro; and

each instance of $R^9$ is independently hydrogen, alkyl, or heterocycloalkyl.

**[00442]** In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound of Formula (III):



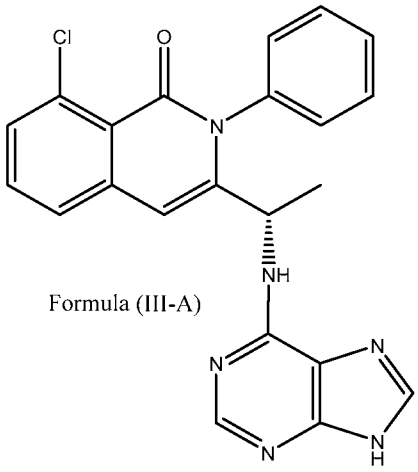

Formula (III)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, where B is a moiety of Formula (II-A),

$R^2$ is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, heteroarylalkyl, alkoxy, amino, halo, cyano, hydroxy or nitro; and

$R^9$ is hydrogen, alkyl, or heterocycloalkyl.

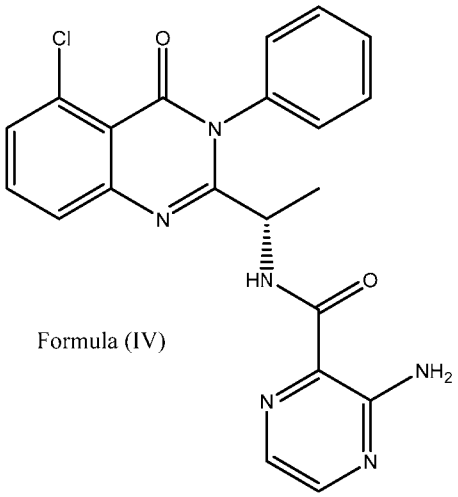
**[00443]** In a preferred embodiment, the PI3K-γ,δ inhibitor is a compound of Formula (III-A):



Formula (III-A)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. Formula (III-A) is also known as IPI-145 or duvelisib (Infinity Pharmaceuticals) and has been studied at doses of 5 mg and 25 mg in clinical trials, including those described in Flinn, *et al.*, *Blood*, **2014,** *124,* 802, and O'Brien, *et al.*, *Blood*, **2014,** *124,* 3334.

**[00444]** In a preferred embodiment, the PI3K inhibitor is a compound of Formula (IV):



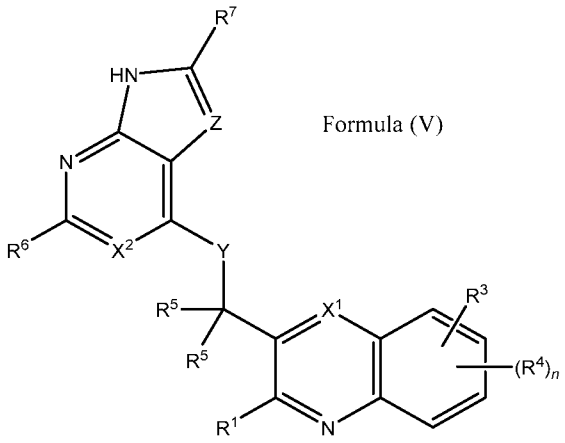
Formula (IV)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

**[00445]** In a preferred embodiment, the PI3K inhibitor is (*S*)-3-(1-((9*H*-purin-6-yl)amino)ethyl)-8-chloro-2-phenylisoquinolin-1(2*H*)-one or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

**[00446]** In a preferred embodiment, the PI3K inhibitor is (*S*)-3-amino-N-(1-(5-chloro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)ethyl)pyrazine-2-carboxamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00447] In an embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound selected from the structures disclosed in U.S. Patent Nos. 8,193,199, 8,586,739, and 8,901,135, the disclosure of each of which is incorporated by reference herein. In an embodiment, the PI3K inhibitor or PI3K-δ inhibitor is a compound of Formula (V):



Formula (V)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein:

$X^1$ is $C(R^9)$ or N;

$X^2$ is $C(R_{10})$ or N;

Y is $N(R^{11})$, O or S;

Z is $CR^8$ or N;

n is 0, 1, 2 or 3;

$R^1$ is a direct-bonded or oxygen -linked saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one 0 or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0 or 1 $R^2$ substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, $(C_{1-4})$alkyl, $O(C_{1-4})$alkyl, $O(C_{1-4})$haloalkyl, $NHC_{1-4}$, $N((C_{1-4})alkyl)(C_{1-4})$alkyl and $(C_{1-4})$haloalkyl;

$R^2$ is selected from halo, $(C_{1-4})$haloalkyl, cyano, nitro, —C(=O)$R^a$, —C(=O)$OR^a$, —C(=O)$NR^aR^a$, —C(=$NR^a$)$NR^aR^a$, —$OR^a$, —OC(=O)$R^a$, —OC(=O)$NR^aR^a$. —OC(=O)N($R^a$)S(=$O)_2R^a$, —$O(C_{2-6})$alkyl$NR^aR^a$, —$O(C_{2-6})$alkyl$OR^a$, —$SR^a$,

$OS(=O)R^a$, $—S(=O)_2R^a$, $—S(=O)_2NR^aR^a$, $—S(=O)_2N(R^a)C(=O)R^a$, $—S(=O)_2N(R^a)C(=O)OR^a$, $—S(=O)_2N(R^a)C(=O)NR^aR^a$, $—NR^aR^a$, $—N(R^a)C(=O)R^a$, $—N(R^a)C(=O)OR^a$, $—N(R^a)C(=O)NR^aR^a$, $—N(R^a)C(=NR^a)NR^aR^a$, $—N(R^a)S(=O)_2R^a$, $—N(R^a)S(=O)_2NR^aR^a$, $—NR^a(C_{2-6}alkylNR^aR^a$ and $—NR^a(C_{2-6})alkylOR^a$; or $R^2$ is selected from $(C_{1-6})$alkyl, phenyl, benzyl, heteroaryl, heterocycle, $—((C_{1-3})alkyl)heteroaryl$, $—((C_{1-3})alkyl)heterocycle$, $—O((C_{1-3})alkyl)heteroaryl$, $—O((C_{1-3})alkyl)heterocycle$, $—NR^a((C_{1-3})alkyl)heteroaryl$, $—NR^a((C_{1-3})alkyl)heterocycle$, $—(C_{1-3})alkyl)phenyl$, $—O((C_{1-3})alkyl)phenyl$ and $—NR^a((C_{1-3})alkyl)phenyl$ all of which are substituted by 0, 1, 2 or 3 substituents selected from $(C_{1-4})$haloalkyl, $O(C_{1-4})$alkyl, Br, Cl, F, I and $(C_{1-4})$alkyl;

$R^3$ is selected from H, halo, $(C_{1-4})$haloalkyl, cyano, nitro, $—C(=O)R^a$, $—C(=O)R^a$, $—C(=O)NR^aR^a$, $—C(=NR^a)NR^aR^a$, $—OR^a$, $—OC(=O)R^a$, $—OC(=O)NR^aR^a$, $—OC(=O)N(R^a)S(=O)_2R^2$, $—O(C_{2-6})alkylNR^aR^a$, $—O(C_{2-6})alkylOR^a$, $—SR^a$, $—S(=O)R^a$, $—S(=O)_2R^a$, $—S(=O)_2NR^aR^a$, $—S(=O)_2N(R^a)C(=O)R^a$, $—S(=O)_2N(R^a)C(=O)OR^a$, $—S(=O)_2N(R^a)C(=O)NR^aR^a$, $—NR^aR^a$, $—N(R^a)C(=O)R^a$, $—N(R^a)C(=O)OR^a$, $—N(R^a)C(=O)NR^aR^a$, $—N(R^a)C(=NR^a)NR^aR^a$, $—N(R^a)S(=O)_2R^a$, $—N(R^a)S(=O)_2NR^aNR^aR^a$, $—NR^a(C_{2-6})alkylOR^a$, $(C_{1-6})$alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the $(C_{1-6})$alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from $(C_{1-6})$haloalkyl, $O(C_{1-6})$alkyl, Br, Cl, F, I and $(C_{1-6})$alkyl;

$R^4$ is, independently, in each instance, halo, nitro, cyano, $(C_{1-4})$alkyl, $O(C_{1-4})$alkyl, $O(C_{1-4})$haloalkyl, $NH(C_{1-4})$alkyl, $N((C_{1-4})alkyl)(C_{1-4})$alkyl or $(C_{1-4})$haloalkyl;

$R^5$ is, independently, in each instance, H, halo, $(C_{1-6})$alkyl, $(C_{1-4})$haloalkyl, or $(C_{1-6})$alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, $O(C_{1-4})$alkyl, $(C_{1-4})$alkyl, $(C_{1-3})$haloalkyl, $O(C_{1-4})$alkyl, $NH_2$, $NHC_{1-4})$alkyl, $N(C_{1-4})alkyl(C_{1-4})$alkyl; or both $R^5$ groups together form a $(C_{3-6})$spiroalkyl substituted by 0, 1, 2 or 3 substituents selected from halo, cyano, OH, $O(C_{1-4})$alkyl, $(C_{1-4})$alkyl, $(C_{1-3})$haloalkyl, $O(C_{1-4})$alkyl, $NH_2$, $NH(C_{1-4})$alkyl, $N((C_{1-4})alkyl)(C_{1-4})$alkyl;

$R^6$ is selected from H, halo, $(C_{1-6})$alkyl, $(C_{1-4})$haloalkyl, cyano, nitro, $—C(=O)R^a$, $—C(=O)OR^a$, $—C(=O)NR^aR^a$, $—C(=NR^a)NR^aR^a$, $—S(=O)R^a$, $—S(=O)_2R^a$, $—S(=O)_2NR^aR^a$, $—S(=O)_2N(R^a)C(=O)R^a$, $—S(=O)_2N(R^a)C(=O)OR^a$, —

$S(=O)_2N(R^a)C(=O)NR^aR^a$;

$R^7$ is selected from H, halo, $(C_{1-6})$alkyl, $(C_{1-4})$haloalkyl, cyano, nitro, —$C(=O)R^a$, —$C(=O)OR^a$, —$C(=O)NR^aR^a$, —$C(=NR^a)NR^aR^a$, —$S(=O)R^a$, —$S(=O)_2R^a$, —$S(=O)_2NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$;

$R^8$ is selected from H, $(C_{1-6})$haloalkyl, Br, Cl, F, I, $OR^a$, $NR^aR^a$, $(C_{1-6})$alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the $(C_{1-6})$alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from $(C_{1-6})$haloalkyl, $O(C_{1-6})$alkyl, Br, Cl, F, I and $(C_{1-6})$alkyl;

$R^9$ is selected from H, halo, $(C_{1-4})$haloalkyl, cyano, nitro, —$C(=O)R^a$, —$C(=O)OR^a$, —$C(=O)NR^aR^aC(=NR^a)NR^aR^a$, —$OR^a$, —$OC(=O)R^a$, —$OC(=O)NR^aR^a$, —$OC(=O)N(R^a)S(=O)_2R^a$, —$O(C_{2-6})$alkyl$OR^a$, —$SR^a$, —$S(=O)R^a$, —$S(=O)_2R^a$, —$S(=O)_2NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$, $NR^aR^a$, —$N(R^a)C(=O)R^a$, —$N(R^a)C(=O)OR^a$, —$N(R^a)C(O)NR^aR^aN(R^aC(=NR^a)NR^aR^a$, —$N(R^a)S(=O)_2R^a$, —$N(R^a)S(=O)_2NR^aR^a$, —$NR^a(C_{2-6}$ alkyl$NR^aR^a$, —$NR^a(C_{1-6})$alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the $(C_{1-6}$ alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from halo, $(C_{1-4})$haloalkyl, cyano, nitro, —$C(=O)R^a$, —$C(=O)OR^a$, —$C(=O)NR^aR^a$, —$C(=NR^a)NR^aR^a$, —$OR^a$, —$OC(=O)R^a$, $OC(=O)NR^aR^a$, —$OC(=O)N(R^a)S(=O)_2R^a$, —$O(C_{2-6})$alkyl$NR^aR^a$, —$O(C_{2-6})$alkyl$OR^a$, —$SR^a$, —$S(=O)R^a$, —$S(=O)_2R^a$, —$S(=O)_2NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$, $NR^aR^a$, —$N(R^a)C(=O)R^a$, —$N(R^a)C(=O)OR^a$, —$N(R^a)C(=O)NR^aR^a$, —$N(R^a)C(=NR^a)NR^aR^a$, —$N(R^a)S(=O)_2R^a$, —$N(R^a)S(=O)_2NR^aR^a$, —$NR^a(C_{2-6})$alkyl$OR^a$, —$NR^a(C_{2-6})$alkyl$OR^a$; or $R^9$ is a saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, $(C_{1-4})$haloalkyl, cyano, nitro, —$C(=O)R^a$, —$C(=O)OR^a$, —$C(=O)NR^aR^a$, —$C(=NR^a)NR^aR^a$, —$OR^a$, —$OC(=O)R^a$, —$OC(=O)NR^aR^a$, —

$OC(=O)N(R^a)S(=O)_2R^a$, —$O(C_{2-6})alkylNR^aR^a$, —$O(C_{2-6})alkylOR^a$, —$SR^a$, —$S(=O)R^a$, —$S(=O)_2R^a$, —$S(=O)_2NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$, —$NR^aR^a$, —$N(R^a)C(=O)R^a$, —$N(R^a)C(=O)OR^a$, —$N(R^a)C(=O)NR^aR^a$, —$N(R^a)C(=NR^a)NR^aR^a$, —$N(R^a)S(=O)_2R^a$, —$N(R^a)S(=O)_2NR^aR^a$, —$NR^a(C_{2-6})alkylNR^aR^a$ and —$NR^a(C_{2-6})alkylOR^a$;

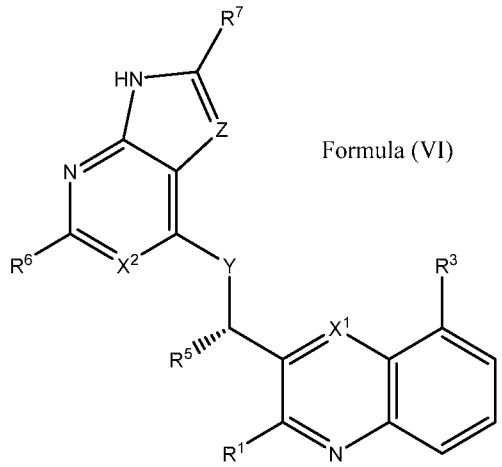
$R^{10}$ is H, $(C_{1-3})$alkyl, $(C_{1-3})$haloalkyl, cyano, nitro, $CO_2R^a$, $C(=O)NR^aR^a$, —$C(=NR^a)NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$, —$S(=O)R^b$, $S(=O)_2R^b$ or $S(=O)_2NR^aR^a$;

$R^{11}$ is H or $(C_{1-4})$alkyl;

$R^a$ is independently, at each instance, H or $R^b$; and

$R^b$ is independently, at each instance, phenyl, benzyl or $(C_{1-6})$alkyl, the phenyl, benzyl and $(C_{1-6})$alkyl being substituted by 0, 1, 2 or 3 substituents selected from halo, $(C_{1-4})$alkyl, $(C_{1-3})$haloalkyl, —$O(C_{1-4})$alkyl, —$NH_2$, —$NHC_{1-4})$alkyl, —$N((C_{1-4})alkyl)(C_{1-4})$alkyl.

**[00448]** In another embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound of Formula (VI):




Formula (VI)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein:

$X^1$ is $C(R^9)$ or N;

$X^2$ is $C(R^{10})$ or N;

Y is $N(R^{11})$, O or S;

Z is $CR^8$ or N;

$R^1$ is a direct-bonded or oxygen-linked saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0 or 1 $R^2$ substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, $(C_{1-4})$alkyl, $O(C_{1-4})$alkyl, $O(C_{1-4})$haloalkyl, $(NHC_{1-4})$alkyl, $N(C_{1-4}$ alkyl$)(C_{1-4})$alkyl and $(C_{1-4})$haloalkyl;

$R^2$ is selected from halo, $(C_{1-4})$haloalkyl, cyano, nitro, —C(=O)$R^a$, —C(=O)$OR^a$, —C(=O)$NR^aR^a$, —C(=$NR^a$)$NR^aR^a$, —$OR^a$, —OC(=O)$R^a$, —OC(=O)$NR^aR^a$, —OC(=O)N($R^a$)S(=O)$_2R^a$, —O$(C_{2-6})$alkyl$NR^aR^a$, —O$(C_{2-6})$alkyl$OR^a$, —S(=O)$R^a$, —S(=O)$_2R^a$, —S(=O)$_2NR^aR^a$, —S(=O)$_2$N($R^a$)C(=O)$R^a$, —S(=O)$_2$N($R^a$)C(=O)$OR^a$, —S(=O)$_2$N($R^a$)C(=O)$NR^aR^a$, —$NR^aR^a$, —N($R^a$)C(=O)$R^a$, —N($R^a$)C(=O)$OR^a$, —N($R^a$)C(=O)$NR^aR^a$, —N($R^a$)C(=$NR^a$)$NR^aR^a$, —N($R^a$)S(=O)$_2R^a$, —N($R^a$)S(=O)$_2NR^aR^a$, —$NR^a(C_{2-6}$ alkyl$NR^aR^a$ and —$NR^a(C_{2-6})$alkyl$OR^a$; or $R^2$ is selected from $(C_{1-6})$alkyl, phenyl, benzyl, heteroaryl, heterocycle, —$((C_{1-3})$alkyl)heteroaryl, —$((C_{1-3})$alkyl)heterocycle, —O$((C_{1-3})$alkyl)heteroaryl, —O$((C_{1-3})$alkyl)heterocycle, —$NR^a((C_{1-3})$alkyl)heteroaryl, —$NR^a((C_{1-3})$alkyl)heterocycle, —$((C_{1-3})$alkyl)phenyl, —O$((C_{1-3})$alkyl)phenyl and —$NR^a(C_{1-3}$ alkyl)phenyl all of which are substituted by 0, 1, 2 or 3 substituents selected from $(C_{1-4})$haloalkyl, $O(C_{1-4})$alkyl, Br, Cl, F, I and $(C_{1-4})$alkyl;

$R^3$ is selected from H, halo, $(C_{1-4})$haloalkyl, cyano, nitro, —C(=O)$R^a$, —C(=O)$OR^a$, C(=O)$NR^aR^a$C(=$NR^a$)$NR^aR^a$, —$OR^a$, —OC(=O)$R^a$, —OC(=O)$NR^aR^a$, —OC(=O)N($R^a$)S(=O)$_2R^a$, —O$(C_{2-6})$alkyl$NR^aR^a$, —O$(C_{2-6})$alkyl$OR^a$, —$SR^a$, —S(=O)$R^a$, —S(=O)$_2R^a$, —S(=O)$_2NR^aR^a$, —S(=O)$_2$N($R^a$)C(=O)$R^a$, —S(=O)$_2$N($R^a$)C(=O)$OR^a$, —S(=O)$_2$N($R^a$)C(=O)$NR^aR^a$, $NR^aR^a$, —N($R^a$)C(=O)$R^a$, —N($R^a$)C(=O)$OR^a$, —N($R^a$)C(=O)$NR^aR^a$, —N($R^a$)C(=$NR^a$)$NR^aR^a$, —N($R^a$)S(=O)$_2R^a$, —N($R^a$)S(=O)$_2NR^aR^a$, —$NR^a(C_{2-6})$alkyl$OR^a$, $(C_{1-6})$alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the $(C_{1-6})$alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from $(C_{1-6})$haloalkyl, $O(C_{1-6})$alkyl, Br, Cl, F, I and $(C_{1-6})$alkyl;

$R^5$ is, independently, in each instance, H, halo, $(C_{1-6})$alkyl, $(C_{1-4})$haloalkyl, or $(C_{1-6})$alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, $O(C_{1-4})$alkyl, $(C_{1-4})$alkyl, $(C_{1-3})$haloalkyl, $O(C_{1-4})$alkyl, $NH_2$, $(NHC_{1-4})$alkyl, $N(C_{1-4})$alkyl$(C_{1-4})$alkyl; or both $R^5$ groups together form a $C_{3-6}$-spiroalkyl substituted by 0, 1, 2 or 3 substituents selected from halo, cyano, OH, $O(C_{1-4})$alkyl, $(C_{1-4})$alkyl, $(C_{1-3})$haloalkyl, $O(C_{1-4})$alkyl, $NH_2$, $(NHC_{1-4})$alkyl, $N((C_{1-4})alkyl)(C_{1-4})$alkyl;

$R^6$ is selected from H, halo, $(C_{1-6})$alkyl, $(C_{1-4})$haloalkyl, cyano, nitro, —$C(=O)R^a$, —$C(=O)OR^a$, —$C(=O)NR^aR^a$, —$C(=NR^a)NR^aR^a$, —$S(=O)R^a$, —$S(=O)_2R^a$, —$S(=O)_2NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$;

$R^7$ is selected from H, halo, $(C_{1-6})$alkyl, $(C_{1-4})$haloalkyl, cyano, nitro, —$C(=O)R^a$, —$C(=O)OR^a$, —$C(=O)NR^aR^a$, —$C(=NR^a)NR^aR^a$, —$S(=O)R^aS(=O)_2R^a$, —$S(=O)_2NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$;

$R^8$ is selected from H, $(C_{1-6})$haloalkyl, Br, Cl, F, I, $OR^a$, $NR^aR^a$, $(C_{1-6})$alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the $(C_{1-6})$alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from $(C_{1-6})$haloalkyl, $O(C_{1-6}$ alkyl, Br, Cl, F, I and $(C_{1-6})$alkyl;

$R^9$ is selected from H, halo, $(C_{1-4})$haloalkyl, cyano, nitro, —$C(=O)R^a$, —$C(=O)OR^a$, —$C(=O)NR^aR^a$, —$C(=NR^a)NR^aR^a$, —$OR^a$, —$OC(=O)R^a$, $OC(=O)NR^aR^a$, —$OC(=O)N(R^a)S(=O)_2R^a$, —$O(C_{2-6})alkylNR^aR^a$, —$O(C_{2-6})alkylOR^a$, —$SR^a$, —$S(=O)R^a$, —$S(=O)_2R^a$, —$S(=O)_2NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$, —$NR^aR^a$, —$N(R^a)C(=O)R^a$, —$N(R^a)C(=O)OR^a$, —$N(R^a)C(=O)NR^aR^a$, —$N(R^a)C(=NR^a)NR^aR^a$, —$N(R^a)S(=O)_2R^a$, —$N(R^a)S(=O)_2NR^aR^a$, —$NR^a(C_{2-6})alkylNR^aR^a$, —$NR^a(C_{2-6})alkylOR^a$, $(C_{1-6})$alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the $(C_{1-6})$alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from halo, $(C_{1-4})$haloalkyl, cyano, nitro, —$C(=O)R^a$, —$C(=O)OR^a$, —$C(=O)NR^aR^a$, —$C(=NR^a)NR^aR^a$, —$OR^a$, —$OC(=O)R^a$, —$OC(=O)NR^aR^a$, —$OC(=O)N(R^a)S(=O)_2R^a$, —$O(C_{2-6})alkylOR^a$, —$SR^a$, —$S(=O)R^a$, —$S(=O)_2R^a$, —$S(=O)_2NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$,

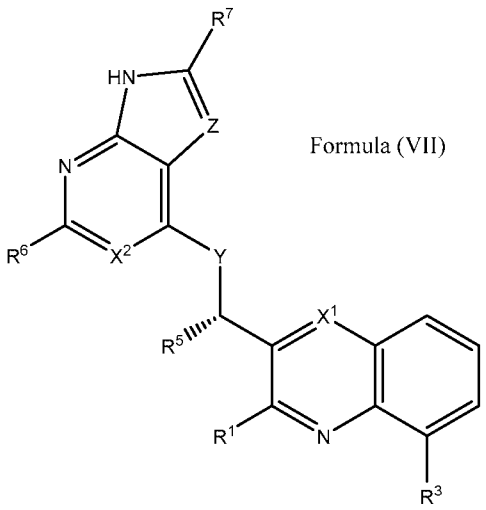
—$S(=O)_2N(R^a)C(=O)NR^aR^a$, $NR^aR^a$, —$N(R^a)C(=O)R^a$, —$N(R^a)C(=O)OR^a$, —$N(R^a)C(=O)NR^aR^a$, —$N(R^a)C(=NR^a)NR^aR^a$, —$N(R^a)S(=O)_2R^a$, —$N(R^a)S(=O)_2NR^aR^a$, —$NR^a(C_{2-6})alkylNR^a$, —$NR^a(C_{2-6})alkylOR^a$; or $R^9$ is a saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, $(C_{1-4})$haloalkyl, cyano, nitro, —$C(=O)R^a$, —$C(=O)OR^a$, —$C(=O)NR^aR^a$, —$C(=NR^a)NR^aR^a$, —$OR^a$, —$OC(=O)R^a$, —$OC(=O)NR^aR^a$, —$OC(=O)N(R^a)S(=O)_2R^a$, —$O(C_{2-6})alkylOR^a$, —$SR^a$, —$S(=O)R^a$, —$S(=O)_2R^a$, —$S(=O)_2NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$, —$NR^aR^a$, —$N(R^a)C(=O)R^a$, —$N(R^a)C(=O)OR^a$, —$N(R^a)C(=O)NR^aR^a$, —$N(R^a)C(=NR^a)NR^aR^a$, —$N(R^a)S(=O)_2R^a$, —$N(R^a)S(=O)_2NR^aR^a$, —$NR^a(C_{2-6}$ $alkylNR^aR^a$ and —$NR^a(C_{2-6})alkylOR^a$;

$R^{10}$ is H, $(C_{1-3})$alkyl, $(C_{1-3})$haloalkyl, cyano, nitro, $CO_2R^a$, $C(=O)NR^aR^a$, —$C(=NR^a)NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$, —$S(=O)R^b$, $S(=O)_2R^b$ or $S(=O)_2NR^aR^a$; —$R^{11}$ is H or $(C_{1-4})$alkyl;

$R^a$ is independently, at each instance, H or $R^b$; and

$R^b$ is independently, at each instance, phenyl, benzyl or $(C_{1-6})$alkyl, the phenyl, benzyl and $(C_{1-6})$alkyl being substituted by 0, 1, 2 or 3 substituents selected from halo, $(C_{1-4})$alkyl, $(C_{1-3})$ haloalkyl, —$O(C_{1-4})$alkyl, —$NH_2$, —$NH(C_{1-4})$alkyl, —$N(C_{1-4})$alkyl$(C_{1-4})$alkyl.

**[00449]** In another embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound of Formula (VII):



Formula (VII)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein:

$X^1$ is $C(R^9)$ or N;

$X^2$ is $C(R^{10})$ or N;

Y is $N(R^{11})$, O or S;

Z is $CR^8$ or N;

$R^1$ is a direct-bonded or oxygen-linked saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0 or 1 $R^2$ substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, $(C_{1-4})$alkyl, $O(C_{1-4})$alkyl, $O(C_{1-4})$haloalkyl, $NH(C_{1-4})$alkyl, $N(C_{1-4})$alkyl$(C_{1-4})$alkyl and $(C_{1-4})$haloalkyl;

$R^2$ is selected from halo, $(C_{1-4})$haloalkyl, cyano, nitro, —$C(=O)R^a$, —$C(=O)OR^a$, —$C(=O)NR^aR^a$, —$C(=NR^a)NR^aR^a$, —$OR^a$, —$OC(=O)R^a$, —$OC(=O)NR^aR^a$, —$OC(=O)N(R^a)S(=O)_2R^a$, —$OC_{2-6})$alkyl$NR^aR^a$, —$OC_{2-6})$alkyl$OR^a$, —$SR^a$, —$S(=O)R^a$, —$S(=O)_2R^a$, —$S(=O)_2NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$, $NR^aR^a$, —$N(R^a)C(=O)R^a$, —$N(R^a)C(=O)OR^a$, —$N(R^a)C(=O)NR^aR^a$, —$N(R^a)C(=NR^a)NR^aR^a$, —$N(R^a)S(=O)_2R^a$, —$N(R^a)S(=O)_2NR^aR^a$, —$NR^a(C_{2-6}$ alkyl$NR^aR^a$ and —$NR^a(C_{2-6})$alkyl$OR^a$; or $R^2$ is selected from $(C_{1-6})$alkyl, phenyl, benzyl, heteroaryl, heterocycle, —$(C_{1-3}$

alkyl)heteroaryl, —($C_{1-3}$ alkyl)heterocycle, —O($C_{1-3}$ alkyl)heteroaryl, —O(($C_{1-3}$)alkyl)heterocycle, —$NR^a$($C_{1-3}$ alkyl)heteroaryl, —$NR^a$($C_{1-3}$ alkyl)heterocycle, —($C_{1-3}$ alkyl)phenyl, —O($C_{1-3}$ alkyl)phenyl and —$NR^a$($C_{1-3}$ alkyl)phenyl all of which are substituted by 0, 1, 2 or 3 substituents selected from ($C_{1-4}$)haloalkyl, O($C_{1-4}$)alkyl, Br, Cl, F, I and ($C_{1-4}$)alkyl;

$R^3$ is selected from H, halo, ($C_{1-4}$)haloalkyl, cyano, nitro, —C(=O)$R^a$, —C(=O)O$R^a$, —C(=O)N$R^a$$R^a$, —C(=N$R^a$)N$R^a$$R^a$, —O$R^a$, —OC(=O)$R^a$, —OC(=O)N$R^a$$R^a$, —OC(=O)N($R^a$)S(=O)$_2$$R^a$, —O$C_{2-6}$)alkylN$R^a$$R^a$, —O$C_{2-6}$)alkylO$R^1$, —S$R^a$, —S(=O)$R^a$, —S(=O)$_2$$R^a$, —S(=O)$_2$N$R^a$$R^a$, —S(=O)$_2$N($R^a$)C(=O)$R^a$, —S(=O)$_2$N($R^a$)C(=O)O$R^a$, —S(=O)$_2$N($R^a$)C(=O)N$R^a$$R^a$, —N$R^a$$R^a$, —N($R^a$)C(=O)$R^a$, —N($R^a$)C(=O)O$R^a$, —N($R^a$)C(=O)N$R^a$$R^a$, —N($R^a$)C(=N$R^a$)N$R^a$$R^a$, —N($R^a$)S(=O)$_2$$R^a$, —N($R^a$)S(=O)$_2$N$R^a$$R^a$, —N$R^a$($C_{2-6}$)alkylN$R^a$$R^a$, —N$R^a$($C_{2-6}$)alkylO$R^a$, ($C_{1-6}$)alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the ($C_{1-6}$)alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from ($C_{1-6}$)haloalkyl, O($C_{1-6}$)alkyl, Br, Cl, F, I and ($C_{1-6}$)alkyl;

$R^5$ is, independently, in each instance, H, halo, ($C_{1-6}$)alkyl, ($C_{1-4}$)haloalkyl, or ($C_{1-6}$)alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, O($C_{1-4}$)alkyl, ($C_{1-4}$)alkyl, ($C_{1-3}$)haloalkyl, O($C_{1-4}$)alkyl, $NH_2$, NH$C_{1-4}$)alkyl, N($C_{1-4}$)alkyl($C_{1-4}$)alkyl; or both $R^5$ groups together form a $C_{3-6}$-spiroalkyl substituted by 0, 1, 2 or 3 substituents selected from halo, cyano, OH, O($C_{1-4}$)alkyl, ($C_{1-4}$)alkyl, ($C_{1-3}$)haloalkyl, O($C_{1-4}$)alkyl, $NH_2$, NH$C_{1-4}$)alkyl, N($C_{1-4}$)alkyl)$C_{1-4}$)alkyl;

$R^6$ is selected from H, halo, ($C_{1-6}$)alkyl, ($C_{1-4}$haloalkyl, cyano, nitro, —C(=O)$R^a$, —C(=O)O$R^a$, —C(=O)N$R^a$$R^a$, —C(=N$R^a$)N$R^a$$R^a$, —S(=O)$R^a$S(=O)$_2$$R^a$, —S(=O)$_2$N$R^a$$R^a$, —S(=O)$_2$N($R^a$)C(=O)$R^a$, —S(=O)$_2$N($R^a$)C(=O)O$R^a$, —S(=O)$_2$N($R^a$)C(=O)N$R^a$$R^a$;

$R^7$ is selected from H, halo, ($C_{1-6}$)alkyl, ($C_{1-4}$haloalkyl, cyano, nitro, —C(=O)$R^a$, —C(=O)O$R^a$, —C(=O)N$R^a$$R^a$, —C(=N$R^a$)N$R^a$$R^a$, —S(=O)$R^a$S(=O)$_2$$R^a$, —S(=O)$_2$N$R^a$$R^a$, —S(=O)$_2$N($R^a$)C(=O)$R^a$, —S(=O)$_2$N($R^a$)C(=O)O$R^a$, —S(=O)$_2$N($R^a$)C(=O)N$R^a$$R^a$;

$R^8$ is selected from H, ($C_{1-6}$)haloalkyl, Br, Cl, F, I, O$R^a$, N$R^a$$R^a$, ($C_{1-6}$)alkyl, phenyl,

benzyl, heteroaryl and heterocycle, wherein the $(C_{1-6})$alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from $(C_{1-6})$haloalkyl, $O(C_{1-6})$alkyl, Br, Cl, F, I and $(C_{1-6})$alkyl;

$R^9$ is selected from H, halo, $(C_{1-4})$haloalkyl, cyano, nitro, —$C(=O)R^a$, —$C(=O)OR^a$, —$C(=O)NR^aR^a$, —$C(=NR^a)NR^aR^a$, —$OR^a$, —$OC(=O)R^a$, —$OC(=O)NR^aR^a$, —$OC(=O)N(R^a)S(=O)_2R^a$, —$OC_{2-6})$alkyl$NR^aR^a$, —$OC_{2-6})$alkyl$OR^a$, —$SR^a$, —$S(=O)R^a$, —$S(=O)_2R^a$, —$S(=O)_2NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$, —$NR^aR^a$, —$N(R^a)C(=O)R^a$, —$N(R^a)C(=O)OR^a$, —$N(R^a)C(=O)NR^aR^a$, —$N(R^a)C(=NR^a)NR^aR^a$, —$N(R^a)S(=O)_2R^a$, —$N(R^a)S(=O)_2NR^aR^a$, —$NR^a(C_{2-6})$alkyl$OR^a$, $(C_{1-6})$alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the $(C_{1-6})$alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from halo, $(C_{1-4})$haloalkyl, cyano, nitro, —$C(=O)R^a$, —$C(=O)OR^a$, —$C(=O)NR^aR^a$, —$C(=NR^a)NR^aR^a$, —$OR^8$, —$OC(=O)R^8$, —$OC(=O)NR^2R^8$, —$OC(=O)N(R^a)S(=O)_2R^a$, —$OC_{2-6})$alkyl$NR^aR^a$, —$OC_{2-6})$alkyl$OR^a$, —$SR^a$, —$S(=O)R^a$, —$S(=O)_2R^8$, —$S(=O)_2NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$, —$NR^aR^a$, —$N(R^a)C(=O)R^a$, —$N(R^a)C(=O)OR^a$, —$N(R^a)C(=O)NR^aR^a$, —$N(R^a)C(=NR^a)NR^aR^a$, —$N(R^a)S(=O)_2R^a$, —$N(R^a)S(=O)_2NR^aR^a$, —$NR^a(C_{2-6})$alkyl$NR^aR^a$, —$NR^a(C_{2-6})$alkyl$OR^a$; or $R^9$ is a saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, $(C_{1-4})$haloalkyl, cyano, nitro, —$C(=O)R^a$, —$C(=O)OR^a$, —$C(=O)NR^aR^a$, —$C(=NR^a)NR^aR^a$, —$OR^a$, —$OC(=O)R^a$, —$OC(=O)NR^aR^a$, —$OC(=O)N(R^a)S(=O)_2R^a$, —$OC_{2-6})$alkyl$NR^aR^a$, —$OC_{2-6})$alkyl$OR^a$, —$SR^a$, —$S(=O)R^a$, —$S(=O)_2R^a$, —$S(=O)_2NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$, —$NR^aR^a$, —$N(R^a)C(=O)R^a$, —$N(R^a)C(=O)OR^a$, —$N(R^a)C(=O)NR^aR^a$, —$N(R^a)C(=NR^a)NR^aR^a$, —$N(R^a)S(=O)_2R^a$, —$N(R^a)S(=O)_2NR^aR^a$, —$NR^a(C_{2-6})$alkyl$NR^aR^a$ and —$NR^a(C_{2-6})$alkyl$OR^a$;

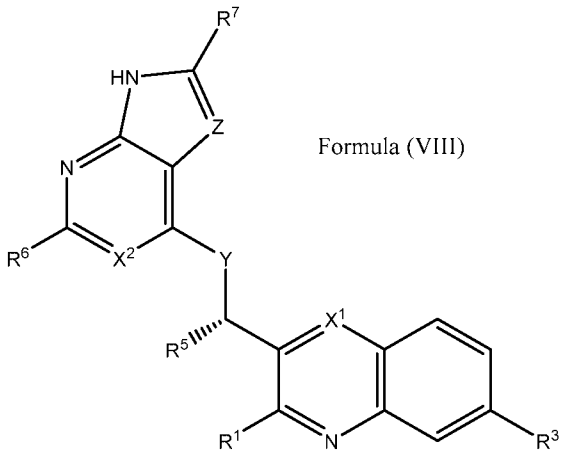
$R^{10}$ is H, ($C_{1-3}$ alkyl, ($C_{1-3}$)haloalkyl, cyano, nitro, $CO_2R^a$, $C(=O)NR^aR^a$, —$C(=NR^a)NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$, —$S(=O)R^b$, $S(=O)_2R^b$ or $S(=O)_2NR^aR^a$;

$R^{11}$ is H or ($C_{1-4}$)alkyl;

$R^a$ is independently, at each instance, H or $R^b$; and

$R^b$ is independently, at each instance, phenyl, benzyl or ($C_{1-6}$)alkyl, the phenyl, benzyl and ($C_{1-6}$)alkyl being substituted by 0, 1, 2 or 3 substituents selected from halo, ($C_{1-4}$)alkyl, ($C_{1-3}$)haloalkyl, —O($C_{1-4}$)alkyl, —$NH_2$, —NH$C_{1-4}$)alkyl, —N($C_{1-4}$)alkyl($C_{1-4}$)alkyl.

**[00450]** In another embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound of Formula (VIII):




Formula (VIII)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein:

$X^1$ is $C(R^9)$ or N;

$X^2$ is $C(R^{10})$ or N;

Y is $N(R^{11})$, O or S;

Z is $CR^8$ or N;

$R^1$ is a direct-bonded or oxygen-linked saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0 or 1 $R^2$ substituents, and the ring is additionally substituted by 0, 1, 2

or 3 substituents independently selected from halo, nitro, cyano, $(C_{1-4})$alkyl, $O(C_{1-4})$alkyl, $O(C_{1-4})$haloalkyl, $NH(C_{1-4})$alkyl, $N(C_{1-4}$ alkyl$)C_{1-4})$alkyl and $(C_{1-4})$haloalkyl;

$R^2$ is selected from halo, $(C_{1-4})$haloalkyl, cyano, nitro, —C(=O)$R^a$, —C(=O)$OR^a$, —C(=O)$NR^aR^a$—C(=$NR^a$)$NR^aR^a$, —$OR^a$, —OC(=O)$R^a$, —OC(=O)$NR^aR^a$, —OC(=O)N($R^a$)S(=O)$_2R^a$, —$OC_{2-6}$alkyl$OR^a$, —$SR^a$, —S(=O)$R^a$, —S(=O)$_2R^a$, —S(=O)$_2NR^aR^a$, —S(=O)$_2$N($R^a$)C(=O)$R^a$, —S(=O)$_2$N($R^a$)C(=O)$OR^a$, —S(=O)$_2$N($R^a$)C(=O)$NR^aR^a$, —$NR^aR^a$, —N($R^a$)C(=O)$R^a$, —N($R^a$)C(=O)$OR^a$, —N($R^a$)C(=O)$NR^aR^a$, —N($R^a$)C(=$NR^a$)$NR^aR^a$, —N($R^a$)S(=O)$_2R^a$, —N($R^a$)S(=O)$_2NR^aR^a$, —$NR^a$($C_{2-6}$ alkyl$NR^aR^a$ and —$NR^a$($C_{2-6}$alkyl$OR^a$; or $R^2$ is selected from ($C_{1-6}$alkyl, phenyl, benzyl, heteroaryl, heterocycle, —($C_{1-3}$ alkyl)heteroaryl, —($C_{1-3}$ alkyl)heterocycle, —O($C_{1-3}$ alkyl)heteroaryl, —O($C_{1-3}$ alkyl)heterocycle, —$NR^a$($C_{1-3}$ alkyl)heteroaryl, —$NR^a$($C_{1-3}$ alkyl)heterocycle, —($C_{1-3}$ alkyl)phenyl, —O($C_{1-3}$ alkyl)phenyl and —$NR^a$($C_{1-3}$ alkyl)phenyl all of which are substituted by 0, 1, 2 or 3 substituents selected from ($C_{1-4}$ haloalkyl, $O(C_{1-4})$alkyl, Br, Cl, F, I and $(C_{1-4})$alkyl;

$R^3$ is selected from H, halo, $(C_{1-4})$haloalkyl, cyano, nitro, —C(=O)$R^a$, —C(=O)$OR^a$, —C(=O)$NR^aR^a$—C(=$NR^a$)$NR^aR^a$, —$OR^a$, —OC(=O)$R^a$, —OC(=O)$NR^aR^a$, —OC(=O)N($R^a$)S(=O)$_2R^a$, —$OC_{2-6}$alkyl$OR^a$, —$SR^a$, —S(=O)$R^a$, —S(=O)$_2R^a$, —S(=O)$_2NR^aR^a$, —S(=O)$_2$N($R^a$)C(=O)$R^a$, —S(=O)$_2$N($R^a$)C(=O)$OR^a$, —S(=O)$_2$N($R^a$)C(=O)$NR^aR^a$, —$NR^aR^a$, —N($R^a$)C(=O)$R^a$, —N($R^a$)C(=O)$OR^a$, —N($R^a$)C(=O)$NR^aR^a$, —N($R^a$)C(=$NR^a$)$NR^aR^a$, —N($R^a$)S(=O)$_2R^a$, —N($R^a$)S(=O)$_2NR^aNR^a$, —$NR^a$, —$NR^a$($C_{2-6}$)alkyl$OR^a$, $(C_{1-6})$alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the $(C_{1-6})$alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from $(C_{1-6})$haloalkyl, $O(C_{1-6})$alkyl, Br, Cl, F, I and $(C_{1-6})$alkyl;

$R^5$ is, independently, in each instance, H, halo, $(C_{1-6})$alkyl, $(C_{1-4})$haloalkyl, or $(C_{1-6})$alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, $O(C_{1-4})$alkyl, $(C_{1-4})$alkyl, $(C_{1-3})$haloalkyl, $O(C_{1-4})$alkyl, $NH_2$, $NH(C_{1-4})$alkyl, $N(C_{1-4})$alkyl$(C_{1-4})$alkyl; or both $R^5$ groups together form a $C_{3-6}$-spiroalkyl substituted by 0, 1, 2 or 3 substituents selected from halo, cyano, OH, $O(C_{1-4})$alkyl, $(C_{1-4})$alkyl, $(C_{1-3})$haloalkyl, $O(C_{1-4})$alkyl, $NH_2$, $NH(C_{1-4})$alkyl, $N(C_{1-4})$alkyl$(C_{1-4})$alkyl;

$R^6$ is selected from H, halo, $(C_{1-6})$alkyl, $(C_{1-4})$haloalkyl, cyano, nitro, —C(=O)$R^a$, —C(=O)$OR^a$, —C(=O)$NR^aR^a$, —C(=$NR^a$)$NR^aR^a$, —S(=O)$R^a$, —$S(=O)_2R^a$, —$S(=O)_2NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$;

$R^7$ is selected from H, halo, $(C_{1-6})$alkyl, $(C_{1-4})$haloalkyl, cyano, nitro, —C(=O)$R^a$, —C(=O)$OR^a$, —C(=O)$NR^aR^a$, —C(=$NR^a$)$NR^aR^a$, —S(=O)$R^a$, —$S(=O)_2R^a$, —$S(=O)_2NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$;

$R^8$ is selected from H, $(C_{1-6})$haloalkyl, Br, Cl, F, I, $OR^a$, $NR^aR^a$, ($C_{1-6}$alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the $(C_{1-6})$alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from $(C_{1-6})$haloalkyl, $OC_{1-6}$ alkyl, Br, Cl, F, I and $(C_{1-6})$alkyl;

$R^9$ is selected from H, halo, $(C_{1-4})$haloalkyl, cyano, nitro, —C(=O)$R^a$, —C(=O)$OR^a$, —C(=O)$NR^aR^a$, —C(=$NR^a$)$NR^aR^a$, —$OR^a$, —OC(=O)$R^a$, —OC(=O)$NR^aR^a$, —OC(=O)$N(R^a)S(=O)_2R^a$, —$OC_{2-6}$alkyl$NR^aR^a$, —$OC_{2-6}$alkyl$OR^a$, —$SR^a$, —S(=O)$R^a$, —$S(=O)_2R^a$, —$S(=O)_2NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$, —$NR^aR^a$, —$N(R^a)C(=O)R^a$, —$N(R^a)C(=O)OR^a$, —$N(R^a)C(=O)NR^aR^a$, —$N(R^a)C(=NR^a)NR^aR^a$, —$N(R^a)S(=O)_2R^a$, —$N(R^a)S(=O)_2NR^aR^a$, —$NR^a(C_{2-6}$alkyl$NR^aR^a$, —$NR^a(C_{2-6}$alkyl$OR^a$, $(C_{1-6})$alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the $(C_{1-6})$alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from halo, $(C_{1-4})$haloalkyl, cyano, nitro, —C(=O)$R^a$, —C(=O)$OR^a$, —C(=O)$NR^aR^a$, —C(=$NR^a$)$NR^aR^a$, —$OR^a$, —OC(=O)$R^a$, OC(=O)$NR^aR^a$, —OC(=O)$N(R^a)S(=O)_2R^a$, —$OC_{2-6}$alkyl$OR^a$, —$SR^a$, —S(=O)$R^a$, —$S(=O)_2R^a$, —$S(=O)_2NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$, —$NR^aR^a$, —$N(R^a)C(=O)R^a$, —$N(R^a)C(=O)OR^a$, —$N(R^a)C(=O)NR^aR^a$, —$N(R^a)C(=NR^a)NR^aR^a$, —$N(R^a)S(=O)_2R^a$, —$N(R^a)S(=O)_2NR^aR^a$, —$NR^a(C_{2-6}$alkyl$NR^aR^a$, —$NR^a(C_{2-6}$alkyl$OR^a$; or $R^9$ is a saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1

or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, ($C_{1-4}$)haloalkyl, cyano, nitro, —$C(O)R^a$, —$C(=O)OR^a$, —$C(=O)NR^aR^a$, —$C(=NR^a)NR^aR^a$, —$OR^a$, —$OC(=O)R^a$, —$OC(=O)NR^aR^a$, —$OC(=O)N(R^a)S(=O)_2R^a$, —$OC_{2-6}$alkyl$NR^aR^a$, —$OC_{2-6}$alkyl$OR^a$, —$SR^a$, —$S(=O)R^a$, —$S(=O)_2R^a$, —$S(=O)_2NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$, —$NR^aR^a$, —$N(R^a)C(=O)R^a$, —$N(R^a)C(=O)OR^a$, —$N(R^a)C(=O)NR^aR^a$, —$N(R^a)C(=NR^a)NR^aR^a$, —$N(R^a)S(=O)_2R^a$, —$N(R^a)S(=O)_2NR^aR^a$, —$NR^a(C_{2-6}$ alkyl$NR^aR^a$ and —$NR^a(C_{2-6}$alkyl$OR^a$;

$R^{10}$ is H, ($C_{1-3}$ alkyl, ($C_{1-3}$)haloalkyl, cyano, nitro, $CO_2R^a$, $C(=O)NR^aR^a$, —$C(=NR^a)NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$, —$S(=O)R^b$, —$S(=O)_2R^b$ or $S(=O)_2NR^aR^a$;

$R^{11}$ is H or ($C_{1-4}$)alkyl;

$R^a$ is independently, at each instance, H or $R^b$; and

$R^b$ is independently, at each instance, phenyl, benzyl or ($C_{1-6}$)alkyl, the phenyl, benzyl and ($C_{1-6}$) alkyl being substituted by 0, 1, 2 or 3 substituents selected from halo, ($C_{1-4}$)alkyl, ($C_{1-3}$ haloalkyl, —$O(C_{1-4})$alkyl, —$NH_2$, —$NH(C_{1-4})$alkyl, —$N(C_{1-4})$alkyl($C_{1-4}$)alkyl.

**[00451]** In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound of Formula (VIII) wherein $X^1$ is $C(R^9)$ and $X^2$ is N.

**[00452]** In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound of Formula (VIII) wherein $X^1$ is $C(R^9)$ and $X^2$ is $C(R^{10})$.

**[00453]** In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound of Formula (VIII) wherein $R^1$ is phenyl substituted by 0, 1, 2, or 3 independently selected $R^2$ substituents.

**[00454]** In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound of Formula (VIII) wherein $R^1$ is phenyl.

**[00455]** In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound of Formula (VIII) wherein $R^1$ is selected from 2-methylphenyl, 2-chlorophenyl, 2-trifluoromethylphenyl, 2-fluorophenyl and 2-methoxyphenyl.

**[00456]** In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound of Formula (VIII) wherein $R^1$ is phenoxy.

**[00457]** In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound of Formula (VIII) wherein $R^1$ is a direct-bonded or oxygen-linked saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0 or 1 $R^2$ substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, $C_{1-4}$alkyl, $OC_{1-4}$alkyl, $OC_{1-4}$haloalkyl, $NHC_{1-4}$alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl and $C_{1-4}$haloalkyl.

**[00458]** In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound of Formula (VIII) wherein $R^1$ is an unsaturated 5- or 6-membered monocyclic ring containing 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the ring is substituted by 0 or 1 $R^2$ substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, $C_{1-4}$alkyl, $OC_{1-4}$alkyl, $OC_{1-4}$haloalkyl, $NHC_{1-4}$alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl and $C_{1-4}$haloalkyl.

**[00459]** In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound of Formula (VIII) wherein $R^1$ is an unsaturated 5- or 6-membered monocyclic ring containing 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the ring is substituted by 0 or 1 $R^2$ substituents, and the ring is additionally substituted by 1, 2 or 3 substituents independently selected from halo, nitro, cyano, $C_{1-4}$alkyl, $OC_{1-4}$alkyl, $OC_{1-4}$haloalkyl, $NHC_{1-4}$alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl and $C_{1-4}$haloalkyl.

**[00460]** In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound of Formula (VIII) wherein $R^1$ is an unsaturated 5- or 6-membered monocyclic ring containing 1, 2, 3 or 4 atoms selected from N, O and S.

**[00461]** In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound of Formula (VIII) wherein $R^1$ is selected from pyridyl and pyrimidinyl.

**[00462]** In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound of Formula (VIII) wherein $R^3$ is selected from halo, $C_{1-4}$haloalkyl, cyano, nitro, —$C(O)R^a$, —$C(=O)OR^a$, —$C(=O)NR^aR^a$, —$C(NR^a)NR^aR^a$, —$OR^a$, —$OC(=O)R^a$, —$OC(=O)NR^aR^a$, —$OC(=O)N(R^a)S(=O)_2R^a$, —$OC_{2-6}$alkyl$NR^aR^a$, —$OC_{2-6}$alkyl$OR^a$, —$SR^a$, —$S(=O)R^a$, —$S(=O)_2R^a$, —$S(=O)NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$, —$NR^aR^a$, —$N(R^a)C(=O)R^a$, —$N(R^a)C(=O)OR^a$, —$N(R^a)C(=O)NR^aR^a$, —$N(R^a)C(=NR^a)NR^aR^a$, —$N(R^a)S(=O)_2R^a$, —$N(R^a)S(=O)_2NR^aR^a$, —$NR^a(C_{2-6}$alkyl$NR^aR^a$, —$NR^a$, $C_{1-6}$alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the $C_{1-6}$alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from $C_{1-6}$)haloalkyl, $OC_{1-6}$alkyl, Br, Cl, F, I and $C_{1-6}$alkyl.

**[00463]** In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound of Formula (VIII) wherein $R^3$ is H.

**[00464]** In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound of Formula (VIII) wherein $R^3$ is selected from F, Cl, $C_{1-6}$alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the $C_{1-6}$alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from $C_{1-6}$)haloalkyl, $OC_{1-6}$alkyl, Br, Cl, F, I and $C_{1-6}$alkyl.

**[00465]** In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound of Formula (VIII)

wherein $R^5$ is, independently, in each instance, H, halo, $C_{1-6}$alkyl, $C_{1-4}$haloalkyl, or $C_{1-6}$alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, $OC_{1-4}$)alkyl, $C_{1-4}$)alkyl, $C_{1-3}$)haloalkyl, $OC_{1-4}$)alkyl, $NH_2$, $NHC_{1-4}$)alkyl, $N(C_{1-4}$)alkyl)$C_{1-4}$)alkyl; or both $R^5$ groups together form a $C_{3-6}$spiroalkyl substituted by 0, 1, 2 or 3 substituents selected from halo, cyano, OH, $OC_{1-4}$)alkyl, $C_{1-4}$)alkyl, $C_{1-3}$)haloalkyl, $OC_{1-4}$)alkyl, $NH_2$, $NHC_{1-4}$)alkyl, $N(C_{1-4}$)alkyl)$C_{1-4}$)alkyl.

**[00466]** In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound of Formula (VIII) wherein $R^5$ is H.

**[00467]** In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound of Formula (VIII) wherein one $R^5$ is S-methyl, the other is H.

**[00468]** In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound of Formula (VIII) wherein at least one $R^5$ is halo, $C_{1-6}$alkyl, $C_{1-4}$haloalkyl, or $C_{1-6}$alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, $OC_{1-4}$)alkyl, $C_{1-4}$)alkyl, $C_{1-3}$)haloalkyl, $OC_{1-4}$)alkyl, $NH_2$, $NHC_{1-4}$)alkyl, $N(C_{1-4}$)alkyl)$C_{1-4}$)alkyl.

**[00469]** In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound of Formula (VIII) wherein $R^6$ is H.

**[00470]** In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound of Formula (VIII) wherein $R^6$ is F, Cl, cyano or nitro.

**[00471]** In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound of Formula (VIII) wherein $R^7$ is H.

**[00472]** In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound of Formula (VIII) wherein $R^7$ is F, Cl, cyano or nitro.

**[00473]** In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound of Formula (VIII) wherein $R^8$ is selected from H, $CF_3$, $C_{1-3}$ alkyl, Br, Cl and F.

**[00474]** In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound of Formula (VIII) wherein $R^8$ is selected from H.

**[00475]** In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound of Formula (VIII) wherein $R^8$ is selected from $CF_3$, $C_{1-3}$ alkyl, Br, Cl and F.

**[00476]** In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound of Formula (VIII) wherein $R^9$ is H.

**[00477]** In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound of Formula (VIII) wherein $R^9$ is selected from halo, $C_{1-4}$haloalkyl, cyano, nitro, —$C(=O)R^a$, —$C(=O)OR^a$, —$C(=O)NR^aR^a$, —$C(=NR^a)NR^aR^a$, —$OR^a$, —$OC(=O)R^a$, —$OC(=O)NR^aR^a$, —$OC(=O)N(R^a)S(=O)_2R^a$, —$OC_{2-6}$alkyl$NR^aR^a$, —$OC_{2-6}$alkyl$OR^a$, —$SR^a$, —$S(=O)R^a$, —$S(=O)_2R^a$, —$S(=O)_2NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$, —$NR^aR^a$, —$N(R^a)C(=O)R^a$, —$N(R^a)C(=O)OR^a$, —$N(R^a)C(=O)NR^aR^a$, —$N(R^a)C(=NR^a)NR^aR^a$, —$N(R^a)S(=O)_2R^a$, —$N(R^a)S(=O)_2NR^aR^a$, —$NR^a(C_{2-6}$alkyl$NR^aR^a$, —$NR^a(C_{2-6}$alkyl$OR^a$, $C_{1-6}$alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the $C_{1-6}$alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from halo, $C_{1-4}$haloalkyl, cyano, nitro, —$C(=O)R^a$, —$C(=O)OR^a$, —$C(=O)NR^aR^a$, —$C(=NR^a)NR^aR^a$, —$OR^a$, —$OC(=O)R^a$, —$OC(=O)NR^aR^a$, —$OC(=O)N(R^a)S(=O)_2R^a$, —$OC_{2-6}$alkyl$OR^a$, —$SR^a$, —$S(=O)R^a$, —$S(=O)_2R^a$, —$S(=O)_2NR^aR^a$, —$S(=O)_2N(R^a)C(=O)R^a$, —$S(=O)_2N(R^a)C(=O)OR^a$, —$S(=O)_2N(R^a)C(=O)NR^aR^a$, —$NR^aR^a$, —$N(R^a)C(=O)R^a$, —$N(R^a)C(=O)OR^a$, —$N(R^a)C(=O)NR^aR^a$, —$N(R^a)C(=NR^a)NR^aR^a$, —$N(R^a)S(=O)_2R^a$, —$N(R^a)S(=O)_2NR^aR^a$, —$NR^a(C_{2-6}$alkyl$NR^aR^a$, —$NR^a(C_{2-6}$alkyl$OR^a$.

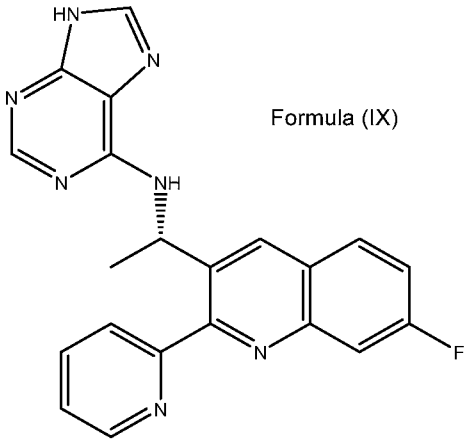
**[00478]** In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound of Formula (VIII) wherein $R^9$ is a saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, $C_{1-4}$haloalkyl, cyano, nitro, —C(=O)$R^a$, —C(=O)$OR^a$, —C(=O)$NR^aR^a$, —C(=$NR^a$)$NR^aR^a$, —$OR^a$, —OC(=O)$R^a$, —OC(=O)$NR^aR^a$, —OC(=O)N($R^a$)S(=O)$_2R^a$, —$OC_{2-6}$alkyl$NR^aR^a$, —$OC_{2-6}$alkyl$OR^a$, —$SR^a$, —S(=O)$R^a$, —S(=O)$_2R^a$, —S(=O)$_2NR^aR^a$, —S(=O)$_2$N($R^a$)C(=O)$R^a$, —S(=O)$_2$N($R^a$)C(=O)$OR^a$, —S(=O)$_2$N($R^a$)C(=O)$NR^aR^a$, —$NR^aR^a$, —N($R^a$)C(=O)$R^a$, —N($R^a$)C(=O)$OR^a$, —N($R^a$)C(=O)$NR^aR^a$, —N($R^a$)C(=$NR^a$)$NR^aR^a$, —N($R^a$)S(=O)$_2R^a$, —N($R^a$)S(=O)$_2NR^aR^a$, —$NR^a$($C_{2-6}$alkyl$NR^aR^a$ and —$NR^a$($C_{2-6}$alkyl$OR^a$.

**[00479]** In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound of Formula (VIII) wherein $R^{10}$ is H.

**[00480]** In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound of Formula (VIII) wherein $R^{10}$ is cyano, nitro, $CO_2R^a$, C(=O)$NR^aR^a$, —C(=$NR^a$)$NR^aR^a$, —S(=O)$_2$N($R^a$)C(=O)$R^a$, —S(=O)$_2$N($R^a$)C(=O)$OR^a$, —S(=O)$_2$N($R^a$)C(=O)$NR^aR^a$, S(=O)$R^b$, S(=O)$_2R^b$ or S(=O)$_2NR^aR^a$.

**[00481]** In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound of Formula (VIII) wherein $R^{11}$ is H.

**[00482]** In a preferred embodiment, the PI3K-δ inhibitor is a compound of Formula (IX):

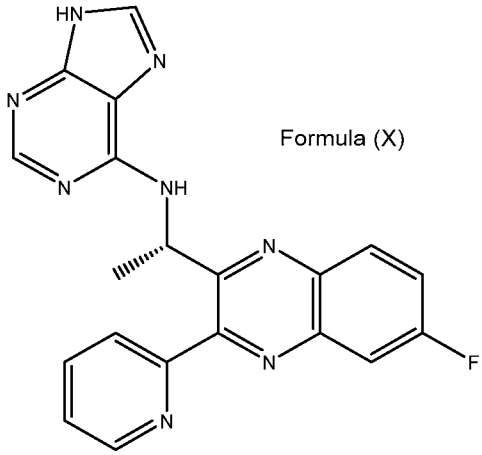


Formula (IX)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

**[00483]** In a preferred embodiment, the PI3K inhibitor or PI3K-δ inhibitor is (*S*)-*N*-(1-(7-fluoro-2-(pyridin-2-yl)quinolin-3-yl)ethyl)-9*H*-purin-6-amine or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

**[00484]** In a preferred embodiment, the PI3K-δ inhibitor is a compound of Formula (X):

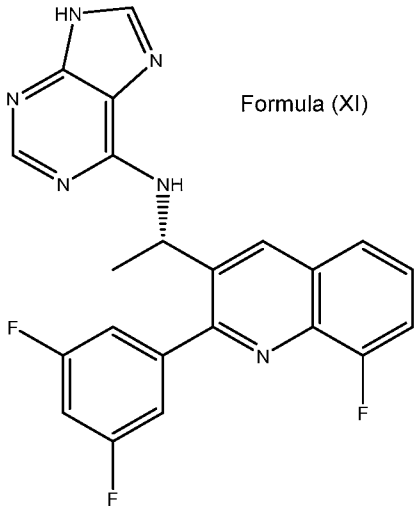


Formula (X)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

**[00485]** In a preferred embodiment, the PI3K inhibitor or PI3K-δ inhibitor is (*S*)-*N*-(1-(6-fluoro-3-(pyridin-2-yl)quinoxalin-2-yl)ethyl)-9*H*-purin-6-amine or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

**[00486]** In a preferred embodiment, the PI3K-δ inhibitor is a compound of Formula (XI):

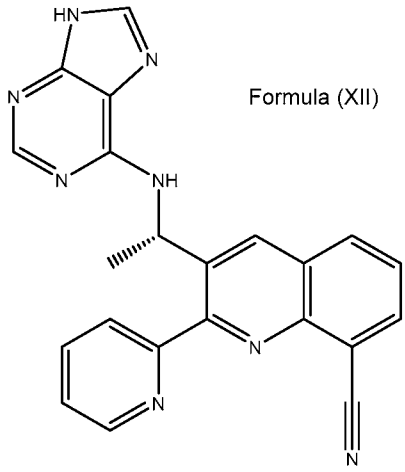



Formula (XI)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

**[00487]** In a preferred embodiment, the PI3K-δ inhibitor is (*S*)-*N*-(1-(2-(3,5-difluorophenyl)-8-fluoroquinolin-3-yl)ethyl)-9*H*-purin-6-amine or a pharmaceutically-acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

**[00488]** In a preferred embodiment, the PI3K-δ inhibitor is a compound of Formula (XII):

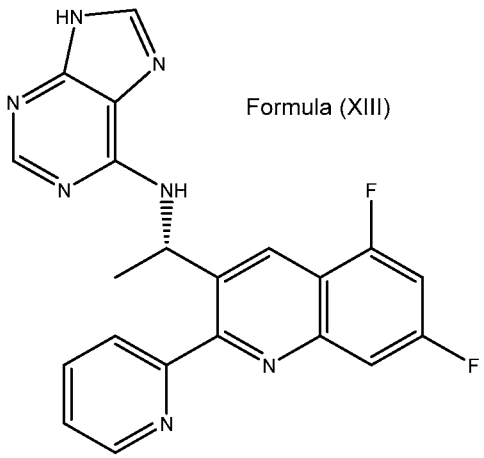



Formula (XII)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

**[00489]** In a preferred embodiment, the PI3K-δ inhibitor is (*S*)-3-(1-((9*H*-purin-6-yl)amino)ethyl)-2-(pyridin-2-yl)quinoline-8-carbonitrile or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

**[00490]** In a preferred embodiment, the PI3K-δ inhibitor is a compound of Formula (XIII):



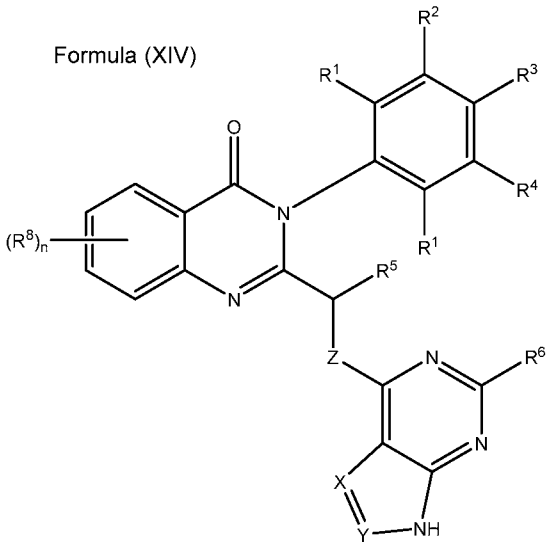

Formula (XIII)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof

**[00491]** In a preferred embodiment, the PI3K-δ inhibitor is (*S*)-*N*-(1-(5,7-difluoro-2-(pyridin-2-yl)quinolin-3-yl)ethyl)-9*H*-purin-6-amine or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

**[00492]** In an embodiment, the PI3K inhibitor or PI3K-δ inhibitor is a compound selected from the structures disclosed in U.S. Patent Nos. 7,932,260 and 8,207,153, the disclosure of which is incorporated by reference herein. In an embodiment, the PI3K inhibitor or PI3K-δ inhibitor is a compound of Formula (XIV):

Formula (XIV)




wherein

X and Y, independently, are N or CH;

Z is N—$R^7$ or O;

$R^1$ are the same and are hydrogen, halo, or $C_{1-3}$ alkyl;

$R^2$ and $R^3$, independently, are hydrogen, halo, or $C_{1-3}$ alkyl;

$R^4$ is hydrogen, halo, $OR^a$, CN, $C_{2-6}$alkynyl, $C(=O)R^a$, $C(=O)NR^aR^b$, $C_{3-6}$heterocycloalkyl, $C_{1-3}$ alkylene$C_{3-6}$heterocycloalkyl, $O(C_{1-3})$alkylene$OR^a$, $O(C_{1-3})$alkylene$NR^aR^b$, $O(C_{1-3})$alkylene$C_{3-6}$ cycloalkyl, $OC_{3-6}$heterocycloalkyl, $O(C_{1-3})$alkyleneC≡CH, or $O(C_{1-3})$alkylene$C(=O)NR^aR^b$;

$R^5$ is $(C_{1-3})$alkyl, $CH_2CF_3$, phenyl, $CH_2C{\equiv}CH$, $(C_{1-3})$alkylene$OR^e$, $(C_{1-4})$alkylene$NR^aR^b$, or $C_{1-4}$ alkyleneNHC(=O)$OR^a$,

$R^6$ is hydrogen, halo, or $NR^aR^b$;

$R^7$ is hydrogen or $R^5$ and $R^7$ are taken together with the atoms to which they are attached to form a five- or six-membered saturated ring;

$R^8$ is $C_{1-3}$ alkyl, halo, $CF_3$, or $CH_2C_{3-6}$heterocycloalkyl;

n is 0, 1, or 2;

$R^a$ is hydrogen, $(C_{1-4})$alkyl, or $CH_2C_6H_5$;

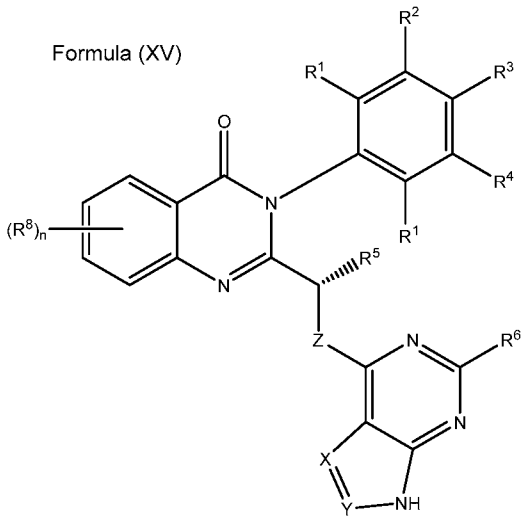
$R^b$ is hydrogen or $C_{1-3}$ alkyl; and

$R^c$ is hydrogen, $C_{1-3}$ alkyl, or halo,

wherein when the $R^1$ groups are different from hydrogen, $R^2$ and $R^4$ are the same; or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

**[00493]** In a preferred embodiment, the PI3K inhibitor or PI3K-δ inhibitor is an enantiomer of Formula (XIV), as shown in Formula (XV):

Formula (XV)



wherein X, Y, Z, $R^1$ through $R^8$, $R^a$, $R^b$, $R^c$, and n are as defined above for Formula (XIV).

**[00494]** In various embodiments exhibiting increased potency relative to other compounds, n = 1, 2, or 3 and $R^8$ is $C_{1-3}$alkyl, F, Cl, or $CF_3$. Alternatively, in such embodiments, n is 0 (such that there is no $R^8$ substituent).

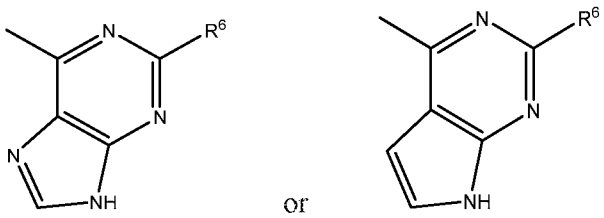
**[00495]** In further embodiments exhibiting increased potency, X is N and Y is CH. Alternatively, X and Y may also both be CH.

**[00496]** In further embodiments exhibiting increased potency, $R^6$ is hydrogen, halo, or $NH_2$. Preferably, $R^6$ is hydrogen.

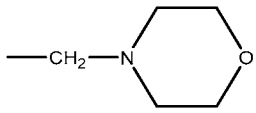
**[00497]** In preferred embodiments exhibiting increased potency, n is 0 or 1; $R^8$ (if n is 1) is $C_{1-3}$alkyl, F, Cl, or $CF_3$; $R^6$ is hydrogen; X is N and Y is CH or X and Y are both CH; Z is NH; $R^1$ are the same and are hydrogen, halo, or $C_{1-3}$alkyl; and $R^2$ and $R^3$, independently, are hydrogen, halo, or $C_{1-3}$alkyl. Preferably, $R^1$, $R^2$, and $R^3$ are hydrogen.

**[00498]** Unexpectedly, potency against PI3K-δ is conserved when $R^1$ is the same. In structural formulae (I) and (II), $R^2$ and $R^4$ may differ provided that $R^1$ is H. When $R^1$ is H, free rotation is unexpectedly permitted about the bond connecting the phenyl ring substituent to the quinazoline ring, and the compounds advantageously do not exhibit atropisomerism (i.e., multiple diasteromer formation is avoided). Alternatively, $R^2$ and $R^4$ can be the same such that the compounds advantageously do not exhibit atropisomerism.

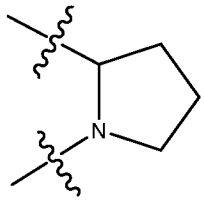
**[00499]** In preferred embodiments, Z is N—$R^7$, and the bicyclic ring system containing X and Y is:



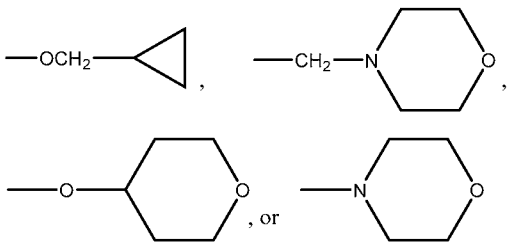
**[00500]** In other preferred embodiments of Formula (XIV) or Formula (XV), X, Y, Z, $R^a$, $R^b$, and $R^c$ are as defined above for Formula (XIV), and $R^1$ is hydrogen, fluoro, chloro, methyl, or



and $R^2$ is hydrogen, methyl, chloro, or fluoro; $R^3$ is hydrogen or fluoro; $R^6$ is $NH_2$, hydrogen, or fluoro; $R^7$ is hydrogen or $R^5$ and $R^7$ are taken together to form



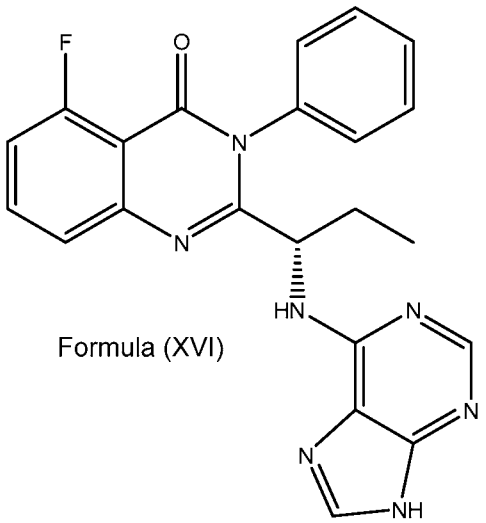
$R^8$ is methyl, trifluoromethyl, chloro, or fluoro; $R^4$ is hydrogen, fluoro, chloro, OH, $OCH_3$, $OCH_2C{\equiv}CH$, $O(CH_2)_2N(CH_3)_2$, $C(=O)CH_3$, $C{\equiv}CH$, CN, $C(=O)NH_2$, $OCH_2C(=O)NH_2$, $O(CH_2)_2OCH_3$, $O(CH_2)_2N(CH_3)_2$,



and $R^5$ is methyl, ethyl, propyl, phenyl, $CH_2OH$, $CH_2OCH_2C_6H_5$, $CH_2CF_3$, $CH_2OC(CH_3)_3$, $CH_2C{\equiv}CH$, $(CH_2)_3N(C_2H_5)_2$, $(CH_2)_3NH_2$, $(CH_2)_4NH_2$, $(CH_2)_3NHC(=O)OCH_2C_6H_5$, or $(CH_2)_4NHC(=O)OCH_2C_6H_5$; $R^c$ is hydrogen, methyl, fluoro, or bromo; and n is 0 or 1.

**[00501]** As used with respect to Formula (XIV) and Formula (XV), the term "alkyl" is defined as straight chained and branched hydrocarbon groups containing the indicated number of carbon atoms, e.g., methyl, ethyl, and straight chain and branched propyl and butyl groups. The terms "$(C_{1-3})$alkylene" and "$(C_{1-4})$alkylene" are defined as hydrocarbon groups containing the indicated number of carbon atoms and one less hydrogen than the corresponding alkyl group. The term "$(C_{2-6})$alkynyl" is defined as a hydrocarbon group containing the indicated number of carbon atoms and a carbon-carbon triple bond. The term "$(C_{3-6})$cycloalkyl" is defined as a cyclic hydrocarbon group containing the indicated number of carbon atoms. The term "$(C_{2-6})$heterocycloalkyl" is defined similarly as cycloalkyl except the ring contains one or two heteroatoms selected from the group consisting of O, $NR^a$, and S. The term "halo" is defined as fluoro, bromo, chloro, and iodo.

**[00502]** In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is idelalisib. In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is the compound of Formula (XVI):




Formula (XVI)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

**[00503]** In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is (*S*)-2-(1-((9*H*-purin-6-

yl)amino)propyl)-5-fluoro-3-phenylquinazolin-4(3*H*)-one or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

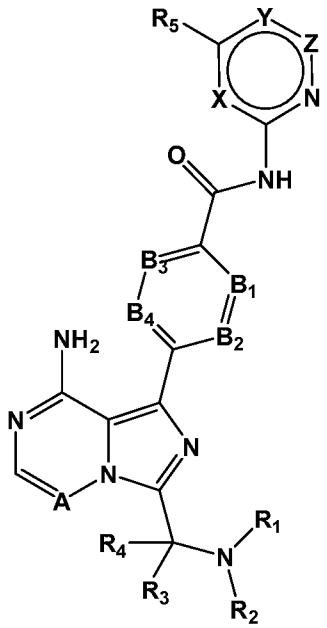
**[00504]** In an embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is 4(3*H*)-quinazolinone, 5-fluoro-3-phenyl-2-[(1*S*)-1-(9*H*-purin-6-ylamino)propyl]-5-fluoro-3-phenyl-2-{(1*S*)-1-[(7*H*-purin-6-yl)amino]propyl}quinazolin-4(3*H*)-one or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof

**[00505]** In an embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is GS-9901. Other PI3K inhibitors suitable for use in the described combination with a BTK inhibitor also include, but are not limited to, those described in, for example, U.S. Patent No. 8,193,182 and U.S. Published Application Nos. 2013/0267521; 2013/0053362; 2013/0029984; 2013/0029982; 2012/0184568; and 2012/0059000, the disclosures of each of which are incorporated by reference in their entireties.

BTK Inhibitors

**[00506]** The BTK inhibitor may be any BTK inhibitor known in the art. In particular, it is one of the BTK inhibitors described in more detail in the following paragraphs. For avoidance of doubt, references herein to a BTK inhibitor may refer to a compound or a pharmaceutically acceptable salt, ester, solvate, hydrate, cocrystal, or prodrug thereof.

**[00507]** In an embodiment, the BTK inhibitor is a compound of Formula (XVII):



Formula (XVII)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof,

wherein:

X is CH, N, O or S;

Y is $C(R_6)$, N, O or S;

Z is CH, N or bond;

A is CH or N;

$B_1$ is N or $C(R_7)$;

$B_2$ is N or $C(R_8)$;

$B_3$ is N or $C(R_9)$;

$B_4$ is N or $C(R_{10})$;

$R_1$ is $R_{11}C(=O)$, $R_{12}S(=O)$, $R_{13}S(=O)_2$ or $(C_{1-6})$alkyl optionally substituted with $R_{14}$;

$R_2$ is H, $(C_{1-3})$alkyl or $(C_{3-7})$cycloalkyl;

$R_3$ is H, $(C_{1-6})$alkyl or $(C_{3-7})$cycloalkyl); or

$R_2$ and $R_3$ form, together with the N and C atom they are attached to, a $(C_{3-7})$heterocycloalkyl optionally substituted with one or more fluorine, hydroxyl, $(C_{1-3})$alkyl, $(C_{1-3})$alkoxy or oxo;

$R_4$ is H or $(C_{1-3})$alkyl;

$R_5$ is H, halogen, cyano, $(C_{1-4})$alkyl, $(C_{1-3})$alkoxy, $(C_{3-6})$cycloalkyl, any alkyl group of

which is optionally substituted with one or more halogen; or $R_5$ is $(C_{6-10})$aryl or $(C_{2-6})$heterocycloalkyl;

$R_6$ is H or $(C_{1-3})$alkyl; or

$R_5$ and $R_6$ together may form a $(C_{3-7})$cycloalkenyl or $(C_{2-6})$heterocycloalkenyl, each optionally substituted with $(C_{1-3})$alkyl or one or more halogens;

$R_7$ is H, halogen, $CF_3$, $(C_{1-3})$alkyl or $(C_{1-3})$alkoxy;

$R_8$ is H, halogen, $CF_3$, $(C_{1-3})$alkyl or $(C_{1-3})$alkoxy; or

$R_7$ and $R_8$ together with the carbon atoms they are attached to, form $(C_{6-10})$aryl or $(C_{1-9})$heteroaryl;

$R_9$ is H, halogen, $(C_{1-3})$alkyl or $(C_{1-3})$alkoxy;

$R_{10}$ is H, halogen, $(C_{1-3})$alkyl or $(C_{1-3})$alkoxy;

$R_{11}$ is independently selected from the group consisting of $(C_{1-6})$alkyl, $(C_{2-6})$alkenyl and $(C_{2-6})$alkynyl, where each alkyl, alkenyl or alkynyl is optionally substituted with one or more substituents selected from the group consisting of hydroxyl, $(C_{1-4})$alkyl, $(C_{3-7})$cycloalkyl, [$(C_{1-4})$alkyl]amino, di[$(C_{1-4})$alkyl]amino, $(C_{1-3})$alkoxy, $(C_{3-7})$cycloalkoxy, $(C_{6-10})$aryl and $(C_{3-7})$heterocycloalkyl; or $R_{11}$ is $(C_{1-3})$alkyl-C(O)-S-$(C_{1-3})$alkyl; or

$R_{11}$ is $(C_{1-5})$heteroaryl optionally substituted with one or more substituents selected from the group consisting of halogen or cyano;

$R_{12}$ and $R_{13}$ are independently selected from the group consisting of $(C_{2-6})$alkenyl or $(C_{2-6})$alkynyl, both optionally substituted with one or more substituents selected from the group consisting of hydroxyl, $(C_{1-4})$alkyl, $(C_{3-7})$cycloalkyl, [$(C_{1-4})$alkyl]amino, di[$(C_{1-4})$alkyl]amino, $(C_{1-3})$alkoxy, $(C_{3-7})$cycloalkoxy, $(C_{6-10})$aryl and $(C_{3-7})$heterocycloalkyl; or a $(C_{1-5})$heteroaryl optionally substituted with one or more substituents selected from the group consisting of halogen and cyano; and

$R_{14}$ is independently selected from the group consisting of halogen, cyano, $(C_{2-6})$alkenyl and $(C_{2-6})$alkynyl, both optionally substituted with one or more substituents selected from the group consisting of hydroxyl, $(C_{1-4})$alkyl, $(C_{3-7})$cycloalkyl, $(C_{1-4})$alkylamino, di[$(C_{1-4})$alkyl]amino, $(C_{1-3})$alkoxy, $(C_{3-7})$cycloalkoxy, $(C_{6-10})$aryl, $(C_{1-5})$heteroaryl and $(C_{3-7})$heterocycloalkyl;

with the proviso that:

0 to 2 atoms of X, Y, Z can simultaneously be a heteroatom;

when one atom selected from X, Y is O or S, then Z is a bond and the other atom selected from X, Y can not be O or S;

when Z is C or N then Y is $C(R_6)$ or N and X is C or N;

0 to 2 atoms of $B_1$, $B_2$, $B_3$ and $B_4$ are N;

with the terms used having the following meanings:

$(C_{1-2})$alkyl means an alkyl group having 1 to 2 carbon atoms, being methyl or ethyl,

$(C_{1-3})$alkyl means a branched or unbranched alkyl group having 1-3 carbon atoms, being methyl, ethyl, propyl or isopropyl;

$(C_{1-4})$alkyl means a branched or unbranched alkyl group having 1-4 carbon atoms, being methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl, $(C_{1-3})$alkyl groups being preferred;

$(C_{1-5})$alkyl means a branched or unbranched alkyl group having 1-5 carbon atoms, for example methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl and isopentyl, $(C_{1-4})$alkyl groups being preferred. $(C_{1-6})$Alkyl means a branched or unbranched alkyl group having 1-6 carbon atoms, for example methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, n-pentyl and n-hexyl. $(C_{1-5})$alkyl groups are preferred, $(C_{1-4})$alkyl being most preferred;

$(C_{1-2})$alkoxy means an alkoxy group having 1-2 carbon atoms, the alkyl moiety having the same meaning as previously defined;

$(C_{1-3})$alkoxy means an alkoxy group having 1-3 carbon atoms, the alkyl moiety having the same meaning as previously defined. $(C_{1-2})$alkoxy groups are preferred;

$(C_{1-4})$alkoxy means an alkoxy group having 1-4 carbon atoms, the alkyl moiety having the same meaning as previously defined. $(C_{1-3})$alkoxy groups are preferred, $(C_{1-2})$alkoxy groups being most preferred;

$(C_{2-4})$alkenyl means a branched or unbranched alkenyl group having 2-4 carbon atoms, such as ethenyl, 2-propenyl, isobutenyl or 2-butenyl;

$(C_{2-6})$alkenyl means a branched or unbranched alkenyl group having 2-6 carbon atoms, such as ethenyl, 2-butenyl, and n-pentenyl, $(C_{2-4})$alkenyl groups being most preferred;

$(C_{2-4})$alkynyl means a branched or unbranched alkynyl group having 2-4 carbon atoms, such as ethynyl, 2-propynyl or 2-butynyl;

($C_{2-6}$)alkynyl means a branched or unbranched alkynyl group having 2-6 carbon atoms, such as ethynyl, propynyl, n-butynyl, n-pentynyl, isopentynyl, isohexynyl or n-hexynyl. ($C_{2-4}$)alkynyl groups are preferred; ($C_{3-6}$)cycloalkyl means a cycloalkyl group having 3-6 carbon atoms, being cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl;

($C_{3-7}$)cycloalkyl means a cycloalkyl group having 3-7 carbon atoms, being cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl;

($C_{2-6}$)heterocycloalkyl means a heterocycloalkyl group having 2-6 carbon atoms, preferably 3-5 carbon atoms, and one or two heteroatoms selected from N, O and/or S, which may be attached via a heteroatom if feasible, or a carbon atom; preferred heteroatoms are N or O; also preferred are piperidine, morpholine, pyrrolidine and piperazine; with the most preferred ($C_{2-6}$)heterocycloalkyl being pyrrolidine; the heterocycloalkyl group may be attached via a heteroatom if feasible;

($C_{3-7}$)heterocycloalkyl means a heterocycloalkyl group having 3-7 carbon atoms, preferably 3-5 carbon atoms, and one or two heteroatoms selected from N, O and/or S. Preferred heteroatoms are N or O; preferred ($C_{3-7}$) heterocycloalkyl groups are azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl; more preferred ($C_{3-7}$)heterocycloalkyl groups are piperidine, morpholine and pyrrolidine; and the heterocycloalkyl group may be attached via a heteroatom if feasible;

($C_{3-7}$)cycloalkoxy means a cycloalkyl group having 3-7 carbon atoms, with the same meaning as previously defined, attached via a ring carbon atom to an exocyclic oxygen atom;

($C_{6-10}$)aryl means an aromatic hydrocarbon group having 6-10 carbon atoms, such as phenyl, naphthyl, tetrahydronaphthyl or indenyl; the preferred ($C_{6-10}$)aryl group is phenyl;

($C_{1-5}$)heteroaryl means a substituted or unsubstituted aromatic group having 1-5 carbon atoms and 1-4 heteroatoms selected from N, O and/or S; the ($C_{1-5}$)heteroaryl may optionally be substituted; preferred ($C_{1-5}$)heteroaryl groups are tetrazolyl, imidazolyl, thiadiazolyl, pyridyl, pyrimidyl, triazinyl, thienyl or furyl, a more preferred ($C_{1-5}$)heteroaryl is pyrimidyl;

($C_{1-9}$)heteroaryl means a substituted or unsubstituted aromatic group having 1-9 carbon

atoms and 1-4 heteroatoms selected from N, O and/or S; the ($C_{1-9}$)heteroaryl may optionally be substituted; preferred ($C_{1-9}$)heteroaryl groups are quinoline, isoquinoline and indole;

[($C_{1-4}$)alkyl]amino means an amino group, monosubstituted with an alkyl group containing 1-4 carbon atoms having the same meaning as previously defined; preferred [($C_{1-4}$)alkyl]amino group is methylamino;

di[($C_{1-4}$)alkyl]amino means an amino group, disubstituted with alkyl group(s), each containing 1-4 carbon atoms and having the same meaning as previously defined; preferred di[($C_{1-4}$)alkyl]amino group is dimethylamino;

halogen means fluorine, chlorine, bromine or iodine;

($C_{1-3}$)alkyl-C(O)-S-($C_{1-3}$)alkyl means an alkyl-carbonyl-thio-alkyl group, each of the alkyl groups having 1 to 3 carbon atoms with the same meaning as previously defined;

($C_{3-7}$)cycloalkenyl means a cycloalkenyl group having 3-7 carbon atoms, preferably 5-7 carbon atoms; preferred ($C_{3-7}$)cycloalkenyl groups are cyclopentenyl or cyclohexenyl; cyclohexenyl groups are most preferred;

($C_{2-6}$)heterocycloalkenyl means a heterocycloalkenyl group having 2-6 carbon atoms, preferably 3-5 carbon atoms; and 1 heteroatom selected from N, O and/or S; preferred ($C_{2-6}$)heterocycloalkenyl groups are oxycyclohexenyl and azacyclohexenyl group.

In the above definitions with multifunctional groups, the attachment point is at the last group.

When, in the definition of a substituent, it is indicated that "all of the alkyl groups" of said substituent are optionally substituted, this also includes the alkyl moiety of an alkoxy group.

A circle in a ring of Formula (XVII) indicates that the ring is aromatic.

Depending on the ring formed, the nitrogen, if present in X or Y, may carry a hydrogen.

**[00508]** In a preferred embodiment, the BTK inhibitor is a compound of Formula (XVII) or a pharmaceutically acceptable salt thereof, wherein:

X is CH or S;

Y is C($R_6$);

Z is CH or bond;

A is CH;

$B_1$ is N or $C(R_7)$;

$B_2$ is N or $C(R_8)$;

$B_3$ is N or CH;

$B_4$ is N or CH;

$R_1$ is $R_{11}C(=O)$,

$R_2$ is $(C_{1-3})$alkyl;

$R_3$ is $(C_{1-3})$alkyl; or

$R_2$ and $R_3$ form, together with the N and C atom they are attached to, a $(C_{3-7})$heterocycloalkyl ring selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, and morpholinyl, optionally substituted with one or more fluorine, hydroxyl, $(C_{1-3})$alkyl, or $(C_{1-3})$alkoxy;

$R_4$ is H;

$R_5$ is H, halogen, cyano, $(C_{1-4})$alkyl, $(C_{1-3})$alkoxy, $(C_{3-6})$cycloalkyl, or an alkyl group which is optionally substituted with one or more halogen;

$R_6$ is H or $(C_{1-3})$alkyl;

$R_7$ is H, halogen or $(C_{1-3})$alkoxy;

$R_8$ is H or $(C_{1-3})$alkyl; or

$R_7$ and $R_8$ form, together with the carbon atom they are attached to a $(C_{6-10})$aryl or $(C_{1-9})$heteroaryl;

$R_5$ and $R_6$ together may form a $(C_{3-7})$cycloalkenyl or $(C_{2-6})$heterocycloalkenyl, each optionally substituted with $(C_{1-3})$alkyl or one or more halogen;

$R_{11}$ is independently selected from the group consisting of $(C_{2-6})$alkenyl and $(C_{2-6})$alkynyl, where each alkenyl or alkynyl is optionally substituted with one or more substituents selected from the group consisting of hydroxyl, $(C_{1-4})$alkyl, $(C_{3-7})$cycloalkyl, [$(C_{1-4})$alkyl]amino, di[$(C_{1-4})$alkyl]amino, $(C_{1-3})$alkoxy, $(C_{3-7})$cycloalkoxy, $(C_{6-10})$aryl and $(C_{3-7})$heterocycloalkyl;

with the proviso that 0 to 2 atoms of $B_1$, $B_2$, $B_3$ and $B_4$ are N.

**[00509]** In an embodiment of Formula (XVII), $B_1$ is $C(R_7)$; $B_2$ is $C(R_8)$; $B_3$ is $C(R_9)$; $B_4$ is $C(R_{10})$; $R_7$, $R_9$, and $R_{10}$ are each H; and $R_8$ is hydrogen or methyl.

**[00510]** In an embodiment of Formula (XVII), the ring containing X, Y and Z is selected from the group consisting of pyridyl, pyrimidyl, pyridazyl, triazinyl, thiazolyl, oxazolyl and isoxazolyl.

**[00511]** In an embodiment of Formula (XVII), the ring containing X, Y and Z is selected from the group consisting of pyridyl, pyrimidyl and pyridazyl.

**[00512]** In an embodiment of Formula (XVII), the ring containing X, Y and Z is selected from the group consisting of pyridyl and pyrimidyl.

**[00513]** In an embodiment of Formula (XVII), the ring containing X, Y and Z is pyridyl.

**[00514]** In an embodiment of Formula (XVII), $R_5$ is selected from the group consisting of hydrogen, fluorine, methyl, methoxy and trifluoromethyl.

**[00515]** In an embodiment of Formula (XVII), $R_5$ is hydrogen.

**[00516]** In an embodiment of Formula (XVII), $R_2$ and $R_3$ together form a heterocycloalkyl ring selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl and morpholinyl, optionally substituted with one or more of fluoro, hydroxyl, $(C_{1-3})$alkyl and $(C_{1-3})$alkoxy.

**[00517]** In an embodiment of Formula (XVII), $R_2$ and $R_3$ together form a heterocycloalkyl ring selected from the group consisting of azetidinyl, pyrrolidinyl and piperidinyl.

**[00518]** In an embodiment of Formula (XVII), $R_2$ and $R_3$ together form a pyrrolidinyl ring.

**[00519]** In an embodiment of Formula (XVII), $R_1$ is independently selected from the group consisting of $(C_{1-6})$alkyl, $(C_{2-6})$alkenyl or $(C_{2-6})$alkynyl, each optionally substituted with one or more substituents selected from the group consisting of hydroxyl, $(C_{1-4})$alkyl, $(C_{3-7})$cycloalkyl, [$(C_{1-4})$alkyl]amino, di[$(C_{1-4})$alkyl] amino, $(C_{1-3})$alkoxy, $(C_{3-7})$cycloalkoxy, $(C_{6-10})$aryl and $(C_{3-7})$heterocycloalkyl.

**[00520]** In an embodiment of Formula (XVII), $B_1$, $B_2$, $B_3$ and $B_4$ are CH; X is N; Y and Z are CH; $R_5$ is $CH_3$; A is N; $R_2$, $R_3$ and $R_4$ are H; and $R_1$ is CO-$CH_3$.

**[00521]** In an embodiment of Formula (XVII), $B_1$, $B_2$, $B_3$ and $B_4$ are CH; X and Y are N; Z is CH; $R_5$ is $CH_3$; A is N; $R_2$, $R_3$ and $R_4$ are H; and $R_1$ is CO-$CH_3$.

**[00522]** In an embodiment of Formula (XVII), $B_1$, $B_2$, $B_3$ and $B_4$ are CH; X and Y are N; Z is CH; $R_5$ is $CH_3$; A is CH; $R_2$ and $R_3$ together form a piperidinyl ring; $R_4$ is H; and $R_1$ is CO-ethenyl.

**[00523]** In an embodiment of Formula (XVII), $B_1$, $B_2$, $B_3$ and $B_4$ are CH; X, Y and Z are CH; $R_5$ is H; A is CH; $R_2$ and $R_3$ together form a pyrrolidinyl ring; $R_4$ is H; and $R_1$ is CO-propynyl.

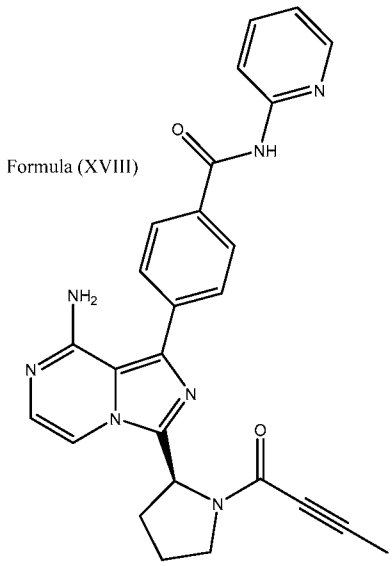
**[00524]** In an embodiment of Formula (XVII), $B_1$, $B_2$, $B_3$ and $B_4$ are CH; X, Y and Z are CH; $R_5$ is $CH_3$; A is CH; $R_2$ and $R_3$ together form a piperidinyl ring; $R_4$ is H; and $R_1$ is CO-propynyl.

**[00525]** In an embodiment of Formula (XVII), $B_1$, $B_2$, $B_3$ and $B_4$ are CH; X and Y are N; Z is CH; $R_5$ is H; A is CH; $R_2$ and $R_3$ together form a morpholinyl ring; $R_4$ is H; and $R_1$ is CO-ethenyl.

**[00526]** In an embodiment of Formula (XVII), $B_1$, $B_2$, $B_3$ and $B_4$ are CH; X and Y are N; Z is CH; $R_5$ is $CH_3$; A is CH; $R_2$ and $R_3$ together form a morpholinyl ring; $R_4$ is H; and $R_1$ is CO-propynyl.

**[00527]** In a preferred embodiment, the BTK inhibitor is a compound of Formula (XVIII):

Formula (XVIII)



or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of this compound is described in International Patent Application Publication No. WO 2013/010868 and U.S. Patent Application Publication No. US 2014/0155385 A1, the disclosures of which are incorporated herein by reference. In brief, Formula (XVIII) and related compounds, such as those according to Formula (XVII), may be prepared as follows.

**[00528]** (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide was made from (*S*)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide and 2-butynoic acid as follows. To a solution of (*S*)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide (19.7 mg, 0.049 mmol), triethylamine (20 mg, 0.197 mmol, 0.027 mL) 2-butynoic acid (4.12 mg, 0.049 mmol) in dichloromethane (2 mL) was added HATU (18.75 mg, 0.049 mmol). The mixture was stirred for 30 min at room temperature. The mixture was washed with water dried over magnesium sulfate and concentrated in vacuo. The residue was purified by preparative HPLC. Fractions containing product were collected and reduced to dryness to afford the title compound (10.5 mg, 18.0%).

**[00529]** (*S*)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide was prepared from the following intermediary compounds.

**[00530]** (a). (3-Chloropyrazin-2-yl)methanamine hydrochloride was prepared as follows. To a solution of 3-chloropyrazine-2-carbonitrile (160 g, 1 .147 mol) in acetic acid (1.5 L)

was added Raney Nickel (50% slurry in water, 70 g, 409 mmol). The resulting mixture was stirred under 4 bar hydrogen at room temperature overnight. Raney Nickel was removed by filtration over decalite and the filtrate was concentrated under reduced pressure and co-evaporated with toluene. The remaining brown solid was dissolved in ethyl acetate at 50°C and cooled on an ice-bath. 2M hydrogen chloride solution in diethyl ether (1 .14 L) was added in 30 min. The mixture was allowed to stir at room temperature over weekend. The crystals were collected by filtration, washed with diethyl ether and dried under reduced pressure at 40°C. The product brown solid obtained was dissolved in methanol at 60°C. The mixture was filtered and partially concentrated, cooled to room temperature and diethyl ether (1000 ml) was added. The mixture was allowed to stir at room temperature overnight. The solids formed were collected by filtration, washed with diethyl ether and dried under reduced pressure at 40°C to give 153.5 g of (3-chloropyrazin-2-yl)methanamine.hydrochloride as a brown solid (74.4 %, content 77 %).

**[00531]** (b). (*S*)-benzyl 2-((3-chloropyrazin-2-yl)methylcarbamoyl)pyrrolidine-1-carboxylate was prepared as follows. To a solution of (3-chloropyrazin-2-yl)methanamine HCl (9.57 g, 21.26 mmol, 40% wt) and Z-Pro-OH (5.3 g, 21.26 mmol) in dichloromethane (250 mL) was added triethylamine (11.85 mL, 85 mmol) and the reaction mixture was cooled to 0°C. After 15 min stirring at 0°C, HATU (8.49 g, 22.33 mmol) was added. The mixture was stirred for 1 hour at 0°C and then overnight at room temperature. The mixture was washed with 0.1 M HCl-solution, 5% NaHC03, water and brine, dried over sodium sulfate and concentrated in vacuo. The product was purified using silica gel chromatography (heptane/ethyl acetate = 1/4 v/v%) to give 5 g of (S)-benzyl 2-((3-chloropyrazin-2-yl)methylcarbamoyl)pyrrolidine-1-carboxylate (62.7%).

**[00532]** (c). (*S*)-Benzyl 2-(8-chloroimidazo[1,5-*a*]pyrazin-3-yl)pyrrolidine-1-carboxylate was prepared as follows. (*S*)-Benzyl 2-((3-chloropyrazin-2-yl)methylcarbamoyl)pyrrolidine-1-carboxylate (20.94 mmol, 7.85 g) was dissolved in acetonitrile (75 ml), 1 ,3-dimethyl-2-imidazolidinone (62.8 mmol, 6.9 ml, 7.17 g) was added and the reaction mixture was cooled to 0°C before POCl3 (84 mmol, 7.81 ml, 12.84 g) was added drop wise while the temperature remained around 5°C. The reaction mixture was refluxed at 60-65°C overnight. The reaction mixture was poured carefully in

ammonium hydroxide 25% in water (250 ml)/crushed ice (500 ml) to give a yellow suspension (pH ~8-9) which was stirred for 15 min until no ice was present in the suspension. Ethyl acetate was added, layers were separated and the aqueous layer was extracted with ethyl acetate (3x). The organic layers were combined and washed with brine, dried over sodium sulfate, filtered and evaporated to give 7.5 g crude product. The crude product was purified using silica gel chromatography (heptane/ethyl acetate = 1/4 v/v%) to give 6.6 g of (S)-benzyl 2-(8- chloroimidazo[1 ,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (88%).

**[00533]** (d). (S)-Benzyl 2-(1-bromo-8-chloroimidazo[1 ,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate was prepared as follows. N-Bromosuccinimide (24.69 mmol, 4.4 g) was added to a stirred solution of (S)-benzyl 2-(8- chloroimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (24.94 mmol, 8.9 g) in DMF (145 mL). The reaction was stirred 3 h at rt. The mixture was poored (slowly) in a stirred mixture of water (145 mL), ethyl acetate (145 mL) and brine (145 mL). The mixture was then transferred into a separating funnel and extracted. The water layer was extracted with 2x145 mL ethyl acetate. The combined organic layers were washed with 3x300 mL water, 300 mL brine, dried over sodium sulfate, filtered and evaporated. The product was purified using silica gel chromatography (ethyl acetate/heptane = 3/1 v/v%) to give 8.95 g of (S)-benzyl 2-(1-bromo-8-chloroimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (82.3%).

**[00534]** (e). (*S*)-Benzyl 2-(8-amino-1-bromoimidazo[1 ,5-*a*]pyrazin-3-yl)pyrrolidine-1-carboxylate was prepared as follows. (S)-Benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (20.54 mmol, 8.95 g) was suspended in 2-propanol (113 ml) in a pressure vessel. 2-propanol (50 ml) was cooled to -78°C in a pre-weighed flask (with stopper and stirring bar) and ammonia gas (646 mmol, 11 g) was lead through for 15 minutes. The resulting solution was added to the suspension in the pressure vessel. The vessel was closed and stirred at room temperature and a slight increase in pressure was observed. Then the suspension was heated to 110 °C which resulted in an increased pressure to 4.5 bar. The clear solution was stirred at 1 10 °C, 4.5 bar overnight. After 18h the pressure remained 4 bar. The reaction mixture was concentrated in vacuum, the residue was suspended in ethyl acetate and subsequent washed with water. The layers were separated and the aqueous layer was extracted with

ethyl acetate. The combined organic layers were washed with water, saturated sodium chloride solution, dried over sodium sulfate and concentrated to give 7.35 g of (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (86%).

**[00535]** (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide was prepared as follows.

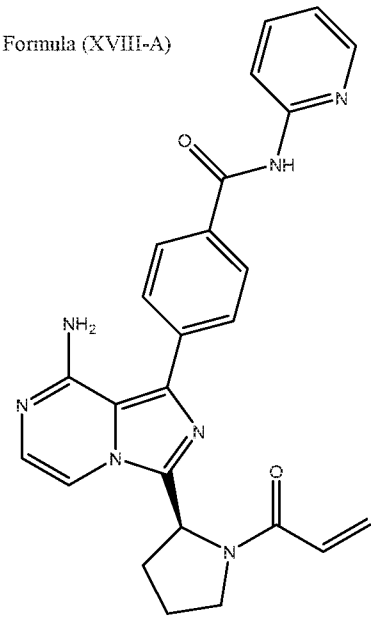
**[00536]** (a). (S)-benzyl 2-(8-amino-1-(4-(pyridin-2-ylcarbamoyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate was prepared as follows. (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (0.237 mmol, 98.5 mg) and 4-(pyridin-2-yl-aminocarbonyl)benzeneboronic acid (0.260 mmol, 63.0 mg) were suspended in a mixture of 2N aqueous potassium carbonate solution (2.37 mmol, 1.18 mL) and dioxane (2.96 mL). Nitrogen was bubbled through the mixture, followed by the addition of 1,1'-bis(diphenylphosphino)ferrocene palladium (ii) chloride (0.059 mmol, 47.8 mg). The reaction mixture was heated for 20 minutes at 140°C in the microwave. Water was added to the reaction mixture, followed by an extraction with ethyl acetate (2x). The combined organic layer was washed with brine, dried over magnesium sulfate and evaporated. The product was purified using silicagel and dichloromethane/methanol = 9/1 v/v% as eluent to afford 97.1 mg of (S)-benzyl 2-(8-amino-1-(4-(pyridin-2-ylcarbamoyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (77%).

**[00537]** (b). (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-alpyrazin-1-yl)-N-(pyridin-2-yl)benzamide was prepared as follows. To (S)-benzyl 2-(8-amino-1-(4-(pyridin-2-ylcarbamoyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1- carboxylate (0.146 mmol, 78 mg) was added a 33% hydrobromic acid/acetic acid solution (1 1.26 mmol, 2 ml) and the mixture was left at room temperature for 1 hour. The mixture was diluted with water and extracted with dichloromethane. The aqueous phase was neutralized using 2N sodium hydroxide solution, and then extracted with dichloromethane. the organic layer was dried over magnesium sulfate, filtered and evaporated to give 34 mg of (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide (58%).

**[00538]** In a preferred embodiment, the BTK inhibitor is (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide or pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug therof.

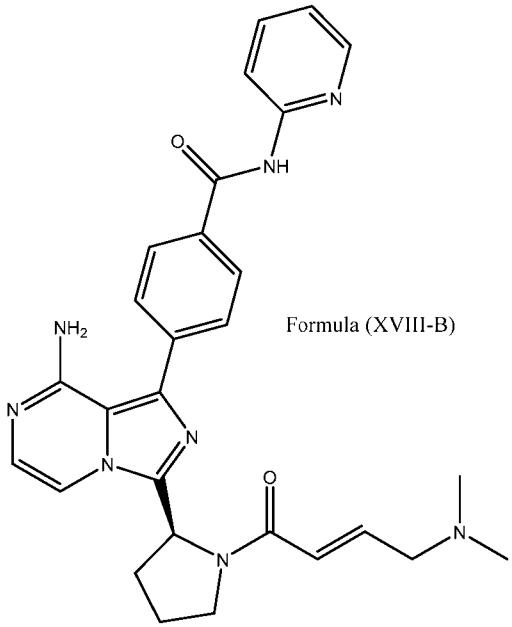
**[00539]** In a preferred embodiment, the BTK inhibitor is a compound of Formula (XVIII-A):

Formula (XVIII-A)




or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of this compound is described in International Patent Application Publication No. WO 2013/010868 and U.S. Patent Application Publication No. US 2014/0155385 A1, the disclosures of which are incorporated herein by reference.

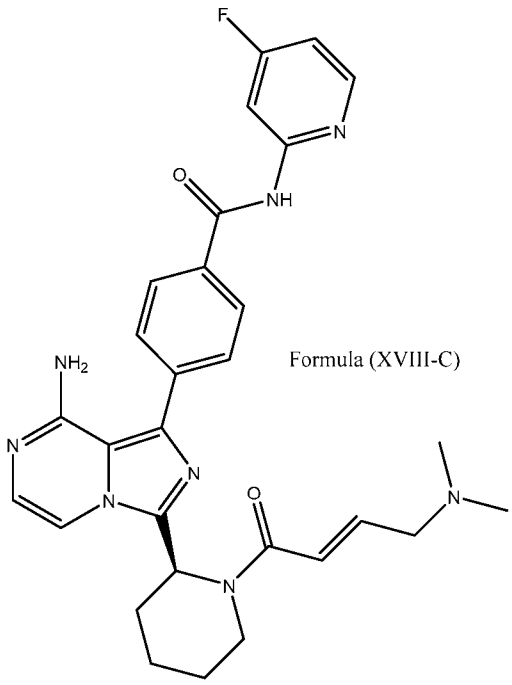
**[00540]** In a preferred embodiment, the BTK inhibitor is a compound of Formula (XVIII-B):



Formula (XVIII-B)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of this compound is described in International Patent Application Publication No. WO 2013/010868 and U.S. Patent Application Publication No. US 2014/0155385 A1, the disclosures of which are incorporated herein by reference.

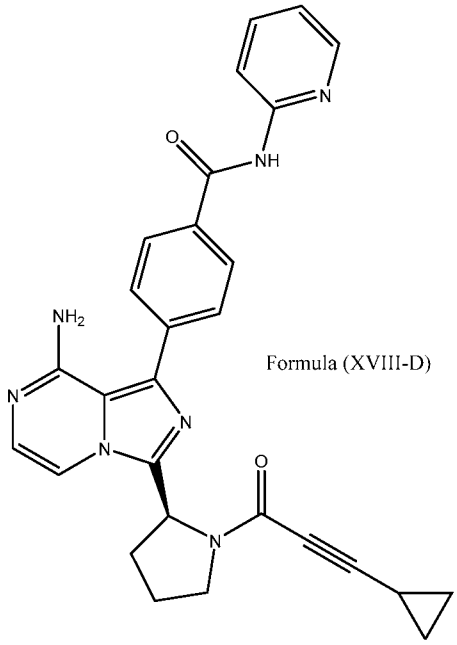
**[00541]** In a preferred embodiment, the BTK inhibitor is a compound of Formula (XVIII-C):



Formula (XVIII-C)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of this compound is described in International Patent Application Publication No. WO 2013/010868 and U.S. Patent Application Publication No. US 2014/0155385 A1, the disclosures of which are incorporated herein by reference.

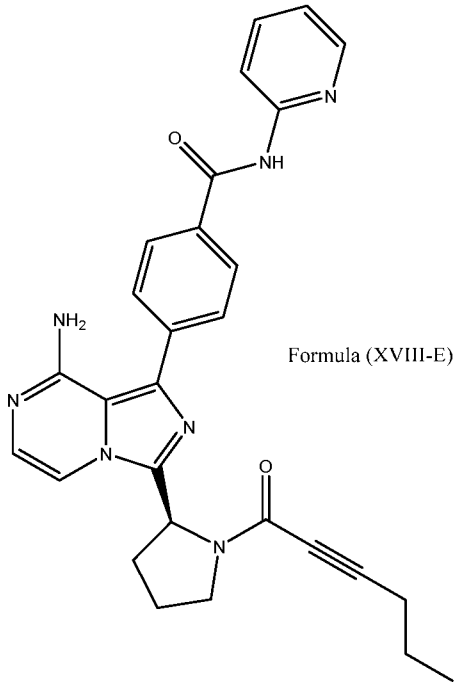
**[00542]** In a preferred embodiment, the BTK inhibitor is a compound of Formula (XVIII-D):



Formula (XVIII-D)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of this compound is described in International Patent Application Publication No. WO 2013/010868 and U.S. Patent Application Publication No. US 2014/0155385 A1, the disclosures of which are incorporated herein by reference.

**[00543]** In a preferred embodiment, the BTK inhibitor is a compound of Formula (XVIII-E):

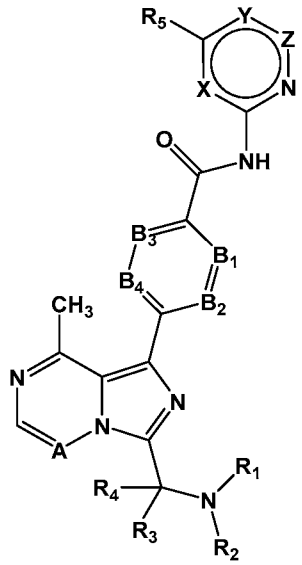


Formula (XVIII-E)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of this compound is described in International Patent Application Publication No. WO 2013/010868 and U.S. Patent Application Publication No. US 2014/0155385 A1, the disclosures of which are incorporated herein by reference.

**[00544]** In other embodiments, the BTK inhibitors include, but are not limited to, those compounds described in International Patent Application Publication No. WO 2013/010868 and U.S. Patent Application Publication No. US 2014/0155385 A1, the disclosures of each of which are specifically incorporated by reference herein.

**[00545]** In an embodiment, the BTK inhibitor is a compound of Formula (XIX) :



Formula (XIX)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof,

wherein:

X is CH, N, O or S;

Y is $C(R_6)$, N, O or S;

Z is CH, N or bond;

A is CH or N;

$B_1$ is N or $C(R_7)$;

$B_2$ is N or $C(R_8)$;

$B_3$ is N or $C(R_9)$;

$B_4$ is N or $C(R_{10})$;

$R_1$ is $R_{11}C(O)$, $R_{12}S(O)$, $R_{13}SO_2$ or $(C_{1-6})$alkyl optionally substituted with $R_{14}$;

$R_2$ is H, $(C_{1-3})$alkyl or $(C_{3-7})$cycloalkyl;

$R_3$ is H, $(C_{1-6})$alkyl or $(C_{3-7})$cycloalkyl); or

$R_2$ and $R_3$ form, together with the N and C atom they are attached to, a $(C_{3-7})$heterocycloalkyl optionally substituted with one or more fluorine, hydroxyl, $(C_{1-3})$alkyl, $(C_{1-3})$alkoxy or oxo;

$R_4$ is H or $(C_{1-3})$alkyl;

$R_5$ is H, halogen, cyano, $(C_{1-4})$alkyl, $(C_{1-3})$alkoxy, $(C_{3-6})$cycloalkyl; all alkyl groups of R5 are optionally substituted with one or more halogen; or $R_5$ is $(C_{6-10})$aryl or $(C_{2-}$

$_6$)heterocycloalkyl;

$R_6$ is H or ($C_{1-3}$)alkyl; or $R_5$ and $R_6$ together may form a ($C_{3-7}$)cycloalkenyl, or ($C_{2-6}$)heterocycloalkenyl; each optionally substituted with ($C_{1-3}$)alkyl, or one or more halogen;

$R_7$ is H, halogen, $CF_3$, ($C_{1-3}$)alkyl or ($C_{1-3}$)alkoxy;

$R_8$ is H, halogen, $CF_3$, ($C_{1-3}$)alkyl or ($C_{1-3}$)alkoxy; or

$R_7$ and $R_8$ together with the carbon atoms they are attached to, form ($C_{6-10}$)aryl or ($C_{1-5}$)heteroaryl;

$R_9$ is H, halogen, ($C_{1-3}$)alkyl or ($C_{1-3}$)alkoxy;

$R_{10}$ is H, halogen, ($C_{1-3}$)alkyl or ($C_{1-3}$)alkoxy;

$R_{11}$ is independently selected from a group consisting of ($C_{1-6}$)alkyl, ($C_{2-6}$)alkenyl and ($C_{2-6}$)alkynyl each alkyl, alkenyl or alkynyl optionally substituted with one or more groups selected from hydroxyl, ($C_{1-4}$)alkyl, ($C_{3-7}$)cycloalkyl, [($C_{1-4}$)alkyl]amino, di[($C_{1-4}$)alkyl]amino, ($C_{1-3}$)alkoxy, ($C_{3-7}$)cycloalkoxy, ($C_{6-10}$)aryl or ($C_{3-7}$)heterocycloalkyl, or

$R_{11}$ is ($C_{1-3}$)alkyl-C(O)-S-($C_{1-3}$)alkyl; or

$R_{11}$ is ($C_{1-5}$)heteroaryl optionally substituted with one or more groups selected from halogen or cyano.

$R_{12}$ and $R_{13}$ are independently selected from a group consisting of ($C_{2-6}$)alkenyl or ($C_{2-6}$)alkynyl both optionally substituted with one or more groups selected from hydroxyl, ($C_{1-4}$)alkyl, ($C_{3-7}$)cycloalkyl, [($C_{1-4}$)alkyl]amino, di[($C_{1-4}$)alkyl]amino, ($C_{1-3}$)alkoxy, ($C_{3-7}$)cycloalkoxy, ($C_{6-10}$)aryl, or ($C_{3-7}$)heterocycloalkyl; or

($C_{1-5}$)heteroaryl optionally substituted with one or more groups selected from halogen or cyano;

$R_{14}$ is independently selected from a group consisting of halogen, cyano or ($C_{2-6}$)alkenyl or ($C_{2-6}$)alkynyl both optionally substituted with one or more groups selected from hydroxyl, ($C_{1-4}$)alkyl, ($C_{3-7}$)cycloalkyl, [($C_{1-4}$)alkyl]amino, di[($C_{1-4}$)alkyl]amino, ($C_{1-3}$)alkoxy, ($C_{3-7}$)cycloalkoxy, ($C_{6-10}$)aryl, ($C_{1-5}$)heteroaryl or ($C_{3-7}$)heterocycloalkyl;

with the proviso that

- 0 to 2 atoms of X, Y, Z can simultaneously be a heteroatom;
- when one atom selected from X, Y is O or S, then Z is a bond and the other atom

selected from

X, Y can not be O or S;

- when Z is C or N then Y is $C(R_6)$ or N and X is C or N;

- 0 to 2 atoms of $B_1$, $B_2$, $B_3$ and $B_4$ are N;

with the terms used having the following meanings:

$(C_{1-3})$alkyl means a branched or unbranched alkyl group having 1-3 carbon atoms, being methyl, ethyl, propyl or isopropyl;

$(C_{1-4})$alkyl means a branched or unbranched alkyl group having 1-4 carbon atoms, being methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl, $(C_{1-3})$alkyl groups being preferred;

$(C_{1-6})$alkyl means a branched or unbranched alkyl group having 1-6 carbon atoms, for example methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, n-pentyl and n-hexyl. $(C_{1-5})$alkyl groups are preferred, $(C_{1-4})$alkyl being most preferred;

$(C_{1-2})$alkoxy means an alkoxy group having 1-2 carbon atoms, the alkyl moiety having the same meaning as previously defined;

$(C_{1-3})$alkoxy means an alkoxy group having 1-3 carbon atoms, the alkyl moiety having the same meaning as previously defined, with $(C_{1-2})$alkoxy groups preferred;

$(C_{2-3})$alkenyl means an alkenyl group having 2-3 carbon atoms, such as ethenyl or 2-propenyl;

$(C_{2-4})$alkenyl means a branched or unbranched alkenyl group having 2-4 carbon atoms, such as ethenyl, 2-propenyl, isobutenyl or 2-butenyl;

$(C_{2-6})$alkenyl means a branched or unbranched alkenyl group having 2-6 carbon atoms, such as ethenyl, 2-butenyl, and n-pentenyl, with $(C_{2-4})$alkenyl groups preferred, and $(C_{2-3})$alkenyl groups even more preferred;

$(C_{2-4})$alkynyl means a branched or unbranched alkynyl group having 2-4 carbon atoms, such as ethynyl, 2-propynyl or 2-butynyl;

$(C_{2-3})$alkynyl means an alkynyl group having 2-3 carbon atoms, such as ethynyl or 2-propynyl;

$(C_{2-6})$alkynyl means a branched or unbranched alkynyl group having $_{2-6}$ carbon atoms, such as ethynyl, propynyl, n-butynyl, n-pentynyl, isopentynyl, isohexynyl or n-hexynyl, wtih $(C_{2-4})$alkynyl groups preferred, and $(C_{2-3})$alkynyl groups more

preferred;

($C_{3-6}$)cycloalkyl means a cycloalkyl group having 3-6 carbon atoms, being cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl;

($C_{3-7}$)cycloalkyl means a cycloalkyl group having 3-7 carbon atoms, being cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl;

($C_{2-6}$)heterocycloalkyl means a heterocycloalkyl group having 2-6 carbon atoms, preferably 3-5 carbon atoms, and one or two heteroatoms selected from N, O and/or S, which may be attached via a heteroatom if feasible, or a carbon atom; preferred heteroatoms are N or O; preferred groups are piperidine, morpholine, pyrrolidine and piperazine; a most preferred ($C_{2-6}$)heterocycloalkyl is pyrrolidine; and the heterocycloalkyl group may be attached via a heteroatom if feasible;

($C_{3-7}$)heterocycloalkyl means a heterocycloalkyl group having 3-7 carbon atoms, preferably 3-5 carbon atoms, and one or two heteroatoms selected from N, O and/or S; preferred heteroatoms are N or O; preferred ($C_{3-7}$) heterocycloalkyl groups are azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl; more preferred ($C_{3-7}$)heterocycloalkyl groups are piperidine, morpholine and pyrrolidine; even more preferred are piperidine and pyrrolodine; and the heterocycloalkyl group may be attached via a heteroatom if feasible;

($C_{3-7}$)cycloalkoxy means a cycloalkyl group having 3-7 carbon atoms, with the same meaning as previously defined, attached via a ring carbon atom to an exocyclic oxygen atom;

($C_{6-10}$)aryl means an aromatic hydrocarbon group having 6-10 carbon atoms, such as phenyl, naphthyl, tetrahydronaphthyl or indenyl; the preferred ($C_{6-10}$)aryl group is phenyl;

($C_{1-5}$)heteroaryl means a substituted or unsubstituted aromatic group having 1-5 carbon atoms and 1-4 heteroatoms selected from N, O and/or S, wherein the ($C_{1-5}$)heteroaryl may optionally be substituted.; preferred ($C_{1-5}$)heteroaryl groups are tetrazolyl, imidazolyl, thiadiazolyl, pyridyl, pyrimidyl, triazinyl, thienyl or furyl, and the more preferred ($C_{1-5}$)heteroaryl is pyrimidyl;

[($C_{1-4}$)alkyl]amino means an amino group, monosubstituted with an alkyl group containing 1-4 carbon atoms having the same meaning as previously defined; the

preferred [($C_{1-4}$)alkyl]amino group is methylamino;

di[($C_{1-4}$)alkyl]amino means an amino group, disubstituted with alkyl group(s), each containing 1-4 carbon atoms and having the same meaning as previously defined; the preferred di[($C_{1-4}$)alkyl]amino group is dimethylamino;

halogen means fluorine, chlorine, bromine or iodine;

($C_{1-3}$)alkyl-C(O)-S-($C_{1-3}$)alkyl means an alkyl-carbonyl-thio-alkyl group, each of the alkyl groups having 1 to 3 carbon atoms with the same meaning as previously defined;

($C_{3-7}$)cycloalkenyl means a cycloalkenyl group having 3-7 carbon atoms, preferably 5-7 carbon atoms; preferred ($C_{3-7}$)cycloalkenyl groups are cyclopentenyl or cyclohexenyl; and cyclohexenyl groups are most preferred;

($C_{2-6}$)heterocycloalkenyl means a heterocycloalkenyl group having 2-6 carbon atoms, preferably 3-5 carbon atoms; and 1 heteroatom selected from N, O and/or S; the preferred ($C_{2-6}$)heterocycloalkenyl groups are oxycyclohexenyl and azacyclohexenyl groups.

In the above definitions with multifunctional groups, the attachment point is at the last group.

When, in the definition of a substituent, is indicated that "all of the alkyl groups" of said substituent are optionally substituted, this also includes the alkyl moiety of an alkoxy group.

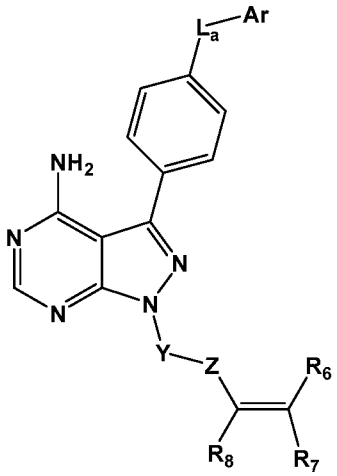
A circle in a ring of Formula (XIX) indicates that the ring is aromatic.

Depending on the ring formed, the nitrogen, if present in X or Y, may carry a hydrogen.

**[00546]** In a preferred embodiment, the invention relates to a compound according to Formula (XIX) wherein $B_1$ is $C(R_7)$; $B_2$ is $C(R_8)$; $B_3$ is $C(R_9)$ and $B_4$ is $C(R_{10})$.

**[00547]** In other embodiments, the BTK inhibitors include, but are not limited to, those compounds described in International Patent Application Publication No. WO 2013/010869 and U.S. Patent Application Publication No. US 2014/0155406 A1, the disclosures of each of which are specifically incorporated by reference herein.

**[00548]** In an embodiment, the BTK inhibitor is a compound of Formula (XX):




Formula (XX)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein:

$L_a$ is $CH_2$, O, NH or S;

Ar is a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

Y is an optionally substituted group selected from the group consisting of alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

Z is C(=O), OC(=O), NRC(=O), C(=S), $S(=O)_x$, $OS(=O)_x$ or $NRS(=O)_x$, where x is 1 or 2;

$R^7$ and $R^8$ are each independently H; or $R^7$ and $R^8$ taken together form a bond;

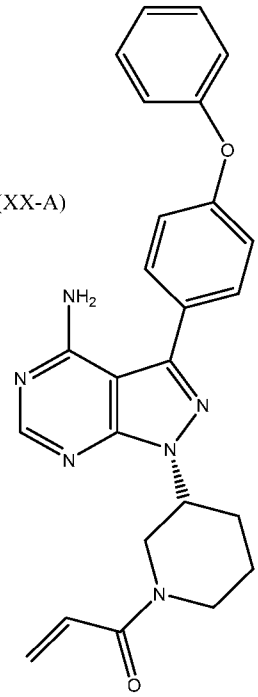
$R^6$ is H; and

R is H or $(C_{1-6})$alkyl.

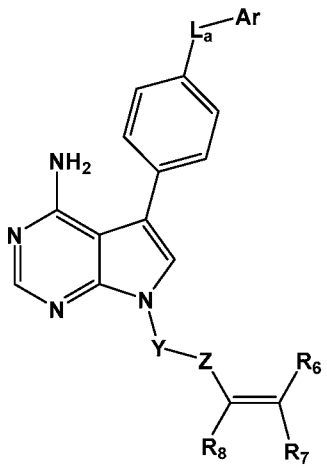
**[00549]** In a preferred embodiment, the BTK inhibitor is ibrutinib or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. In a preferred embodiment, the BTK inhibitor is (*R*)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one. In a preferred embodiment, the BTK inhibitor is 1-[(3*R*)-3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidin-1-yl]prop-2-en-1-one. In a preferred embodiment, the BTK inhibitor is (*S*)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one. In a preferred embodiment, the BTK inhibitor has the structure of Formula (XX-A), or an enantiomer

thereof, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

Formula (XX-A)



**[00550]** In a preferred embodiment, the BTK inhibitor is a compound of Formula (XXI):



Formula (XXI)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein:

$L_a$ is $CH_2$, O, NH or S;

Ar is a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

Y is an optionally substituted group selected from the group consisting of alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

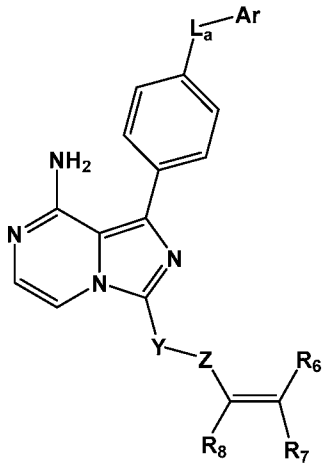
Z is C(=O), OC(=O), NRC(=O), C(=S), $S(=O)_x$, $OS(=O)_x$ or $NRS(=O)_x$, where x is 1 or 2;

$R^7$ and $R^8$ are each H; or $R^7$ and $R^8$ taken together form a bond;

$R^6$ is H; and

R is H or $(C_{1-6})$alkyl.

**[00551]** In an embodiment, the BTK inhibitor is a compound of Formula (XXII):




Formula (XXII)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein:

$L_a$ is $CH_2$, O, NH or S;

Ar is a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

Y is an optionally substituted group selected from the group consisting of alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

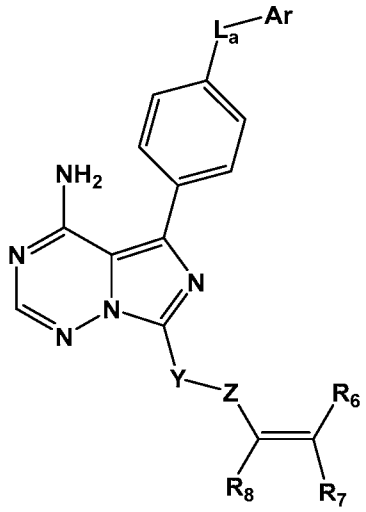
Z is C(=O), OC(=O), NRC(=O), C(=S), $S(=O)_x$, $OS(=O)_x$ or $NRS(=O)_x$, where x is 1 or 2;

$R^7$ and $R^8$ are each H; or $R^7$ and $R^8$ taken together form a bond;

$R^6$ is H; and

R is H or $(C_{1-6})$alkyl.

**[00552]** In an embodiment, the BTK inhibitor is a compound of Formula (XXIII):




Formula (XXIII)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein:

$L_a$ is $CH_2$, O, NH or S;

Ar is a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

Y is an optionally substituted group selected from the group consisting of alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

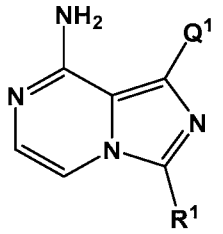
Z is C(=O), OC(=O), NRC(=O), C(=S), $S(=O)_x$, $OS(=O)_x$ or $NRS(=O)_x$, where x is 1 or 2;

$R^7$ and $R^8$ are each H; or $R^7$ and $R^8$ taken together form a bond;

$R^6$ is H; and

R is H or $(C_{1-6})$alkyl.

**[00553]** In an embodiment, the BTK inhibitor is a compound disclosed in U.S. Patent No. 7,459,554, the disclosure of which is specifically incorporated herein by reference. In an embodiment, the BTK inhibitor is a compound of Formula (XXIV):




Formula (XXIV)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein:

$Q^1$ is $aryl^1$, $heteroaryl^1$, cycloalkyl, heterocyclyl, cycloalkenyl, or heterocycloalkenyl, any of which is optionally substituted by one to five independent $G^1$ substituents;

$R^1$ is alkyl, cycloalkyl, bicycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocyclyl, or heterobicycloalkyl, any of which is optionally substituted by one or more independent $G^{11}$ substituents;

$G^1$ and $G^{41}$ are each independently halo, oxo, $-CF_3$, $-OCF_3$, $-OR^2$, $-NR^2R^3(R^{3a})_{j1}$, $-C(O)R^2$, $-CO_2R^2$, $-CONR^2R^3$, $-NO_2$, $-CN$, $-S(O)_{j1}R^2$, $-SO_2NR^2R^3$, $NR^2(C=O)R^3$, $NR^2(C=O)OR^3$, $NR^2(C=O)NR^2R^3$, $NR^2S(O)_{j1}R^3$, $-(C=S)OR^2$, $-(C=O)SR^2$, $-NR^2(C=NR^3)NR^{2a}R^{3a}$, $-NR^2(C=NR^3)OR^{2a}$, $-NR^2(C=NR^3)SR^{3a}$, $-O(C=O)OR^2$, $-O(C=O)NR^2R^3$, $-O(C=O)SR^2$, $-S(C=O)OR^2$, $-S(C=O)NR^2R^3$, $(C_{0-10})$alkyl, $(C_{2-10})$alkenyl, $(C_{2-10})$alkynyl, $(C_{1-10})$alkoxy$(C_{1-10})$alkyl, $(C_{1-10})$alkoxy$(C_{2-10})$alkenyl, $(C_{1-10})$alkoxy$(C_{2-10})$alkynyl, $(C_{1-10})$alkylthio$(C_{1-10})$ alkyl, $(C_{1-10})$alkylthio$(C_{2-10})$alkenyl, $(C_{1-10})$alkylthio$(C_{2-10})$alkynyl, cyclo$(C_{3-8})$alkyl, cyclo$(C_{3-8})$alkenyl, cyclo$(C_{3-8})$alkyl$(C_{1-10})$alkyl, cyclo$(C_{3-8})$alkenyl$(C_{1-10})$alkyl, cyclo$(C_{3-8})$ alkyl$(C_{2-10})$alkenyl, cyclo$(C_{3-8})$alkenyl$(C_{2-10})$alkenyl, cyclo$(C_{3-8})$alkyl$(C_{2-10})$alkynyl, cyclo$(C_{3-8})$alkenyl$(C_{2-10})$alkynyl, heterocyclyl-$(C_{0-10})$alkyl, heterocyclyl-$(C_{2-10})$alkenyl, or heterocyclyl-$(C_{2-10})$alkynyl, any of which is optionally substituted with one or more independent halo, oxo, $-CF_3$, $-OCF_3$, $-OR^{222}$, $-NR^{222}R^{333}(R^{333}a)_{j1a}$, $-C(O)R^{222}$, $-CO_2R^{222}$, $-CONR^{222}R^{333}$, $-NO_2$, $-CN$, $-S(O)_{j1a}R^{222}$, $-SO_2NR^{222}R^{333}$, $NR^{222}(C=O)R^{333}$, $NR^{222}(C=O)OR^{333}$, $NR^{222}(C=O)NR^{222}R^{333}$, $NR^{222}S(O)_{j1a}R^{333}$, $-(C=S)OR^{222}$, $-(C=O)SR^{222}$, $-NR^{222}(C=NR^{333})NR^{222a}R^{333a}$, $-NR^{222}(C=NR^{333})OR^{222a}$, $-NR^{222}(C=NR^{333})SR^{333a}$, $-O(C=O)OR^{222}$, $-O(C=O)NR^{222}R^{333}$, $-O(C=O)SR^{222}$, $-S(C=O)OR^{222}$, or $-S(C=O)NR^{222}R^{333}$ substituents; or $-(X^1)_n-(Y^1)_m-R^4$; or aryl-$(C_{0-}$

$_{10}$)alkyl, aryl-($C_{2-10}$)alkenyl, or aryl-($C_{2-10}$) alkynyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{222}$, $-NR^{222}R^{333}(R^{333a})_{j2a}$, $-C(O)R^{222}$, $-CO_2R^{222}$, $-CONR^{222}R^{333}$, $-NO_2$, -CN, $-S(O)_{j2a}R^{222}$, $-SO_2NR^{222}R^{333}$, $NR^{222}(C=O)R^{333}$, $NR^{222}(C=O)OR^{333}$, $NR^{222}(C=O)NR^{222}R^{333}$, $NR^{222}S(O)_{j2a}R^{333}$, $-(C=S)OR^{222}$, $-(C=O)SR^{222}$, $-NR^{222}(C=NR^{333})NR^{222a}R^{333a}$, $-NR^{222}(C=NR^{333})OR^{222a}$, $-NR^{222}(C=NR^{333})SR^{333a}$, $-O(C=O)OR^{222}$, $-O(C=O)NR^{222}R^{333}$, $-O(C=O)SR^{222}$, $-S(C=O)OR^{222}$, or $-S(C=O)NR^{222}R^{333}$ substituents; or hetaryl-($C_{0-10}$)alkyl, hetaryl-($C_{2-10}$)alkenyl, or hetaryl-($C_{2-10}$)alkynyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{222}$, $-NR^{222}$, $R^{333}(R^{333a})_{j3a}$, $-C(O)R^{222}$, $-CO_2R^{222}$, $-CONR^{222}R^{333}$, $-NO_2$, -CN, $-S(O)_{j3a}R^{222}$, $-SO_2NR^{222}R^{333}$, $NR^{222}(C=O)R^{333}$, $NR^{222}(C=O)OR^{333}$, $NR^{222}(C=O)NR^{222}R^{333}$, $NR^{222}S(O)_{j3a}R^{333}$, $-(C=S)OR^{222}$, $-(C=O)SR^{222}$, $-NR^{222}(C=NR^{333})NR^{222}aR^{333}a$, $-NR^{222}(C=NR^{333})OR^{222a}$, $-NR^{222}(C=NR^{333})SR^{333}a$, $-O(C=O)OR^{222}$, $-O(C=O)NR^{222}R^{333}$, $-O(C=O)SR^{222}$, $-S(C=O)OR^{222}$, or $-S(C=O)NR^{222}R^{333}$ substituents;

$G^{11}$ is halo, oxo, $-CF_3$, $-OCF_3$, $-OR^{21}$, $-NR^{21}R^{31}(R^{3a1})_{j4}$, $-C(O)R^{21}$, $-CO_2R^{21}$, $-CONR^{21}R^{31}$, $-NO_2$, -CN, $-S(O)_{j4}R^{21}$, $-SO_2NR^{21}R^{31}$, $NR^{21}(C=O)R^{31}$, $NR^{21}(C=O)OR^{31}$, $NR^{21}(C=O)NR^{21}R^{31}$, $NR^{21}S(O)_{j4}R^{31}$, $-(C=S)OR^{21}$, $-(C=O)SR^{21}$, $-NR^{21}(C=NR^{31})NR^{2a1}R^{3a1}$, $-NR^{21}(C=NR^{31})OR^{2a1}$, $-NR^{21}(C=NR^{31})SR^{3a1}$, $-O(C=O)OR^{21}$, $-O(C=O)NR^{21}R^{31}$, $-O(C=O)SR^{21}$, $-S(C=O)OR^{21}$, $-S(C=O)NR^{21}R^{31}$, $-P(O)OR^{21}OR^{31}$, ($C_{0-10}$)alkyl, ($C_{2-10}$)alkenyl, ($C_{2-10}$)alkynyl, ($C_{1-10}$) alkoxy($C_{1-10}$)alkyl, ($C_{1-10}$)alkoxy($C_{2-10}$)alkenyl, ($C_{1-10}$)alkoxy($C_{2-10}$)alkynyl, ($C_{1-10}$) alkylthio($C_{1-10}$)alkyl, ($C_{1-10}$)alkylthio($C_{2-10}$)alkenyl, ($C_{1-10}$)alkylthio($C_{2-10}$)alkynyl, cyclo($C_{3-8}$)alkyl, cyclo($C_{3-8}$)alkenyl, cyclo($C_{3-8}$)alkyl($C_{1-10}$)alkyl, cyclo($C_{3-8}$)alkenyl($C_{1-10}$) alkyl, cyclo($C_{3-8}$)alkyl($C_{2-10}$)alkenyl, cyclo($C_{3-8}$)alkenyl($C_{2-10}$)alkenyl, cyclo($C_{3-8}$) alkyl($C_{2-10}$) alkynyl, cyclo($C_{3-8}$)alkenyl($C_{2-10}$)alkynyl, heterocyclyl-($C_{0-10}$)alkyl, heterocyclyl-($C_{2-10}$) alkenyl, or heterocyclyl-($C_{2-10}$)alkynyl, any of which is optionally substituted with one or more independent halo, oxo, $-CF_3$, $-OCF_3$, $-OR^{2221}$, $-NR^{2221}R^{3331}(R^{333a1})_{j4a}$, $-C(O)R^{2221}$, $-CO_2R^{2221}$, $-CONR^{2221}R^{3331}$, $-NO_2$, -CN, $-S(O)_{j4a}R^{2221}$, $-SO_2NR^{2221}R^{3331}$, $NR^{2221}(C=O)R^{3331}$, $NR^{2221}(C=O)OR^{3331}$, $NR^{2221}(C=O)NR^{2221}R^{3331}$, $NR^{2221}S(O)_{j4a}R^{3331}$, $-(C=S)OR^{2221}$, $-(C=O)SR^{2221}$, -

$NR^{2221}(C=NR^{3331})NR^{222a1}R^{333a1}$, $-NR^{2221}(C=NR^{3331})OR^{222a1}$, $-NR^{2221}(C=NR^{3331})SR^{333a1}$, $-O(C=O)OR^{2221}$, $-O(C=O)NR^{2221}R^{3331}$, $-O(C=O)SR^{2221}$, $-S(C=O)OR^{2221}$, $-P(O)OR^{2221}OR^{3331}$, or $-S(C=O)NR^{2221}R^{3331}$ substituents; or aryl-($C_{0-10}$)alkyl, aryl-($C_{2-10}$)alkenyl, or aryl-($C_{2-10}$)alkynyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{2221}$, $-NR^{2221}R^{3331}(R^{333a1})_{j5a}$, $-C(O)R^{2221}$, $-CO_2R^{2221}$, $-CONR^{2221}R^{3331}$, $-NO_2$, -CN, $-S(O)_{j5a}R^{2221}$, $-SO_2NR^{2221}R^{3331}$, $NR^{2221}(C=O)R^{3331}$, $NR^{2221}(C=O)OR^{3331}$, $NR^{2221}(C=O)NR^{2221}R^{3331}$, $NR^{2221}S(O)_{j5a}R^{3331}$, $-(C=S)OR^{2221}$, $-(C=O)SR^{2221}$, $-NR^{2221}(C=NR^{3331})NR^{222a1}R^{333a1}$, $-NR^{2221}(C=NR^{3331})OR^{222a1}$, $-NR^{2221}(C=NR^{3331})SR^{333a1}$, $-O(C=O)OR^{2221}$, $-O(C=O)NR^{2221}R^{3331}$, $-O(C=O)SR^{2221}$, $-S(C=O)OR^{2221}$, $-P(O)OR^{2221}R^{3331}$, or $-S(C=O)NR^{2221}R^{3331}$ substituents; or hetaryl-($C_{0-10}$) alkyl, hetaryl-($C_{2-10}$)alkenyl, or hetaryl-($C_{2-10}$)alkynyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{2221}$, $-NR^{2221}R^{3331}(R^{333a1})_{j6a}$, $-C(O)R^{2221}$, $-CO_2R^{2221}$, $-CONR^{2221}R^{3331}$, $-NO_2$, -CN, $-S(O)_{j6a}R^{2221}$, $-SO_2NR^{2221}R^{3331}$, $NR^{2221}(C=O)R^{3331}$, $NR^{2221}(C=O)OR^{3331}$, $NR^{2221}(C=O)NR^{2221}R^{3331}$, $NR^{2221}S(O)_{j6a}R^{3331}$, $-(C=S)OR^{2221}$, $-(C=O)SR^{2221}$, $-NR^{2221}(C=NR^{3331})NR^{222a1}R^{333a1}$, $-NR^{2221}(C=NR^{3331})OR^{222a1}$, $-NR^{2221}(C=NR^{3331})SR^{333a1}$, $-O(C=O)OR^{2221}$, $-O(C=O)NR^{2221}R^{3331}$, $-O(C=O)SR^{2221}$, $-S(C=O)OR^{2221}$, $-P(O)OR^{2221}OR^{3331}$, or $-S(C=O)NR^{2221}R^{3331}$ substituents; or $G^{11}$ is taken together with the carbon to which it is attached to form a double bond which is substituted with $R^5$ and $G^{111}$;

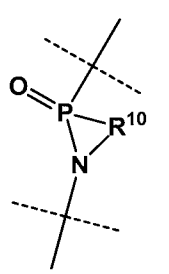
$R^2$, $R^{2a}$, $R^3$, $R^{3a}$, $R^{222}$, $R^{222}a$, $R^{333}$, $R^{333a}$, $R^{21}$, $R^{2a1}$, $R^{31}$, $R^{3a1}$, $R^{2221}$, $R^{222a1}$, $R^{3331}$, and $R^{333a1}$ are each independently equal to ($C_{0-10}$)alkyl, ($C_{2-10}$)alkenyl, ($C_{2-10}$)alkynyl, ($C_{1-10}$)alkoxy($C_{1-10}$)alkyl, ($C_{1-10}$)alkoxy($C_{2-10}$)alkenyl, ($C_{1-10}$)alkoxy($C_{2-10}$)alkynyl, ($C_{1-10}$)alkylthio($C_{1-10}$)alkyl, ($C_{1-10}$)alkylthio($C_{2-10}$)alkenyl, ($C_{1-10}$)alkylthio($C_{2-10}$)alkynyl, cyclo($C_{3-8}$)alkyl, cyclo($C_{3-8}$)alkenyl, cyclo($C_{3-8}$)alkyl($C_{1-10}$)alkyl, cyclo($C_{3-8}$)alkenyl($C_{1-10}$)alkyl, cyclo($C_{3-8}$)alkyl($_{2-10}$)alkenyl, cyclo($C_{3-8}$)alkenyl($C_{2-10}$)alkenyl, cyclo($C_{3-8}$)alkyl($C_{2-10}$)alkynyl, cyclo($C_{3-8}$)alkenyl($C_{2-10}$)alkynyl, heterocyclyl-($C_{0-10}$)alkyl, heterocyclyl-($C_{2-10}$)alkenyl, or heterocyclyl-($C_{2-10}$)alkynyl, any of which is optionally substituted by one or more $G^{111}$ substituents; or aryl-($C_{0-10}$)alkyl, aryl-($C_{2-10}$)alkenyl, or aryl-($C_{2-10}$)alkynyl, hetaryl-($C_{0-10}$)alkyl, hetaryl-($C_{2-10}$)alkenyl, or

hetaryl-($C_{2-10}$)alkynyl, any of which is optionally substituted by one or more $G^{111}$ substituents; or in the case of $-NR^2R^3(R^{3a})_{j1}$ or $-NR^{222}R^{333}(R^{333}a)_{j1a}$ or $-NR^{222}R^{333}(R^{333}a)_{j2a}$ or $-NR^{2221}R^{3331}(R^{333a1})_{j3a}$ or $-NR^{2221}R^{3331}(R^{333a1})_{j4a}$ or $-NR^{2221}R^{3331}(R^{333a1})_{j5a}$ or $-NR^{2221}R^{3331}(R^{333a1})_{j6a}$, $R^2$ and $R^3$ or $R^{222}$ and $R^{333}3$ or $R^{2221}$ and $R^{3331}$ taken together with the nitrogen atom to which they are attached form a 3-10 membered saturated ring, unsaturated ring, heterocyclic saturated ring, or heterocyclic unsaturated ring, wherein said ring is optionally substituted by one or more $G^{111}$ substituents;

$X^1$ and $Y^1$ are each independently -O-, $-NR^7$-, $-S(O)_{j7}$-, $-CR^5R^6$-, $-N(C(O)OR^7)$-, $-N(C(O)R^7)$-, $-N(SO_2R^7)$-, $-CH_2O$-, $-CH_2S$-, $-CH_2N(R^7)$-, $-CH(NR^7)$-, $-CH_2N(C(O)R^7)$-, $-CH_2N(C(O)OR^7)$-, $-CH_2N(SO_2R^7)$-, $-CH(NHR^7)$-, $-CH(NHC(O)R^7)$-, $-CH(NHSO_2R^7)$-, $-CH(NHC(O)OR^7)$-, $-CH(OC(O)R^7)$-, $-CH(OC(O)NHR^7)$-, -CH=CH-, -C.ident.C-, $-C(=NOR^7)$-, -C(O)-, $-CH(OR^7)$-, $-C(O)N(R^7)$-, $-N(R^7)C(O)$-, $-N(R^7)S(O)$-, $-N(R^7)S(O)_2$- $-OC(O)N(R^7)$-, $-N(R^7)C(O)N(R^7)$-, $-NR^7C(O)O$-, $-S(O)N(R^7)$-, $-S(O)_2N(R^7)$-, $-N(C(O)R^7)S(O)$-, $-N(C(O)R^7)S(O)_2$-, $-N(R^7)S(O)N(R^7)$-, $-N(R^7)S(O)_2N(R^7)$-, $-C(O)N(R^7)C(O)$-, $-S(O)N(R^7)C(O)$-, $-S(O)_2N(R^7)C(O)$-, $-OS(O)N(R^7)$-, $-OS(O)_2N(R^7)$-, $-N(R^7)S(O)O$-, $-N(R^7)S(O)_2O$-, $-N(R^7)S(O)C(O)$-, $-N(R^7)S(O)_2C(O)$-, $-SON(C(O)R^7)$-, $-SO_2N(C(O)R^7)$-, $-N(R^7)SON(R^7)$-, $-N(R^7)SO_2N(R^7)$-, -C(O)O-, $-N(R^7)P(OR^8)O$-, $-N(R^7)P(OR^8)$-, $-N(R^7)P(O)(OR^8)O$-, $-N(R^7)P(O)(OR^8)$-, $-N(C(O)R^7)P(OR^8)O$-, $-N(C(O)R^7)P(OR^8)$-, $-N(C(O)R^7)P(O)(OR^8)O$-, $-N(C(O)R^7)P(OR^8)$-, $-CH(R^7)S(O)$-, $-CH(R^7)S(O)_2$-, $-CH(R^7)N(C(O)OR^7)$-, $-CH(R^7)N(C(O)R^7)$-, $-CH(R^7)N(SO_2R^7)$-, $-CH(R^7)O$-, $-CH(R^7)S$-, $-CH(R^7)N(R^7)$-, $-CH(R^7)N(C(O)R^7)$-, $-CH(R^7)N(C(O)OR^7)$-, $-CH(R^7)N(SO_2R^7)$-, $-CH(R^7)C(=NOR^7)$-, $-CH(R^7)C(O)$-, $-CH(R^7)CH(OR^7)$-, $-CH(R^7)C(O)N(R^7)$-, $-CH(R^7)N(R^7)C(O)$-, $-CH(R^7)N(R^7)S(O)$-, $-CH(R^7)N(R^7)S(O)_2$-, $-CH(R^7)OC(O)N(R^7)$-, $-CH(R^7)N(R^7)C(O)N(R^7)$-, $-CH(R^7)NR^7C(O)O$-, $-CH(R^7)S(O)N(R^7)$-, $-CH(R^7)S(O)_2N(R^7)$-, $-CH(R^7)N(C(O)R^7)S(O)$-, $-CH(R^7)N(C(O)R^7)S(O)$-, $-CH(R^7)N(R^7)S(O)N(R^7)$-, $-CH(R^7)N(R^7)S(O)_2N(R^7)$-, $-CH(R^7)C(O)N(R^7)C(O)$-, $-CH(R^7)S(O)N(R^7)C(O)$-, $-CH(R^7)S(O)_2N(R^7)C(O)$-, $-CH(R^7)OS(O)N(R^7)$-, $-CH(R^7)OS(O)_2N(R^7)$-, $-CH(R^7)N(R^7)S(O)O$-, $-CH(R^7)N(R^7)S(O)_2O$-, $-CH(R^7)N(R^7)S(O)C(O)$-, $-CH(R^7)N(R^7)S(O)_2C(O)$-, -

$CH(R^7)SON(C(O)R^7)$-, -$CH(R^7)SO_2N(C(O)R^7)$-, -$CH(R^7)N(R^7)SON(R^7)$-, -$CH(R^7)N(R^7)SO_2N(R^7)$-, -$CH(R^7)C(O)O$-, -$CH(R^7)N(R^7)P(OR^8)O$-, -$CH(R^7)N(R^7)P(OR^8)$-, -$CH(R^7)N(R^7)P(O)(OR^8)O$-, -$CH(R^7)N(R^7)P(O)(OR^8)$-, -$CH(R^7)N(C(O)R^7)P(OR^8)O$-, -$CH(R^7)N(C(O)R^7)P(OR^8)$-, -$CH(R^7)N(C(O)R^7)P(O)(OR^8)O$-, or -$CH(R^7)N(C(O)R^7)P(OR^8)$-;

or $X^1$ and $Y^1$ are each independently represented by one of the following structural formulas: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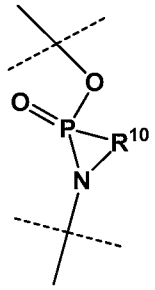
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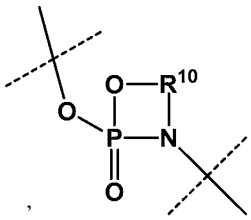
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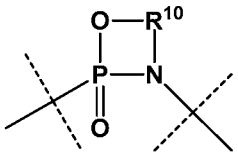
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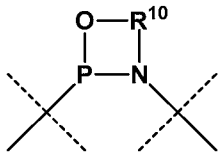
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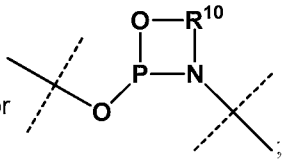

;

$R^{10}$, taken together with the phosphinamide or phosphonamide, is a 5-, 6-, or 7-membered aryl, heteroaryl or heterocyclyl ring system;

$R^5$, $R^6$, and $G^{111}$ are each independently a $(C_{0\text{-}10})$alkyl, $(C_{2\text{-}10})$alkenyl, $(C_{2\text{-}10})$alkynyl, $(C_{1\text{-}10})$alkoxy$(C_{1\text{-}10})$alkyl, $(C_{1\text{-}10})$alkoxy$(C_{2\text{-}10})$alkenyl, $(C_{1\text{-}10})$alkoxy$(C_{2\text{-}10})$alkynyl, $(C_{1\text{-}10})$alkylthio$(C_{1\text{-}10})$alkyl, $(C_{1\text{-}10})$alkylthio$(C_{2\text{-}10})$alkenyl, $(C_{1\text{-}10})$alkylthio$(C_{2\text{-}10})$alkynyl, cyclo$(C_{3\text{-}8})$alkyl, cyclo$(C_{3\text{-}8})$alkenyl, cyclo$(C_{3\text{-}8})$alkyl$(C_{1\text{-}10})$alkyl, cyclo$(C_{3\text{-}8})$alkenyl$(C_{1\text{-}10})$alkyl, cyclo$(C_{3\text{-}8})$alkyl$(C_{2\text{-}10})$alkenyl, cyclo$(C_{3\text{-}8})$alkenyl$(C_{2\text{-}10})$alkenyl, cyclo$(C_{3\text{-}8})$alkyl$(C_{2\text{-}10})$alkynyl, cyclo$(C_{3\text{-}8})$alkenyl$(C_{2\text{-}10})$alkynyl, heterocyclyl-$(C_{0\text{-}10})$alkyl, heterocyclyl-$(C_{2\text{-}10})$alkenyl, or heterocyclyl-$(C_{2\text{-}10})$alkynyl, any of which is optionally substituted with one or more independent halo, -$CF_3$, -$OCF_3$, -$OR^{77}$, -$NR^{77}R^{87}$, -$C(O)R^{77}$, -$CO_2R^{77}$, -$CONR^{77}R^{87}$, -$NO_2$, -CN, -$S(O)_{j5a}R^{77}$, -$SO_2NR^{77}R^{87}$, $NR^{77}(C{=}O)R^{87}$, $NR^{77}(C{=}O)OR^{87}$, $NR^{77}(C{=}O)NR^{78}R^{87}$, $NR^{77}S(O)_{j5a}R^{87}$,

-(C=S)OR$^{77}$, -(C=O)SR$^{77}$, -NR$^{77}$(C=NR$^{87}$)NR$^{78}$R$^{88}$, -NR$^{77}$(C=NR$^{87}$)OR$^{78}$, -NR$^{77}$(C=NR$^{87}$)SR$^{78}$, -O(C=O)OR$^{77}$, -O(C=O)NR$^{77}$R$^{87}$, -O(C=O)SR$^{77}$, -S(C=O)OR$^{77}$, -P(O)OR$^{77}$OR$^{87}$, or -S(C=O)NR$^{77}$R$^{87}$ substituents; or aryl-($C_{0-10}$)alkyl, aryl-($C_{2-10}$)alkenyl, or aryl-($C_{2-10}$)alkynyl, any of which is optionally substituted with one or more independent halo, -$CF_3$, -$OCF_3$, -OR$^{77}$, -NR$^{77}$R$^{87}$, -C(O)R$^{77}$, -$CO_2$R$^{77}$, -CONR$^{77}$R$^{87}$, -$NO_2$, -CN, -S(O)$_{j5a}$R$^{77}$, -$SO_2$NR$^{77}$R$^{87}$, NR$^{77}$(C=O)R$^{87}$, NR$^{77}$(C=O)OR$^{87}$, NR$^{77}$(C=O)NR$^{78}$R$^{87}$, NR$^{77}$S(O)$_{j5a}$R$^{87}$, -(C=S)OR$^{77}$, -(C=O)SR$^{77}$, -NR$^{77}$(C=NR$^{87}$)NR$^{78}$R$^{88}$, -NR$^{77}$(C=NR$^{87}$)OR$^{78}$, -NR$^{77}$(C=NR$^{87}$)SR$^{78}$, -O(C=O)OR$^{77}$, -O(C=O)NR$^{77}$R$^{87}$, -O(C=O)SR$^{77}$, -S(C=O)OR$^{77}$, -P(O)OR$^{77}$R$^{87}$, or -S(C=O)NR$^{77}$R$^{87}$ substituents; or hetaryl-($C_{0-10}$)alkyl, hetaryl-($C_{2-10}$)alkenyl, or hetaryl-($C_{2-10}$)alkynyl, any of which is optionally substituted with one or more independent halo, -$CF_3$, -$OCF_3$, -OR$^{77}$, -NR$^{77}$R$^{87}$, -C(O)R$^{77}$, -$CO_2$R$^{77}$, -CONR$^{77}$R$^{87}$, -$NO_2$, -CN, -S(O)$_{j5a}$R$^{77}$, -$SO_2$NR$^{77}$R$^{87}$, NR$^{77}$(C=O)R$^{87}$, NR$^{77}$(C=O)OR$^{87}$, NR$^{77}$(C=O)NR$^{78}$R$^{87}$, NR$^{77}$S(O)$_{j5a}$R$^{87}$, -(C=S)OR$^{77}$, -(C=O)SR$^{77}$, -NR$^{77}$(C=NR$^{87}$)NR$^{78}$R$^{88}$, -NR$^{77}$(C=NR$^{87}$)OR$^{78}$, -NR$^{77}$(C=NR$^{87}$)SR$^{78}$, -O(C=O)OR$^{77}$, -O(C=O)NR$^{77}$R$^{87}$, -O(C=O)SR$^{77}$, -S(C=O)OR$^{77}$, -P(O)OR$^{77}$OR$^{87}$, or -S(C=O)NR$^{77}$R$^{87}$ substituents; or R$^5$ with R$^6$ taken together with the respective carbon atom to which they are attached, form a 3-10 membered saturated or unsaturated ring, wherein said ring is optionally substituted with R$^{69}$; or R$^5$ with R$^6$ taken together with the respective carbon atom to which they are attached, form a 3-10 membered saturated or unsaturated heterocyclic ring, wherein said ring is optionally substituted with R$^{69}$;

R$^7$ and R$^8$ are each independently H, acyl, alkyl, alkenyl, aryl, heteroaryl, heterocyclyl or cycloalkyl, any of which is optionally substituted by one or more G$^{111}$ substituents;

R$^4$ is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, cycloalkenyl, or heterocycloalkenyl, any of which is optionally substituted by one or more G$^{41}$ substituents;

R$^{69}$ is equal to halo, -OR$^{78}$, -SH, -NR$^{78}$R$^{88}$, -$CO_2$R$^{78}$, -CONR$^{78}$R$^{88}$, -$NO_2$, -CN, -S(O)$_{j8}$R$^{78}$, -$SO_2$NR$^{78}$R$^{88}$, ($C_{0-10}$)alkyl, ($C_{2-10}$)alkenyl, ($C_{2-10}$)alkynyl, ($C_{1-10}$)alkoxy($C_{1-10}$)alkyl, ($C_{1-10}$)alkoxy($C_{2-10}$)alkenyl, ($C_{1-10}$)alkoxy($C_{2-10}$)alkynyl, ($C_{1-10}$)alkylthio($C_{1-10}$)alkyl, ($C_{1-10}$)alkylthio($C_{2-10}$)alkenyl, ($C_{1-10}$)alkylthio($C_{2-10}$)alkynyl, cyclo($C_{3-8}$)alkyl, cyclo($C_{3-8}$)alkenyl, cyclo($C_{3-8}$)alkyl($C_{1-10}$)alkyl, cyclo($C_{3-}$

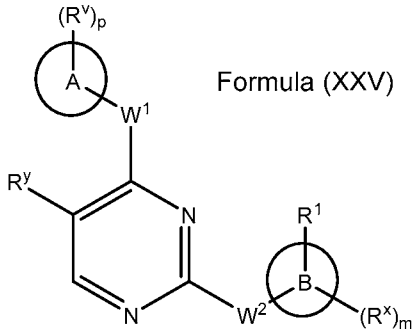
$_{8}$)alkenyl($C_{1-10}$)alkyl, cyclo($C_{3-8}$)alkyl($C_{2-10}$)alkenyl, cyclo($C_{3-8}$)alkenyl($C_{2-10}$)alkenyl, cyclo($C_{3-8}$)alkyl($C_{2-10}$)alkynyl, cyclo($C_{3-8}$)alkenyl($C_{2-10}$)alkynyl, heterocyclyl-($C_{0-10}$)alkyl, heterocyclyl-($C_{2-10}$)alkenyl, or heterocyclyl-($C_{2-10}$)alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, -$OR^{778}$, -$SO_2NR^{778}R^{888}$, or -$NR^{778}R^{888}$ substituents; or aryl-($C_{0-10}$)alkyl, aryl-($C_{2-10}$)alkenyl, or aryl-($C_{2-10}$)alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, -$OR^{778}$, ($C_{1-10}$)alkyl, ($C_{2-10}$)alkenyl, ($C_{2-10}$)alkynyl, halo($C_{1-10}$)alkyl, halo($C_{2-10}$)alkenyl, halo($C_{2-10}$)alkynyl, -COOH, ($C_{1-4}$)alkoxycarbonyl, -$CONR^{778}R^{888}$, -$SO_2NR^{778}R^{888}$, or -$NR^{778}R^{888}$ substituents; or hetaryl-($C_{0-10}$)alkyl, hetaryl-($C_{2-10}$)alkenyl, or hetaryl-($C_{2-10}$)alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, -$OR^{778}$, ($C_{1-10}$)alkyl, ($C_{2-10}$)alkenyl, ($C_{2-10}$)alkynyl, halo($C_{1-10}$)alkyl, halo($C_{2-10}$)alkenyl, halo($C_{2-10}$)alkynyl, -COOH, ($C_{1-4}$)alkoxycarbonyl, -$CONR^{778}R^{888}$, -$SO_2NR^{778}R^{888}$, or -$NR^{778}R^{888}$ substituents; or mono($C_{1-6}$alkyl)amino($C_{1-6}$)alkyl, di(($C_{1-6}$)alkyl)amino($C_{1-6}$)alkyl, mono(aryl)amino($C_{1-6}$)alkyl, di(aryl)amino($C_{1-6}$)alkyl, or -N(($C_{1-6}$)alkyl)-($C_{1-6}$)alkyl-aryl, any of which is optionally substituted with one or more independent halo, cyano, nitro, -$OR^{778}$, ($C_{1-10}$)alkyl, ($C_{2-10}$)alkenyl, ($C_{2-10}$)alkynyl, halo($C_{1-10}$)alkyl, halo($C_{2-10}$)alkenyl, halo($C_{2-10}$)alkynyl, -COOH, ($C_{1-4}$)alkoxycarbonyl, -$CONR^{778}R^{888}$ $SO_2NR^{778}R^{888}$, or -$NR^{778}R^{888}$ substituents; or in the case of -$NR^{78}R^{88}$, $R^{78}$ and $R^{88}$ taken together with the nitrogen atom to which they are attached form a 3-10 membered saturated ring, unsaturated ring, heterocyclic saturated ring, or heterocyclic unsaturated ring, wherein said ring is optionally substituted with one or more independent halo, cyano, hydroxy, nitro, ($C_{1-10}$)alkoxy, -$SO_2NR^{778}R^{888}$, or -$NR^{778}R^{888}$ substituents;

$R^{77}$, $R^{78}$, $R^{87}$, $R^{88}$, $R^{778}$, and $R^{888}$ are each independently ($C_{0-10}$)alkyl, ($C_{2-10}$)alkenyl, ($C_{2-10}$)alkynyl, ($C_{1-10}$)alkoxy($C_{1-10}$)alkyl, ($C_{1-10}$)alkoxy$C_{2-10}$)alkenyl, ($C_{1-10}$)alkoxy($C_{2-10}$)alkynyl, ($C_{1-10}$)alkylthio($C_{1-10}$)alkyl, ($C_{1-10}$)alkylthio($C_{2-10}$)alkenyl, ($C_{1-10}$)alkylthio($C_{2-10}$)alkynyl, cyclo($C_{3-8}$)alkyl, cyclo($C_{3-8}$)alkenyl, cyclo($C_{3-8}$)alkyl($C_{1-10}$)alkyl, cyclo($C_{3-8}$)alkenyl($C_{1-10}$)alkyl, cyclo($C_{3-8}$)alkyl($C_{2-10}$)alkenyl, cyclo($C_{3-8}$)alkenyl($C_{2-10}$)alkenyl, cyclo($C_{3-8}$)alkyl($C_{2-10}$)alkynyl, cyclo($C_{3-8}$)alkenyl($C_{2-10}$)alkynyl, heterocyclyl-($C_{0-10}$)alkyl, heterocyclyl-($C_{2-10}$)alkenyl, heterocyclyl-($C_{2-10}$)alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, -$OR^{778}$, -$SO_2NR^{778}R^{888}$, or -$NR^{778}R^{888}$ substituents; or aryl-($C_{0-10}$)alkyl, aryl-($C_{2-10}$)alkenyl, or aryl-($C_{2-10}$)alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, -$OR^{778}$, ($C_{1-10}$)alkyl, ($C_{2-10}$)alkenyl, ($C_{2-10}$)alkynyl, halo($C_{1-10}$)alkyl, halo($C_{2-10}$)alkenyl, halo($C_{2-10}$)alkynyl, -COOH, ($C_{1-4}$)alkoxycarbonyl, -$CONR^{778}R^{888}$, -$SO_2NR^{778}R^{888}$, or -$NR^{778}R^{888}$ substituents; or hetaryl-($C_{0-10}$)alkyl, hetaryl-($C_{2-10}$)alkenyl, or hetaryl-($C_{2-10}$)alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, -$OR^{778}$, ($C_{1-10}$)alkyl, ($C_{2-10}$)alkenyl, ($C_{2-10}$)alkynyl, halo($C_{1-10}$)alkyl, halo($C_{2-10}$)alkenyl, halo($C_{2-10}$)alkynyl, -COOH, ($C_{1-4}$)alkoxycarbonyl, -$CONR^{778}R^{888}$, -$SO_2NR^{778}R^{888}$, or -$NR^{778}R^{888}$ substituents; or mono($C_{1-6}$alkyl)amino($C_{1-6}$)alkyl, di(($C_{1-6}$)alkyl)amino($C_{1-6}$)alkyl, mono(aryl)amino($C_{1-6}$)alkyl, di(aryl)amino($C_{1-6}$)alkyl, or -N(($C_{1-6}$)alkyl)-($C_{1-6}$)alkyl-aryl, any of which is optionally substituted with one or more independent halo, cyano, nitro, -$OR^{778}$, ($C_{1-10}$)alkyl, ($C_{2-10}$)alkenyl, ($C_{2-10}$)alkynyl, halo($C_{1-10}$)alkyl, halo($C_{2-10}$)alkenyl, halo($C_{2-10}$)alkynyl, -COOH, ($C_{1-4}$)alkoxycarbonyl, -$CONR^{778}R^{888}$ $SO_2NR^{778}R^{888}$, or -$NR^{778}R^{888}$ substituents; or in the case of -$NR^{78}R^{88}$, $R^{78}$ and $R^{88}$ taken together with the nitrogen atom to which they are attached form a 3-10 membered saturated ring, unsaturated ring, heterocyclic saturated ring, or heterocyclic unsaturated ring, wherein said ring is optionally substituted with one or more independent halo, cyano, hydroxy, nitro, ($C_{1-10}$)alkoxy, -$SO_2NR^{778}R^{888}$, or -$NR^{778}R^{888}$ substituents;

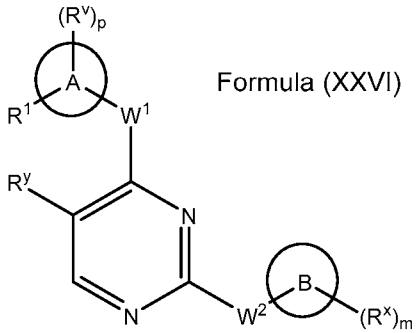
$_{10}$)alkynyl, ($C_{1-10}$)alkylcarbonyl, ($C_{2-10}$)alkenylcarbonyl, ($C_{2-10}$)alkynylcarbonyl, ($C_{1-10}$)alkoxycarbonyl, ($C_{1-10}$)alkoxycarbonyl($C_{1-10}$)alkyl, mono($C_{1-6}$)alkylaminocarbonyl, di($C_{1-6}$)alkylaminocarbonyl, mono(aryl)aminocarbonyl, di(aryl)aminocarbonyl, or ($C_{1-10}$)alkyl(aryl)aminocarbonyl, any of which is optionally substituted with one or more independent halo, cyano, hydroxy, nitro, ($C_{1-10}$)alkoxy, -$SO_2$N(($C_{0-4}$)alkyl)(($C_{0-4}$)alkyl), or -N(($C_{0-4}$)alkyl)(($C_{0-4}$)alkyl) substituents; or aryl-($C_{0-10}$)alkyl, aryl-($C_{2-10}$)alkenyl, or aryl-($C_{2-10}$)alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, -O(($C_{0-4}$)alkyl), ($C_{1-10}$)alkyl, ($C_{2-10}$)alkenyl, ($C_{2-10}$)alkynyl, halo($C_{1-10}$)alkyl, halo($C_{2-10}$)alkenyl, halo($C_{2-10}$)alkynyl, -COOH, ($C_{1-4}$)alkoxycarbonyl, -CON(($C_{0-4}$)alkyl)(($C_{0-10}$)alkyl), -$SO_2$N(($C_{0-4}$)alkyl)(($C_{0-4}$)alkyl), or -N(($C_{0-4}$)alkyl)(($C_{0-4}$)alkyl) substituents; or hetaryl-($C_{0-10}$)alkyl, hetaryl-($C_{2-10}$)alkenyl, or hetaryl-($C_{2-10}$)alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, -O(($C_{0-4}$)alkyl), ($C_{1-10}$)alkyl, ($C_{2-10}$)alkenyl, ($C_{2-10}$)alkynyl, halo($C_{1-10}$)alkyl, halo($C_{2-10}$)alkenyl, halo($C_{2-10}$)alkynyl, -COOH, ($C_{1-4}$)alkoxycarbonyl, -CON(($C_{0-4}$)alkyl)(($C_{0-4}$)alkyl), -$SO_2$N(($C_{0-4}$)alkyl)(($C_{0-4}$)alkyl), or -N(($C_{0-4}$)alkyl)(($C_{0-4}$)alkyl) substituents; or mono(($C_{1-6}$)alkyl)amino($C_{1-6}$)alkyl, di(($C_{1-6}$)alkyl)amino($C_{1-6}$)alkyl, mono(aryl)amino($C_{1-6}$)alkyl, di(aryl)amino($C_{1-6}$)alkyl, or -N(($C_{1-6}$)alkyl)-($C_{1-6}$)alkyl-aryl, any of which is optionally substituted with one or more independent halo, cyano, nitro, -O(($C_{0-4}$)alkyl), ($C_{1-10}$)alkyl, ($C_{2-10}$)alkenyl, ($C_{2-10}$)alkynyl, halo($C_{1-10}$)alkyl, halo($C_{2-10}$)alkenyl, halo($C_{2-10}$)alkynyl, -COOH, ($C_{1-4}$)alkoxycarbonyl, -CON(($C_{0-4}$)alkyl)(($C_{0-4}$)alkyl), -$SO_2$N(($C_{0-4}$)alkyl)(($C_{0-4}$)alkyl), or -N(($C_{0-4}$)alkyl)(($C_{0-4}$)alkyl) substituents; and

n, m, j1, j1a, j2a, j3a, j4, j4a, j5a, j6a, j7, and j8 are each independently equal to 0, 1, or 2.

**[00554]** In an embodiment, the BTK inhibitor is a compound selected from the structures disclosed in U.S. Patent Nos. 8,450,335 and 8,609,679, and U.S. Patent Application Publication Nos. 2010/0029610 A1, 2012/0077832 A1, 2013/0065879 A1, 2013/0072469 A1, and 2013/0165462 A1, the disclosures of which are incorporated by reference herein. In an embodiment, the BTK inhibitor is a compound of Formula (XXV) or Formula (XXVI):




Formula (XXV)




Formula (XXVI)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein:

Ring A is an optionally substituted group selected from phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated or aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an optionally substituted 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ring B is an optionally substituted group selected from phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated or aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 4-7

membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an optionally substituted 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

$R^1$ is a warhead group;

$R^y$ is hydrogen, halogen, —CN, —$CF_3$, $C_{1-4}$ aliphatic, $C_{1-4}$ haloaliphatic, —OR, —C(O)R, or —$C(O)N(R)_2$;

each R group is independently hydrogen or an optionally substituted group selected from $C_{1-6}$ aliphatic, phenyl, an optionally substituted 4-7 membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

$W^1$ and $W^2$ are each independently a covalent bond or a bivalent $C_{1-3}$ alkylene chain wherein one methylene unit of $W^1$ or $W^2$ is optionally replaced by —$NR^2$—, —$N(R^2)C(O)$—, —$C(O)N(R^2)$—, —$N(R^2)SO_2$—, —$SO_2N(R^2)$—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —SO— or —$SO_2$—;

$R^2$ is hydrogen, optionally substituted $C_{1-6}$ aliphatic, or —C(O)R, or:

$R^2$ and a substituent on Ring A are taken together with their intervening atoms to form a 4-6 membered saturated, partially unsaturated, or aromatic fused ring, or:

$R^2$ and $R^y$ are taken together with their intervening atoms to form an optionally substituted 4-7 membered partially unsaturated or aromatic fused ring;

m and p are independently 0-4; and

$R^x$ and $R^v$ are independently selected from —R, halogen, —OR, —$O(CH_2)_qOR$, —CN, —$NO_2$, —$SO_2R$, —$SO_2N(R)_2$, —SOR, —C(O)R, —$CO_2R$, —$C(O)N(R)_2$, —NRC(O)R, —$NRC(O)NR_2$, —$NRSO_2R$, or —$N(R)_2$, wherein q is 1-4; or:

$R^x$ and $R^1$ when concurrently present on Ring B are taken together with their intervening atoms to form an optionally substituted 5-7 membered saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with a warhead group and

0-3 groups independently selected from oxo, halogen, —CN, or $C_{1-6}$ aliphatic; or

$R^v$ and $R^1$ when concurrently present on Ring A are taken together with their intervening atoms to form an optionally substituted 5-7 membered saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with a warhead group and 0-3 groups independently selected from oxo, halogen, —CN, or $C_{1-6}$ aliphatic.

**[00555]** In an embodiment, the BTK inhibitor is a compound of Formula (XXV) or Formula (XXVI), wherein:

Ring A is selected from phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated or aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an optionally substituted 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an optionally substituted 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ring B is selected from phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated or aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an optionally substituted 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an optionally substituted 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

$R^1$ is -L-Y, wherein:

L is a covalent bond or a bivalent $C_{1-8}$ saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene units of L are optionally and

independently replaced by cyclopropylene, —NR—, —N(R)C(O)—, —C(O)N(R)—, —N(R)$SO_2$—, —$SO_2$N(R)—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —SO—, —$SO_2$—, —C(=S)—, —C(=NR)—, —N=N—, or —C(=$N_2$)—;

Y is hydrogen, $C_{1-6}$ aliphatic optionally substituted with oxo, halogen, or CN, or a 3-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein said ring is substituted with at 1-4 groups independently selected from -Q-Z, oxo, $NO_2$, halogen, CN, or $C_{1-6}$ aliphatic, wherein:

Q is a covalent bond or a bivalent $C_{1-6}$ saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one or two methylene units of Q are optionally and independently replaced by —NR—, —S—, —O—, —C(O)—, —SO—, or —$SO_2$—; and

Z is hydrogen or $C_{1-6}$ aliphatic optionally substituted with oxo, halogen, or CN;

$R^y$ is hydrogen, halogen, —CN, —$CF_3$, $C_{1-4}$ aliphatic, $C_{1-4}$ haloaliphatic, —OR, —C(O)R, or —C(O)N($R_2$);

each R group is independently hydrogen or an optionally substituted group selected from $C_{1-6}$ aliphatic, phenyl, an optionally substituted 4-7 membered heterocylic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

$W^1$ and $W^2$ are each independently a covalent bond or a bivalent $C_{1-3}$ alkylene chain wherein one methylene unit of $W^1$ or $W^2$ is optionally replaced by —$NR^2$—, —$N(R^2)$C(O)—, —C(O)N($R^2$)—, —N($R^2$)$SO_2$—, —$SO_2$N($R^2$)—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —SO— or —$SO_2$—;

$R^2$ is hydrogen, optionally substituted $C_{1-6}$ aliphatic, or —C(O)R, or:

$R^2$ and a substituent on Ring A are taken together with their intervening atoms to form a 4-6 membered partially unsaturated or aromatic fused ring; or

$R^2$ and $R^y$ are taken together with their intervening atoms to form a 4-6 membered saturated, partially unsaturated, or aromatic fused ring;

m and p are independently 0-4; and

$R^x$ and $R^y$ are independently selected from —R, halogen, —OR, —O($CH_2$)$_q$OR, —CN,

—$NO_2$, —$SO_2R$, —$SO_2N(R)_2$, —SOR, —C(O)R, —$CO_2R$, —$C(O)N(R)_2$, —NRC(O)R, —$NRC(O)NR_2$, —$NRSO_2R$, or —$N(R)_2$, wherein R is independently selected from the group consisting of hydrogen, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, and heterocycly; or:

$R^x$ and $R^1$ when concurrently present on Ring B are taken together with their intervening atoms to form a 5-7 membered saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with a warhead group and 0-3 groups independently selected from oxo, halogen, —CN, or $C_{1-6}$ aliphatic; or

$R^y$ and $R^1$ when concurrently present on Ring A are taken together with their intervening atoms to form a 5-7 membered saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with a warhead group and 0-3 groups independently selected from oxo, halogen, —CN, or $C_{1-6}$ aliphatic.

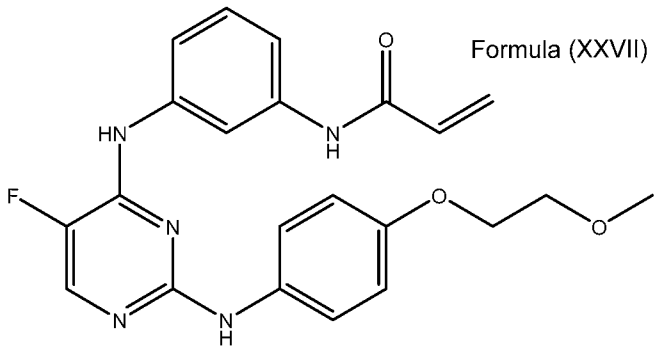
**[00556]** As defined generally above, Ring A is selected from phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated or aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an optionally substituted 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an optionally substituted 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

**[00557]** In preferred embodiments, Ring A is an optionally substituted phenyl group. In some embodiments, Ring A is an optionally substituted naphthyl ring or an optionally substituted bicyclic 8-10 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In certain other embodiments, Ring A is an optionally substituted 3-7 membered carbocyclic ring. In yet other embodiments, Ring A is an optionally substituted 4-7 membered heterocyclic ring having

1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In preferred embodiments, Ring B is an optionally substituted phenyl group.

**[00558]** In certain embodiments, Ring A in Formula (XXV) or Formula (XXVI) is substituted as defined herein. In some embodiments, Ring A is substituted with one, two, or three groups independently selected from halogen, $R^{\circ}$, or $—(CH_2)_{0-4}OR^{\circ}$, or $—O(CH_2)_{0-4}R^{\circ}$, wherein each $R^{\circ}$ is independently selected from the group consisting of cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl. Exemplary substituents on Ring A include Br, I, Cl, methyl, $—CF_3$, —C≡CH, $—OCH_2$phenyl, $—OCH_2$(fluorophenyl), or $—OCH_2$pyridyl.

**[00559]** In a preferred embodiment, the BTK inhibitor is CC-292, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, preferably a hydrochloride salt or a besylate salt thereof. In a preferred embodiment, the BTK inhibitor is a compound of Formula (XXVII):




Formula (XXVII)

,

which is *N*-(3-((5-fluoro-2-((4-(2-methoxyethoxy)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, or in a preferred embodiment is a hydrochloride salt or a besylate salt thereof. The preparation of this compound is described in U.S. Patent Application Publication No. 2010/0029610 A1 at Example 20, the disclosure of which is incorporated by reference herein. The preparation of the besylate salt of this compound is described in U.S. Patent Application Publication No. 2012/0077832 A1, the disclosure of which is incorporated by reference herein. In an embodiment, the BTK inhibitor is a compound selected from the structures disclosed in U.S. Patent Application Publication No. 2010/0029610 A1 or No. 2012/0077832 A1, the disclosures of which are

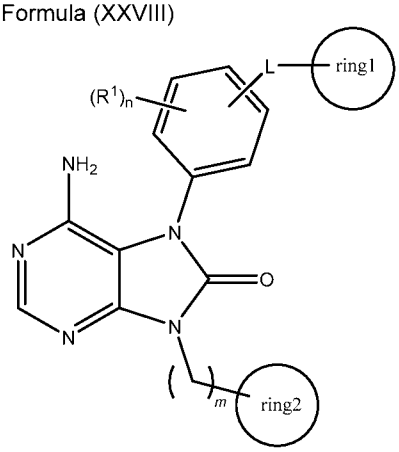
incorporated by reference herein.

**[00560]** In a preferred embodiment, the BTK inhibitor is *N*-(3-((5-fluoro-2-((4-(2-methoxyethoxy)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, or a hydrochloride salt thereof. The preparation of this compound is described in U.S. Patent Application Publication Nos. 2010/0029610 A1 and 2012/0077832 A1, the disclosure of which is incorporated by reference herein.

**[00561]** In a preferred embodiment, the BTK inhibitor is (N-(3-(5-fluoro-2-(4-(2-methoxyethoxy)phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide), or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, or preferably a besylate salt thereof. The preparation of this compound is described in U.S. Patent Application Publication No. 2010/0029610 A1 at Example 20, the disclosure of which is incorporated by reference herein. The preparation of its besylate salt is described in U.S. Patent Application Publication No. 2012/0077832 A1, the disclosure of which is incorporated by reference herein.

**[00562]** In an embodiment, the BTK inhibitor is a compound of Formula (XXVIII):

Formula (XXVIII)




or a pharmaceutically acceptable salt, hydrate, solvate, cocrystal, or prodrug thereof, wherein

L represents (1) –O–, (2) –S–, (3) –SO–, (4) $–SO_2–$ (5) –NH–, (6) –C(O)–, (7) $–CH_2O–$, (8) $–O–CH_2–$, (9) $–CH_2–$, or (10) –CH(OH)–;

$R^1$ represents (1) a halogen atom, (2) a $C_{1-4}$ alkyl group, (3) a $C_{1-4}$ alkoxy group, (4) a $C_{1-4}$

haloalkyl group, or (5) a $C_{1-4}$ haloalkoxy group;

ring1 represents a 4- to 7-membered cyclic group, which may be substituted by from one to five substituents each independently selected from the group consisting of (1) halogen atoms, (2) $C_{1-4}$ alkyl groups, (3) $C_{1-4}$ alkoxy groups, (4) nitrile, (5) $C_{1-4}$ haloalkyl groups, and (6) $C_{1-4}$ haloalkoxy groups, wherein when two or more substituents are present on ring1, these substituents may form a 4- to 7-membered cyclic group together with the atoms in ring1 to which these substituents are bound;

ring2 represents a 4- to 7-membered saturated heterocycle, which may be substituted by from one to three –K–$R^2$; K represents (1) a bond, (2) a $C_{1-4}$ alkylene, (3) –C(O)–, (4) –C(O)–$CH_2$–, (5) –$CH_2$–C(O)–, (6) –C(O)O–, or (7) –$SO_2$– (wherein the bond on the left is bound to the ring2);

$R^2$ represents (1) a $C_{1-4}$ alkyl, (2) a $C_{2-4}$ alkenyl, or (3) a $C_{2-4}$ alkynyl group, each of which may be substituted by from one to five substituents each independently selected from the group consisting of (1) $NR^3R^4$, (2) halogen atoms, (3) $CONR^5R^6$, (4) $CO_2R^7$, and (5) $OR^8$;

$R^3$ and $R^4$ each independently represent (1) a hydrogen atom, or (2) a $C_{1-4}$ alkyl group which may be substituted by $OR^9$ or $CONR^{10}R^{11}$; $R^3$ and $R^4$ may, together with the nitrogen atom to which they are bound, form a 4- to 7-membered nitrogenous saturated heterocycle, which may be substituted by an oxo group or a hydroxyl group;

$R^5$ and $R^6$ each independently represent (1) a hydrogen atom, (2) a $C_{1-4}$ alkyl group, or (3) a phenyl group;

$R^7$ represents (1) a hydrogen atom or (2) a $C_{1-4}$ alkyl group;

$R^8$ represents (1) a hydrogen atom, (2) a $C_{1-4}$ alkyl group, (3) a phenyl group, or (4) a benzotriazolyl group; $R^9$ represents (1) a hydrogen atom or (2) a $C_{1-4}$ alkyl group;

$R^{10}$ and $R^{11}$ each independently represent (1) a hydrogen atom or (2) a $C_{1-4}$ alkyl group;

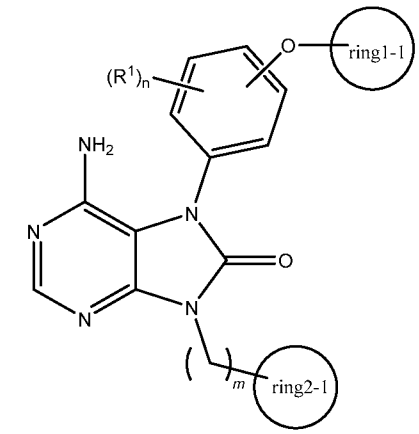
n represents an integer from 0 to 4;

m represents an integer from 0 to 2; and

when n is two or more, the $R^1$'s may be the same as each other or may differ from one another).

**[00563]** In an embodiment, the BTK inhibitor is a compound of Formula (XXVIII-A):

Formula (XXVIII-A)




or a pharmaceutically acceptable salt, hydrate, solvate, cocrystal, or prodrug thereof, wherein

$R^1$ represents (1) a halogen atom, (2) a $C_{1-4}$ alkyl group, (3) a $C_{1-4}$ alkoxy group, (4) a $C_{1-4}$ haloalkyl group, or (5) a $C_{1-4}$ haloalkoxy group;

ring1 represents a benzene, cyclohexane, or pyridine ring, each of which may be substituted by from one to five substituents each independently selected from the group consisting of (1) halogen atoms, (2) $C_{1-4}$ alkyl groups, (3) $C_{1-4}$ alkoxy groups, (4) nitrile, (5) $CF_3$;

ring2 represents a 4- to 7-membered nitrogenous saturated heterocycle, which may be substituted by from one to three $-K-R^2$; wherein K represents (1) a bond, (2) a $C_{1-4}$ alkylene, (3) $-C(O)-$, (4) $-C(O)-CH_2-$, (5) $-CH_2-C(O)-$, (6) $-C(O)O-$, or (7) $-SO_2-$ (wherein the bond on the left is bound to the ring2);

$R^2$ represents (1) a $C_{1-4}$ alkyl, (2) a $C_{2-4}$ alkenyl, or (3) a $C_{2-4}$ alkynyl group, each of which may be substituted by from one to five substituents each independently selected from the group consisting of (1) $NR^3R^4$, (2) halogen atoms, (3) $CONR^5R^6$, (4) $CO_2R^7$, and (5) $OR^8$;

$R^3$ and $R^4$ each independently represent (1) a hydrogen atom, or (2) a $C_{1-4}$ alkyl group which may be substituted by $OR^9$ or $CONR^{10}R^{11}$; $R^3$ and $R^4$ may, together with the nitrogen atom to which they are bound, form a 4- to 7-membered nitrogenous saturated heterocycle, which may be substituted by an oxo group or a hydroxyl group;

$R^5$ and $R^6$ each independently represent (1) a hydrogen atom, (2) a $C_{1-4}$ alkyl group, or (3) a phenyl group;

$R^7$ represents (1) a hydrogen atom or (2) a $C_{1-4}$ alkyl group;

$R^8$ represents (1) a hydrogen atom, (2) a $C_{1-4}$ alkyl group, (3) a phenyl group, or (4) a benzotriazolyl group; $R^9$ represents (1) a hydrogen atom or (2) a $C_{1-4}$ alkyl group;

$R^{10}$ and $R^{11}$ each independently represent (1) a hydrogen atom or (2) a $C_{1-4}$ alkyl group;

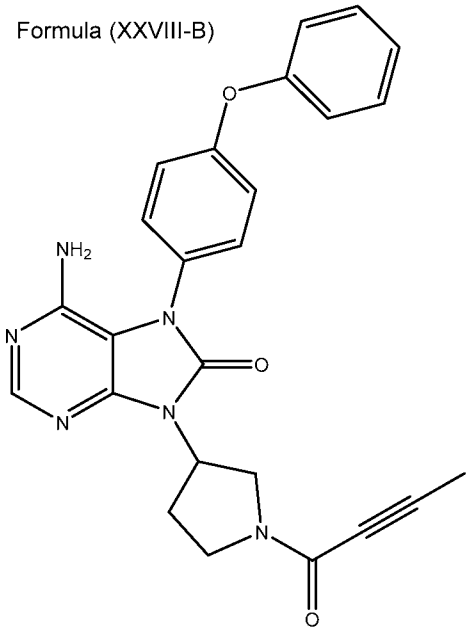
n represents an integer from 0 to 4;

m represents an integer from 0 to 2; and

when n is two or more, the $R^1$'s may be the same as each other or may differ from one another).

**[00564]** In a preferred embodiment, the BTK inhibitor is a compound of Formula (XXVIII-B):

Formula (XXVIII-B)

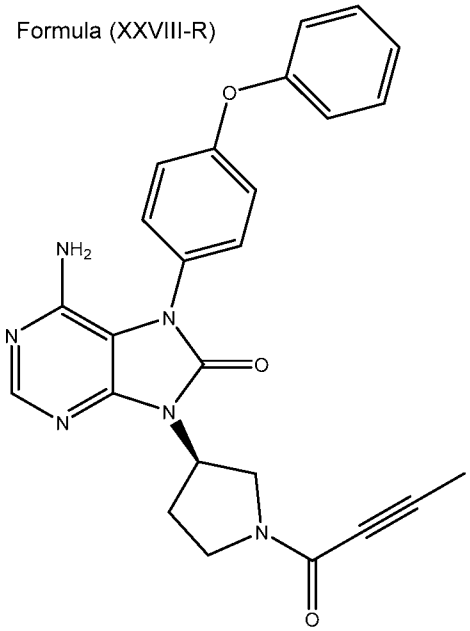



or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, preferably a hydrochloride salt thereof. The preparation of this compound is described in International Patent Application Publication No. WO 2013/081016 A1, the disclosure of which is incorporated by reference herein. In an embodiment, the BTK inhibitor is 6-amino-9-(1-(but-2-ynoyl)pyrrolidin-3-yl)-7-(4-phenoxyphenyl)-7,9-dihydro-8*H*-purin-8-one or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, or preferably a hydrochloride salt thereof. In an embodiment, the BTK inhibitor is 6-amino-9-[(3*S*)-1-(2-butynoyl)-3-pyrrolidinyl]-7-(4-phenoxyphenyl)-7,9-dihydro-8*H*-

purin-8-one or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, or a hydrochloride salt thereof.

**[00565]** The *R*-enantiomer of Formula (XXVIII-B) is also known as ONO-4059, and is given by Formula (XXVIII-R). In a preferred embodiment, the BTK inhibitor is a compound of Formula (XXVIII-R):

Formula (XXVIII-R)



or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, preferably a hydrochloride salt thereof.

**[00566]** In an embodiment, the BTK inhibitor is 6-amino-9-[(3*R*)-1-(2-butynoyl)-3-pyrrolidinyl]-7-(4- phenoxyphenyl)-7,9-dihydro-8*H*-purin-8-one or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, preferably a hydrochloride salt thereof.

**[00567]** The preparation of Formula (XXVII-R) is described in International Patent Application Publication No. WO 2013/081016 A1, the disclosure of which is incorporated by reference herein. In brief, the BTK inhibitor of Formula (XXVIII-R) can be prepared by the following procedure.

**[00568]** Step 1: A solution of dibenzylamine (10.2 g) in dichloromethane (30 mL) is dripped into a solution of 4,6-dichloro-5-nitropyrimidine (10 g) in dichloromethane (70

mL) on an ice bath. Then triethylamine (14.4 mL) is added, and the mixture is stirred for 1 hour. Water is added to the reaction mixture, the organic layer is washed with a saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate, and the solvent is concentrated under reduced pressure to obtain *N*,*N*-dibenzyl-6-chloro-5-nitropyrimidine-4-amine (19.2 g).

**[00569]** Step 2: The compound prepared in Step 1 (19 g) and tert-butyl (3R)-3-aminopyrrolidine-1-carboxylate (10.5 g) are dissolved in dioxane (58 mL). Triethylamine (8.1 mL) is added, and the mixture is stirred for 5 hours at 50° C. The reaction mixture is returned to room temperature, the solvent is distilled off, water is added, and extraction is performed with ethyl acetate. The organic layer is washed with saturated aqueous sodium chloride solution, then dried over anhydrous sodium sulfate, and the solvent is distilled off. The residue is purified by silica gel column chromatography to obtain *tert*-butyl (3*R*)-3-{[6-(dibenzylamino)-5-nitropyrimidin-4-yl]amino}pyrrolid- ine-1-carboxylate (27.0 g).

**[00570]** Step 3: An ethyl acetate (360 mL) solution of the compound prepared in Step 2 (17.5 g) is dripped into a mixture of zinc (23.3 g) and a 3.0 M aqueous ammonium chloride solution (11.4 g) on an ice bath, and the temperature is immediately raised to room temperature. After stirring for 2 hours, the reaction mixture is filtered through CELITE and the solvent is distilled off. The residue is purified by silica gel column chromatography to obtain *tert*-butyl (3*R*)-3-{[5-amino-6-(dibenzylamino)pyrimidin-4-yl]amino}pyrrolidine-1-carboxylate (12.4 g).

**[00571]** Step 4: The compound prepared in Step 3 (8.4 g) and 1,1'-carbonyl diimidazole (5.9 g) are dissolved in tetrahydrofuran (120 mL) and the solution is stirred for 15 hours at 60° C. The solvent is distilled off from the reaction mixture, water is added, and extraction with ethyl acetate is performed. The organic layer is washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and the solvent is distilled off. The residue is purified by silica gel column chromatography to obtain *tert*-butyl (3*R*)-3-[6-(dibenzylamino)-8-oxo-7,8-dihydro-9*H*-purin-9-yl]pyrrolidin-1-carboxylate (7.8 g).

**[00572]** Step 5: The compound prepared in Step 4 (7.8 g) is dissolved in methanol (240 mL) and ethyl acetate (50 mL), 20% Pearlman's catalyst ($Pd(OH)_2/C$) (8.0 g, 100 wt %) is added, hydrogen gas replacement is carried out, and stirring is performed for 7.5 hours at 60° C. The reaction mixture is filtered through CELITE and the solvent is distilled off to obtain *tert*-butyl (3*R*)-3-(6-amino-8-oxo-7,8-dihydro-9*H*-purin-9-yl)pyrrolidine-1-carboxylate (5.0 g).

**[00573]** Step 6: At room temperature p-phenoxy phenyl boronic acid (2.1 g), copper(II) acetate (1.48 g), molecular sieve 4A (2.5 g), and pyridine (0.82 mL) are added to a dichloromethane suspension (200 mL) of the compound prepared in Step 5 (2.5 g), followed by stirring for 21 hours. The reaction mixture is filtered through CELITE and the residue is purified by silica gel column chromatography to obtain *tert*-butyl (3*R*)-3-[6-amino-8-oxo-7-(4-phenoxyphenyl)-7,8-dihydro-9*H*-purin-9-yl]pyrrolidine-1-carboxylate (1.3 g).

**[00574]** Step 7: At room temperature 4 N HCl/dioxane (13 mL) is added to a methanol (13 mL) suspension of the compound prepared in Step 6 (1.3 g 2.76 mmol, 1.0 equivalent), and the mixture is stirred for 1 hour. The solvent is then distilled off to obtain (3R)-6-amino-9-pyrrolidin-3-yl-7-(4-phenoxyphenyl)-7,9-dihydro-8*H*-purin-8-one dihydrochloride (1.5 g).

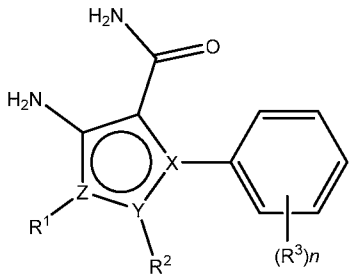
**[00575]** Step 8: After 2-butylnoic acid (34 mg), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC) (78 mg), 1-hydroxybenzotriazole (HOBt) (62 mg), and triethylamine (114 mL) are added to a solution of the compound prepared in Step 7 (100 mg) in dimethyl formamide (3 mL), the mixture is stirred at room temperature for 3 hours. Water is added to the reaction mixture and extraction with ethyl acetate is performed. The organic layer is washed with saturated sodium carbonate solution and saturated aqueous sodium chloride solution, then dried over anhydrous sodium sulfate, and the solvent is distilled off. The residue is purified by thin layer chromatography (dichloromethane:methanol:28% ammonia water=90:10:1) to obtain 6-amino-9-[(3*R*)-1-(2-butynoyl)-3-pyrrolidinyl]-7-(4-phenoxyphenyl)-7,9-dihydro-8H-purin-8-one (Formula (XXVIII-R)) (75 mg).

**[00576]** The hydrochloride salt of the compound of Formula (XXVIII-R) can be prepared as follows: 6-amino-9-[(3*R*)-1-(2-butynoyl)-3-pyrrolidinyl]-7-(4-phenoxyphenyl)-7,9-dihydro-8*H*-purin-8-one (3.0 g) (which may be prepared as described above) is placed in a 300 mL 3-neck pear-shaped flask, ethyl acetate (30 mL) and 1-propanol (4.5 mL) are added, and the external temperature is set at 70° C (internal temperature 61° C). After it is confirmed that the compound prepared in Step 8 has dissolved completely, 10% HCl/methanol (3.5 mL) is added, and after precipitation of crystals is confirmed, the crystals are ripened by the following sequence: external temperature 70° C for 30 min, external temperature 60° C for 30 min, external temperature 50° C for 60 min, external temperature 40° C for 30 min, room temperature for 30 min, and an ice bath for 30 min. The resulting crystals are filtered, washed with ethyl acetate (6 mL), and dried under vacuum at 50° C to obtain white crystals of 6-amino-9-[(3*R*)-1-(2-butynoyl)-3-pyrrolidinyl]-7-(4-phenoxyphenyl)-7,9-dihydro-8*H*-purin-8-one hydrochloride (2.76 g).

**[00577]** In an embodiment, the BTK inhibitor is a compound selected from the structures disclosed in U.S. Patent Application Publication No. US 2014/0330015 A1, the disclosure of which is incorporated by reference herein.

**[00578]** In an embodiment, the BTK inhibitor is a compound of Formula (B):

Formula (B)




or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein:

X-Y-Z is N-C-C and $R^2$ is present, or C-N-N and $R^2$ is absent;

$R^1$ is a 3-8 membered, N-containing ring, wherein the N is unsubstituted or substituted with $R^4$;

$R^2$ is H or lower alkyl, particularly methyl, ethyl, propyl or butyl; or

$R^1$ and $R^2$ together with the atoms to which they are attached, form a 4-8 membered ring, preferably a 5-6 membered ring, selected from cycloalkyl, saturated or unsaturated heterocycle, aryl, and heteroaryl rings unsubstituted or substituted with at least one substituent L-$R^4$;

$R^3$ is in each instance, independently halogen, alkyl, S-alkyl, CN, or $OR^5$;

n is 1, 2, 3, or 4, preferably 1 or 2;

L is a bond, NH, heteroalkyl, or heterocyclyl;

$R^4$ is COR', $CO_2R'$, or $SO_2R'$, wherein R' is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl;

$R^5$ is H or unsubstituted or substituted heteroalkyl, alkyl, cycloalkyl, saturated or unsaturated heterocyclyl, aryl, or heteroaryl.

**[00579]** In some embodiments, the BTK inhibitor is one of the following particular embodiments of Formula B:

X--Y--Z is C--N--N and $R^2$ is absent; and $R^1$ is 3-8 membered, N-containing ring, N-substituted with $R^4$;

X--Y--Z is N--C--C and $R^2$ is present, $R^1$ is 3-8 membered, N-containing ring, N-substituted with $R^4$; and $R^2$ is H or lower alkyl;

X--Y--Z is N--C--C and $R^2$ is present; and $R^1$ and $R^2$ together with the atoms to which they are attached, form a 4-8 membered ring selected from cycloalkyl, saturated or unsaturated heterocycle, aryl, and heteroaryl rings unsubstituted or substituted with at least one substituent L-$R^4$, wherein preferred rings of $R^1$ and $R^2$ are 5-6-membered, particularly dihydropyrrole, tetrahydropyridine, tetrahydroazepine, phenyl, or pyridine;

X--Y--Z is N--C--C and $R^2$ is present; and $R^1$ and $R^2$ together with the atoms to which they are attached, form a 5-6 membered ring, preferably (a) phenyl substituted with a single -L-$R^4$, or (b) dihydropyrrole or tetrahydropyridine, N-substituted with a single -L-$R^4$ wherein L is bond;

$R^1$ is piperidine or azaspiro[3.3]heptane, preferably N-substituted with $R^4$;

$R^4$ is COR' or $SO_2R'$, particularly wherein R' is substituted or unsubstituted alkenyl, particularly substituted or unsubstituted ethenyl; or

$R^5$ is unsubstituted or substituted alkyl or aryl, particularly substituted or unsubstituted phenyl or methyl, such as cyclopropyl-substituted methyl with or tetrabutyl-substituted phenyl.

**[00580]** In some embodiments, the BTK inhibitor is one of the following particular embodiments of Formula B:

$R^1$ is piperidine or azaspiro[3.3]heptane, N-substituted with $R^4$, wherein $R^4$ is H, COR' or $SO_2R'$, and R' is substituted or unsubstituted alkenyl, particularly substituted or unsubstituted ethenyl;

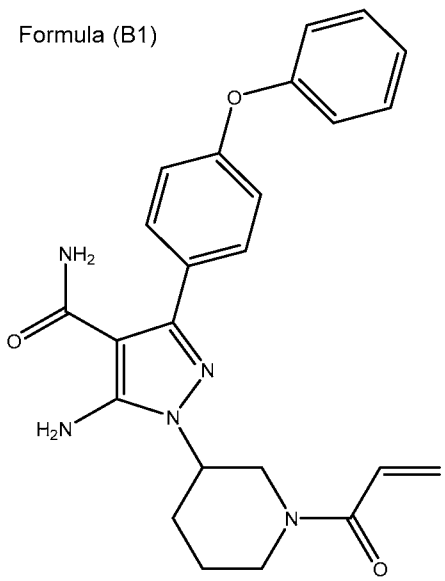
$R^3$ is $-OR^5$, $R^5$ is phenyl, and n is 1;

$R^1$ and $R^2$, together with the atoms to which they are attached, form a 5-6 membered ring, preferably (a) phenyl substituted with a single -L-$R^4$, or (b) dihydropyrrole or tetrahydropyridine, N-substituted with a single -L-$R^4$ wherein L is bond; $R^3$ is $-OR^5$; n is 1; $R^4$ is COR', and R' is ethenyl; and $R^5$ is phenyl; and

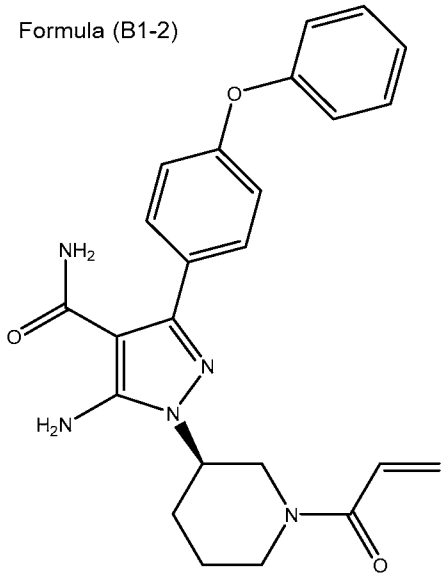
X--Y--Z is C--N--N and $R^2$ is absent; $R^1$ is piperidine, N-substituted with $R^4$; $R^3$ is $-OR^5$; n is 1; $R^4$ is COR', and R' is unsubstituted or substituted alkenyl, particularly ethenyl; and $R^5$ is substituted or unsubstituted aryl, particularly phenyl.

**[00581]** In a preferred embodiment, the BTK inhibitor is a compound of Formula (B1), Formula (B1-2), or Formula (B1-3):

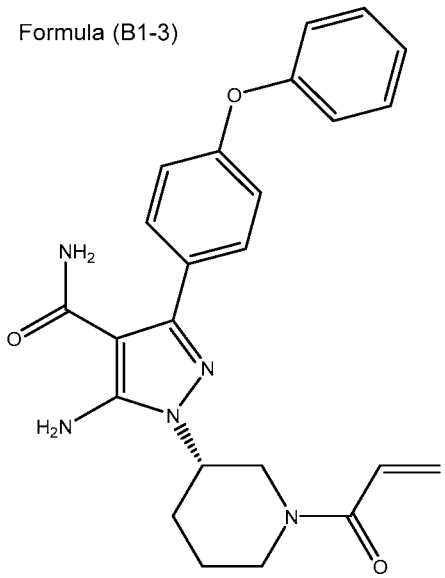
Formula (B1)



Formula (B1-2)



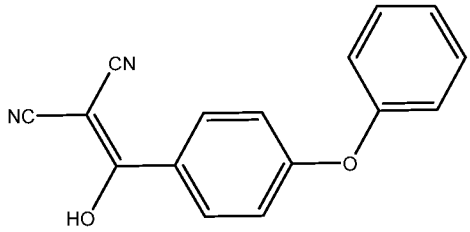
Formula (B1-3)



or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. Formula (B1-2) is also known as BGB-3111. The preparation of these compounds is described in International Patent Application Publication No. WO 2014/173289 A1 and U.S. Patent Application Publication No. US 2015/0005277 A1, the disclosure of which is incorporated by reference herein.

**[00582]** In brief, the BTK inhibitor of Formula (B1) can be prepared by the following procedure.

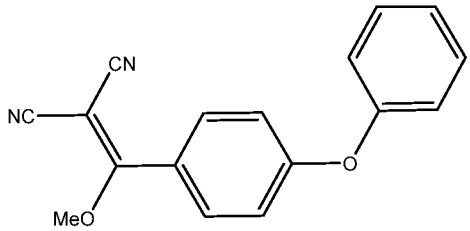
**[00583]** Step 1. Preparation of 2-(hydroxy(4-phenoxyphenyl)methylene)malononitrile:




**[00584]** A solution of 4-phenoxybenzoic acid (300 g, 1.4 mol) in $SOCl_2$ (1.2 L) is stirred at 80° C under $N_2$ for 3 hours. The mixture is concentrated in vacuum to give the intermediate (315 g) which is used for next step without further purification.

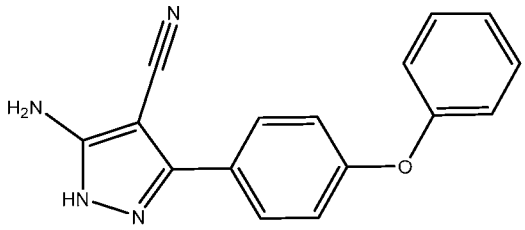
**[00585]** To a solution of propanedinitrile (89.5 g, 1355 mmol) and DIEA (350 g, 2710 mmol) in THF (800 mL) is dropwise a solution of the intermediate (315 g) in toluene (800 mL) at 0-5° C. over 2 hours. The resultant mixture is allowed to warm to RT and stirred for 16 hours. The reaction is quenched with water (2.0 L) and extracted with of EA (2.0 L × 3). The combined organic layers are washed with 1000 mL of 3 N HCl aqueous solution, brine (2.0 L × 3), dried over $Na_2SO_4$ and concentrated to give the crude product (330 g, 93%).

**[00586]** Step 2. Preparation of 2-(Methoxy(4-phenoxyphenyl)methylene)malononitrile:



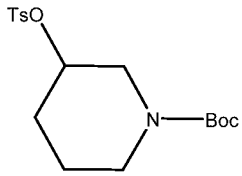

**[00587]** A solution of 2-(hydroxy(4-phenoxyphenyl)methylene)malononitrile (50 g, 190.8 mmol) in $CH(OMe_3)$ (500 mL) is heated to 75°C for 16 hours. Then the mixture is concentrated to a residue and washed with MeOH (50 mL) to give 25 g (47.5%) of 2-(methoxy(4-phenoxyphenyl)methylene)malononitrile as a yellow solid.

**[00588]** Step 3. Preparation of 5-amino-3-(4-phenoxyphenyl)-1*H*-pyrazole-4-carbonitrile:



**[00589]** To a solution of 2-(methoxy(4-phenoxyphenyl)methylene)malononitrile (80 g, 290 mmol) in ethanol (200 mL) is added hydrazine hydrate (20 mL). The mixture is stirred at RT for 16 hours then is concentrated to give the crude product and washed with MeOH (30 mL) to afford 55 g (68.8%) of 5-amino-3-(4-phenoxyphenyl)-1*H*-pyrazole-4-carbonitrile as a off-white solid.

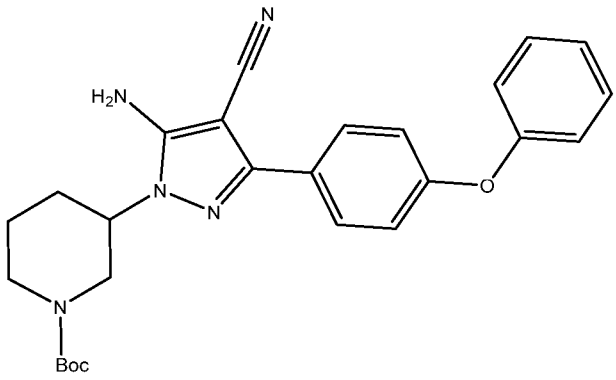
**[00590]** Step 4. Preparation of *tert*-butyl 3-(tosyloxy)piperidine-1-carboxylate:



wherein "Boc" represents a *tert*-butyloxycarbonyl protecting group.

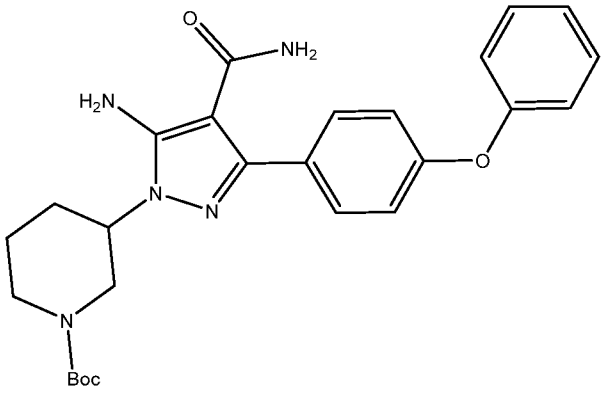
**[00591]** To a solution of *tert*-butyl 3-hydroxypiperidine-1-carboxylate (1.05 g, 5.0 mmol) in pyridine (8 mL) is added TsCl (1.425 g, 7.5 mmol). The mixture is stirred at RT under $N_2$ for two days. The mixture is concentrated and partitioned between 100 mL of EA and 100 mL of HCl (1 N) aqueous solution. The organic layer is separated from aqueous layer, washed with saturated $NaHCO_3$ aqueous solution (100 mL × 2), brine (100 mL × 3) and dried over $Na_2SO_4$. The organic layer is concentrated to afford 1.1 g (60%) of *tert*-butyl 3-(tosyloxy)piperidine-1-carboxylate as a colorless oil.

**[00592]** Step 5. Preparation of *tert*-butyl 3-(5-amino-4-cyano-3-(4-phenoxyphenyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate:




**[00593]** To a solution of *tert*-butyl 3-(tosyloxy)piperidine-1-carboxylate (355 mg, 1.0 mmol) and 5-amino-3-(4-phenoxyphenyl)-1*H*-pyrazole-4-carbonitrile (276 mg, 1.0 mmol) in 5 mL of DMF is added $Cs_2CO_3$ (650 mg, 2.0 mmol). A tosyloxy leaving group is employed in this reaction. The mixture is stirred at RT for 16 hours, 75° C for 3 hours and 60°C for 16 hours. The mixture is concentrated washed with brine (100 mL × 3) and dried over $Na_2SO_4$. The material is concentrated and purified by chromatography column on silica gel (eluted with petroleum ether/ethyl actate = 3/1) to afford 60 mg (13%) of *tert*-butyl 3-(5-amino-4-cyano-3-(4-phenoxyphenyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate as a yellow oil.

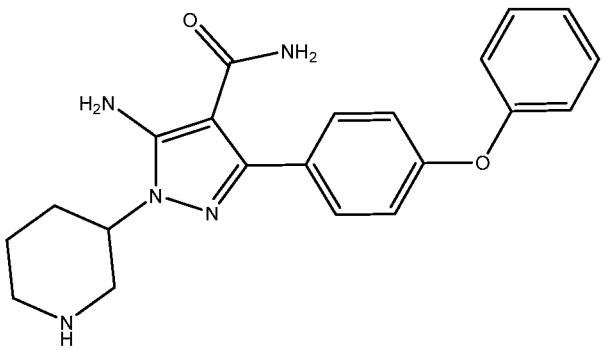
**[00594]** Step 6. Preparation of *tert*-butyl 3-(5-amino-4-carbamoyl-3-(4-phenoxyphenyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate:




**[00595]** To a solution of *tert*-butyl 3-(5-amino-4-cyano-3-(4-phenoxyphenyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate (100 mg, 0.22 mmol) in DMSO (2 mL) and ethanol (2 mL) was added the solution of NaOH (200 mg, 5 mmol) in water (1 mL) and $H_2O_2$ (1 mL). The mixture is stirred at 60° C for 15 min and concentrated to remove EtOH, after which 10 mL of water and 50 mL of ethyl acetate are added. The organic

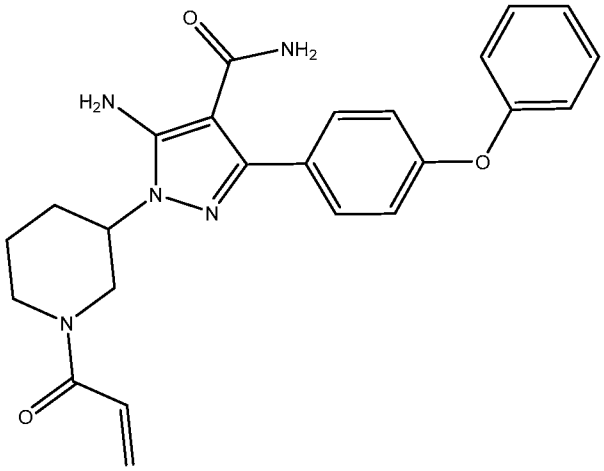
layer is separated from aqueous layer, washed with brine (30 mL × 3) and dried over $Na_2SO_4$. After concentration, 50 mg of residue is used directly in the next step, wherein 50 mg of residue is purified by pre-TLC (eluted with petroleum ether/ethyl actate = 1/1) to afford 12 mg (30%) of *tert*-butyl 3-(5-amino-4-carbamoyl-3-(4-phenoxyphenyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate as a white solid.

**[00596]** Step 7. Preparation of 5-amino-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1*H*-pyrazole-4-carboxamide:




**[00597]** To a solution of *tert*-butyl 3-(5-amino-4-carbamoyl-3-(4-phenoxyphenyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate (50 mg, 0.11 mmol) in ethyl acetate (1 mL) is added concentrated HCl (0.75 mL). The mixture is stirred at RT for 1 hour. Then saturated $NaHCO_3$ is added until pH > 7, followed by ethyl acetate (50 mL). The organic layer is separated from aqueous layer, washed with brine (50 mL × 3) and dried over $Na_2SO_4$. The resulting product is concentrated and purified by Pre-TLC (eluted with dichloromethane/MeOH/$NH_3$-$H_2O$=5/1/0.01) to afford 10 mg (25%) of 5-amino-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1*H*-pyrazole-4-carboxamide as a white solid.

**[00598]** Step 8. Preparation of 1-(1-acryloylpiperidin-3-yl)-5-amino-3-(4-phenoxyphenyl)-1*H*-pyrazole-4-carboxamide:



**[00599]** To a solution of 5-amino-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1*H*-pyrazole-4-carboxamide (63 mg, 0.17 mmol) in dichloromethane (4 mL) is added pyridine (27 mg, 0.34 mmol). Then a solution of acryloyl chloride (12 mg, 0.17 mmol) in dichloromethane (1 mL) is added dropwise. After stirring at RT for 4 hours, the mixture is partitioned between 100 mL of dichloromethane and 100 mL of brine. The organic layer is separated from aqueous layer, washed with brine (100 mL × 2) and dried over $Na_2SO_4$. The material is concentrated and purified by Pre-TLC (eluted with dichloromethane/MeOH=10/1) to afford 4 mg (5.5%) of 1-(1-acryloylpiperidin-3-yl)-5-amino-3-(4-phenoxyphenyl)-1*H*-pyrazole-4-carboxamide as a white solid.

**[00600]** The enantiomers of Formula (B1) provided by the procedure above may be prepared from 5-amino-3-(phenoxyphenyl)-1*H*-pyrazole-4-carbonitrile and (*S*)-*tert*-butyl 3-hydroxypiperidine-1-carboxylate using a similar procedure (step 4 to 8) for Formula (B1-2), or from (*R*)-*tert*-butyl 3-hydroxypiperidine-1-carboxylate using a similar procedure (step 4 to 8) for Formula (B1-3). Under appropriate conditions recognized by one of ordinary skill in the art, a racemic mixture of Formula (B1) may be separated by chiral HPLC, the crystallization of chiral salts, or other means described above to yield Formula (B1-2) and Formula (B1-3) of high enantiomeric purity.

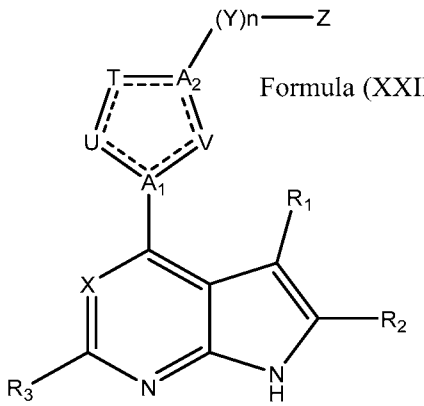
**[00601]** In an embodiment, the BTK inhibitor is a compound selected from the structures disclosed in U.S. Patent Application Publication No. US 2015/0005277A1, the disclosure of which is incorporated by reference herein.

**[00602]** Other BTK inhibitors suitable for use in the described combination with a JAK-2 inhibitor or a PI3K inhibitor, the PI3K inhibitor being preferably selected from the group consisting of a PI3K-γ inhibitor, a PI3K-δ inhibitor, and a PI3K-γ,δ inhibitor, also include, but are not limited to, those described in, for example, International Patent Application Publication Nos. WO 2013/010868, WO 2012/158843, WO 2012/135944, WO 2012/135937, U.S. Patent Application Publication No. 2011/0177011, and U.S. Patent Nos. 8,501,751, 8,476,284, 8,008,309, 7,960,396, 7,825,118, 7,732,454, 7,514,444, 7,459,554, 7,405,295, and 7,393,848, the disclosures of each of which are incorporated herein by reference.

JAK-2 Inhibitors

**[00603]** The JAK-2 inhibitor may be any JAK-2 inhibitor known in the art. In particular, it is one of the JAK-2 inhibitors described in more detail in the following paragraphs. For avoidance of doubt, references herein to a JAK-2 inhibitor may refer to a compound or a pharmaceutically acceptable salt, ester, solvate, hydrate, cocrystal, or prodrug thereof.

**[00604]** In an embodiment, the JAK-2 inhibitor is a compound of Formula (XXIX):




Formula (XXIX)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein:

$A^1$ and $A^2$ are independently selected from C and N;

T, U, and V are independently selected from O, S, N, $CR^5$, and $NR^6$;

wherein the 5-membered ring formed by $A^1$, $A^2$, U, T, and V is aromatic;

X is N or $CR^4$;

Y is $C_{1-8}$ alkylene, $C_{2-8}$ alkenylene, $C_{2-8}$ alkynylene, $(CR^{11}R^{12})_p$—($C_{3-10}$ cycloalkylene)-$(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_p$-(arylene)-$(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_p$—($C_{1-10}$ heterocycloalkylene)-$(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_p$-(heteroarylene)-$(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_pO(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_pS(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_pC(O)(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_pC(O)NR^c(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_pC(O)O(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_pOC(O)(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_pOC(O)NR^c(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_pNR^c(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_pNR^cC(O)NR^d(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_pS(O)(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_pS(O)NR^c(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_pS(O)_2(CR^{11}R^{12})_q$, or $(CR^{11}R^{12})_pS(O)_2NR^c(CR^{11}R^{12})_q$, wherein said $C_{1-8}$ alkylene, $C_{2-8}$ alkenylene, $C_{2-8}$ alkynylene, cycloalkylene, arylene, heterocycloalkylene, or heteroarylene, is optionally substituted with 1, 2, or 3 substituents independently selected from $-D^1-D^2-D^3-D^4$;

Z is H, halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, halosulfanyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, =C—$R^i$, =N—$R^i$, $Cy^1$, CN, $NO_2$, $OR^a$, $SR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $C(=NR^i)NR^cR^d$, $NR^cC(=NR^i)NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $C(=NOH)R^b$, $C(=NO(C_{1-6}\text{ alkyl})R^b$, and $S(O)_2NR^cR^d$, wherein said $C_{1-8}$ alkyl, $C_{2-8}$ alkenyl, or $C_{2-8}$ alkynyl, is optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, halosulfanyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^1$, CN, $NO_2$, $OR^a$, $SR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $C(=NR^i)NR^cR^d$, $NR^cC(=NR^i)NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $C(=NOH)R^b$, $C(=NO(C_{1-6}\text{ alkyl})R^b$, and $S(O)_2NR^cR^d$;

wherein when Z is H, n is 1;

or the —$(Y)_n$—Z moiety is taken together with i) $A^2$ to which the moiety is attached, ii) $R^5$ or $R^6$ of either T or V, and iii) the C or N atom to which the $R^5$ or $R^6$ of either T or V is attached to form a 4- to 20-membered aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring fused to the 5-membered ring formed by $A^1$, $A^2$, U, T, and V, wherein said 4- to 20-membered aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring is optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from —

$(W)_m$-Q;

W is $C_{1-8}$ alkylenyl, $C_{2-8}$ alkenylenyl, $C_{2-8}$ alkynylenyl, O, S, C(O), $C(O)NR^{c'}$, C(O)O, OC(O), $OC(O)NR^{c'}$, $NR^{c'}$, $NR^{c'}C(O)NR^{d'}$, S(O), $S(O)NR^{c'}$, $S(O)_2$, or $S(O)_2NR^{c'}$;

Q is H, halo, CN, $NO_2$, $C_{1-8}$ alkyl, $C_{2-8}$ alkenyl, $C_{2-8}$ alkynyl, $C_{1-8}$ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl, wherein said $C_{1-8}$ alkyl, $C_{2-8}$ alkenyl, $C_{2-8}$ alkynyl, $C_{1-8}$ haloalkyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, halosulfanyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^2$, CN, $NO_2$, $OR^{a'}$, $SR^{a'}$, $C(O)R^{b'}$, $C(O)NR^{c'}R^{d'}$, $C(O)OR^{a'}$, $OC(O)R^{b'}$, $OC(O)NR^{c'}R^{d'}$, $NR^{c'}R^{d'}$, $NR^{c'}C(O)R^{b'}$, $NR^{c'}C(O)NR^{c'}R^{d'}$, $NR^{c'}C(O)OR^{a'}$, $S(O)R^{b'}$, $S(O)NR^{c'}R^{d'}$, $S(O)_2R^{b'}$, $NR^{c'}S(O)_2R^{b'}$, and $S(O)_2NR^{c'}R^{d'}$;

$Cy^1$ and $Cy^2$ are independently selected from aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, each optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, halosulfanyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, CN, $NO_2$, $OR^{a''}$, $SR^{a''}$, $C(O)R^{b''}$, $C(O)NR^{c''}R^{d''}$, $C(O)OR^{a''}$, $OC(O)R^{b''}OC(O)NR^{c''}R^{d''}$, $NR^{c''}R^{d''}$, $NR^{c''}C(O)R^{b''}$, $NR^{c''}C(O)OR^{a''}$, $NR^{c''}S(O)R^{b''}$, $NR^{c''}S(O)_2R^{b''}$, $S(O)R^{b''}$, $S(O)NR^{c''}R^{d''}$, $S(O)_2R^{b''}$, and $S(O)_2NR^{c''}R^{d''}$;

$R^1$, $R^2$, $R^3$, and $R^4$ are independently selected from H, halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, $NO_2$, $OR^7$, $SR^7$, $C(O)R^8$, $C(O)NR^9R^{10}$, $C(O)OR^7OC(O)R^8$, $OC(O)NR^9R^{10}$, $NR^9R^{10}$, $NR^9C(O)R^8$, $NR^cC(O)OR^7$, $S(O)R^8$, $S(O)NR^9R^{10}$, $S(O)_2R^8$, $NR^9S(O)_2R^8$, and $S(O)_2NR^9R^{10}$;

$R^5$ is H, halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, halosulfanyl, CN, $NO_2$, $OR^7$, $SR^7$, $C(O)R^8$, $C(O)NR^9R^{10}$, $C(O)OR^7$, $OC(O)R^8$, $OC(O)NR^9R^{10}$, $NR^9R^{10}$, $NR^9C(O)R^8$, $NR^9C(O)OR^7$, $S(O)R^8$, $S(O)NR^9R^{10}$, $S(O)_2R^8$, $NR^9S(O)_2R^8$, or $S(O)_2NR^9R^{10}$;

$R^6$ is H, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, $OR^7$, $C(O)R^8$, $C(O)NR^9R^{10}$, $C(O)OR^7$, $S(O)R^8$, $S(O)NR^9R^{10}$, $S(O)_2R^8$, or $S(O)_2NR^9R^{10}$;

$R^7$ is H, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl;

$R^8$ is H, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl;

$R^9$ and $R^{10}$ are independently selected from H, $C_{1-10}$ alkyl, $C_{1-6}$ haloalkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{1-6}$ alkylcarbonyl, arylcarbonyl, $C_{1-6}$ alkylsulfonyl, arylsulfonyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl;

or $R^9$ and $R^{10}$ together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group;

$R^{11}$ and $R^{12}$ are independently selected from H and $-E^1-E^2-E^3-E^4$;

$D^1$ and $E^1$ are independently absent or independently selected from $C_{1-6}$ alkylene, $C_{2-6}$ alkenylene, $C_{2-6}$ alkynylene, arylene, cycloalkylene, heteroarylene, and heterocycloalkylene, wherein each of the $C_{1-6}$ alkylene, $C_{2-6}$ alkenylene, $C_{2-6}$ alkynylene, arylene, cycloalkylene, heteroarylene, and heterocycloalkylene is optionally substituted by 1, 2 or 3 substituents independently selected from halo, CN, $NO_2$, $N_3$, SCN, OH, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, $C_{2-8}$ alkoxyalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ haloalkoxy, amino, $C_{1-6}$ alkylamino, and $C_{2-8}$ dialkylamino;

$D^2$ and $E^2$ are independently absent or independently selected from $C_{1-6}$ alkylene, $C_{2-6}$ alkenylene, $C_{2-6}$ alkynylene, $(C_{1-6}\text{ alkylene})_r\text{-O}\text{---}(C_{1-6}\text{ alkylene})_s$, $(C_{1-6}\text{ alkylene})_r\text{-S}\text{---}(C_{1-6}\text{ alkylene})_s$, $(C_{1-6}\text{ alkylene})_s\text{---}NR^e\text{---}(C_{1-6}\text{ alkylene})_s$, $(C_{1-6}\text{ alkylene})_r\text{-CO}\text{---}(C_{1-6}\text{ alkylene})_s$, $(C_{1-6}\text{ alkylene})_r\text{-COO}\text{---}(C_{1-6}\text{ alkylene})_s$, $(C_{1-6}\text{ alkylene})_r\text{-CONR}^e\text{---}(C_{1-6}\text{ alkylene})_s$, $(C_{1-6}\text{ alkylene})_r\text{-SO}\text{---}(C_{1-6}\text{ alkylene})_s$, $(C_{1-6}\text{ alkylene})_r\text{-SO}_2\text{---}(C_{1-6}\text{ alkylene})_s$, $(C_{1-6}\text{ alkylene})_r\text{-SONR}^e\text{---}(C_{1-6}\text{ alkylene})_s$, and $(C_{1-6}\text{ alkylene})_r\text{-NR}^e\text{CONR}^f\text{---}(C_{1-6}\text{ alkylene})_s$, wherein each of the $C_{1-6}$ alkylene, $C_{2-6}$ alkenylene, and $C_{2-6}$ alkynylene is optionally substituted by 1, 2 or 3 substituents independently selected from halo, CN, $NO_2$, $N_3$, SCN, OH, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, $C_{2-8}$ alkoxyalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ haloalkoxy, amino, $C_{1-6}$ alkylamino, and $C_{2-8}$ dialkylamino;

$D^3$ and $E^3$ are independently absent or independently selected from $C_{1-6}$ alkylene, $C_{2-6}$ alkenylene, $C_{2-6}$ alkynylene, arylene, cycloalkylene, heteroarylene, and heterocycloalkylene, wherein each of the $C_{1-6}$ alkylene, $C_{2-6}$ alkenylene, $C_{2-6}$ alkynylene, arylene, cycloalkylene, heteroarylene, and heterocycloalkylene is

optionally substituted by 1, 2 or 3 substituents independently selected from halo, CN, $NO_2$, $N_3$, SCN, OH, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, $C_{2-8}$ alkoxyalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ haloalkoxy, amino, $C_{1-6}$ alkylamino, and $C_{2-8}$ dialkylamino;

$D^4$ and $E^4$ are independently selected from H, halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, halosulfanyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^1$, CN, $NO_2$, $OR^a$, $SR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $C(=NR^i)NR^cR^d$, $NR^cC(=NR^i)NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $C(=NOH)R^b$, $C(=NO(C_{1-6}$ alkyl$)R^b$, and $S(O)_2NR^cR^d$, wherein said $C_{1-8}$ alkyl, $C_{2-8}$ alkenyl, or $C_{2-8}$ alkynyl, is optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, halosulfanyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^1$, CN, $NO_2$, $OR^a$, $SR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $C(=NR^i)NR^cR^d$, $NR^cC(=NR^i)NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $C(=NOH)R^b$, $C(=NO(C_{1-6}$ alkyl$))R^b$, and $S(O)_2NR^cR^d$,

$R^a$ is H, $Cy^1$, —($C_{1-6}$ alkyl)-$Cy^1$, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, wherein said $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, $C_{2-6}$ alkenyl, or $C_{2-6}$ alkynyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, halosulfanyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl and heterocycloalkyl;

$R^b$ is H, $Cy^1$, —($C_{1-6}$ alkyl)-$Cy^1$, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, wherein said $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, $C_{2-6}$ alkenyl, or $C_{2-6}$ alkynyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ haloalkyl, halosulfanyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl and heterocycloalkyl;

$R^{a'}$ and $R^{a''}$ are independently selected from H, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein said $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, $C_{1-6}$

alkyl, $C_{1-6}$ haloalkyl, halosulfanyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl and heterocycloalkyl;

$R^{b'}$ and $R^{b''}$ are independently selected from H, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein said $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ haloalkyl, halosulfanyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl and heterocycloalkyl;

$R^c$ and $R^d$ are independently selected from H, $Cy^1$, —($C_{1-6}$ alkyl)-$Cy^1$, $C_{1-10}$ alkyl, $C_{1-6}$ haloalkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, wherein said $C_{1-10}$ alkyl, $C_{1-6}$ haloalkyl, $C_{2-6}$ alkenyl, or $C_{2-6}$ alkynyl, is optionally substituted with 1, 2, or 3 substituents independently selected from $Cy^1$, —($C_{1-6}$ alkyl)-$Cy^1$, OH, CN, amino, halo, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ haloalkyl, and halosulfanyl;

or $R^c$ and $R^d$ together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from $Cy^1$, —($C_{1-6}$ alkyl)-$Cy^1$, OH, CN, amino, halo, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ haloalkyl, and halosulfanyl;

$R^{c'}$ and $R^{d'}$ are independently selected from H, $C_{1-10}$ alkyl, $C_{1-6}$ haloalkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein said $C_{1-10}$ alkyl, $C_{1-6}$ haloalkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ haloalkyl, halosulfanyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl and heterocycloalkyl;

or $R^{c'}$ and $R^{d'}$ together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ haloalkyl, halosulfanyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl and

heterocycloalkyl;

$R^{c''}$ and $R^{d''}$ are independently selected from H, $C_{1-10}$ alkyl, $C_{1-6}$ haloalkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein said $C_{1-10}$ alkyl, $C_{1-6}$ haloalkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, halosulfanyl, $C_{1-6}$ haloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl and heterocycloalkyl;

or $R^{c''}$ and $R^{d''}$ together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ haloalkyl, halosulfanyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl and heterocycloalkyl;

$R^i$ is H, CN, $NO_2$, or $C_{1-6}$ alkyl;

$R^e$ and $R^f$ are independently selected from H and $C_{1-6}$ alkyl;

$R^i$ is H, CN, or $NO_2$;

m is 0 or 1;

n is 0 or 1;

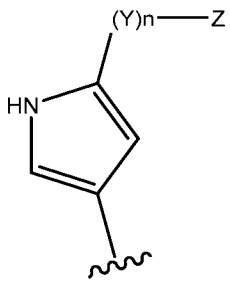
p is 0, 1, 2, 3, 4, 5, or 6;

q is 0, 1, 2, 3, 4, 5 or 6;

r is 0 or 1; and

s is 0 or 1.

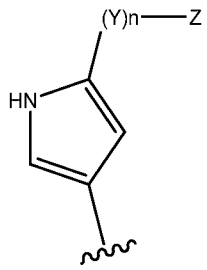
**[00605]** In some embodiments, when X is N, n is 1, and the moiety formed by $A^1$, $A^2$, U, T, V, and —$(Y)_n$—Z has the formula:



then Y is other than $(CR^{11}R^{12})_pC(O)NR^c(CR^{11}R^{12})_q$.

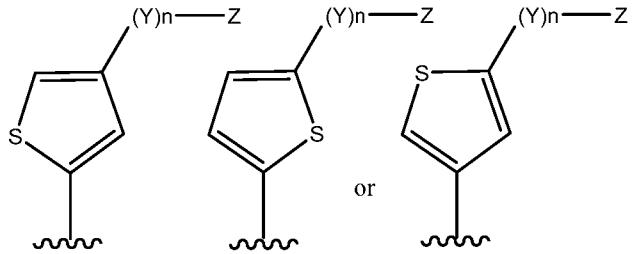
**[00606]** In some embodiments, when X is N, the 5-membered ring formed by $A^1$, $A^2$, U, T, and V is other than pyrrolyl.

**[00607]** In some embodiments, when X is CH, n is 1, and the moiety formed by $A^1$, $A^2$, U, T, V, and $—(Y)_n—Z$ has the formula:



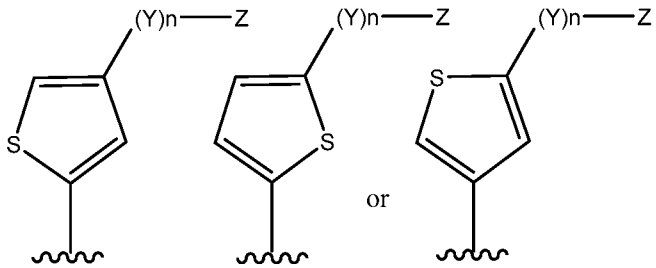

then $—(Y)_n—Z$ is other than COOH.

**[00608]** In some embodiments, when X is CH or C-halo, $R^1$, $R^2$, and $R^3$ are each H, n is 1, and the moiety formed by $A^1$, $A^2$, U, T, V, and $—(Y)_n—Z$ has the formula:



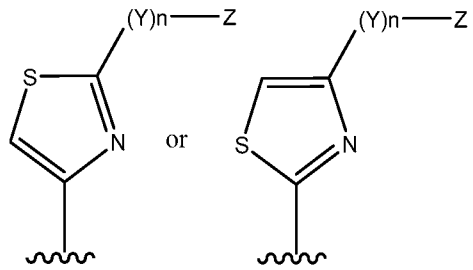

then Y is other than $(CR^{11}R^{12})_pC(O)NR^c(CR^{11}R^{12})_q$ or $(CR^{11}R^{12})_pC(O)(CR^{11}R^{12})_q$.

**[00609]** In some embodiments, when X is CH or C-halo, $R^1$, $R^2$, and $R^3$ are each H, n is 0, and the moiety formed by $A^1$, $A^2$, U, T, V, and $—(Y)_n—Z$ has the formula:



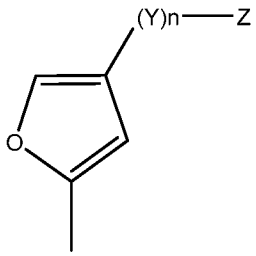

then Z is other than CN, halo, or $C_{1-4}$ alkyl.

**[00610]** In some embodiments, when X is CH or C-halo, $R^1$, $R^2$, and $R^3$ are each H, n is 1, and the moiety formed by $A^1$, $A^2$, U, T, V, and —$(Y)_n$—Z has the formula:



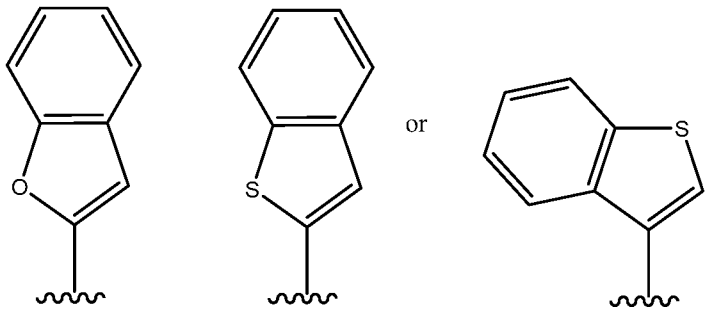

then Y is other than $(CR^{11}R^{12})_pC(O)NR^c(CR^{11}R^{12})_q$ or $(CR^{11}R^{12})_pC(O)(CR^{11}R^{12})_q$.

**[00611]** In some embodiments, when X is CH or C-halo, $R^1$, $R^2$, and $R^3$ are each H, n is 1, and the moiety formed by $A^1$, $A^2$, U, T, V, and —$(Y)_n$—Z has the formula:




then Y is other than $(CR^{11}R^{12})_pNR^c(CR^{11}R^{12})_q$.

**[00612]** In some embodiments, when X is CH or C-halo and $R^1$, $R^2$, and $R^3$ are each H, then the moiety formed by $A^1$, $A^2$, U, T, V, and —$(Y)_n$—Z has a formula other than:




**[00613]** In some embodiments:

Z is H, halo, CN, $NO_2$, $C_{1-8}$ alkyl, $C_{2-8}$ alkenyl, $C_{2-8}$ alkynyl, $C_{1-8}$ haloalkyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl, wherein said $C_{1-8}$ alkyl, $C_{2-8}$ alkenyl, $C_{2-8}$ alkynyl, $C_{1-8}$ haloalkyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally

substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^1$, CN, $NO_2$, $OR^a$, $SR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $C(=NR^i)NR^cR^d$, $NR^cC(=NR^i)NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$;

Q is H, halo, CN, $NO_2$, $C_{1-8}$ alkyl, $C_{2-8}$ alkenyl, $C_{2-8}$ alkynyl, $C_{1-8}$ haloalkyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl, wherein said $C_{1-8}$ alkyl, $C_{2-8}$ alkenyl, $C_{2-8}$ alkynyl, $C_{1-8}$ haloalkyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^2$, CN, $NO_2$, $OR^{a'}$, $SR^{a'}$, $C(O)R^{b'}$, $C(O)NR^{c'}R^{d'}$, $C(O)OR^{a'}$, $OC(O)R^{b'}$, $OC(O)NR^{c'}R^{d'}$, $NR^{c'}R^{d'}$, $NR^{c'}C(O)R^{b'}$, $NR^{c'}C(O)NR^{c'}R^{d'}$, $NR^{c'}C(O)OR^{a'}$, $S(O)R^{b'}$, $S(O)NR^{c'}R^{d'}$, $S(O)_2R^{b'}$, $NR^{c'}S(O)_2R^{b'}$, and $S(O)_2NR^{c'}R^{d'}$;

$Cy^1$ and $Cy^1$ are independently selected from aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, each optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, CN, $NO_2$, $OR^{a''}$, $SR^{a''}$, $C(O)R^{b''}$, $C(O)NR^{c''}R^{d''}$, $C(O)OR^{a''}$, $OC(O)R^{b''}$, $OC(O)NR^{c''}R^{d''}$, $NR^{c''}R^{d''}$, $NR^{c''}C(O)R^{b''}$, $NR^{c''}C(O)OR^{a''}$, $NR^{c''}S(O)R^{b''}$, $NR^{c''}S(O)_2R^{b''}$, $S(O)R^{b''}$, $S(O)NR^{c''}R^{d''}$, $S(O)_2R^{b''}$, and $S(O)_2NR^{c''}R^{d''}$;

$R^1$, $R^2$, $R^3$, and $R^4$ are independently selected from H, halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, $NO_2$, $OR^7$, $SR^7$, $C(O)R^8$, $C(O)NR^9R^{10}$, $C(O)OR^7OC(O)R^8$, $OC(O)NR^9R^{10}$, $NR^9R^{10}$, $NR^9C(O)R^8$, $NR^cC(O)OR^7$, $S(O)R^8$, $S(O)NR^9R^{10}$, $S(O)_2R^8$, $NR^9S(O)_2R^8$, and $S(O)_2NR^9R^{10}$;

$R^5$ is H, halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, CN, $NO_2$, $OR^7$, $SR^7$, $C(O)R^8$, $C(O)NR^9R^{10}$, $C(O)OR^7$, $OC(O)R^8$, $OC(O)NR^9R^{10}$, $NR^9R^{10}$, $NR^9C(O)R^8$, $NR^9C(O)OR^7$, $S(O)R^8$, $S(O)NR^9R^{10}$, $S(O)_2R^8$, $NR^9S(O)_2R^8$, or $S(O)_2NR^9R^{10}$;

$R^6$ is H, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, $OR^7$, $C(O)R^8$, $C(O)NR^9R^{10}$, $C(O)OR^7$, $S(O)R^8$, $S(O)NR^9R^{10}$, $S(O)_2R^8$, or $S(O)_2NR^9R^{10}$;

$R^7$ is H, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl;

$R^8$ is H, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, aryl, cycloalkyl, heteroaryl,

heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl;

$R^9$ and $R^{10}$ are independently selected from H, $C_{1-10}$ alkyl, $C_{1-6}$ haloalkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{1-6}$ alkylcarbonyl, arylcarbonyl, $C_{1-6}$ alkylsulfonyl, arylsulfonyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl;

or $R^9$ and $R^{10}$ together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group;

$R^{11}$ and $R^{12}$ are independently selected from H, halo, OH, CN, $C_{1-4}$ alkyl, $C_{1-4}$ haloalkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl;

$R^a$, $R^{a'}$, and $R^{a''}$ are independently selected from H, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein said $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl and heterocycloalkyl;

$R^b$, $R^{b'}$ and $R^{b''}$ are independently selected from H, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein said $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ haloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl and heterocycloalkyl;

$R^c$ and $R^d$ are independently selected from H, $C_{1-10}$ alkyl, $C_{1-6}$ haloalkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein said $C_{1-10}$ alkyl, $C_{1-6}$ haloalkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl is optionally substituted

with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ haloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl or heterocycloalkyl;

or $R^c$ and $R^d$ together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ haloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl and heterocycloalkyl;

$R^{c'}$ and $R^{d'}$ are independently selected from H, $C_{1-10}$ alkyl, $C_{1-6}$ haloalkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein said $C_{1-10}$ alkyl, $C_{1-6}$ haloalkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ haloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl and heterocycloalkyl;

or $R^{c'}$ and $R^{d'}$ together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ haloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl and heterocycloalkyl;

$R^{c''}$ and $R^{d''}$ are independently selected from H, $C_{1-10}$ alkyl, $C_{1-6}$ haloalkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein said $C_{1-10}$ alkyl, $C_{1-6}$ haloalkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ haloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl and heterocycloalkyl;

or $R^{c''}$ and $R^{d''}$ together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ haloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl and heterocycloalkyl.

**[00614]** In some embodiments, X is N.

**[00615]** In some embodiments, X is $CR^4$.

**[00616]** In some embodiments, $A^1$ is C.

**[00617]** In some embodiments, $A^1$ is N.

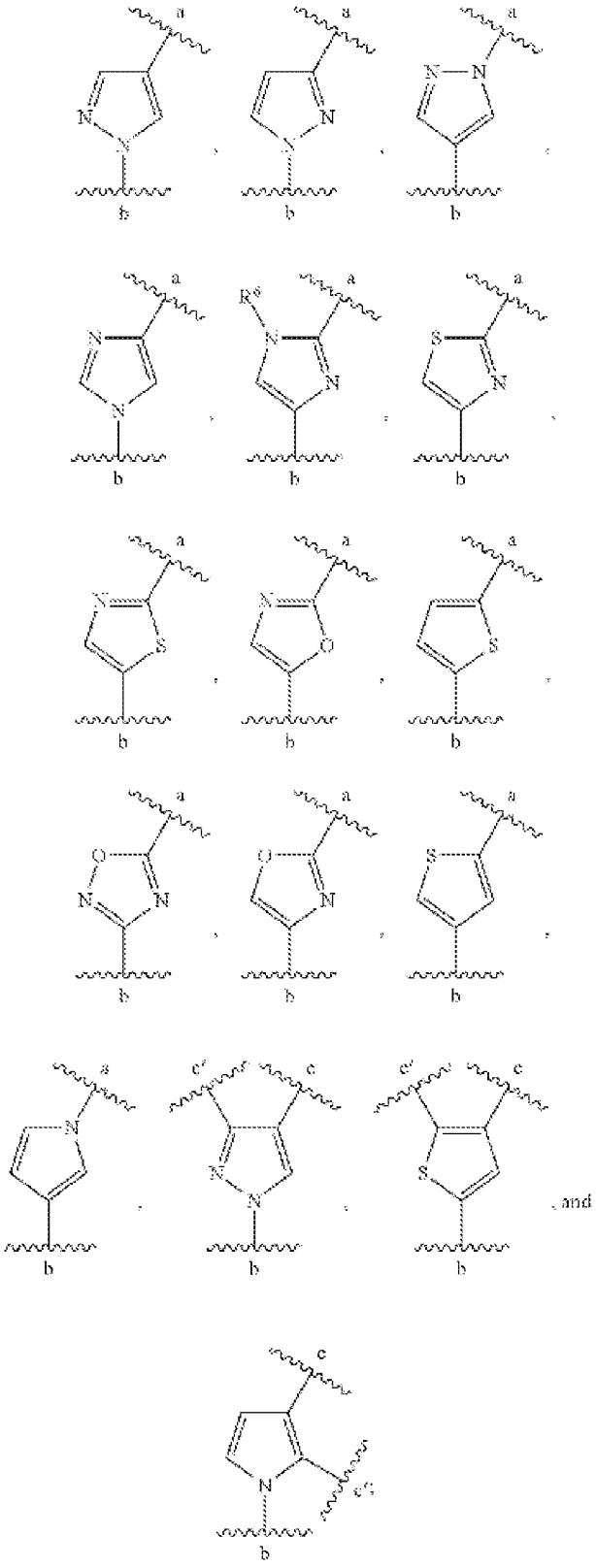
**[00618]** In some embodiments, $A^2$ is C.

**[00619]** In some embodiments, $A^2$ is N.

**[00620]** In some embodiments, at least one of $A^1$, $A^2$, U, T, and V is N.

**[00621]** In some embodiments, the 5-membered ring formed by $A^1$, $A^2$, U, T, and V is pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, or oxadiazolyl.

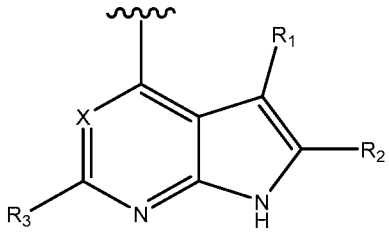
**[00622]** In some embodiments, the 5-membered ring formed by $A^1$, $A^2$, U, T, and V is selected from:



wherein:

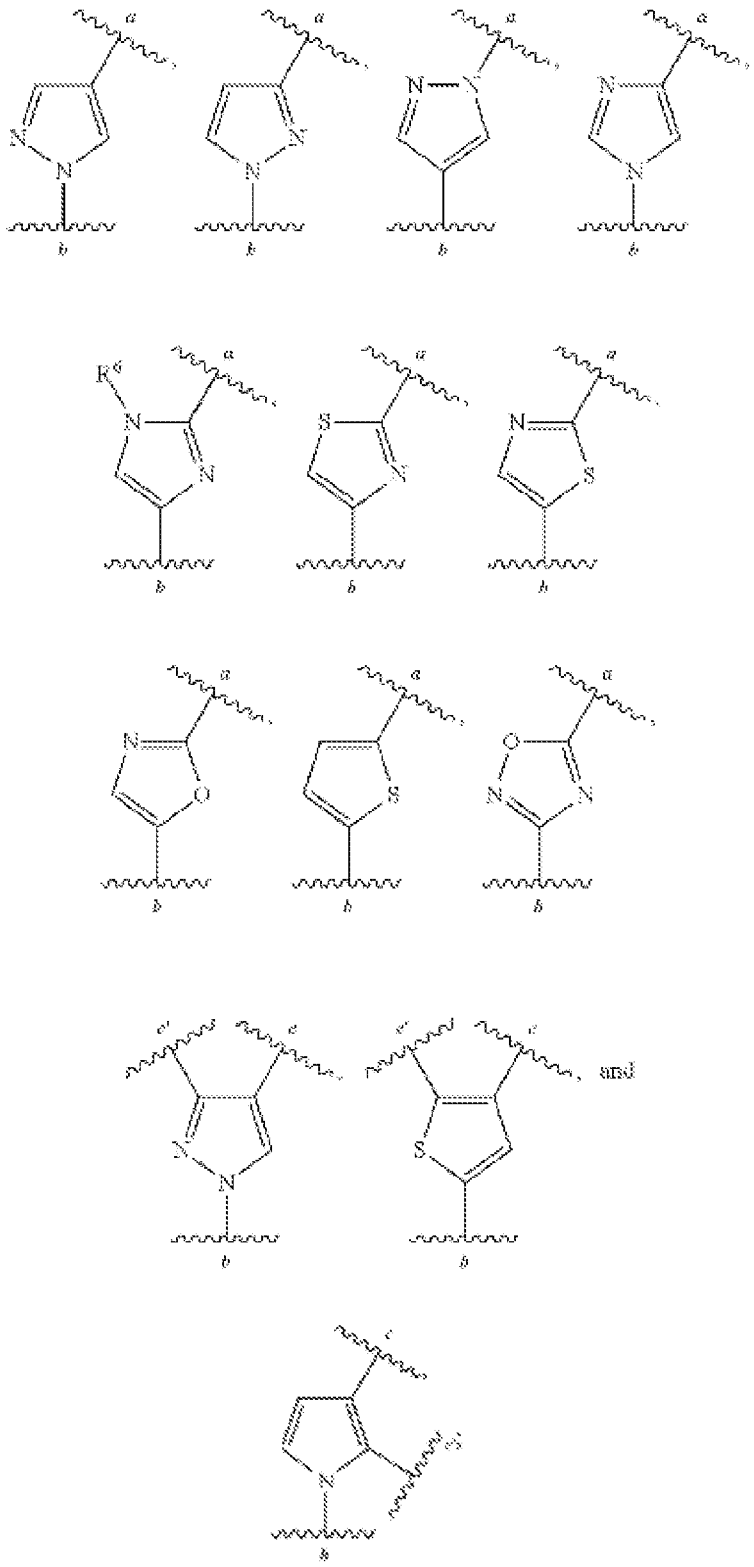
a designates the site of attachment of moiety —$(Y)_n$—Z;

b designates the site of attachment to the core moiety:




and c and c' designate the two sites of attachment of the fused 4- to 20-membered aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring.

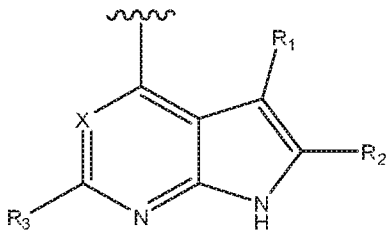
**[00623]** In some embodiments, the 5-membered ring formed by $A^1$, $A^2$, U, T, and V is:



wherein:

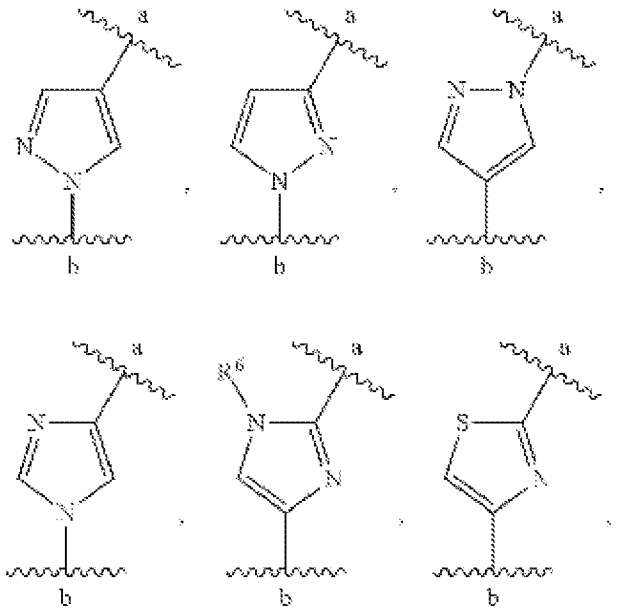
a designates the site of attachment of moiety —$(Y)_n$—Z;

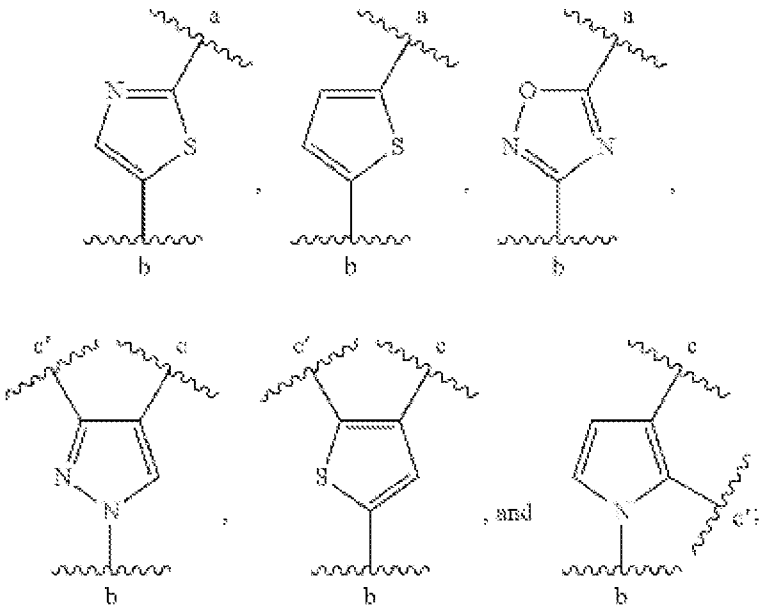
b designates the site of attachment to the core moiety.




and c and c′ designate the two sites of attachment of the fused 4- to 20-membered aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring.

**[00624]** In some embodiments, the 5-membered ring formed by $A^1$, $A^2$, U, T, and V is selected from:

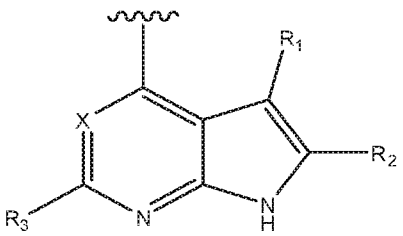





wherein:

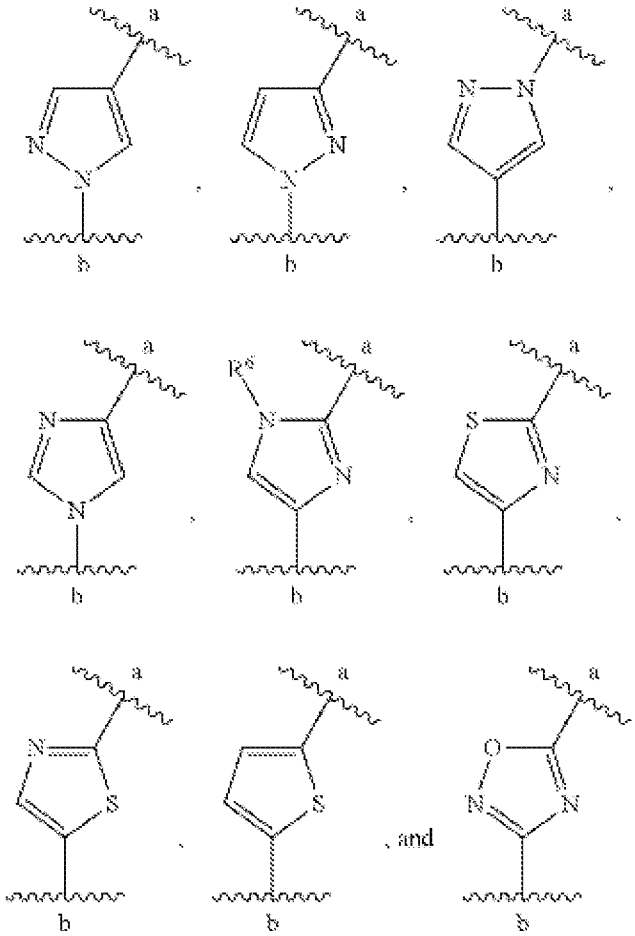
a designates the site of attachment of moiety $—(Y)_n—Z$;

b designates the site of attachment to the core moiety:




and c and c′ designate the two sites of attachment of the fused 4- to 20-membered aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring.

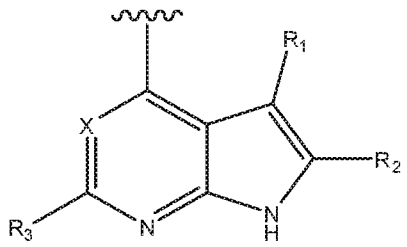
**[00625]** In some embodiments, the 5-membered ring formed by $A^1$, $A^2$, U, T, and V is selected from:



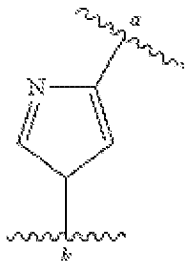
wherein:

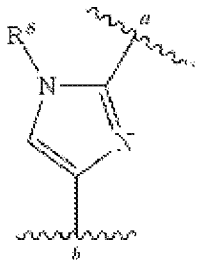
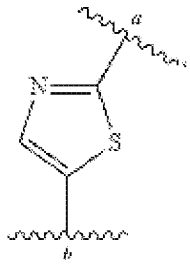
a designates the site of attachment of moiety —(Y)$_n$—Z;

b designates the site of attachment to the core moiety:



**[00626]** In some embodiments, the 5-membered ring formed by $A^1$, $A^2$, U, T, and V is selected from:

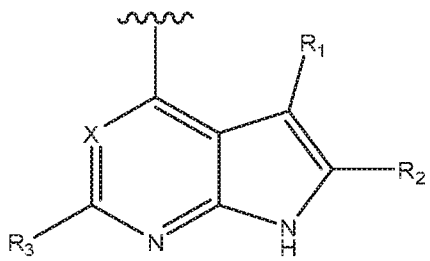




and


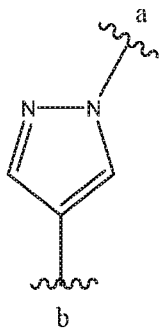
wherein:

a designates the site of attachment of moiety —$(Y)_n$—Z;

b designates the site of attachment to the core moiety:



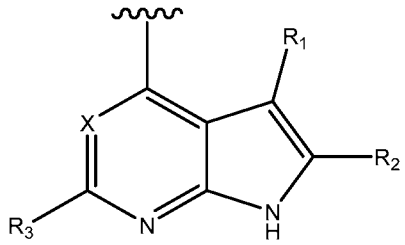
**[00627]** In some embodiments, the 5-membered ring formed by $A^1$, $A^2$, U, T, and V is selected from:



wherein:

a designates the site of attachment of moiety —$(Y)_n$—Z;

b designates the site of attachment to the core moiety:




**[00628]** In some embodiments, n is 0.

**[00629]** In some embodiments, n is 1.

**[00630]** In some embodiments, n is 1 and Y is $C_{1-8}$ alkylene, $C_{2-8}$ alkenylene, $(CR^{11}R^{12})_pC(O)(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_pC(O)NR^c(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_pC(O)O(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_pOC(O)(CR^{11}R^{12})_q$, wherein said $C_{1-8}$ alkylene or $C_{2-8}$ alkenylene, is optionally substituted with 1, 2, or 3 halo, OH, CN, amino, $C_{1-4}$ alkylamino, or $C_{2-8}$ dialkylamino.

**[00631]** In some embodiments, n is 1 and Y is $C_{1-8}$ alkylene, $(CR^{11}R^{12})_pC(O)(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_pC(O)NR^c(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_pC(O)O(CR^{11}R^{12})_q$, wherein said $C_{1-8}$ alkylene is optionally substituted with 1, 2, or 3 halo, OH, CN, amino, $C_{1-4}$ alkylamino, or $C_{2-8}$ dialkylamino.

**[00632]** In some embodiments, n is 1 and Y is $C_{1-8}$ alkylene optionally substituted with 1, 2, or 3 halo, OH, CN, amino, $C_{1-4}$ alkylamino, or $C_{2-8}$ dialkylamino.

**[00633]** In some embodiments, n is 1 and Y is ethylene optionally substituted with 1, 2, or 3 halo, OH, CN, amino, $C_{1-4}$ alkylamino, or $C_{2-8}$ dialkylamino.

**[00634]** In some embodiments, n is 1 and Y is $(CR^{11}R^{12})_pC(O)(CR^{11}R^{12})_q$ $(CR^{11}R^{12})_pC(O)NR^c(CR^{11}R^{12})_q$, or $(CR^{11}R^{12})_pC(O)O(CR^{11}R^{12})_q$.

**[00635]** In some embodiments, Y is $C_{1-8}$ alkylene, $C_{2-8}$ alkenylene, $C_{2-8}$ alkynylene, $(CR^{11}R^{12})_p$—($C_{3-10}$ cycloalkylene)-$(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_p$-(arylene)-$(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_p$—($C_{1-10}$ heterocycloalkylene)-$(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_p$-(heteroarylene)-$(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_pO(CR^{11}R^{12})_q$, or $(CR^{11}R^{12})_pS(CR^{11}R^{12})_q$, wherein said $C_{1-8}$ alkylene, $C_{2-8}$ alkenylene, $C_{2-8}$ alkynylene, cycloalkylene, arylene, heterocycloalkylene, or

heteroarylene, is optionally substituted with 1, 2, or 3 substituents independently selected from $-D^1-D^2-D^3-D^4$.

**[00636]** In some embodiments, Y is $C_{1-8}$ alkylene, $C_{2-8}$ alkenylene, $C_{2-8}$ alkynylene, $(CR^{11}R^{12})_p$—($C_{3-10}$ cycloalkylene)-$(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_p$-(arylene)-$(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_p$—($C_{1-10}$ heterocycloalkylene)-$(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_p$-(heteroarylene)-$(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_pO(CR^{11}R^{12})_q$, or $(CR^{11}R^{12})_pS(CR^{11}R^{12})_q$, wherein said $C_{1-8}$ alkylene, $C_{2-8}$ alkenylene, $C_{2-8}$ alkynylene, cycloalkylene, arylene, heterocycloalkylene, or heteroarylene, is optionally substituted with 1, 2, or 3 substituents independently selected from $D^4$.

**[00637]** In some embodiments, Y is $C_{1-8}$ alkylene, $C_{2-8}$ alkenylene, $C_{2-8}$ alkynylene, or $(CR^{11}R^{12})_p$—($C_{3-10}$ cycloalkylene)-$(CR^{11}R^{12})_q$, wherein said $C_{1-8}$ alkylene, $C_{2-8}$ alkenylene, $C_{2-8}$ alkynylene, or cycloalkylene, is optionally substituted with 1, 2, or 3 substituents independently selected from $-D^1-D^2-D^3-D^4$.

**[00638]** In some embodiments, Y is $C_{1-8}$ alkylene, $C_{2-8}$ alkenylene, $C_{2-8}$ alkynylene, or $(CR^{11}R^{12})_p$—($C_{3-10}$ cycloalkylene)-$(CR^{11}R^{12})_q$, wherein said $C_{1-8}$ alkylene, $C_{2-8}$ alkenylene, $C_{2-8}$ alkynylene, or cycloalkylene, is optionally substituted with 1, 2, or 3 substituents independently selected from $D^4$.

**[00639]** In some embodiments, Y is $C_{1-8}$ alkylene, $C_{2-8}$ alkenylene, or $C_{2-8}$ alkynylene, each optionally substituted with 1, 2, or 3 substituents independently selected from $-D^1-D^2-D^3-D^4$.

**[00640]** In some embodiments, Y is $C_{1-8}$ alkylene optionally substituted with 1, 2, or 3 substituents independently selected from $-D^1-D^2-D^3-D^4$.

**[00641]** In some embodiments, Y is $C_{1-8}$ alkylene optionally substituted with 1, 2, or 3 substituents independently selected from $D^4$.

**[00642]** In some embodiments, Y is $C_{1-8}$ alkylene, $C_{2-8}$ alkenylene, $C_{2-8}$ alkynylene, $(CR^{11}R^{12})_pO$—$(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_pS(CR^{11}R^{12})_q$, $(CR^{11}R^{12})C(O)(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_pC(O)NR^c(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_pC(O)O(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_pOC(O)(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_pOC(O)NR^c(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_pNR^c(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_pNR^cC(O)NR^d(CR^{11}R^{12})_q$,

$(CR^{11}R^{12})_pS(O)(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_pS(O)NR^c(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_pS(O)_2(CR^{11}R^{12})_q$, or $(CR^{11}R^{12})_pS(O)_2NR^c(CR^{11}R^{12})_q$, wherein said $C_{1-8}$ alkylene, $C_{2-8}$ alkenylene, $C_{2-8}$ alkynylene is optionally substituted with 1, 2, or 3 substituents independently selected from halo, OH, CN, amino, $C_{1-4}$ alkylamino, and $C_{2-8}$ dialkylamino.

**[00643]** In some embodiments, Y is $C_{1-8}$ alkylene, $C_{2-8}$ alkenylene, $C_{2-8}$ alkynylene, $(CR^{11}R^{12})_p$—($C_{3-10}$ cycloalkylene)-$(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_p$-(arylene)-$(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_p$—($C_{1-10}$ heterocycloalkylene)-$(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_p$-(heteroarylene)-$(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_pO(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_pS(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_pC(O)(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_pC(O)NR^c(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_pC(O)O(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_pOC(O)(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_pOC(O)NR^c(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_pNR^c(CR^{11}R^{12})_q$ $(CR^{11}R^{12})_pNR^cC(O)NR^d(CR^{11}R^{12})_q$, $(CR^{11}R^{12})S(O)(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_pS(O)NR^c(CR^{11}R^{12})_q$, $(CR^{11}R^{12})_pS(O)_2(CR^{11}R^{12})_q$, or $(CR^{11}R^{12})_pS(O)_2NR^c(CR^{11}R^{12})_q$, wherein said $C_{1-8}$ alkylene, $C_{2-8}$ alkenylene, $C_{2-8}$ alkynylene, cycloalkylene, arylene, heterocycloalkylene, or heteroarylene, is optionally substituted with 1, 2, or 3 substituents independently selected from halo, OH, CN, amino, $C_{1-4}$ alkylamino, and $C_{2-8}$ dialkylamino.

**[00644]** In some embodiments, p is 0.

**[00645]** In some embodiments, p is 1.

**[00646]** In some embodiments, p is 2.

**[00647]** In some embodiments, q is 0.

**[00648]** In some embodiments, q is 1.

**[00649]** In some embodiments, q is 2.

**[00650]** In some embodiments, one of p and q is 0 and the other of p and q is 1, 2, or 3.

**[00651]** In some embodiments, Z is H, halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, halosulfanyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^1$, CN, $NO_2$, $OR^a$, $SR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $C(=NR^i)NR^cR^d$, $NR^cC(=NR^i)NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $C(=NOH)R^b$, $C(=NO(C_{1-6}\text{ alkyl})R^b$, and $S(O)_2NR^cR^d$, wherein said $C_{1-8}$ alkyl, $C_{2-8}$ alkenyl, or $C_{2-8}$ alkynyl, is optionally

substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, halosulfanyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^1$, CN, $NO_2$, $OR^a$, $SR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $C(=NR^i)NR^cR^d$, $NR^cC(=NR^i)NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $C(=NOH)R^b$, $C(=NO(C_{1-6}\text{ alkyl}))R^b$, and $S(O)_2NR^cR^d$.

**[00652]** In some embodiments, Z is aryl, cycloalkyl, heteroaryl, or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, halosulfanyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^1$, CN, $NO_2$, $OR^a$, $SR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $C(=NR^i)NR^cR^d$, $NR^cC(=NR^i)NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$.

**[00653]** In some embodiments, Z is aryl, cycloalkyl, heteroaryl, or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^1$, CN, $NO_2$, $OR^a$, $SR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $C(=NR^i)NR^cR^d$, $NR^cC(=NR^i)NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$.

**[00654]** In some embodiments, Z is aryl or heteroaryl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, halosulfanyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^1$, CN, $NO_2$, $OR^a$, $SR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $C(=NR^i)NR^cR^d$, $NR^cC(=NR^i)NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$.

**[00655]** In some embodiments, Z is aryl or heteroaryl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^1$, CN, $NO_2$, $OR^a$, $SR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $C(=NR^i)NR^cR^d$, $NR^cC(=NR^i)NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$.

**[00656]** In some embodiments, Z is phenyl or 5- or 6-membered heteroaryl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, halosulfanyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^1$, CN, $NO_2$, $OR^a$, $SR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $C(=NR^i)NR^cR^d$, $NR^cC(=NR^i)NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$.

**[00657]** In some embodiments, Z is phenyl or 5- or 6-membered heteroaryl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^1$, CN, $NO_2$, $OR^a$, $SR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $C(=NR^i)NR^cR^d$, $NR^cC(=NR^i)NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$.

**[00658]** In some embodiments, Z is phenyl optionally substituted with 1, 2, 3, 4, 5, or 6 substituents selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, halosulfanyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^1$, CN, $NO_2$, $OR^a$, $SR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $C(=NR^i)NR^cR^d$, $NR^cC(=NR^i)NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$.

**[00659]** In some embodiments, Z is phenyl optionally substituted with 1, 2, 3, 4, 5, or 6 substituents selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^1$, CN, $NO_2$, $OR^a$, $SR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^c$, $C(=NR^i)NR^cR^d$, $NR^cC(=NR^i)NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$.

**[00660]** In some embodiments, Z is cycloalkyl or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, halosulfanyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^1$, CN, $NO_2$, $OR^a$, $SR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $C(=NR^i)NR^cR^d$, $NR^cC(=NR^i)NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$.

**[00661]** In some embodiments, Z is cycloalkyl or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^1$, CN, $NO_2$, $OR^a$, $SR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $C(=NR^i)NR^cR^d$, $NR^cC(=NR^1)NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$.

**[00662]** In some embodiments, Z is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, halosulfanyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^1$, CN, $NO_2$, $OR^a$, $SR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $C(=NR^i)NR^cR^d$, $NR^cC(=NR^i)NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$.

**[00663]** In some embodiments, Z is $C_{1-8}$ alkyl, $C_{2-8}$ alkenyl, or $C_{2-8}$ alkynyl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, halosulfanyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^1$, CN, $NO_2$, $OR^a$, $SR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $C(=NR^i)NR^cR^d$, $NR^cC(=NR^i)NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$.In some embodiments, Z is $C_{1-8}$ alkyl, $C_{2-8}$ alkenyl, or $C_{2-8}$ alkynyl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^1$, CN, $NO_2$, $OR^a$, $SR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $C(=NR^i)NR^cR^d$, $NR^cC(=NR^i)NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$.

**[00664]** In some embodiments, Z is aryl, cycloalkyl, heteroaryl, or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, halosulfanyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^1$, CN, $NO_2$, $OR^a$, $SR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$.

**[00665]** In some embodiments, Z is aryl, cycloalkyl, heteroaryl, or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^1$, CN, $NO_2$, $OR^a$, $SR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$.

**[00666]** In some embodiments, Z is aryl or heteroaryl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, halosulfanyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^1$, CN, $NO_2$, $OR^a$, $SR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$.

**[00667]** In some embodiments, Z is aryl or heteroaryl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^1$, CN, $NO_2$, $OR^a$, $SR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$.

**[00668]** In some embodiments, Z is phenyl or 5- or 6-membered heteroaryl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, halosulfanyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^1$, CN, $NO_2$, $OR^a$, $SR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$.

**[00669]** In some embodiments, Z is phenyl or 5- or 6-membered heteroaryl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^1$, CN, $NO_2$, $OR^a$, $SR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$.

**[00670]** In some embodiments, Z is phenyl optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, halosulfanyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^1$, CN, $NO_2$, $OR^a$, $SR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$.

**[00671]** In some embodiments, Z is phenyl optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^1$, CN, $NO_2$, $OR^a$, $SR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$.

**[00672]** In some embodiments, Z is cycloalkyl or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, halosulfanyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^1$, CN, $NO_2$, $OR^a$, $SR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$.

**[00673]** In some embodiments, Z is cycloalkyl or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^1$, CN, $NO_2$, $OR^a$, $SR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$.

**[00674]** In some embodiments, Z is $C_{1-8}$ alkyl, $C_{2-8}$ alkenyl, or $C_{2-8}$ alkynyl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, halosulfanyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^1$, CN, $NO_2$, $OR^a$, $SR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$.

**[00675]** In some embodiments, Z is $C_{1-8}$ alkyl, $C_{2-8}$ alkenyl, or $C_{2-8}$ alkynyl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, $C_{1-4}$, hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^1$, CN, $NO_2$, $OR^a$, $SR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$.

**[00676]** In some embodiments, Z is $C_{1-8}$ alkyl, $C_{2-8}$ alkenyl, $C_{2-8}$ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, $C_{1-4}$ alkyl, $C_{1-4}$ haloalkyl, halosulfanyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^1$, CN, $NO_2$, $OR^a$, $C(O)NR^cR^d$, $C(O)OR^a$, $NR^cR^d$, $NR^cC(O)R^b$, and $S(O)_2R^b$.

**[00677]** In some embodiments, Z is $C_{1-8}$ alkyl, $C_{2-8}$ alkenyl, $C_{2-8}$ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, $C_{1-4}$ alkyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^1$, CN, $NO_2$, $OR^a$, $C(O)NR^cR^d$, $C(O)OR^a$, $NR^cR^d$, $NR^cC(O)R^b$, and $S(O)_2R^b$.

**[00678]** In some embodiments, Z is $C_{1-8}$ alkyl, $C_{2-8}$ alkenyl, $C_{2-8}$ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl, each optionally substituted with 1, 2, or 3 substituents independently selected from halo, $C_{1-4}$ alkyl, $C_{1-4}$ haloalkyl, halosulfanyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^1$, CN, $NO_2$, $OR^a$, $C(O)NR^cR^d$, $C(O)OR^a$, $NR^cR^d$, $NR^cC(O)R^b$, and $S(O)_2R^b$.

**[00679]** In some embodiments, Z is $C_{1-8}$ alkyl, $C_{2-8}$ alkenyl, $C_{2-8}$ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl, each optionally substituted with 1, 2, or 3 substituents independently selected from halo, $C_{1-4}$ alkyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^1$, CN, $NO_2$, $OR^a$, $C(O)NR^cR^d$, $C(O)OR^a$, $NR^cR^d$, $NR^cC(O)R^b$, and $S(O)_2R^b$.

**[00680]** In some embodiments, Z is substituted with at least one substituent comprising at least one CN group.

**[00681]** In some embodiments, Z is $C_{1-8}$ alkyl, $C_{2-8}$ alkenyl, $C_{2-8}$ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl, each substituted with at least one CN or $C_{1-4}$ cyanoalkyl and optionally substituted with 1, 2, 3, 4, or 5 further substituents selected from halo, $C_{1-4}$ alkyl, $C_{2-8}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, halosulfanyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^1$, CN, $NO_2$, $OR^a$, $SR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$.

**[00682]** In some embodiments, Z is $C_{1-8}$ alkyl, $C_{2-8}$ alkenyl, $C_{2-8}$ alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl, each substituted with at least one CN or $C_{1-4}$ cyanoalkyl and optionally substituted with 1, 2, 3, 4, or 5 further substituents selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^1$, CN, $NO_2$, $OR^a$, $SR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, and $S(O)_2NR^cR^d$.

**[00683]** In some embodiments, wherein the —$(Y)_n$—Z moiety is taken together with i) $A^2$ to which said moiety is attached, ii) $R^5$ or $R^6$ of either T or V, and iii) the C or N atom to which said $R^5$ or $R^6$ of either T or V is attached to form a 4- to 20-membered aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring fused to the 5-membered ring formed by $A^1$, $A^2$, U, T, and V, wherein said 4- to 20-membered aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring is optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from —$(W)_m$-Q.

**[00684]** In some embodiments, wherein the —$(Y)_n$—Z moiety is taken together with i) $A^2$ to which said moiety is attached, ii) $R^5$ or $R^6$ of either T or V, and iii) the C or N atom to which said $R^5$ or $R^6$ of either T or V is attached to form a 4- to 8-membered aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring fused to the 5-membered ring formed by $A^1$, $A^2$, U, T, and V, wherein said 4- to 8-membered aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring is optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from —$(W)_m$-Q.

**[00685]** In some embodiments, the —$(Y)_n$—Z moiety is taken together with i) $A^2$ to which said moiety is attached, ii) $R^5$ or $R^6$ of either T or V, and iii) the C or N atom to

which said $R^5$ or $R^6$ of either T or V is attached to form a 6-membered aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring fused to the 5-membered ring formed by $A^1$, $A^2$, U, T, and V, wherein said 6-membered aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring is optionally substituted by 1, 2, or 3 substituents independently selected from halo, CN, $NO_2$, $C_{1-8}$ alkyl, $C_{2-8}$ alkenyl, $C_{2-8}$ alkynyl, $C_{1-8}$ haloalkyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl wherein said $C_{1-8}$ alkyl, $C_{2-8}$ alkenyl, $C_{2-8}$ alkynyl, $C_{1-8}$ haloalkyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted by 1, 2 or 3 CN.

**[00686]** In some embodiments, $Cy^1$ and $Cy^2$ are independently selected from aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, each optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, CN, $NO_2$, $OR^{a''}$, $SR^{a''}$, $C(O)R^{b''}$, $C(O)NR^{c''}R^{d''}$, $C(O)OR^{a''}$, $OC(O)R^{b''}$, $OC(O)NR^{c''}R^{d''}$, $NR^{c''}R^{d''}$, $NR^{c''}C(O)R^{b''}$, $NR^{c''}C(O)OR^{a''}$, $S(O)R^{b''}$, $S(O)NR^{c''}R^{d''}$, $S(O)_2R^{b''}$, and $S(O)_2NR^{c''}R^{d''}$.

**[00687]** In some embodiments, $Cy^1$ and $Cy^2$ are independently selected from aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, each optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, CN, $NO_2$, $OR^{a''}$, $SR^{a''}$, $C(O)R^{b''}$, $C(O)NR^{c''}R^{d''}$, $C(O)OR^{a''}$, $OC(O)R^{b''}$, $OC(O)NR^{c''}R^{d''}$, $NR^{c''}R^{d''}$, $NR^{c''}C(O)R^{b''}$, $NR^{c''}C(O)OR^{a''}S(O)R^{b''}$, $S(O)NR^{c''}R^{d''}$, $S(O)_2R^{b''}$, and $S(O)_2NR^{c''}R^{d''}$.

**[00688]** In some embodiments, $Cy^1$ and $Cy^2$ are independently selected from cycloalkyl and heterocycloalkyl, each optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, CN, $NO_2$, $OR^{a''}$, $SR^{a''}$, $C(O)R^{b''}$, $C(O)NR^{c''}R^{d''}$, $C(O)OR^{a''}$, $OC(O)R^{b''}OC(O)NR^{c''}R^{d''}$, $NR^{C''}R^{d''}$, $NR^{c''}C(O)R^{b'', NR\ c''}C(O)OR^{a''}$, $S(O)R^{b''}$, $S(O)NR^{c''}R^{d''}$, $S(O)_2R^{b''}$, and $S(O)_2NR^{c''}R^{d''}$.

**[00689]** In some embodiments, $Cy^1$ and $Cy^2$ are independently selected from cycloalkyl optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, CN, $NO_2$, $OR^{a''}$, $SR^{a''}$, $C(O)R^{b''}$, $C(O)NR^{c''}R^{d''}$, $C(O)OR^{a''}$, $OC(O)R^{b''}$, $OC(O)NR^{c''}R^{d''}$, $NR^{c''}R^{d''}$, $NR^{c''}C(O)R^{b''}$, $NR^{c''}C(O)OR^{a''}S(O)R^{b''}$, $S(O)NR^{c''}R^{d''}$, $S(O)_2R^{b''}$, and $S(O)_2NR^{c''}R^{d''}$.

**[00690]** In some embodiments, $R^1$, $R^2$, $R^3$, and $R^4$ are independently selected from H, halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, $NO_2$, $OR^7$, $SR^7$, $C(O)R^8$, $C(O)NR^9R^{10}$, $C(O)OR^7OC(O)R^8$, $OC(O)NR^9R^{10}$, $NR^9R^{10}$, $NR^9C(O)R^8$, $NR^cC(O)OR^7$, $S(O)R^8$, $S(O)NR^9R^{10}$, $S(O)_2R^8$, $NR^9S(O)_2R^8$, and $S(O)_2NR^9R^{10}$.

**[00691]** In some embodiments, $R^1$, $R^2$, $R^3$, and $R^4$ are independently selected from H, halo, and $C_{1-4}$ alkyl.

**[00692]** In some embodiments, $R^1$, $R^2$, $R^3$, and $R^4$ are each H.

**[00693]** In some embodiments, $R^1$ is H, halo, or $C_{1-4}$ alkyl.

**[00694]** In some embodiments, $R^5$ is H, halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, CN, $NO_2$, $OR^7$, $SR^7$, $C(O)R^8$, $C(O)NR^9R^{10}$, $C(O)OR^7$, $OC(O)R^8$, $OC(O)NR^9R^{10}$, $NR^9R^{10}$, $NR^9C(O)R^8$, $NR^9C(O)OR^7$, $S(O)R^8$, $S(O)NR^9R^{10}$, $S(O)_2R^8$, $NR^9S(O)_2R^8$, or $S(O)_2NR^9R^{10}$.

**[00695]** In some embodiments, $R^5$ is H, halo, $C_{1-4}$ alkyl, $C_{1-4}$ haloalkyl, halosulfanyl, CN, or $NR^9R^{10}$.

**[00696]** In some embodiments, $R^5$ is H, halo, $C_{1-4}$ alkyl, $C_{1-4}$ haloalkyl, CN, or $NR^9R^{10}$.

**[00697]** In some embodiments, $R^5$ is H.

**[00698]** In some embodiments, $R^6$ is H or $C_{1-4}$ alkyl.

**[00699]** In some embodiments, $R^6$ is H.

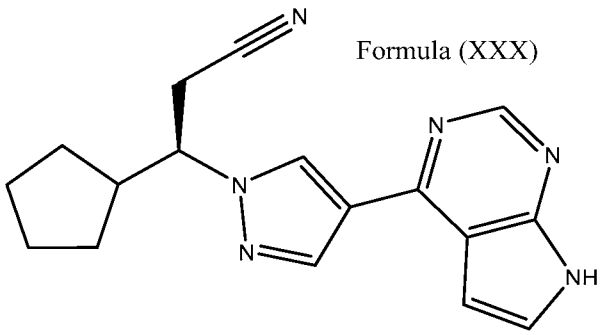
**[00700]** In some embodiments, $R^{11}$ and $R^{12}$ are independently selected from H, halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, halosulfanyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^i$, CN, $NO_2$, $OR^a$, $SR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $C(=NR^i)NR^cR^d$, $NR^cC(=NR^i)NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $C(=NOH)R^b$, $C(=NO(C_{1-6}\text{ alkyl})R^b$, and $S(O)_2NR^cR^d$, wherein said $C_{1-g}$ alkyl, $C_{2-8}$ alkenyl, or $C_{2-8}$ alkynyl, is optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, $C_{1-4}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl, $C_{1-4}$ haloalkyl, halosulfanyl, $C_{1-4}$ hydroxyalkyl, $C_{1-4}$ cyanoalkyl, $Cy^i$, CN, $NO_2$, $OR^a$, $SR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$,

$OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $C(=NR^i)NR^cR^d$, $NR^cC(=NR^i)NR^cR^d$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $C(=NOH)R^b$, $C(=NO(C_{1\text{-}6}\text{alkyl}))R^b$, and $S(O)_2NR^cR^d$.

**[00701]** In some embodiments, $R^{11}$ and $R^{12}$ are independently selected from H, halo, OH, CN, $(C_{1\text{-}4})$alkyl, $(C_{1\text{-}4})$haloalkyl, halosulfanyl, SCN, $(C_{2\text{-}4})$alkenyl, $(C_{2\text{-}4})$alkynyl, $(C_{1\text{-}4})$hydroxyalkyl, $(C_{1\text{-}4})$cyanoalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl.

**[00702]** In some embodiments, $R^{11}$ and $R^{12}$ are independently selected from H, halo, OH, CN, $(C_{1\text{-}4})$alkyl, $(C_{1\text{-}4})$haloalkyl, $(C_{2\text{-}4})$alkenyl, $(C_{2\text{-}4})$alkynyl, $(C_{1\text{-}4})$hydroxyalkyl, $(C_{1\text{-}4})$cyanoalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl.

**[00703]** In a preferred embodiment, the JAK-2 inhibitor is ruxolitinib (available from Incyte Corp. and Novartis AG). In a preferred embodiment, the JAK-2 inhibitor is ruxolitinib phosphate (available from Incyte Corp. and Novartis AG). In a preferred embodiment, the JAK-2 inhibitor is (*R*)-3-(4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-3-cyclopentylpropanenitrile. In a preferred embodiment, the JAK-2 inhibitor is the phosphate salt of (*R*)-3-(4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-3-cyclopentylpropanenitrile. In a preferred embodiment, the JAK-2 inhibitor is (3*R*)-3-cyclopentyl-3-[4-(7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]propanenitrile. In a preferred embodiment, the JAK-2 inhibitor is a compound of Formula (XXX):




Formula (XXX)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of this compound is described in U.S. Patent Nos. 8,604,043, 7,834,022, 8,486,902, 8,530,485, 7,598,257, 8,541,425, and 8,410,265 and U.S. Patent Application Publication Nos. 2010/0298355 A1, 2008/0312258 A1, 2011/0082159 A1, 2011/0086810

A1, 2013/0345157 A1, 2014/0018374 A1, 2014/0005210 A1, 2011/0223210 A1, 2011/0224157 A1, 2007/0135461 A1, 2010/0022522 A1, 2013/0253193 A1, 2013/0253191 A1, 2013/0253190 A1, 2010/0190981 A1, 2013/0338134 A1, 2008/0312259 A1, 2014/0094477 A1, and 2014/0094476 A1, the disclosures of which are incorporated by reference herein. In an embodiment, the JAK-2 inhibitor is a compound selected from the structures disclosed in U.S. Patent Nos. 8,604,043, 7,834,022, 8,486,902, 8,530,485, 7,598,257, 8,541,425, and 8,410,265 and U.S. Patent Application Publication Nos. 2010/0298355 A1, 2008/0312258 A1, 2011/0082159 A1, 2011/0086810 A1, 2013/0345157 A1, 2014/0018374 A1, 2014/0005210 A1, 2011/0223210 A1, 2011/0224157 A1, 2007/0135461 A1, 2010/0022522 A1, 2013/0253193 A1, 2013/0253191 A1, 2013/0253190 A1, 2010/0190981 A1, 2013/0338134 A1, 2008/0312259 A1, 2014/0094477 A1, and 2014/0094476 A1, the disclosures of which are incorporated by reference herein.

**[00704]** Ruxolitinib may be prepared according to the procedures given in the references above, or by the procedure of Example 67 of U.S. Patent No. 7598257, the disclosure of which is specifically incorporated by reference herein. Briefly, the preparation is as follows:

**[00705]** Step 1. (2*E*)- and (2*Z*)-3-Cyclopentylacrylonitrile. To a solution of 1.0 M potassium tert-butoxide in THF (235 mL) at 0° C. was added dropwise a solution of diethyl cyanomethylphosphonate (39.9 mL, 0.246 mol) in TBF (300 mL). The cold bath was removed and the reaction was warmed to room temperature followed by recooling to 0° C., at which time a solution of cyclopentanecarbaldehyde (22.0 g, 0.224 mol) in THF (60 mL) was added dropwise. The bath was removed and the reaction warmed to ambient temperature and stirred for 64 hours. The mixture was partitioned between diethyl ether and water, the aqueous was extracted with three portions of ether, followed by two portions of ethyl acetate. The combined extracts were washed with brine, then dried over sodium sulfate, filtered and concentrated in vacuo to afford a mixture containing 24.4 g of olefin isomers which was used without further purification (89%). $^1$H NMR (400 MHz, CDCl3): δ 6.69 (dd, 1H, trans olefin), 6.37 (t, 1H, cis olefin), 5.29 (dd, 1H, trans olefin), 5.20 (d, 1H, cis olefin), 3.07-2.95 (m, 1H, cis product), 2.64-2.52 (m, 1H, trans product), 1.98-1.26 (m, 16H).

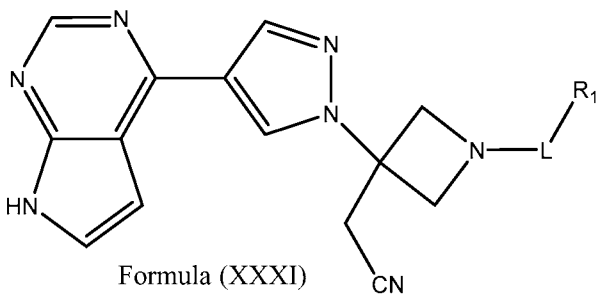
**[00706]** Step 2. (3*R*)- and (3*S*)-3-Cyclopentyl-3-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7*H*-pyrrolo[2,3-*d*]-pyrimidin-4-yl)-1*H*-pyrazol-1-yl]propanenitrile. To a solution of 4-(1*H*-pyrazol-4-yl)-7-[2-(trimethylsilyl)ethoxy]methyl-7*H*-pyrrolo[2,3-d]-pyrimidine (15.0 g, 0.0476 mol) in ACN (300 mL) was added 3-cyclopentylacrylonitrile (15 g, 0.12 mol) (as a mixture of cis and trans isomers), followed by DBU (15 mL, 0.10 mol). The resulting mixture was stirred at room temperature overnight. The ACN was evaporated. The mixture was diluted with ethyl acetate, and the solution was washed with 1.0 N HCl. The aqueous layer was back-extracted with three portions of ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered and concentrated. The crude product was purified by silica gel chromatography (gradient of ethyl acetate/hexanes) to yield a viscous clear syrup, which was dissolved in ethanol and evaporated several times to remove ethyl acetate, to afford 19.4 g of racemic adduct (93%). The enantiomers were separated by preparative-HPLC, (OD-H column, 15% ethanol/hexanes) and used separately in the next step to generate their corresponding final product. The final products (see Step 3) stemming from each of the separated enantiomers were found to be active JAK inhibitors; however, the final product stemming from the second peak to elute from the preparative-HPLC was more active than its enantiomer. The products may be isolated by preparative HPLC or other means known to those of skill in the art for use in Step 3 below. $^1$H NMR (300 MHz, CDCl3): δ 8.85 (s, 1H), 8.32 (s, 2H), 7.39 (d, 1H), 6.80 (d, 1H), 5.68 (s, 2H), 4.26 (dt, 1H), 3.54 (t, 2H), 3.14 (dd, 1H), 2.95 (dd, 1H), 2.67-2.50 (m, 1H), 2.03-1.88 (m, 1H), 1.80-1.15 (m, 7H), 0.92 (t, 2H), −0.06 (s, 9H); MS(ES): 437 (M+1).

**[00707]** Step 3. To a solution of 3-cyclopentyl-3-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]-pyrimidin-4-yl)-1*H*-pyrazol-1-yl]propanenitrile (6.5 g, 0.015 mol, *R* or *S* enantiomer as isolated above) in DCM (40 mL) was added TFA (16 mL) and this was stirred for 6 hours. The solvent and TFA were removed in vacuo. The residue was dissolved in DCM and concentrated using a rotary evaporator two further times to remove as much as possible of the TFA. Following this, the residue was stirred with ethylenediamine (4 mL, 0.06 mol) in methanol (30 mL) overnight. The solvent was removed in vacuo, water was added and the product was extracted into three portions of ethyl acetate. The combined extracts were washed with

brine, dried over sodium sulfate, decanted and concentrated to afford the crude product which was purified by flash column chromatography (eluting with a gradient of methanol/DCM). The resulting mixture was further purified by preparative-HPLC/MS (C18 eluting with a gradient of ACN/H2O containing 0.15% NH4OH) to afford product (2.68 g, 58%). $^1$H NMR (400 MHz, D6-dmso): δ 12.11 (br s, 1H), 8.80 (s, 1H), 8.67 (s, 1H), 8.37 (s, 1H), 7.60 (d, 1H), 6.98 (d, 1H), 4.53 (dt, 1H), 3.27 (dd, 1H), 3.19 (dd, 1H), 2.48-2.36 (m, 1H), 1.86-1.76 (m, 1H), 1.68-1.13 (m, 7H); MS(ES): 307 (M+1).

**[00708]** Ruxolitinib prepared according to the steps above, or any other procedure, may be used as its free base for the compositions and methods described heren. Ruxolitinib may also be used in a salt form. For example, a crystalline phosphoric acid salt of (*R*)-3-(4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-3-cyclopentylpropanenitrile may be prepared from the free base as follows according to the procedure given in Example 2 of U.S. Patent No. 8,722,693, the disclosure of which is specifically incorporated herein by reference. To a test tube was added (*R*)-3-(4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-3-cyclopentylpropanenitrile (153.5 mg) and phosphoric acid (56.6 mg) followed by isopropyl alcohol (IPA) (5.75 mL). The resulting mixture was heated to clear, cooled to room temperature, and then stirred for another 2 hours. The precipitate was collected by filtration and the cake was washed with 0.6 mL of cold IPA. The cake was dried under vacuum to constant weight to provide the final salt product (171.7 mg). The phosphroic acid salt is a 1:1 salt by $^1$H NMR and crystallinity is confirmed by X-ray powder diffraction (XRPD). Differential scanning calorimetry (DSC) of the produce yields a sharp melting peak at about 198.7° C.

**[00709]** In an embodiment, the JAK-2 inhibitor is a compound of Formula (XXXI):




Formula (XXXI)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof,

wherein:

L is $SO_2$ or CO;

$R^1$ is $C_{1-6}$ alkyl, $C_{3-7}$ cycloalkyl, phenyl, 5- or 6-membered heteroaryl, indolyl, $NR^2R^3$, or $OR^4$, wherein said alkyl, cycloalkyl, phenyl, or heteroaryl is optionally substituted with 1, 2, or 3 substituents independently selected from F, CN, and $C_{1-4}$ alkyl;

$R^2$ and $R^3$ are independently selected from H, $C_{1-4}$ alkyl, and phenyl; and

$R^4$ is $C_{1-6}$ alkyl, phenyl, or benzyl.

In some embodiments, when L is $SO_2$, then $R^1$ is other than $OR^4$.

In some embodiments, when L is $SO_2$, then $R^1$ is $C_{1-6}$ alkyl, $C_{3-7}$ cycloalkyl, phenyl, 5- or 6-membered heteroaryl, or $NR^2R^3$, wherein said alkyl, cycloalkyl, phenyl, or heteroaryl is optionally substituted with 1, 2, or 3 substituents independently selected from F and $C_{1-4}$ alkyl.

In some embodiments, when L is CO, then $R^1$ is $C_{3-7}$ cycloalkyl, phenyl, 5- or 6-membered heteroaryl, indolyl, $NR^2R^3$, or $OR^4$, wherein said cycloalkyl, phenyl, or heteroaryl is optionally substituted with 1, 2, or 3 substituents independently selected from CN and $C_{1-4}$ alkyl.

In some embodiments, L is $SO_2$.

In some embodiments, L is CO.

In some embodiments, $R^1$ is methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, 2-methylprop-1-yl, 1-methylprop-1-yl, each optionally substituted with 1, 2, or 3 F.

In some embodiments, $R^1$ is $C_{1-4}$ alkyl.

In some embodiments, $R^1$ is ethyl.

In some embodiments, $R^1$ is $C_{3-7}$ cycloalkyl optionally substituted by $C_{1-4}$ alkyl.

In some embodiments, $R^1$ is phenyl optionally substituted with F, methyl, or CN.

In some embodiments, $R^1$ is 5-membered heteroaryl selected from thienyl, pyrazolyl, pyrrolyl, 1,2,4-oxadiazolyl, and isoxazolyl, each optionally substituted with $C_{1-4}$ alkyl.

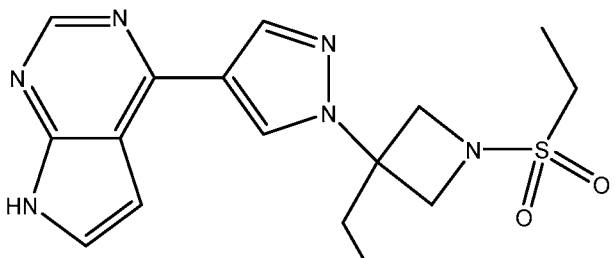
In some embodiments, $R^1$ is pyridinyl.

In some embodiments, $R^1$ is $NR^2R^3$ or $OR^4$.

In some embodiments, L is $SO_2$ and $R^1$ is $C_{1-6}$ alkyl.

**[00710]** In an embodiment, the JAK-2 inhibitor is baricitinib (available from Incyte Corp. and Eli Lilly & Co.). In an embodiment, the JAK-2 inhibitor is 2-(3-(4-(7*H*-

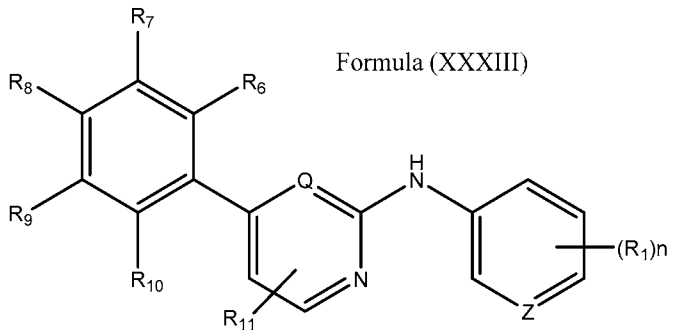
pyrrolo[2,3-d]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-1-(ethylsulfonyl)azetidin-3-yl)acetonitrile. In an embodiment, the JAK-2 inhibitor is a compound of Formula (XXXII):



Formula (XXXII)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of this compound is described in U.S. Patent Nos. 8,158,616 and 8,420,629, U.S. Patent Application Publication Nos. 2009/0233903 A1; 2013/0225556 A1; and, 2012/0077798 A1, and International Patent Application Publication No. WO 2014/0028756, the disclosures of which are incorporated by reference herein. In an embodiment, the JAK-2 inhibitor is a compound described in U.S. Patent Nos. 8,158,616 and 8,420,629, U.S. Patent Application Publication Nos. 2009/0233903 A1; 2013/0225556 A1; and, 2012/0077798 A1, and International Patent Application Publication No. WO 2014/0028756, the disclosures of which are incorporated by reference herein.

**[00711]** In an embodiment, the JAK-2 inhibitor is a compound of Formula (XXXIII):



Formula (XXXIII)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein:

Q and Z are independently selected from N and $CR^1$; n is 1, 2 or 3;

$R^1$ is independently selected from hydrogen, halogen, $R^2$, $OR^2$, OH, $R^4$, $OR^4$, CN, $CF_3$,

$(CH_2)_nN(R^2)_2$, $NO_2$, $R^2R^4$, $SO_2R^4$, $NR^2SO_2R^3$, $COR^4$, $NR^2COR^3$, $CO_2H$, $CO_2R^2$, $NR^2COR^4$, $R^2CN$, $R^2CN$, $R^2OH$, $R^2OR^3$ and $OR^5R^4$; or two $R^1$ substituents together with the carbons which they are attached to form an unsaturated 5 or 6 membered heterocyclyl;

$R^2$ is substituted or unsubstituted $C_{1-4}$alkyl or substituted or unsubstituted $C_{1-4}$ alkylene where up to 2 carbon atoms can be optionally replaced with CO, $NR^Y$, $CONR^Y$, S, $SO_2$ or O;

$R^3$ is $R^2$, $C_{2-4}$ alkenyl or substituted or unsubstituted aryl;

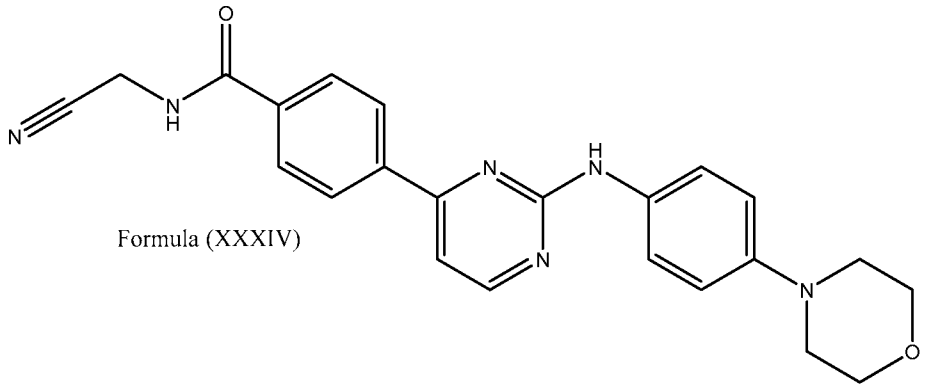
$R^4$ is $NH_2$, $NHR^2$, $N(R')_2$, substituted or unsubstituted morpholino, substituted or unsubstituted thiomorpholino, substituted or unsubstituted thiomorpholino-1-oxide, substituted or unsubstituted thiomorpholino-1, 1-dioxide, substituted or unsubstituted piperazinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted tetrahydrofuranyl and substituted or unsubstituted tetrahydropyranyl;

$R^5$ is substituted or unsubstituted $C_{1-4}$alkylene;

$R^6$-$R^{10}$ are independently selected from H, $R^XCN$, halogen, substituted or unsubstituted $C_M$alkyl, $OR^1$, $CO_2R^1$, $N(R')_2$, $NO_2$, $CON(R')_{2J}$ $SO_2N(R^Y)_2$, $N(SO_2R^\wedge_2$, substituted or unsubstituted piperazinyl, $N(R^Y)SO_2R^2$ and $CF_3$, $R^x$ is absent or substituted or unsubstituted $Ci_{-6}$alkylene wherein up to 2 carbon atoms can be optionally replaced with CO, $NSO_2R^1$, $NR^Y$, $CONR^Y$, S, $SO_2$ or O; $R^Y$ is H or substituted or unsubstituted $C_{1-4}$ alkyl; and

$R^{11}$ is selected from H, halogen, substituted or unsubstituted $C_{1-4}$ alkyl, $OR^2$, $CO_2R^2$, CN, $CON(R')_2$ and $CF_3$, or an enantiomer thereof.

**[00712]** In a preferred embodiment, the JAK-2 inhibitor is momelotinib (Gilead Sciences). Momelotinib is also known as CYT-387. In a preferred embodiment, the JAK-2 inhibitor is *N*-(cyanomethyl)-4-(2-((4-morpholinophenyl)amino)pyrimidin-4-yl)benzamide. In a preferred embodiment, the JAK-2 inhibitor is a compound of Formula (XXXIV):

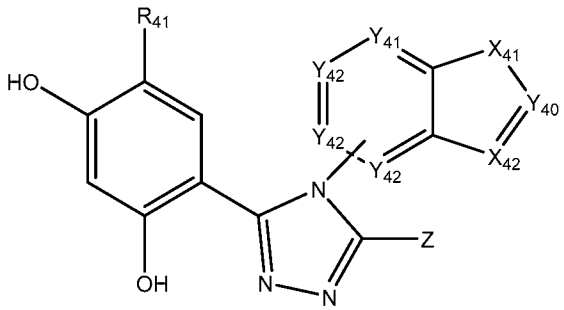


Formula (XXXIV)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of this compound is described in U.S. Patent No. 8,486,941 and U.S. Patent Application Publication Nos. 2010/0197671 A1; 2014/0005180 A1; 2014/0011803 A1; and, 2014/0073643 A1, the disclosures of which are incorporated by reference herein. In an embodiment, the JAK-2 inhibitor is a compound described in U.S. Patent No. 8,486,941 and U.S. Patent Application Publication Nos. 2010/0197671 A1; 2014/0005180 A1; 2014/0011803 A1; and, 2014/0073643 A1, the disclosures of which are incorporated by reference herein.

**[00713]** In an embodiment, the JAK-2 inhibitor is a compound of Formula (XXXV):

Formula (XXXV)



or a tautomer thereof, or a clathrate thereof, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein:

$X_{41}$ is O, S, or $NR_{42}$;

$X_{42}$ is $CR_{44}$ or N;

$Y_{40}$ is N or $CR_{43}$;

$Y_{41}$ is N or $CR_{45}$;

$Y_{42}$, for each occurrence, is independently N, C or $CR_{46}$;

Z is OH SH, or $NHR_7$;

$R_{41}$ is —H, —OH, —SH, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, halo, cyano, nitro, guanadino, a haloalkyl, a heteroalkyl, an alkoxy or cycloalkoxy, a haloalkoxy, —$NR_{10}R_{11}$, —$OR_7$, —$C(O)R_7$, —$C(O)OR_7$, —$C(S)R_7$, —$C(O)SR_7$, —$C(S)SR_7$, —$C(S)OR_7$, —$C(S)NR_{10}R_{11}$, —$C(NR_8)OR_7$, —$C(NR_8)R_7$, —$C(NR_8)NR_{10}R_{11}$, —$C(NR_8)SR_7$, —$OC(O)R_7$, —$OC(O)OR_7$, —$OC(S)OR_7$, —$OC(_8)OR_7$, —$SC(O)R_7$, —$SC(O)OR_7$, —$SC(NR_8)OR_7$, —$OC(S)R_7$, —$SC(S)R_7$, —$SC(S)OR_7$, —$OC(O)NR_{10}R_{11}$, —$OC(S)NR_{10}R_{11}$, —$OC(NR_8)NR_{10}R_{11}$, —$SC(O)NR_{10}R_{11}$, —$SC(NR_8)NR_{10}R_{11}$, —$SC(S)NR_{10}R_{11}$, —$OC(NR_8)R_7$, —$SC(NR_8)R_7$, —$C(O)NR_{10}R_{11}$, —$NR_8C(O)R_7$, —$NR_7C(S)R_7$, —$NR_7C(S)OR_7$, —$NR_7C(NR_8)R_7$, —$NR_7C(O)OR_7$, —$NR_7C(NR_8)OR_7$, —$NR_7C(O)NR_{10}R_{11}$, —$NR_7C(S)NR_{10}R_{11}$, —$NR_7C(NR_8)NR_{10}R_{11}$, —$SR_7$, —$S(O)_pR_7$, —$OS(O)_pR_7$, —$OS(O)_pOR_7$, —$OS(O)_pNR_{10}R_{11}$, —$S(O)_pOR_7$, —$NR_8S(O)_pR_7$, —$NR_7S(O)_pNR_{10}R_{11}$, —$NR_7S(O)_pOR_7$, —$S(O)_pNR_{10}R_{11}$, —$SS(O)_pR_7$, —$SS(O)_pOR_7$, —$SS(O)_pNR_{10}R_{11}$, —$OP(O)(OR_7)_2$, or —$SP(O)(OR_7)_2$;

$R_{42}$ is —H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, hydroxyalkyl, alkoxyalkyl, a haloalkyl, a heteroalkyl, —$C(O)R_7$, —$(CH_2)_mC(O)OR_7$, —$C(O)OR_7$, —$OC(O)R_7$, —$C(O)NR_{10}R_{11}$, —$S(O)_pR_7$, —$S(O)_pOR_7$, or —$S(O)_pNR_{10}R_{11}$;

$R_{43}$ and $R_{44}$ are, independently, —H, —OH, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, hydroxyalkyl,

alkoxyalkyl, halo, cyano, nitro, guanadino, a haloalkyl, a heteroalkyl, —$C(O)R_7$, —$C(O)OR_7$, —$OC(O)R_7$, —$C(O)NR_{10}R_{11}$, —$NR_8C(O)R_7$, —$SR_7$, —$S(O)_pR_7$, —$OS(O)_pR_7$, —$S(O)_pOR_7$, —$NR_8S(O)_pR_7$, —$S(O)_pNR_{10}R_{11}$, or $R_{43}$ and $R_{44}$ taken together with the carbon atoms to which they are attached form an optionally substituted cycloalkenyl, an optionally substituted aryl, an optionally substituted heterocyclyl, or an optionally substituted heteroaryl;

$R_{45}$ is —H, —OH, —SH, —$NR_7H$, —$OR_{26}$, —$SR_{26}$, —$NHR_{26}$, —$O(CH_2)_mOH$, —$O(CH_2)_mSH$, —$O(CH_2)_mNR_7H$, —$S(CH_2)_mOH$, —$S(CH_2)_mSH$, —$S(CH_2)_mNR_7H$, —$OC(O)NR_{10}R_{11}$, —$SC(O)NR_{10}R_{11}$, —$NR_7C(O)NR_{10}R_{11}$, —$OC(O)R_7$, —$SC(O)R_7$, —$NR_7C(O)R_7$, —$OC(O)OR_7$, —$SC(O)OR_7$, —$NR_7C(O)OR_7$, —$OCH_2C(O)R_7$, —$SCH_2C(O)R_7$, —$NR_7CH_2C(O)R_7$, —$OCH_2C(O)OR_7$, —$SCR_2C(O)OR_7$, —$NR_7CH_2C(O)OR_7$, —$OCH_2C(O)NR_{10}R_{11}$, —$SCH_2C(O)NR_{10}R_{11}$, —$NR_7CH_2C(O)NR_{10}R_{11}$, —$OS(O)_pR_7$, —$SS(O)_pR_7$, —$NR_7S(O)_pR_7$, —$OS(O)_pNR_{10}R_{11}$, —$SS(O)_pNR_{10}R_{11}$, —$NR_7S(O)_pNR_{10}R_{11}$, —$OS(O)_pOR_7$, —$SS(O)_pOR_7$, —$NR_7S(O)_pOR_7$, —$OC(S)R_7$, —$SC(S)R_7$, —$NR_7C(S)R_7$, —$OC(S)OR_7$, —$SC(S)OR_7$, —$NR_7C(S)OR_7$, —$OC(S)NR_{10}R_{11}$, —$SC(S)NR_{10}R_{11}$, —$NR_7C(S)NR_{10}R_{11}$, —$OC(NR_8)R_7$, —$SC(NR_8)R_7$, —$NR_7C(N_8)R_7$, —$OC(NR_8)OR_7$, —$SC(NR_8)OR_7$, —$NR_7C(NR_8)OR_7$, —$OC(NR_8)NR_{10}R_{11}$, —$SC(NR_8)NR_{10}R_{11}$, or —$NR_7C(N_8)NR_{10}R_{11}$;

$R_{46}$, for each occurrence, is independently, selected from the group consisting of H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, halo, cyano, nitro, guanadino, a haloalkyl, a heteroalkyl, —$NR_{10}R_{11}$, —$OR_7$, —$C(O)R_7$, —$C(O)OR_7$, —$OC(O)R_7$, —$C(O)NR_{10}R_{11}$, —$NR_8C(O)R_7$, —$SR_7$, —$S(O)_pR_7$, —$OS(O)_pR_7$, —$S(O)_pOR_7$, —$NR_8S(O)_pR_7$, or —$S(O)_pNR_{10}R_{11}$;

$R_7$ and $R_8$, for each occurrence, are, independently, —H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted

heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

$R_{10}$ and $R_{11}$, for each occurrence, are independently —H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; or $R_{10}$ and $R_{11}$, taken together with the nitrogen to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl;

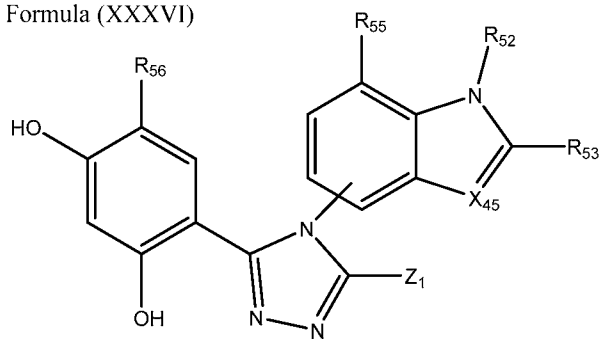
$R_{26}$, for each occurrence is, is independently, a lower alkyl;

p, for each occurrence, is, independently, 1 or 2; and

m, for each occurrence, is independently, 1, 2, 3, or 4.

**[00714]** In an embodiment, the JAK-2 inhibitor is a compound of Formula (XXXVI):

Formula (XXXVI)




or a tautomer thereof, or a clathrate thereof, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein:

$X_{45}$ is $CR_{54}$ or N;

Z1 is —OH or —SH;

$R_{56}$ is selected from the group consisting of —H, methyl, ethyl, isopropyl, and cyclopropyl;

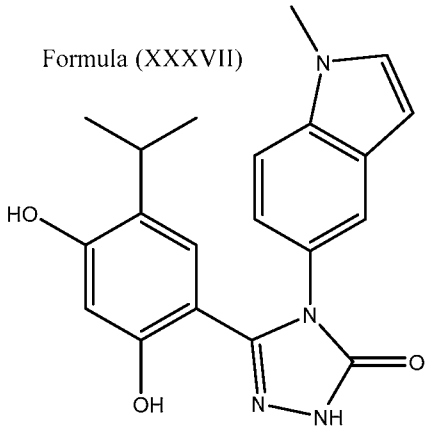
$R_{52}$ is selected from the group consisting of —H, methyl, ethyl, n-propyl, isopropyl, n-butyl, n-pentyl, n-hexyl, —$(CH_2)_2OCH_3$, —$CH_2C(O)OH$, and —$C(O)N(CH_3)_2$;

$R_{53}$ and $R_{54}$ are each, independently, —H, methyl, ethyl, or isopropyl; or $R_{53}$ and $R_{54}$ taken together with the carbon atoms to which they are attached form a phenyl, cyclohexenyl, or cyclooctenyl ring; and

$R_{55}$ is selected from the group consisting of —H, —OH, —$OCH_3$, and —$OCH_2CH_3$.

**[00715]** In a preferred embodiment, the JAK-2 inhibitor is ganetespib. In a preferred embodiment, the JAK-2 inhibitor is 5-(2,4-dihydroxy-5-isopropylphenyl)-4-(1-methyl-1*H*-indol-5-yl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one. In a preferred embodiment, the JAK-2 inhibitor is a compound of Formula (XXXVII):

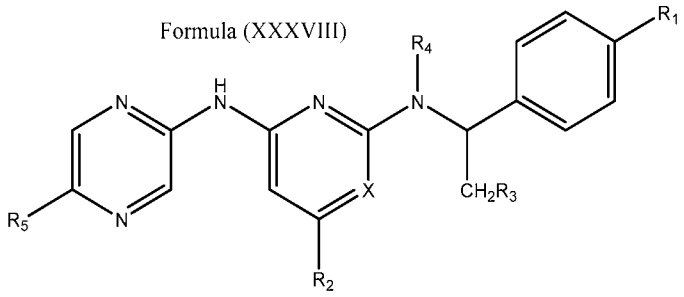
Formula (XXXVII)




or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of this compound is described in U.S. Patent Nos. 7,825,148 and 8,628,752, U.S. Patent Application Publication Nos. 2006/0167070 A1; 2014/0024030 A1; 2014/0051665 A1; 2014/0045908 A1; 2012/0128665 A1; 2013/0109045 A1, and 2014/0079636 A1, and, International Patent Application Publication No. WO 2013/170182; WO 2013/028505; WO 2013/067162; WO 2013/173436; WO 2013/006864; WO 2012/162584; WO 2013/170159; WO 2013/067165; WO 2013/074594; WO 2012/162372; WO 2012/162293; and WO 2012/155063, the disclosures of which are incorporated by reference herein. In an embodiment, the JAK-2 inhibitor is a compound described in U.S. Patent Nos. 7,825,148 and 8,628,752, U.S. Patent Application Publication Nos. 2006/0167070 A1; 2014/0024030 A1; 2014/0051665 A1; 2014/0045908 A1; 2012/0128665 A1; 2013/0109045 A1, and 2014/0079636 A1, and, International Patent Application Publication No. WO 2013/170182; WO 2013/028505; WO 2013/067162; WO 2013/173436; WO 2013/006864; WO 2012/162584; WO 2013/170159; WO 2013/067165; WO 2013/074594; WO 2012/162372; WO 2012/162293; and WO 2012/155063, the disclosures of which are incorporated by reference herein.

**[00716]** In an embodiment, the JAK-2 inhibitor is a compound of Formula (XXXVIII):

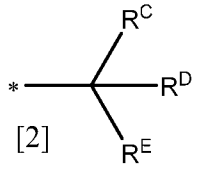
Formula (XXXVIII)



or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein the compound is defined by the following (I) or (II).

(I): X represents CH or N; $R_1$ represents a halogen;

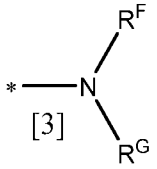
$R_2$ represents: (1) H, (2) a halogen, (3) cyano,(4) a group represented by the following general formula [2]:



[2]

(wherein * indicates the binding position; and $R^C$, $R^D$ and $R^E$ are the same or different and each represents (a) H, or (b) alkyl optionally substituted by hydroxy or alkoxy, or alternatively two of $R^C$, $R^D$ and $R^E$ are taken together with the adjacent C to represent a N-containing saturated heterocyclic group and the other one is H, the saturated heterocyclic group optionally substituted by alkylsulfonyl),

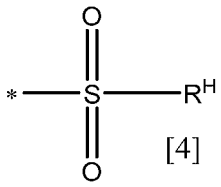
(5) a group represented by the following general formula [3]:



[3]

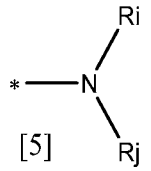
(wherein * has the same meaning as described above; and $R^F$ and $R^G$ are the same or different and each represents (a) H, (b) alkyl optionally substituted by one or two groups selected from the group consisting of hydroxy, amino, dialkylamino, a saturated cyclic amino group, alkylcarbonylamino, alkylsulfonylamino, aryl, heteroaryl optionally substituted by alkyl, tetrahydrofuranyl, and carbamoyl, (c) alkylcarbonyl, (d) alkylsulfonyl, (e) carbamoyl, or (f) heteroaryl optionally substituted by alkyl, or

alternatively $R^F$ and $R^G$ are taken together with the adjacent N to represent a saturated cyclic amino group, which may optionally be substituted by one or two groups selected from the group consisting of (a) halogen, (b) cyano, (c) hydroxy, (d) alkyl optionally substituted by one or two groups selected from the group consisting of hydroxy, alkoxy, amino, alkoxycarbonylamino, alkylsulfonylamino, and alkylcarbonylamino, (e) cycloalkyl, (f) haloalkyl, (g) alkoxy, (h) oxo, (i) a group represented by the following general formula [4]:



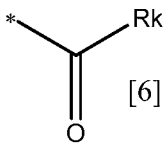
[4]

(wherein * has the same meaning as described above; and $R^H$ represents alkyl or aryl), (j) a group represented by the following general formula [5]:



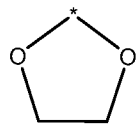
[5]

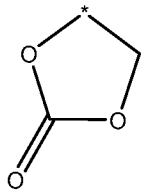
(wherein * has the same meaning as described above; and $R^I$ and $R^J$ are the same or different and each represents H, alkyl, carbamoyl, alkylcarbonyl, or alkylsulfonyl), (k) a group represented by the following general formula [6]:



[6]

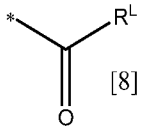
(wherein * has the same meaning as described above; and $R^K$ represents alkyl, hydroxy, amino, alkylamino, dialkylamino, cycloalkylamino, (cycloalkyl)alkylamino, (hydroxyalkyl)amino, (alkoxyalkyl)amino, alkoxy, alkylsulfonylamino, or a saturated cyclic amino group), and (l) a saturated cyclic amino group optionally substituted by hydroxy; and the saturated cyclic amino group, which is formed by combining $R^F$, $R^G$ and the adjacent N, may form a spiro-linkage with a group represented by the following general formula [7A] or [7B]:


[7A]


[7B]

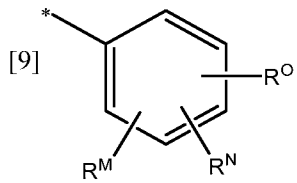
(wherein has the same meaning as described above)),

(6) a group represented by the following general formula [8]:


[8]

(wherein * has the same meaning as described above; and $R^L$ represents (a) alkyl, (b) hydroxy, (c) alkoxy, (d) saturated cyclic amino group optionally substituted by alkyl or alkylsulfonyl, or (e) an amino optionally substituted by one or two groups selected from the group consisting of alkyl, cycloalkyl, (cycloalkyl)alkyl, aralkyl; haloalkyl, dialkylaminoalkyl, alkoxyalkyl, and hydroxyalkyl),

(7) a group represented by the following general formula [9]:


[9]

(wherein * has the same meaning as described above; and $R^M$, $R^N$ and $R^O$ are the same or different and each represents H, halogen, cyano, alkoxy, carbamoyl, sulfamoyl, monoalkylaminosulfonyl, or alkylsulfonyl, or alternatively two of $R^M$, $R^N$ and $R^O$ are taken together to represent methylenedioxy),

(8) —$OR^P$ ($R^P$ represents an alkyl optionally substituted by a group selected from the group consisting of hydroxy, dialkylamino, alkoxy, tetrahydrofuranyl, and cycloalkyl, or an optionally O-containing saturated cyclic group optionally substituted by hydroxy), or

(9) a heteroaryl optionally substituted by one or two groups selected from the group consisting of cyano, halogen, hydroxy, alkoxy, alkylcarbonyl, carbamoyl, alkyl, cycloalkyl, (cycloalkyl)alkyl, aralkyl, hydroxycarbonyl and alkoxyalkyl;

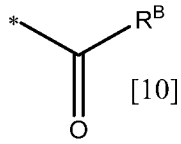
$R_3$ represents H or hydroxy;

$R_2$ represents H or alkyl; and

$R_5$ represents H or alkyl;

(II): X represents —$CR^A$;

$R^A$ represents a group represented by the following general formula [10]:




[10]

(wherein * has the same meaning as described above; and $R^B$ represents (a) amino optionally substituted by one or two groups selected from the group consisting of alkyl, cycloalkyl, (cycloalkyl)alkyl, and alkoxyalkyl, (b) alkoxy, (c) hydroxy, or (d) a saturated cyclic amino group);

$R_1$ represents a halogen;

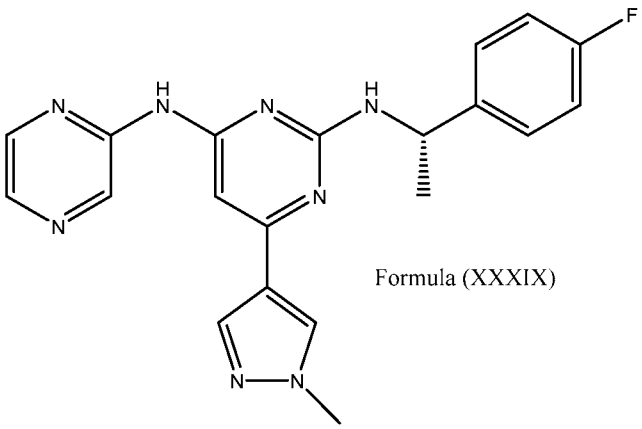
$R_2$ represents H;

$R_3$ represents E or hydroxy;

$R_4$ represents H or alkyl; and

$R_5$ represents H or alkyl.

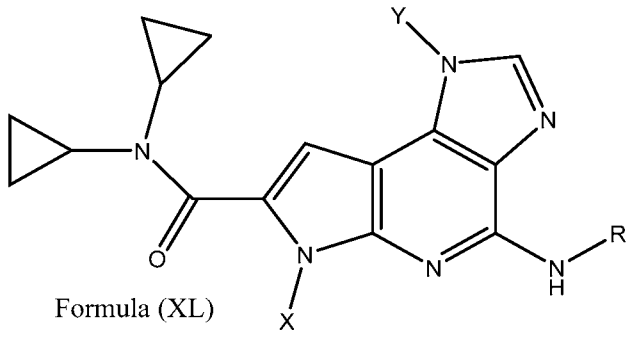
**[00717]** In a preferred embodiment, the JAK-2 inhibitor is NS-018. In an embodiment, the JAK-2 inhibitor is (*S*)-$N^2$-(1-(4-fluorophenyl)ethyl)-6-(1-methyl-1*H*-pyrazol-4-yl)-$N^4$-(pyrazin-2-yl)pyrimidine-2,4-diamine. NS-018 has been described in Nakaya, *et al.*, *Blood Cancer J.* **2014,** *4,* e174. In an embodiment, the JAK-2 inhibitor has the chemical structure shown in Formula (XXXIX):




Formula (XXXIX)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of this compound is described in U.S. Patent Nos. 8,673,891 and 8,586,591, U.S. Patent Application Publication Nos. 2011/0288065 A1 and 2013/0131082 A1, and International Patent Application Publication No. WO 2012/020787 and WO 2012/020786, the disclosures of which are incorporated by reference herein. In an embodiment, the JAK-2 inhibitor is a compound described in U.S. Patent Nos. 8,673,891 and 8,586,591, U.S. Patent Application Publication Nos. 2011/0288065 A1 and 2013/0131082 A1, and International Patent Application Publication No. WO 2012/020787 and WO 2012/020786, the disclosures of which are incorporated by reference herein.

**[00718]** In an embodiment, the JAK-2 inhibitor is a compound of Formula (XL):



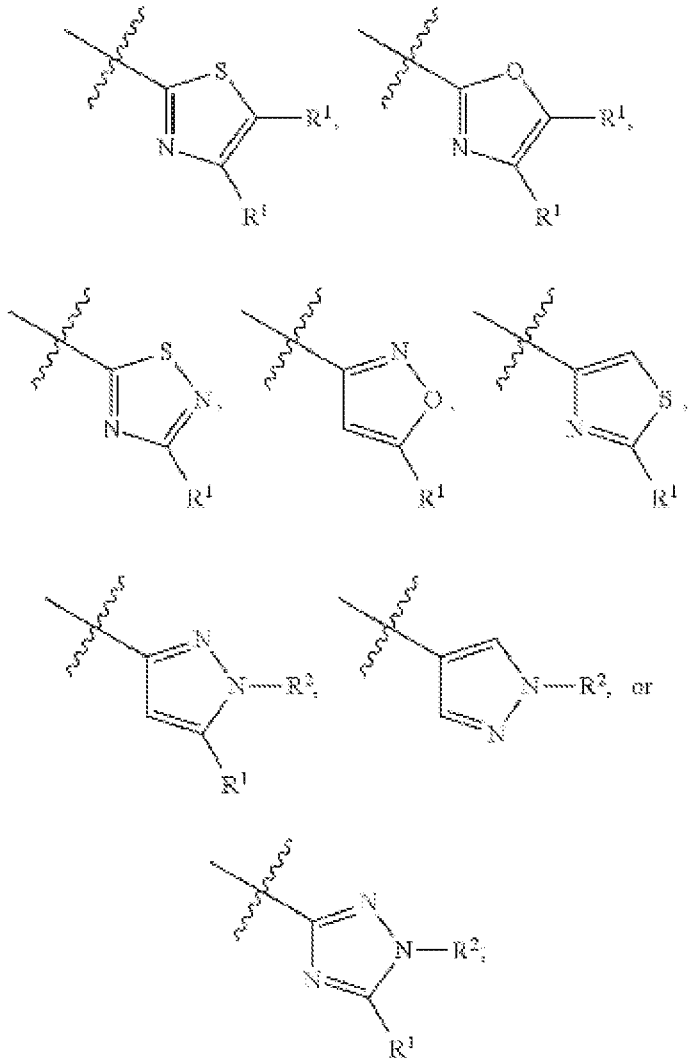

Formula (XL)

or a stereoisomer, tautomer, or pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein:

Y is $C_{1-4}$ alkyl;

X is $C_{1-4}$ alkyl;

R is



any of which are optionally fused with a 5 or 6 membered carbocycle or heterocycle having one heteroatom selected from $NR^3$ or S, said fused carbocycle or heterocycle being optionally substituted with 0-3 $R^1$.

$R^1$ is H, halo, CN, $C_{1-6}$ alkyl substituted with 0-3 $R^c$, $CF_3$, $CONR^aR^a$, $NR^aR^a$, $COOR^b$, $SO_2$—$(C_{1-4})$alkyl, $C(O)R^d$, cycloalkyl substituted with 0-3 $R^e$, furanyl, tetrahydropyranyl, or pyridinyl;

$R^2$ is absent, H, $C_{1-6}$ alkyl substituted with 0-3 $R^c$, C(O)O—$(C_{1-4})$alkyl, $SO_2$—$(C_{1-4})$alkyl, cycloalkyl substituted with 0-3 $R^e$, or tetrahydropyranyl;

$R^3$ is absent, H, or C(O)O—$(C_{1-4})$alkyl;

$R^a$ is H, $C_{1-6}$ alkyl substituted with 0-3 $R^e$, $C_{3-6}$ cycloalkyl substituted with 0-3 $R^e$, tetrahydropyranyl, or dioxotetrahydrothiophenyl;

$R^b$ is H or $C_{1-6}$ alkyl;

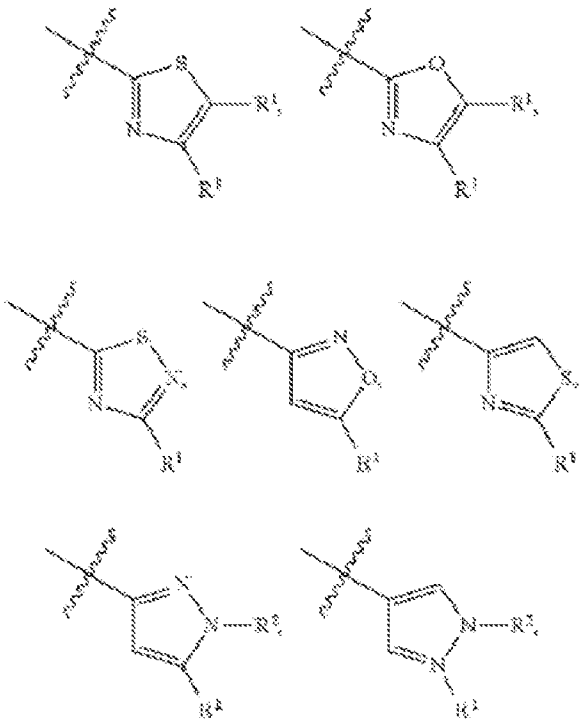
$R^c$ is H, halo, CN, OH, O—($C_{1-4}$)alkyl, O—($C_{1-4}$)alkyl-O—($C_{1-4}$)alkyl, $NH_2$, N($C_{1-4}$ alkyl)$_2$, C(O)N($C_{1-4}$ alkyl)$_2$, $SO_2$—($C_{1-4}$)alkyl, or morpholinyl or piperazinyl, either of which are optionally substituted with 0-1 $C_{1-4}$ alkyl;

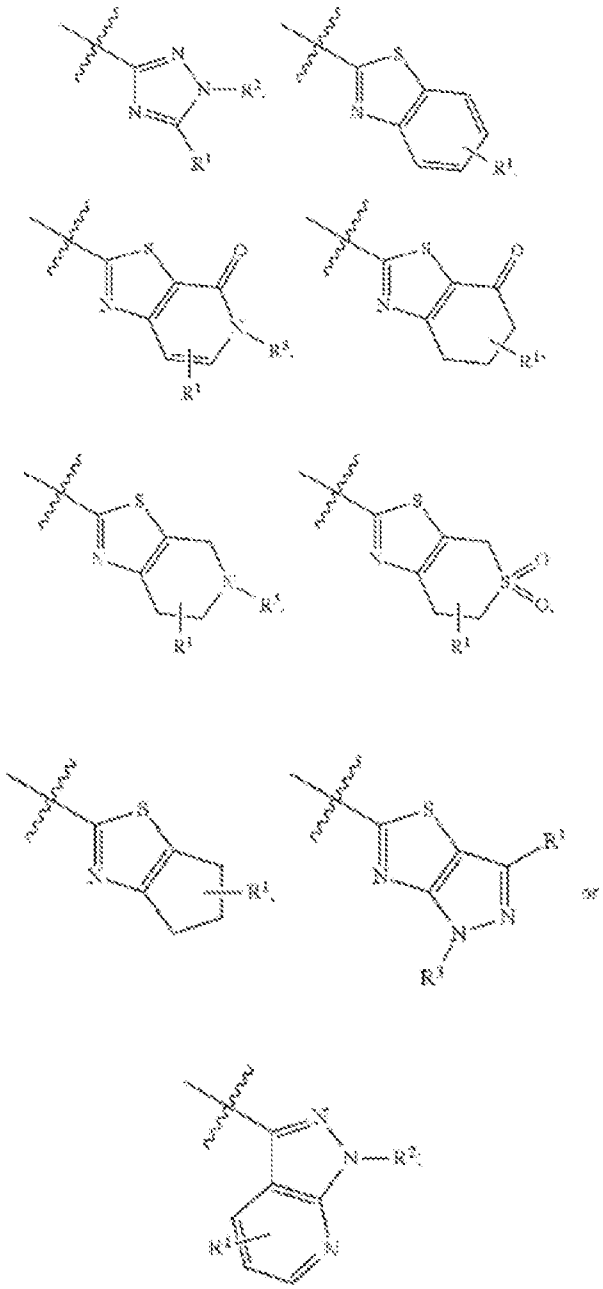
$R^d$ is $C_{1-6}$ alkyl, or azeridinyl, azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, dioxidothiomorpholinyl or tetrahydropyranyl, any of which are substituted with 0-2 $R^e$; and

$R^e$ is H, halo, CN, $C_{1-4}$ alkyl, OH, O—($C_{1-4}$)alkyl, $SO_2$—($C_{1-4}$)alkyl, NHC(O)—($C_{1-4}$)alkyl, morpholinyl, OC(O)—($C_{1-4}$)alkyl, C(O)N($C_{1-4}$ alkyl)$_2$, or O—($C_{1-4}$)alkyl-O—($C_{1-4}$)alkyl.

**[00719]** In an embodiment, the JAK-2 inhibitor is a compound of Formula (XL), wherein:

R is:



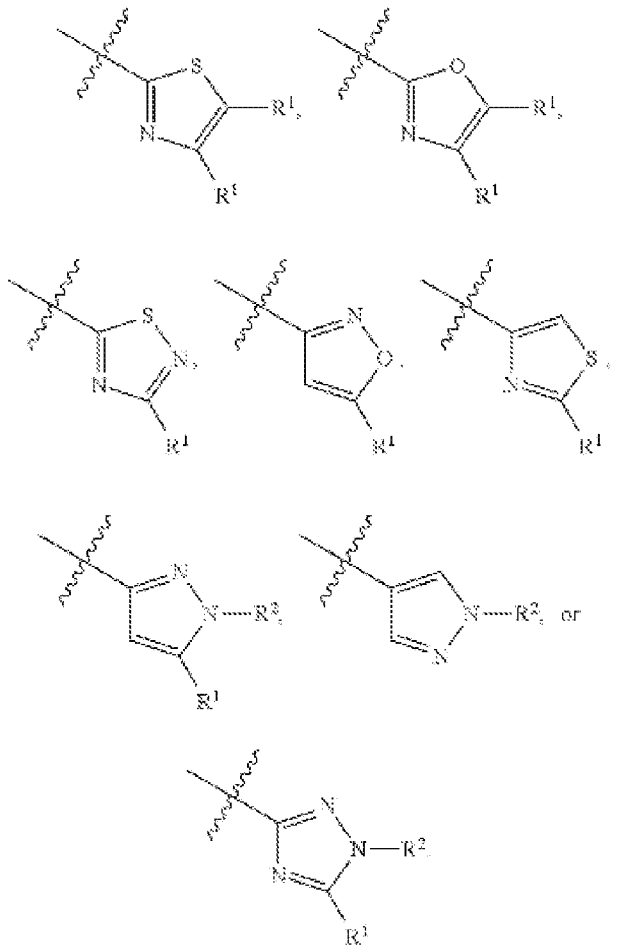


any of which are optionally substituted with 0-3 $R^1$.

**[00720]** In an embodiment, the JAK-2 inhibitor is a compound of Formula (XL), wherein Y is methyl and X is ethyl.

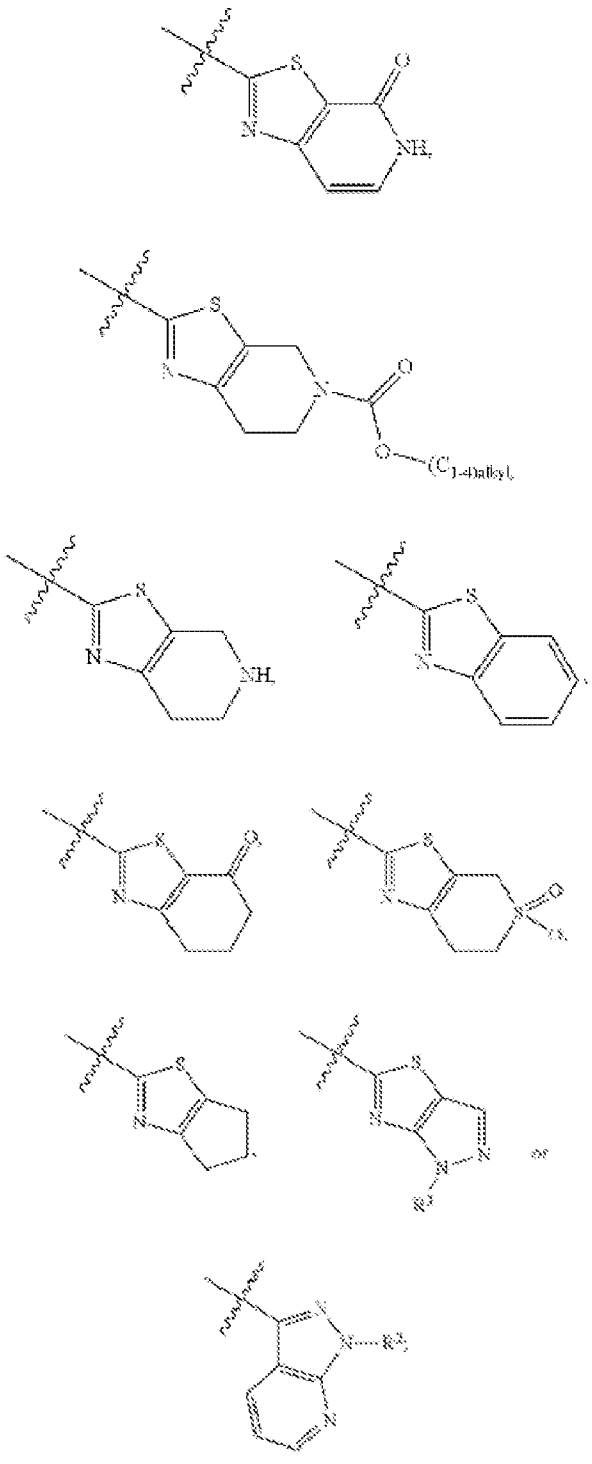
**[00721]** In another embodiment, the JAK-2 inhibitor is a compound of Formula (XL), wherein:

R is:



**[00722]** In an embodiment, the JAK-2 inhibitor is a compound of Formula (XL), wherein:

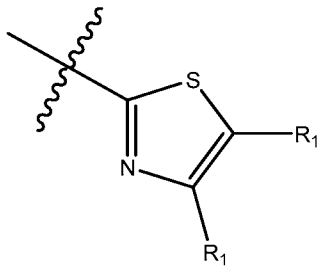
R is:



any of which are optionally substituted with 0-2 $R^1$.

**[00723]** In an embodiment, the JAK-2 inhibitor is a compound of Formula (XL), wherein

R is:




$R^1$ is H, halo, CN, $C_{1-6}$ alkyl substituted with 0-3 $R^c$, $CF_3$, $CONR^aR^a$, $COOR^b$, $SO_2$—($C_{1-4}$)alkyl, $C(O)R^d$, cycloalkyl substituted with 0-3 $R^e$, or pyridinyl;

$R^a$ is H, $C_{1-6}$ alkyl substituted with 0-3 $R^e$, $C_{3-6}$ cycloalkyl substituted with 0-3 $R^e$, tetrahydropyranyl or dioxotetrahydrothiophenyl;

$R^b$ is H or $C_{1-6}$ alkyl;

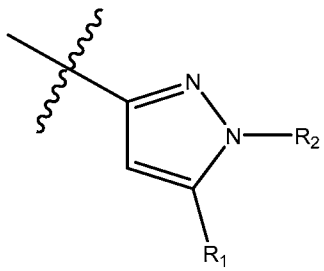
$R^c$ is H, halo, OH, O—($C_{1-4}$)alkyl, $SO_2$—($C_{1-4}$)alkyl or morpholinyl;

$R^d$ is $C_{1-6}$ alkyl, or azetidinyl, pyrrolidinyl, morpholinyl, piperazinyl or dioxidothiomorpholinyl, any of which are substituted with 0-2 $R^e$;

$R^e$ is H, halo, CN, OH, O—($C_{1-4}$)alkyl, $SO_2$—($C_{1-4}$)alkyl, NHC(O)—($C_{1-4}$)alkyl or morpholinyl.

**[00724]** In an embodiment, the JAK-2 inhibitor is a compound of Formula (XL), wherein:

R is:




$R^1$ is H, halo, $C_{1-6}$ alkyl substituted with 0-3 $R^c$, $CF_3$, $CONR^aR^a$, $COOR^b$, $C(O)R^d$, cycloalkyl substituted with 0-3 $R^e$ or furanyl;

$R^2$ is H, $C_{1-6}$ alkyl substituted with 0-3 $R^c$, $SO_2$—$(C_{1-4})$alkyl, cycloalkyl substituted with 0-3 $R^e$, or tetrahydropyranyl;

$R^a$ is H, or $C_{1-6}$ alkyl substituted with 0-3 $R^e$;

$R^b$ is H or $C_{1-6}$ alkyl;

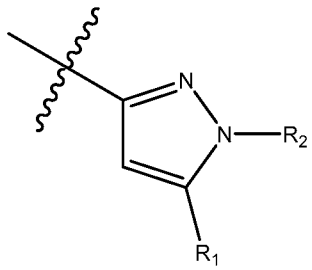
$R^c$ is H, halo, CN, OH, O—$(C_{1-4})$alkyl, O—$(C_{1-4})$alkyl-O—$(C_{1-4})$alkyl, $NH_2$, $N(C_{1-4}$ alkyl$)_2$, $C(O)N(C_{1-4}$ alkyl$)_2$, $SO_2$—$(C_{1-4})$alkyl, or morpholinyl or piperazinyl, either of which are optionally substituted with 0-1 $C_{1-4}$ alkyl;

$R^d$ is $C_{1-6}$ alkyl, or morpholinyl, piperazinyl or dioxidothiomorpholinyl, any of which are substituted with 0-2 $R^e$; and

$R^e$ is H, $C_{1-4}$ alkyl, CN, OH, NHC(O)—$(C_{1-4})$alkyl or morpholinyl.

**[00725]** In an embodiment, the JAK-2 inhibitor is a compound of Formula (XL), wherein:

R is:

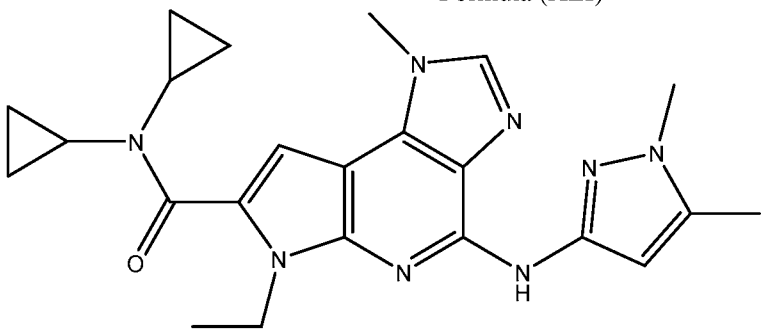



$R^1$ is $C_{1-6}$ alkyl substituted with 0-3 $R^c$; and

$R^2$ is $C_{1-6}$ alkyl.

**[00726]** In a preferred embodiment, the JAK-2 inhibitor is BMS-911543. In a preferred embodiment, the JAK-2 inhibitor is *N*,*N*-dicyclopropyl-4-((1,5-dimethyl-1*H*-pyrazol-3-yl)amino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridine-7-carboxamide. In a preferred embodiment, the JAK-2 inhibitor is a compound of Formula (XLI):

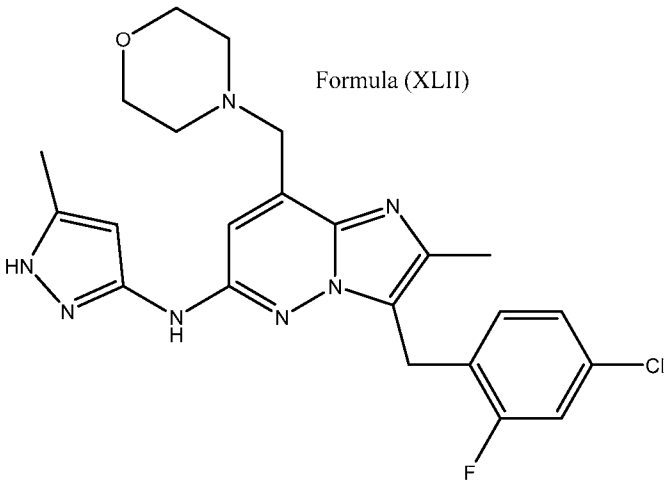
Formula (XLI)



or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of this compound is described in U.S. Patent Nos. 8,673,933 and 8,202,881 and U.S. Patent Application Publication Nos. 2013/0225551 A1 and 2011/0059943 A1, the disclosures of which are incorporated by reference herein. In an embodiment, the JAK-2 inhibitor is a compound described in U.S. Patent Nos. 8,673,933 and 8,202,881 and U.S. Patent Application Publication Nos. 2013/0225551 A1 and 2011/0059943 A1, the disclosures of which are incorporated by reference herein.

**[00727]** In a preferred embodiment, the JAK-2 inhibitor is gandotinib. In a preferred embodiment, the JAK-2 inhibitor is 3-(4-chloro-2-fluorobenzyl)-2-methyl-*N*-(5-methyl-1*H*-pyrazol-3-yl)-8-(morpholinomethyl)imidazo[1,2-*b*]pyridazin-6-amine. In a preferred embodiment, the JAK-2 inhibitor is a compound of Formula (XLII):

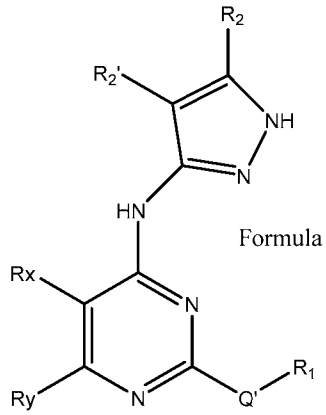
Formula (XLII)



or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of this compound is described in U.S. Patent No. 7,897,600 and U.S. Patent Application Publication Nos. 2010/0152181 A1 and 2010/0286139 A1, the disclosures of

which are incorporated by reference herein. In an embodiment, the JAK-2 inhibitor is a compound described in U.S. Patent No. 7,897,600 and U.S. Patent Application Publication Nos. 2010/0152181 A1 and 2010/0286139 A1, the disclosures of which are incorporated by reference herein.

**[00728]** In an embodiment, the JAK-2 inhibitor is a compound of Formula (XLIII):




Formula (XLIII)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein:

$R^x$ and $R^y$ are independently selected from the group consisting of -T-$R^3$ and -L-Z-$R^3$;

Q' is selected from the group consisting of —$CR^{6''}$=$CR^{6''}$— and wherein said —$CR^{6''}$=$CR^{6''}$— may be a cis or trans double bond or a mixture thereof,

$R^1$ is -T-(Ring D);

Ring D is a 5-7 membered monocyclic ring or 8-10 membered bicyclic ring selected from the group consisting of aryl, heteroaryl, heterocyclyl, and carbocyclyl, said heteroaryl or heterocyclyl ring having 1-4 ring heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, wherein each substitutable ring carbon of Ring D is independently substituted by oxo, -T-$R^5$ or —V-Z-$R^5$, and each substitutable ring nitrogen of Ring D is independently substituted by —$R^4$;

T is a valence bond or —$(C(R^{6'})_2)$-A-;

A is a valence bond or a $C_1$-$C_3$ alkylidene chain wherein a methylene unit of said $C_{1-3}$ alkylidene chain is optionally replaced by —O—, —S—, —$N(R^4)$—, —CO—, —CONH—, —NHCO—, —$SO_2$—, —$SO_2$NH—, —$NHSO_2$—, —$CO_2$—, —OC(O)—, —OC(O)NH—, or —$NHCO_2$—;

Z is a $C_{1-4}$ alkylidene chain;

L is selected from the group consisting of —O—, —S—, —SO—, —$SO_2$—, —$N(R^6)SO_2$—$SO_2N(R^6)$—, —$N(R^6)$—, —CO—, —$CO_2$—, —$N(R^6)CO$—, —$N(R^6)C(O)O$—, —$N(R^6)CON(R^6)$—, —$N(R^6)SO_2N(R^6)$—, —$N(R^6)N(R^6)$—, —$C(O)N(R^6)$—, —$OC(O)N(R^6)$—, —$C(R^6)_2$—O—, —$C(R^6)_2$—, —$C(R^6)_2SO$—, —$C(R^6)_2SO_2$—, —$C(R^6)_2SO_2N(R^6)$—, —$C(R^6)_2N(R^6)$—, —$C(R^6)_2N(R^6)C(O)$—, —$C(R^6)_2N(R^6)C(O)O$—, —$C(R^6)$=$NN(R^6)$—, —$C(R^6)$=N—O—, —$C(R^6)_2N(R^6)N(R^6)$—, —$C(R^6)_2N(R^6)SO_2N(R^6)$—, and —$C(R^6)_2N(R^6)CON(R^6)$—;

$R^2$ and $R^{2'}$ are independently selected from the group consisting of —R and -T-W—$R^6$, or $R^2$ and $R^{2'}$ taken together with their intervening atoms form a fused, 5-8 membered, unsaturated or partially unsaturated ring having 0-3 ring heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, wherein each substitutable ring carbon of said fused ring formed by $R^2$ and $R^{2'}$ is independently substituted by halo, oxo, —CN, —$NO_2$, $R^7$, or —V—$R^6$, and each substitutable ring nitrogen of said ring formed by $R^2$ and $R^{2'}$ is independently substituted by —$R^4$;

$R^3$ is selected from the group consisting of —R, -halo, —OR, —C(=O)R, —$CO_2$R, —COCOR, —$COCH_2COR$, —$NO_2$, —CN, —S(O)R, —$S(O)_2$R, —SR, —$N(R^4)_2$, —$CON(R^7)_2$, —$SO_2N(R^7)_2$, —OC(=O)R, —$N(R^7)COR$, —$N(R^7)CO_2$($C_{1-6}$ aliphatic), —$N(R^4)N(R^4)_2$, —C=$NN(R^4)_2$, —C=N—OR, —$N(R^7)CON(R^7)_2$, —$N(R^7)SO_2N(R^7)_2$, —$N(R^4)SO_2$R, and —OC(=O)$N(R)_2$;

each R is independently hydrogen or an optionally substituted group selected from the group consisting of $C_{1-6}$ aliphatic, $C_{6-10}$ aryl, a heteroaryl ring having 5-10 ring atoms, and a heterocyclyl ring having 5-10 ring atoms;

each $R^4$ is independently selected from the group consisting of —$R^7$, —$COR^7$, —$CO_2$(optionally substituted $C_{1-6}$ aliphatic), —$CON(R^7)_2$, and —$SO_2R^7$;

each $R^5$ is independently selected from the group consisting of —R, halo, —OR, —C(=O)R, —$CO_2$R, —COCOR, —$NO_2$, —CN, —S(O)R, —$SO_2$R, —SR, —$N(R^4)_2$, —$CON(R^4)_2$, —$SO_2N(R^4)_2$, —OC(=O)R, —$N(R^4)COR$, —$N(R^4)CO_2$ (optionally substituted $C_{1-6}$ aliphatic), —$N(R^4)N(R^4)_2$, —C=$NN(R^4)_2$, —C=N—OR, —$N(R^4)CON(R^4)_2$, —$N(R^4)SO_2N(R^4)_2$, —$N(R^4)SO_2$R, and —OC(=O)$N(R^4)_2$;

V is selected from the group consisting of —O—, —S—, —SO—, —$SO_2$—, —

$N(R^6)SO_2$—, —$SO_2N(R^6)$—, —$N(R^6)$—, —CO—, —$CO_2$—, —$N(R^6)CO$—, —$N(R^6)C(O)O$—, —$N(R^6)CON(R^6)$—, —$N(R^6)SO_2N(R^6)$—, —$N(R^6)N(R^6)$—, —$C(O)N(R^6)$—, —$OC(O)N(R^6)$—, —$C(R^6)_2O$—, —$C(R^6)_2S$—, —$C(R^6)_2SO$—, —$C(R^6)_2SO_2$—, —$C(R^6)_2SO_2N(R^6)$—, —$C(R^6)_2N(R^6)$—, —$C(R^6)_2N(R^6)C(O)$—, —$C(R^6)_2N(R^6)C(O)O$—, —$C(R^6)$═$NN(R^6)$—, —$C(R^6)$═N—O—, —$C(R^6)_2N(R^6)N(R^6)$—, —$C(R^6)_2N(R^6)SO_2N(R^6)$—, and —$C(R^6)_2N(R^6)CON(R^6)$—;

W is selected from the group consisting of —$C(R^6)_2O$—, —$C(R^6)_2S$—, —$C(R^6)_2SO$—, —$C(R^6)_2SO_2$—, —$C(R^6)_2SO_2N(R^6)$—, —$C(R^6)_2N(R^6)$—, —CO—, —$CO_2$—, —$C(R^6)OC(O)$—, —$C(R^6)OC(O)N(R^6)$—, —$C(R^6)_2N(R^6)CO$—, —$C(R^6)_2N(R^6)C(O)O$—, —$C(R^6)$═$NN(R^6)$—, —$C(R^6)$═N—O—, —$C(R^6)_2N(R^6)N(R^6)$—, —$C(R^6)_2N(R^6)SO_2N(R^6)$—, —$C(R^6)_2N(R^6)CON(R^6)$—, and —$CON(R^6)$—;

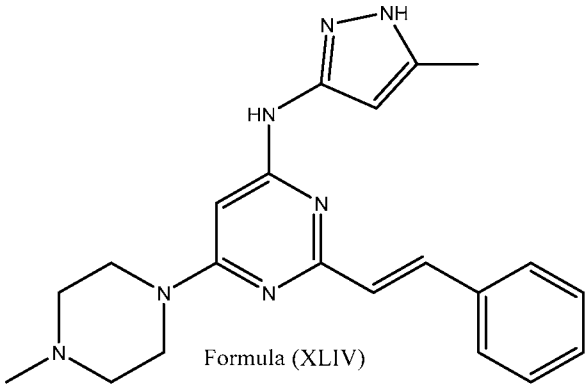
each $R^6$ is independently selected from the group consisting of hydrogen and an optionally substituted $C_{1-4}$ aliphatic group, or two $R^6$ groups on the same nitrogen atom may be taken together with the nitrogen atom to form a 3-6 membered heterocyclyl or heteroaryl ring;

each $R^{6'}$ is independently selected from the group consisting of hydrogen and a $C_{1-4}$ aliphatic group, or two $R^{6'}$ on the same carbon atom are taken together to form a 3-8 membered carbocyclic ring;

each $R^{6''}$ is independently selected from the group consisting of hydrogen, a $C_{1-4}$ aliphatic group, halogen, optionally substituted aryl, and optionally substituted heteroaryl, or two $R^6$ on adjacent carbon atoms are taken together to form a 5-7 membered carbocyclic ring; and

each $R^7$ is independently selected from the group consisting of hydrogen and an optionally substituted $C_{1-6}$ aliphatic group, or two $R^7$ on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclyl or heteroaryl ring.

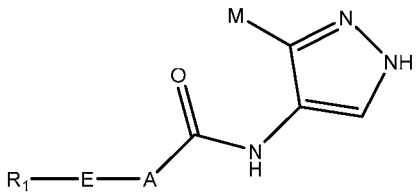
**[00729]** In a preferred embodiment, the JAK-2 inhibitor is ENMD-2076. In a preferred embodiment, the JAK-2 inhibitor is (*E*)-*N*-(5-methyl-1*H*-pyrazol-3-yl)-6-(4-methylpiperazin-1-yl)-2-styrylpyrimidin-4-amine. In a preferred embodiment, the JAK-2 inhibitor is a compound of Formula (XLIV):



Formula (XLIV)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of this compound is described in U.S. Patent Nos. 8,153,630; 7,563,787; and, 8,114,870 and U.S. Patent Application Publication Nos. 2008/0200485 A1; 2007/0142368 A1; 2009/0264422 A1; 2011/0318393 A1; and, 2009/0029992 A1, the disclosures of which are incorporated by reference herein. In an embodiment, the JAK-2 inhibitor is a compound described in U.S. Patent Nos. 8,153,630; 7,563,787; and, 8,114,870 and U.S. Patent Application Publication Nos. 2008/0200485 A1; 2007/0142368 A1; 2009/0264422 A1; 2011/0318393 A1; and, 2009/0029992 A1, the disclosures of which are incorporated by reference herein.

**[00730]** In an embodiment, the JAK-2 inhibitor is a compound of Formula (XLV):

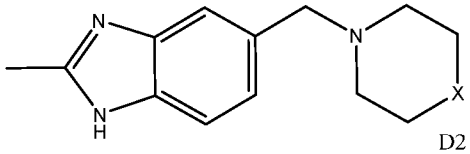


Formula (XLV)

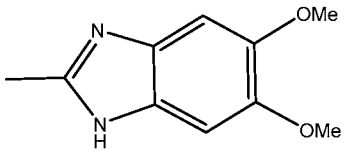
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, prodrug, tautomer or N-oxide thereof,

wherein M is selected from a group D1 and a group D2:

D1



D2



and wherein:

(A) when M is a group D1:

X is selected from O, NH and $NCH_3$;

A is selected from a bond and a group $NR_2$ where $R_2$ is hydrogen or methyl;

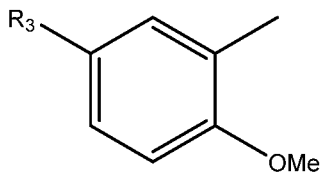
E is selected from a bond, $CH_2$, CH(CN) and $C(CH_3)_2$;

$R_1$ is selected from:

(i) a cycloalkyl group of 3 to 5 ring members optionally substituted by hydroxy, fluorine, amino, methylamino, methyl or ethyl;

(ii) a saturated heterocyclic group of 4 to 6 ring members containing 1 or 2 heteroatom ring members selected from O, N, S and $SO_2$, the heterocyclic group being optionally substituted by $(C_{1-4})$alkyl, amino or hydroxy; but excluding unsubstituted 4-morpholinyl, unsubstituted tetrahydropyran-4-yl, unsubstituted 2-pyrrolidinyl, and unsubstituted and 1-substituted piperidine-4-yl;

(iii) a 2,5-substituted phenyl group of the formula:



wherein (a) when X is NH or N—$CH_3$, $R_3$ is selected from chlorine and cyano;

and (b) when X is O, $R_3$ is CN;

(iv) a group $CR_6R_7R_8$ wherein $R_6$ and $R_7$ are each selected from hydrogen and methyl, and $R_8$ is selected from hydrogen, methyl, $(C_{1-4})$alkylsulphonylmethyl, hydroxymethyl and cyano;

(v) a pyridazin-4-yl group optionally substituted by one or two substituents selected from methyl, ethyl, methoxy and ethoxy;

(vi) a substituted imidazothiazole group wherein the substituents are selected from methyl, ethyl, amino, fluorine, chlorine, amino and methylamino; and
(vii) an optionally substituted 1,3-dihydro-isoindol-2-yl or optionally substituted 2,3-dihydro-indol-1-yl group wherein the optional substituents in each case are selected from halogen, cyano, amino, $C_{1-4}$ mono- and dialkylamino, $CONH_2$ or CONH—($C_{1-4}$)alkyl, $C_{1-4}$ alkyl and $C_{1-4}$ alkoxy wherein the $C_{1-4}$ alkyl and $C_{1-4}$ alkoxy groups are optionally substituted by hydroxy, methoxy, or amino;
(viii) 3-pyridyl optionally substituted by one or two substituents selected from hydroxy, halogen, cyano, amino, $C_{1-4}$ mono- and dialkylamino, $CONH_2$ or CONH—$C_{1-4}$ alkyl, $C_{1-4}$ alkyl and $C_{1-4}$ alkoxy wherein the $C_{1-4}$ alkyl and $C_{1-4}$ alkoxy groups are optionally substituted by hydroxy, methoxy, or amino, but excluding the compounds 2-oxo-1,2-dihydro-pyridine-3-carboxylic acid [3-(5-morpholin-4-ylmethyl-*1H*-benzoimidazol-2-yl)-*1H*-pyrazol-4-yl]-amide and 2,6-dimethoxy-N-[3-(5-morpholin-4-ylmethyl-*1H*-benzoimidazol-2-yl)-*1H*-pyrazol-4-yl]-nicotinamide;
(ix) thiomorpholine or an S-oxide or S,S-dioxide thereof optionally substituted by one or two substituents selected from halogen, cyano, amino, $C_{1-4}$ mono- and dialkylamino, $CONH_2$ or CONH—$C_{1-4}$ alkyl, $C_{1-4}$ alkyl and $C_{1-4}$ alkoxy wherein the $C_{1-4}$ alkyl and $C_{1-4}$ alkoxy groups are optionally substituted by hydroxy, methoxy, or amino; and
when E-A is $NR_2$, $R_1$ is additionally selected from:
(x) 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 3,4-difluorophenyl, 2,5-difluorophenyl, 3,5-difluorophenyl, 2,4,6-trifluorophenyl, 2-methoxyphenyl, 5-chloro-2-methoxyphenyl, cyclohexyl, unsubstituted 4-tetrahydropyranyl and tert-butyl;
(xi) a group $NR_{10}R_{11}$ where $R_{10}$ and $R_{11}$ are each $C_{1-4}$ alkyl or $R_{10}$ and $R_{11}$ are linked so that $NR_{10}R_{11}$ forms a saturated heterocyclic group of 4 to 6 ring members optionally containing a second heteroatom ring member selected from O, N, S and $SO_2$, the heterocyclic group being optionally substituted by C1-4 alkyl, amino or hydroxy;
(xii) pyridone optionally substituted by one or two substituents selected from hydroxy, halogen, cyano, amino, $C_{1-4}$ mono- and dialkylamino, CONH2, CONH—$C_{1-4}$ alkyl, $C_{1-4}$ alkyl and $C_{1-4}$ alkoxy wherein the $C_{1-4}$ alkyl and $C_{1-4}$ alkoxy groups are optionally substituted by hydroxy, methoxy, or amino;

when E-A is $C(CH_3)_2NR_2$ or $CH_2$-$NR_2$, $R_1$ is additionally selected from:

(xiii) unsubstituted 2-furyl and 2,6-difluorophenyl; and

when E-A is $C(CH3)_2NR_2$, $R_1$ is additionally selected from:

(xiv) unsubstituted phenyl; and

when E is $CH_2$, $R_1$ is additionally selected from:

(xv) unsubstituted tetrahydropyran-4-yl; and

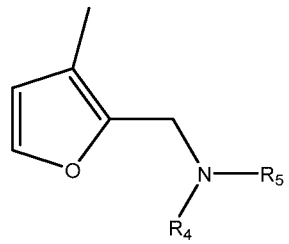
(B) when M is a group D2:

A is selected from a bond and a group $NR_2$ where $R_2$ is hydrogen or methyl;

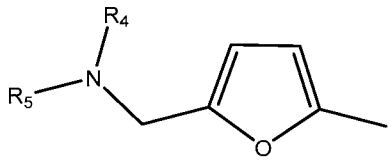
E is selected from a bond, $CH_2$, CH(CN) and $C(CH_3)_2$;

$R_1$ is selected from:

(xvi) a 2-substituted 3-furyl group of the formula:




wherein $R_4$ and $R_5$ are the same or different and are selected from hydrogen and $C_{1-4}$ alkyl, or $R_4$ and $R_5$ are linked so that $NR_4R_5$ forms a 5- or 6-membered saturated heterocyclic group optionally containing a second heteroatom or group selected from O, NH, NMe, S or $SO_2$, the 5- or 6-membered saturated ring being optionally substituted by hydroxy, fluorine, amino, methylamino, methyl or ethyl; (xvii) a 5-substituted 2-furyl group of the formula:

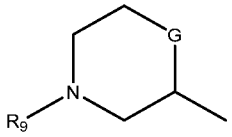



wherein $R_4$ and $R_5$ are the same or different and are selected from hydrogen and $C_{1-4}$ alkyl, or $R_4$ and $R_5$ are linked so that $NR_4R_5$ forms a 5- or 6-membered saturated heterocyclic group optionally containing a second heteroatom or group selected from O, NH, NMe, S or $SO_2$, the 5- or 6-membered saturated heterocyclic group being optionally substituted by hydroxy, fluorine, amino, methylamino, methyl or ethyl;

with the proviso that the compound is not 5-piperidin-1-ylmethyl-furan-2-carboxylic acid

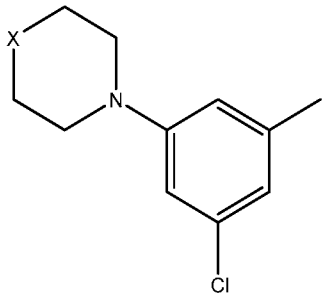
[3-(5,6-dimethoxy-1*H*-benzoimidazol-2-yl)-1*H*-pyrazol-4-yl]-amide;

(xviii) a group of the formula:




wherein $R_9$ is hydrogen, methyl, ethyl or isopropyl; G is CH, O, S, SO, $SO_2$ or NH and the group is optionally substituted by one, two or three substituents selected from $C_{1-4}$ hydrocarbyl, hydroxy, $C_{1-4}$ hydrocarbyloxy, fluorine, amino, mono- and di-$C_{1-4}$ alkylamino and wherein the $C_{1-4}$ hydrocarbyl and $C_{1-4}$ hydrocarbyloxy groups are each optionally substituted by hydroxy, fluorine, amino, mono- or di-$C_{1-4}$ alkylamino; and

(xix) a 3,5-disubstituted phenyl group of the formula:




wherein X is selected from O, NH and $NCH_3$; and

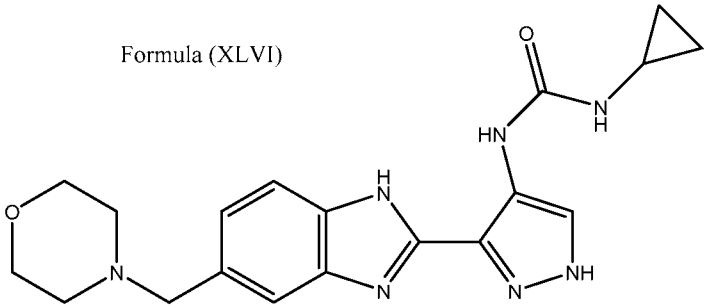
(C) when M is a group D1:

and X is O; A is a group $NR_2$ where $R_2$ is hydrogen; E is a bond; and $R_1$ is 2,6-difluorophenyl; then the compound of the Formula (XLV) is an acid addition salt selected from salts formed with an acid selected from the group consisting of acetic, adipic, alginic, ascorbic (e.g. L-ascorbic), aspartic (e.g. L-aspartic), benzenesulphonic, benzoic, camphoric (e.g. (+) camphoric), capric, caprylic, carbonic, citric, cyclamic, dodecanoate, dodecylsulphuric, ethane-1,2-disulphonic, ethanesulphonic, fumaric, galactaric, gentisic, glucoheptonic, D-gluconic, glucuronic (e.g. D-glucuronic), glutamic (e.g. L-glutamic), α-oxoglutaric, glycolic, hippuric, hydrochloric, isethionic, isobutyric, lactic (e.g. (+)-L-lactic and (±)-DL-lactic), lactobionic, laurylsulphonic, maleic, malic, (−)-L-malic, malonic, methanesulphonic, mucic, naphthalenesulphonic (e.g. naphthalene-2-sulphonic), naphthalene-1,5-disulphonic, nicotinic, oleic, orotic, oxalic, palmitic, pamoic, phosphoric, propionic, sebacic, stearic, succinic, sulphuric, tartaric (e.g. (+)-L-tartaric),

thiocyanic, toluenesulphonic (e.g. p-toluenesulphonic), valeric and xinafoic acids.

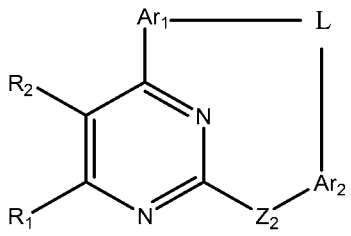
**[00731]** In a preferred embodiment, the JAK-2 inhibitor is AT-9283. In a preferred embodiment, the JAK-2 inhibitor is 1-cyclopropyl-3-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)urea. In a preferred embodiment, the JAK-2 inhibitor is a compound of Formula (XLVI):

Formula (XLVI)



or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of this compound is described in U.S. Patent Nos. 8,399,442 and 7,977,477 and U.S. Patent Application Publication Nos. 2010/0004232 A1; 2014/0010892 A1; 2011/0224203 A1; and, 2007/0135477, the disclosures of which are incorporated by reference herein. In an embodiment, the JAK-2 inhibitor is a compound described in U.S. Patent Nos. 8,399,442 and 7,977,477 and U.S. Patent Application Publication Nos. 2010/0004232 A1; 2014/0010892 A1; 2011/0224203 A1; and, 2007/0135477, the disclosures of which are incorporated by reference herein.

**[00732]** In an embodiment, the JAK-2 inhibitor is a compound of Formula (XLVII):



Formula (XLVII)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein:

$R^1$ and $R^2$ are each independently selected from the group consisting of: H, halogen, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, heteroalkyl, cycloalkyl, cycloalkenyl,

heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, cycloalkylheteroalkyl, heterocycloalkylheteroalkyl, heteroarylheteroalkyl, arylheteroalkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, alkoxyaryl, alkenyloxy, alkynyloxy, cycloalkylkoxy, heterocycloalkyloxy, aryloxy, arylalkyloxy, phenoxy, benzyloxy, heteroaryloxy, amino, alkylamino, aminoalkyl, acylamino, arylamino, sulfonylamino, sulfinylamino, —COOH, —$COR^3$, —$COOR^3$, —$CONHR^3$, —$NHCOR^3$, —$NHCOOR^3$, —$NHCONHR^3$, alkoxycarbonyl, alkylaminocarbonyl, sulfonyl, alkylsulfonyl, alkylsulfinyl, arylsulfonyl, arylsulfinyl, aminosulfonyl, —$SR^3$, $R^4S(O)R^6$—, $R^4S(O)_2R^6$—, $R^4C(O)N(R^5)R^6$—, $R^4SO_2N(R^5)R^6$—, $R^4N(R^5)C(O)R^6$—, $R^4N(R^5)SO_2R^6$—, $R^4N(R^5)C(O)N(R^5)R^6$— and acyl, each of which may be optionally substituted;

each $R^3$, $R^4$, and $R^5$ is independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl and acyl, each of which may be optionally substituted;

each $R^6$ is independently selected from the group consisting of a bond, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl and acyl, each of which may be optionally substituted;

$Z^2$ is independently selected from the group consisting of a bond, O, S, —$N(R^7)$—, —$N(R^7)C_{1\text{-}2}$alkyl-, and —$C_{1\text{-}2}$alkyl$N(R^7)$—;

each $R^7$ is independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl and acyl, each of which may be optionally substituted;

$Ar^1$ and $Ar^2$ are each independently selected from the group consisting of aryl and heteroaryl, each of which may be optionally substituted;

L is a group of formula:

—$X^1$—Y—$X^2$—

wherein $X^1$ is attached to $Ar^1$ and $X^2$ is attached to $Ar^2$, and wherein $X^1$, $X^2$ and Y are

selected such that the group L has between 5 and 15 atoms in the normal chain,

$X^1$ and $X^2$ are each independently a heteroalkyl group containing at least one oxygen atom in the normal chain,

Y is a group of formula —$CR^a$=$CR^b$— or an optionally substituted cycloalkyl group,

wherein $R^a$ and $R^b$ are each independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl and acyl, each of which may be optionally substituted, or

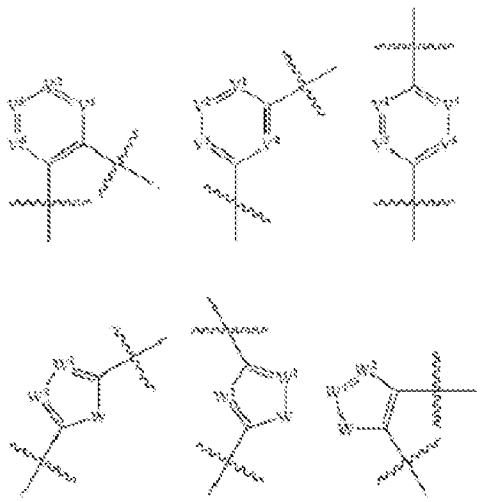
$R^a$ and $R^b$ may be joined such that when taken together with the carbon atoms to which they are attached they form a cycloalkenyl or cycloheteroalkenyl group;

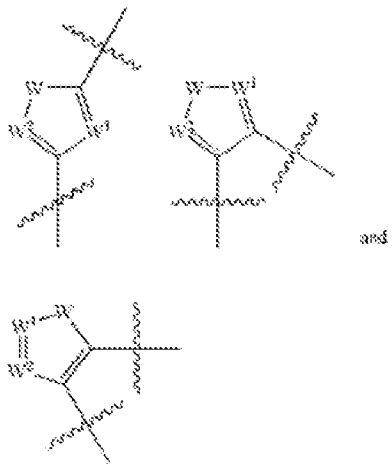
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, or an N-oxide thereof.

In certain embodiments $Z^2$ is selected from the group consisting of a bond, —$N(R^7)$—, and —S—. In one specific embodiment $Z^2$ is —$N(R^7)$—. In an even more specific embodiment $Z^2$ is —N(H)—.

$Ar^1$ and $Ar^2$ are each independently selected from the group consisting of aryl and heteroaryl and may be monocyclic, bicyclic or polycyclic moieties. In certain embodiments each of $Ar^1$ and $Ar^2$ is a monocyclic or bicyclic moiety. In certain embodiments each of $Ar^1$ and $Ar^2$ are a monocyclic moiety.

In certain embodiments $Ar^1$ is selected from the group consisting of:





wherein $V^1$, $V^2$, $V^3$ and $V^4$ are each independently selected from the group consisting of N, and $C(R^{10})$;

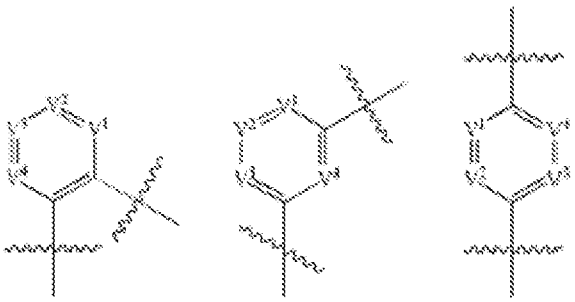
W is selected from the group consisting of O, S and $NR^{10}$;

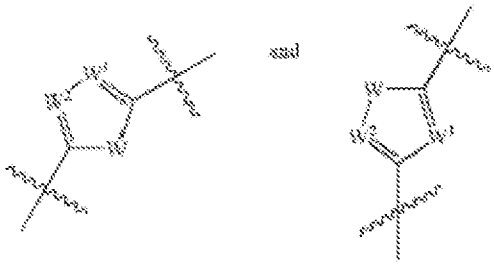
$W^1$ and $W^2$ are each independently selected from the group consisting of N and $CR^{10}$;

wherein each $R^{10}$ is independently selected from the group consisting of: H, halogen, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, heteroalkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, cycloalkylheteroalkyl, heterocycloalkylheteroalkyl, heteroarylheteroalkyl, arylheteroalkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, alkoxyaryl, alkenyloxy, alkynyloxy, cycloalkylkoxy, heterocycloalkyloxy, aryloxy, arylalkyloxy, phenoxy, benzyloxy, heteroaryloxy, amino, alkylamino, aminoalkyl, acylamino, arylamino, sulfonylamino, sulfinylamino, —COOH, —$COR^3$, —$COOR^3$, —$CONHR^3$, —$NHCOR^3$, —$NHCOOR^3$, —$NHCONHR^3$, alkoxycarbonyl, alkylaminocarbonyl, sulfonyl, alkylsulfonyl, alkylsulfinyl, arylsulfonyl, arylsulfinyl, aminosulfonyl, —$SR^3$, $R^4S(O)R^6$—, $R^4S(O)_2R^6$—, $R^4C(O)N(R^5)R^6$—, $R^4SO_2N(R^5)R^6$—, $R^4N(R^5)C(O)R^6$—, $R^4N(R^5)SO_2R^6$—, $R^4N(R^5)C(O)N(R^5)R^6$— and acyl, each of which may be optionally substituted,

wherein $R^3$, $R^4$, $R^5$ and $R^6$ are as defined above.

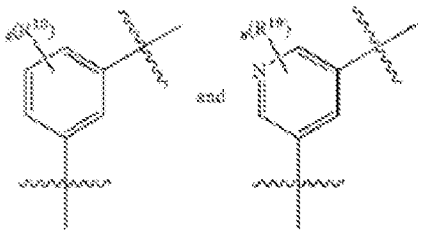
In certain embodiments $Ar^1$ is selected from the group consisting of:





wherein $V^1$, $V^2$, $V^3$, $V^4$, W, $W^1$, $W^2$, $R^3$, $R^4$, $R^5$ and $R^6$ are as defined above.

In certain embodiments $Ar^1$ is selected from the group consisting of:

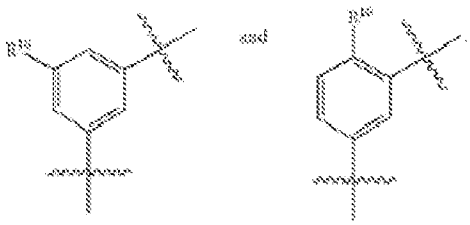


wherein each $R^{10}$ is independently as defined above,

k is an integer selected from the group consisting of 0, 1, 2, 3, and 4; and

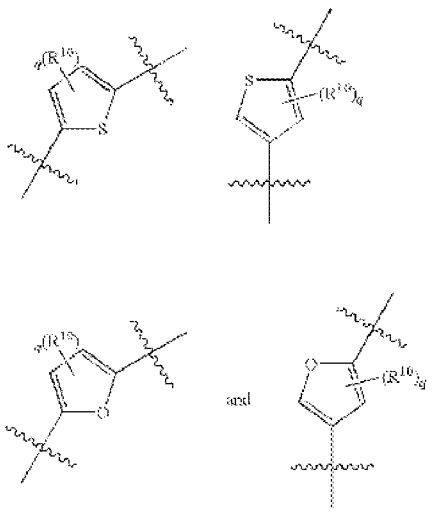
n is an integer selected from the group consisting of 0, 1, and 2.

In yet an even further embodiment $Ar^1$ is selected from the group consisting of:



wherein $R^{10}$ is as defined above.

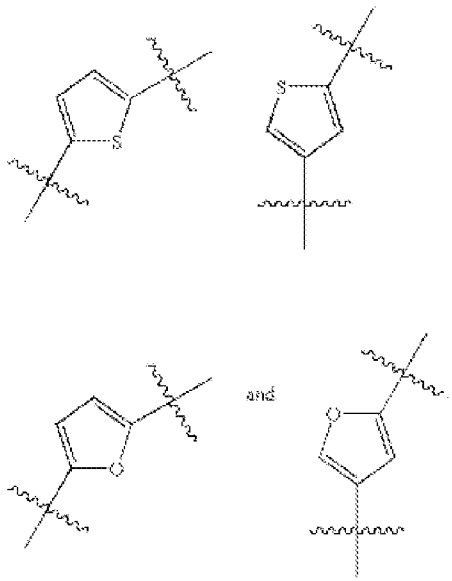
In certain embodiments $Ar^1$ is selected from the group consisting of:



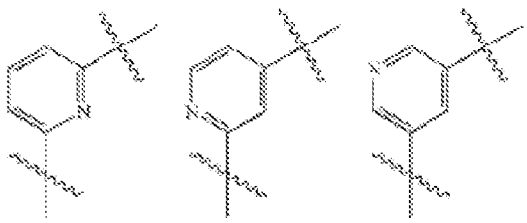
wherein each $R^{10}$ is independently as defined above, and

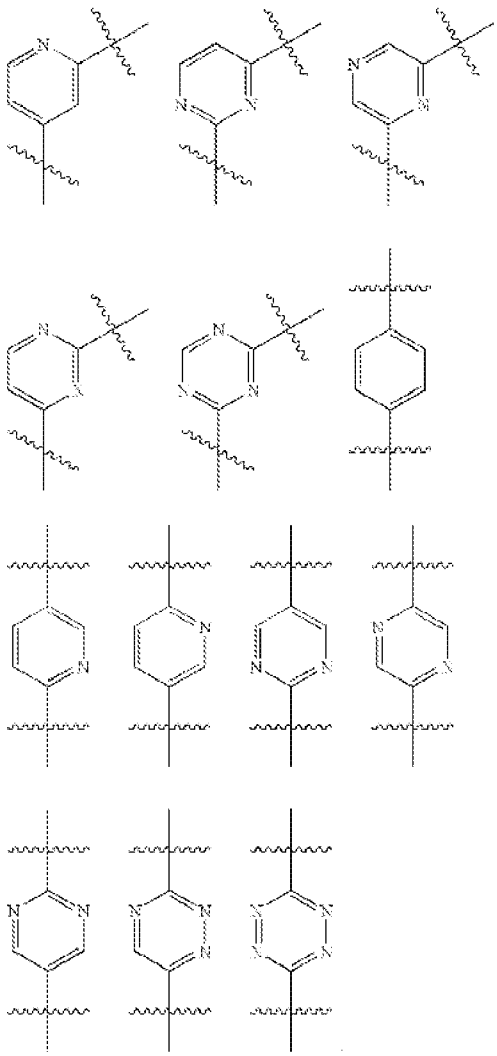
q is an integer selected from the group consisting of 0, 1 and 2.

In certain embodiments $Ar^1$ is selected from the group consisting of:

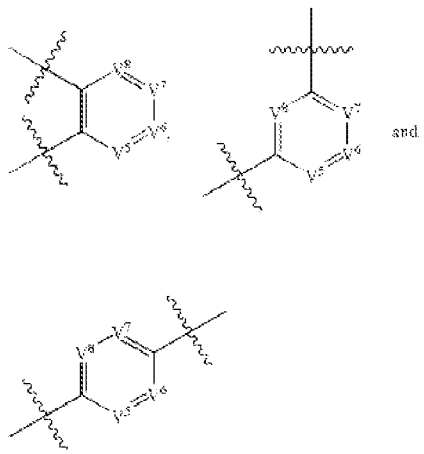


In certain embodiments $Ar^1$ is selected from the group consisting of:





In certain embodiments $Ar^2$ is selected from the group consisting of:

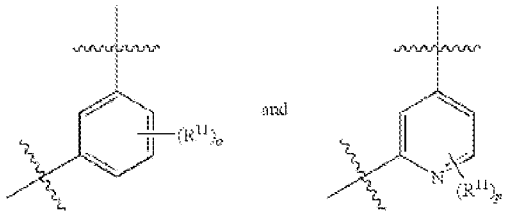


wherein $V^5$, $V^6$, $V^7$ and $V^8$ are independently selected from the group consisting of N, and

$C(R^{11})$;

wherein each $R^{11}$ is independently selected from the group consisting of: H, halogen, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, heteroalkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, cycloalkylheteroalkyl, heterocycloalkylheteroalkyl, heteroarylheteroalkyl, arylheteroalkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, alkoxyaryl, alkenyloxy, alkynyloxy, cycloalkylkoxy, heterocycloalkyloxy, aryloxy, arylalkyloxy, phenoxy, benzyloxy, heteroaryloxy, amino, alkylamino, aminoalkyl, acylamino, arylamino, sulfonylamino, sulfinylamino, —COOH, $—COR^3$, $—COOR^3$, $—CONHR^3$, $—NHCOR^3$, $—NHCOOR^3$, $—NHCONHR^3$, alkoxycarbonyl, alkylaminocarbonyl, sulfonyl, alkylsulfonyl, alkylsulfinyl, arylsulfonyl, arylsulfinyl, aminosulfonyl, $—SR^3$, $R^4S(O)R^6—$, $R^4S(O)_2R^6—$, $R^4C(O)N(R^5)R^6—$, $R^4SO_2N(R^5)R^6—$, $R^4N(R^5)C(O)R^6—$, $R^4N(R^5)SO_2R^6—$, $R^4N(R^5)C(O)N(R^5)R^6—$ and acyl, each of which may be optionally substituted.

In certain embodiments $Ar^2$ is selected from the group consisting of:

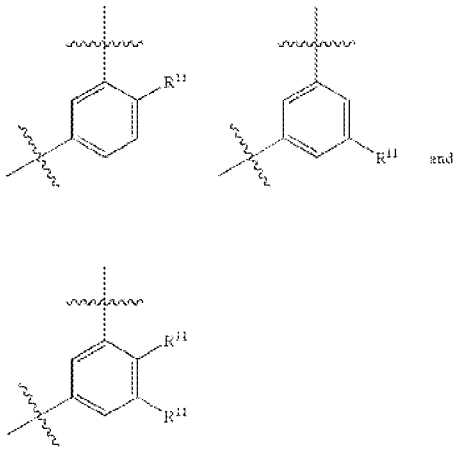



wherein each $R^{11}$ is independently as defined above

o is an integer selected from the group consisting of 0, 1, 2, 3, and 4; and

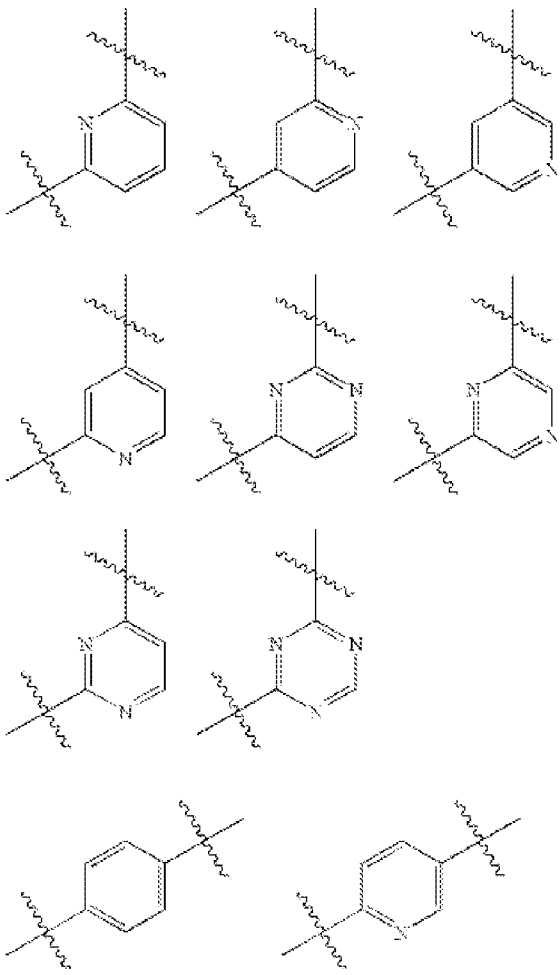
p is an integer selected from the group consisting of 0, 1, 2, and 3.

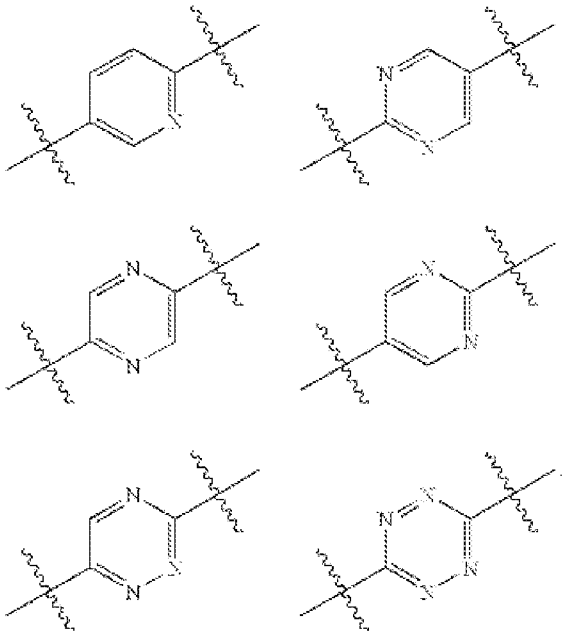
In certain embodiments $Ar^2$ is selected from the group consisting of:



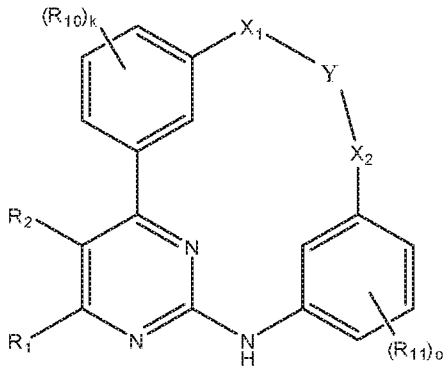
wherein each $R^{11}$ is as defined above.

In a further embodiment $Ar^2$ is selected from the group consisting of:





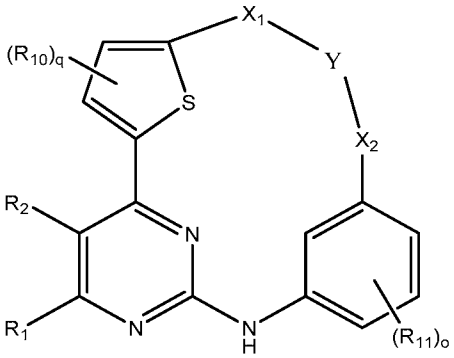
**[00733]** In an embodiment, the JAK-2 inhibitor is a compound of Formula (XLVIII):



Formula (XLVIII)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein $R^1$, $R^2$, $R^{10}$, $R^{11}$, $X^1$, $X^2$, Y, k and o are as defined above.

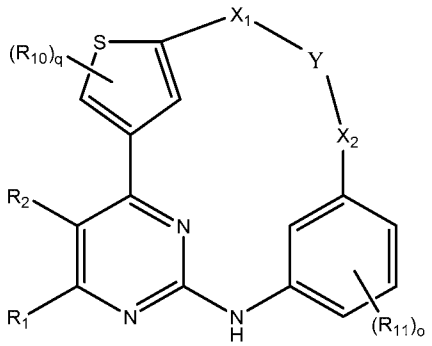
**[00734]** In an embodiment, the JAK-2 inhibitor is a compound of Formula (XLIX):



Formula (XLIX)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof wherein $R^1$, $R^2$, $R^{10}$, $R^{11}$, $X^1$, $X^2$, Y, q and o are as defined above.

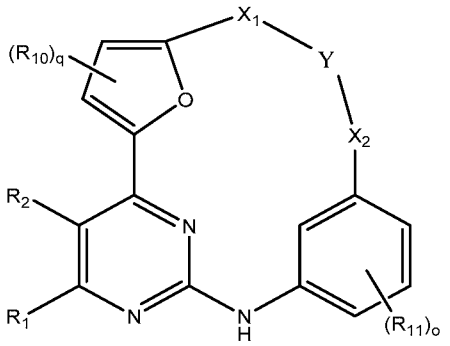
**[00735]** In an embodiment, the JAK-2 inhibitor is a compound of Formula (L):



Formula (L)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein $R^1$, $R^2$, $R^{10}$, $R^{11}$, $X^1$, $X^2$, Y, q and o are as defined above.

**[00736]** In an embodiment, the JAK-2 inhibitor is a compound of Formula (LI):

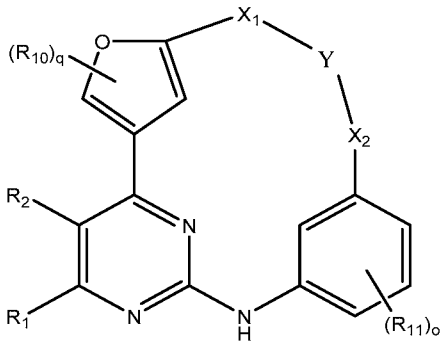


Formula (LI)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof,

wherein $R^1$, $R^2$, $R^{10}$, $R^{11}$, $X^1$, $X^2$, Y, q and o are as defined above.

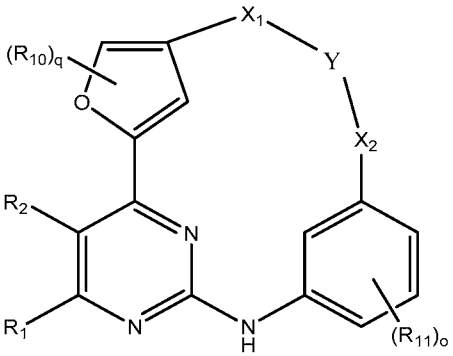
**[00737]** In an embodiment, the JAK-2 inhibitor is a compound of Formula (LII):



Formula (LII)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein $R^1$, $R^2$, $R^{10}$, $R^{11}$, $X^1$, $X^2$, Y, q and o are as defined above.

**[00738]** In an embodiment, the JAK-2 inhibitor is a compound of Formula (LIII):



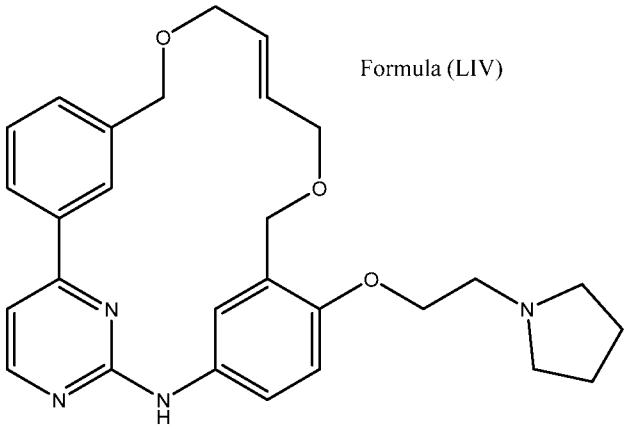
Formula (LIII)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein $R^1$, $R^2$, $R^{10}$, $R^{11}$, $X^1$, $X^2$, Y, q and o are as defined above.

**[00739]** In embodiments where the JAK-2 inhibitor is a compound of Formulas (XLVII)-(LIII), $X^1$, $X^2$ and Y are chosen such that there are between 5 and 15 atoms in the normal chain. In one embodiment, $X^1$, $X^2$ and Y are chosen such that there are between 6 and 15 atoms in the normal chain. In one specific embodiment, $X^1$, $X^2$ and Y are chosen such that there are 7 atoms in the normal chain. In another specific embodiment, $X^1$, $X^2$ and Y are chosen such that there are 8 atoms in the normal chain.

[00740] In embodiments where the JAK-2 inhibitor is a compound of Formulas (XLVII)-(LIII), $X^1$ and $X^2$ are each independently a heteroalkyl group containing at least one oxygen atom in the normal chain. In certain embodiments $X^1$ is selected from the group consisting of: (a) —$O(C_{1-5})$alkyl-, (b) —$(C_{1-5})$alkylO-, and (c) —$(C_{1-5})$alkyl$O(C_{1-5})$alkyl. In certain embodiments $X^1$ is selected from the group consisting of: (a) —$OCH_2$— (b) —$CH_2O$—, (c) —$OCH_2CH_2$—, (d) —$CH_2CH_2O$—, (e) —$CH_2OCH_2$—, and (f) —$CH_2CH_2OCH_2$—. In one specific embodiment $X^1$ is —$OCH_2$—. In another specific embodiment $X^1$ is —$CH_2O$—. In another specific embodiment $X^1$ is —$OCH_2CH_2$—. In another specific embodiment $X^1$ is —$CH_2CH_2O$—. In another specific embodiment $X^1$ is —$CH_2OCH_2$—. In another specific embodiment $X^1$ is —$CH_2CH_2OCH_2$—. In certain embodiments $X^2$ is selected from the group consisting of: (a) —$O(C_{1-5})$alkyl-, (b) —$(C_{1-5})$alkylO-, and (c) —$(C_{1-5})$alkyl$O(C_{1-5})$alkyl. In certain embodiments $X^2$ is selected from the group consisting of: (a) —$OCH_2$— (b) —$CH_2O$—, (c) —$OCH_2CH_2$—, (d) —$CH_2CH_2O$—, (e) —$CH_2OCH_2$—, and (f) —$CH_2CH_2OCH_2$—. In one specific embodiment $X^2$ is —$OCH_2$—. In another specific embodiment $X^1$ is —$CH_2O$—. In another specific embodiment $X^2$ is —$OCH_2CH_2$—. In another specific embodiment $X^2$ is —$CH_2CH_2O$—. In another specific embodiment $X^2$ is —$CH_2OCH_2$—. In another specific embodiment $X^2$ is —$CH_2CH_2OCH_2$—.

**[00741]** In a preferred embodiment, the JAK-2 inhibitor is pacritinib. Pacritinib is also known as SB1518. In a preferred embodiment, the JAK-2 inhibitor is (*E*)-$4^4$-(2-(pyrrolidin-1-yl)ethoxy)-6,11-dioxa-3-aza-2(4,2)-pyrimidina-1,4(1,3)-dibenzenacyclododecaphan-8-ene. In a preferred embodiment, the JAK-2 inhibitor is 14,19-dioxa-5,7,27-triazatetracyclo[19.3.1.$1^{2,6}$.$1^{8,12}$]heptacosa-1(25),2,4,6(27),8,10,12(26),16,21,23-decaene, 11-[2-(1-pyrrolidinyl)ethoxy]-, (16E)-. In a preferred embodiment, the JAK-2 inhibitor is (16E)-11-[2-(pyrrolidin-1-yl)ethoxy]-14,19-dioxa-5,7,27-triazatetracyclo[19.3.1.$1^{2,6}$.$1^{8,12}$]heptacosa-1(24),2,4,6,8,10,12(26),16,21(25),22-decaene. In an embodiment, the JAK-2 inhibitor is a compound of Formula (LIV):

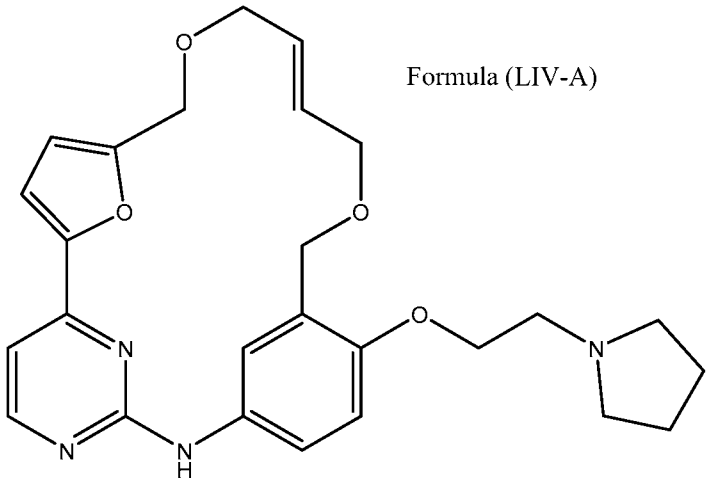


Formula (LIV)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. In an embodiment, the structure of Formula (LIV) may be a tautomeric form. The preparation of Formula (LIV) is described in U.S. Patent Nos. 8,143,255; 8,153,632; and, 8,415,338 and U.S. Patent Application Publication Nos. 2009/0258886 A1; 2012/0142680 A1; 2012/0196855 A1; and 2013/0172338 A1, the disclosures of which are incorporated by reference herein. The preparation and properties of this JAK-2 inhibitor are known to those of ordinary skill in the art, and for example are described in: Hart, *et al.*, SB1518, a novel macrocyclic pyrimidine-based JAK2 inhibitor for the treatment of myeloid and lymphoid malignancies, *Leukemia* **2011,** *25,* 1751-1759; Hart, *et al.*, Pacritinib (SB1518), a JAK2/FLT3 inhibitor for the treatment of acute myeloid leukemia, *Blood Cancer J.*, **2011,** *1(11)*, e44; William, *et al.*, Discovery of the macrocycle 11-(2-pyrrolidin-1-yl-ethoxy)-14,19-dioxa-5,7,26-triaza-tetracyclo[19.3.1.1(2,6).1(8,12)]heptacosa-1(25),2(26),3,5,8,10,12(27),16,21,23-decaene (SB1518), a potent Janus kinase 2/fms-like tyrosine kinase-3 (JAK2/FLT3) inhibitor for the treatment of myelofibrosis and lymphoma. *J. Med. Chem.* **2011,** *54,* 4638-4658; Poulsen, *et al.* Structure-based design of oxygen-linked macrocyclic kinase inhibitors: discovery of SB1518 and SB1578, potent inhibitors of Janus kinase 2 (JAK2) and Fms-like tyrosine kinase-3 (FLT3). *J. Comput. Aided Mol. Des.* **2012,** *26,* 437-450.

**[00742]** In an embodiment, the JAK-2 inhibitor is selected from the structures disclosed in U.S. Patent Nos. 8,143,255; 8,153,632; and 8,415,338 and U.S. Patent Application Publication Nos. 2009/0258886 A1; 2012/0142680 A1; 2012/0196855 A1; and 2013/0172338 A1, the disclosures of which are incorporated by reference herein.

**[00743]** In a preferred embodiment, the JAK-2 inhibitor is (*E*)-4$^4$-(2-(pyrrolidin-1-yl)ethoxy)-6,11-dioxa-3-aza-2(4,2)-pyrimidina-1(2,5)-furana-4(1,3)-benzenacyclododecaphan-8-ene. In a preferred embodiment, the JAK-2 inhibitor is (9E)-15-(2-(pyrrolidin-1-yl)ethoxy)-7,12,25-trioxa-19,21,24-triaza-tetracyclo[18.3.1.1(2,5).1(14,18)]hexacosa-1(24),2,4,9,14(26),15,17,20,22-nonaene. In a preferred embodiment, the JAK-2 inhibitor is a compound of Formula (LIV-A):

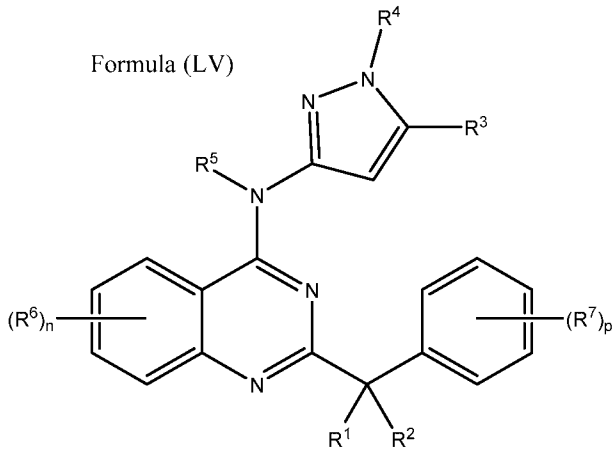


Formula (LIV-A)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The preparation and properties of this JAK-2 inhibitor are known to those of ordinary skill in the art, and for example are described in: Madan, *et al.*, SB1578, a novel inhibitor of JAK2, FLT3, and c-Fms for the treatment of rheumatoid arthritis, *J. Immunol.* **2012,** *189,* 4123-4134 and William et al., Discovery of the macrocycle (9E)-15-(2-(pyrrolidin-1-yl)ethoxy)-7,12,25-trioxa-19,21,24-triaza-tetracyclo[18.3.1.1(2,5).1(14,18)]hexacosa-1(24),2,4,9,14(26),15,17,20,22-nonaene (SB1578), a potent inhibitor of janus kinase 2/fms-like tyrosine kinase-3 (JAK2/FLT3) for the treatment of rheumatoid arthritis. *J. Med. Chem.* **2012,** 55, 2623-2640.

**[00744]** In an embodiment, the JAK-2 inhibitor is a compound selected from the structures disclosed in U.S. Patent No. 8,349,851 and U.S. Patent Application Publication Nos. 2010/0317659 A1, 2013/0245014, 2013/0296363 A1, the disclosures of which are incorporated by reference herein. In an embodiment, the JAK-2 inhibitor is a compound of Formula (LV):

Formula (LV)



or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein

$R^1$ and $R^2$ are selected from (i), (ii), (iii), (iv), and (v) as follows:

(i) $R^1$ and $R^2$ together form =O, =S, =$NR^9$ or =$CR^{10}R^{11}$;

(ii) $R^1$ and $R^2$ are both —$OR^8$, or $R^1$ and $R^2$, together with the carbon atom to which they are attached, form dioxacycloalkyl;

(iii) $R^1$ is hydrogen or halo; and $R^2$ is halo; and

(iv) $R^1$ is alkyl, alkenyl, alkynyl, cycloalkyl or aryl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl and aryl is optionally substituted with one or more substituents selected from halo, cyano, alkyl, —$R^xOR^w$, —$R^xS(O)_qR^v$, —$R^xNR^yR^z$ and —$C(O)OR^w$; and $R^2$ is halo or —$OR^8$; and

(v) $R^1$ is halo, deutero, —$OR^{12}$, —$NR^{13}R^{14}$, or —$S(O)_qR^{15}$; and $R^2$ is hydrogen, deutero, alkyl, alkenyl, alkynyl, cycloalkyl or aryl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl and aryl, is optionally substituted with one or more substitutents selected from halo, cyano, alkyl, —$R^xOR^w$, —$R^xS(O)_qR^v$ and —$R^xNR^yR^z$;

$R^3$ is hydrogen, halo, alkyl, cyano, haloalkyl, cycloalkyl, cycloalkylalkyl, hydroxy or alkoxy;

$R^4$ and $R^5$ are each independently hydrogen or alkyl;

each $R^6$ is independently selected from halo, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, —$R^xOR^{18}$, —$R^xNR^{19}R^{20}$, and —$R^xS(O)_qR^v$;

each $R^7$ is independently halo, alkyl, haloalkyl or —$R^xOR^w$;

$R^8$ is alkyl, alkenyl or alkynyl;

$R^9$ is hydrogen, alkyl, haloalkyl, hydroxy, alkoxy or amino;

$R^{10}$ is hydrogen or alkyl;

$R^{11}$ is hydrogen, alkyl, haloalkyl or —C(O)$OR^8$;

$R^{12}$ is selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, —C(O)$R^v$, —C(O)$OR^w$ and —C(O)$NR^yR^z$, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl are each optionally substituted with one or more substituents independently selected from halo, oxo, alkyl, hydroxy, alkoxy, amino and alkylthio;

$R^{13}$ and $R^{14}$ are selected as follows:

(i) $R^{13}$ is hydrogen or alkyl; and $R^{14}$ is selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, alkoxy, —C(O)$R^v$, —C(O)$OR^w$, —C(O)$NR^yR^z$ and —$S(O)_qR^v$, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl are each optionally substituted with one or more substituents independently selected from halo, oxo, alkyl, hydroxy, alkoxy, amino and alkylthio; or

(ii) $R^{13}$ and $R^{14}$, together with the nitrogen atom to which they are attached, form heterocyclyl or heteroaryl wherein the heterocyclyl or heteroaryl is optionally substituted with one or more substituents independently selected from halo, alkyl, hydroxy, alkoxy, amino and alkylthio and wherein the heterocyclyl is also optionally substituted with oxo;

$R^{15}$ is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, —C(O)$NR^yR^z$ or —$NR^yR^z$, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl are each optionally substituted with one or more substituents independently selected from halo, oxo, alkyl, hydroxy, alkoxy, amino and alkylthio;

$R^{18}$ is hydrogen, alkyl, haloalkyl, hydroxy($C_{2-6}$)alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroarylalkyl; wherein $R^{18}$ is optionally substituted with 1 to 3 groups $Q^1$, each $Q^1$ independently selected from alkyl, hydroxyl, halo, haloalkyl, alkoxy, aryloxy,

alkoxyalkyl, alkoxycarbonyl, alkoxysulfonyl, hydroxycarbonyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloaryl and amino;

$R^{19}$ and $R^{20}$ are selected as follows:

(i) $R^{19}$ and $R^{20}$ are each independently hydrogen or alkyl; or

(ii) $R^{19}$ and $R^{20}$, together with the nitrogen atom to which they are attached, form a heterocyclyl or heteroaryl which is optionally substituted with 1 to 2 groups each independently selected from halo, alkyl, haloalkyl, hydroxyl and alkoxy;

each $R^x$ is independently alkylene or a direct bond;

$R^y$ is hydrogen, alkyl, alkenyl or alkynyl;

$R^w$ is independently hydrogen, alkyl, alkenyl, alkynyl or haloalkyl;

$R^y$ and $R^z$ are selected as follows:

(i) $R^y$ and $R^z$ are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or haloalkyl;

(ii) $R^y$ and $R^z$, together with the nitrogen atom to which they are attached, form a heterocyclyl or heteroaryl which is optionally substituted with 1 to 2 groups each independently selected from halo, alkyl, haloalkyl, hydroxyl and alkoxy;

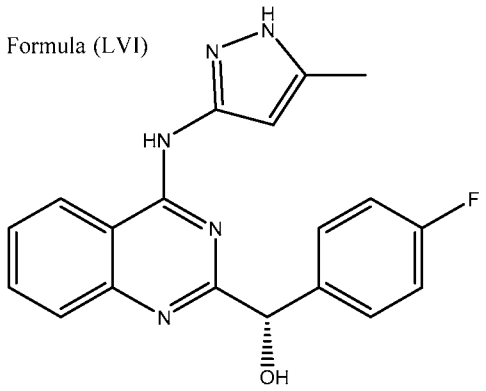
n is 0-4;

p is 0-5; and

each q is independently 0, 1 or 2.

**[00745]** In a preferred embodiment, the JAK-2 inhibitor is AC-410 (available from Ambit Biosciences). In a preferred embodiment, the JAK-2 inhibitor is (*S*)-(4-fluorophenyl)(4-((5-methyl-1*H*-pyrazol-3-yl)amino)quinazolin-2-yl)methanol. In a preferred embodiment, the JAK-2 inhibitor is a compound of Formula (LVI):

Formula (LVI)



or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of racemic (4-fluorophenyl)(4-((5-methyl-1*H*-pyrazol-3-yl)amino)quinazolin-2-yl)methanol hydrochloride is described in Examples 3 and 12 of U.S. Patent No. 8,349,851, the disclosure of which is incorporated by reference herein. Other preparation methods known to one of skill in the art also may be used. The preparation of the compound of Formula (LVI) is also described in the following paragraphs.

**[00746]** The preparation of (4-fluorophenyl)(4-(5-methyl-1*H*-pyrazol-3-ylamino)quinazolin-2-yl)methanone is accomplished by the following two steps (A and B). Step A: To a solution of ethyl 4-chloroquinazoline-2-carboxylate (0.6 g, 2.53 mmol) in THF (6 mL) at −40 °C, was added dropwise a 1 M solution of 4-fluorophenylmagnesium bromide in THF (3 mL, 3.0 mmol, 1.2 eq). The mixture was stirred at −40 °C for 4 h. The reaction was quenched by adding 0.5 N HCl solution (5 mL) and the mixture was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The crude product was purified on a silica gel column using a mixture of EtOAc-hexanes as eluent. (4-chloroquinazoline-2-yl)(4-fluorophenyl)methanone was obtained as a light yellow solid (440 mg, 60%). $^1H$ NMR (300 MHz, DMSO-d6) δ 7.45-740 (m, 2H), 8.07-8.03 (m, 1H), 8.17-8.13 (m, 2H), 8.23 (m, 2H), 8.42 (d, 1H); LC-MS (ESI) m/z 287 $(M+H)^+$. Step B: To a solution of (4-chloroquinazolin-2-yl)(4-fluorophenyl)methanone (84 mg, 0.30 mmol) in DMF (3mL) were added DIEA (0.103 mL, 0.6 mmol) and 5-methyl-1*H*-pyrazol-3-amine (88 mg, 0.9 mmol at rt. The reaction mixture was heated at 40 °C overnight. The reaction was quenched by adding water and the yellow precipitate was collected by filtration and washed with water. The crude product was purified by silica gel chromatography eluting with DCM/MeOH to give (4-fluorophenyl)(4-(5-methyl-1*H*-pyrazol-3-ylamino)quinazolin-2-yl)methanone (30 mg, 29%). $^1H$ NMR (300 MHz, DMSO-d6) δ 2.19 (s, 3H), 6.54 (s, 1H), 7.40 (m, 2H), 7.68 (t, 1H), 7.9-7.7 (m, 2H), 8.08 (m, 2H), 8.74 (d, 1H), 10.66 (s, 1H), 12.20 (s, 1H);LC-MS (ESI) m/z 348 $(M+H)^+$.

**[00747]** To a solution of 4-fluorophenyl)(4-(5-methyl-1*H*-pyrazol-3-ylamino)quinazolin-2-yl)methanone (60 mg, 0.172 mmol) in 1:1 MeOH/THF (10 mL) at 0 °C, was added $NaBH_4$ (64 mg, 1.69 mmol). The reaction mixture was stirred at 0° C. for 1.5 h. The reaction mixture was quenched by adding a few drops of acetone and

concentrated to dryness. The crude solid was purified on HPLC to afford (4-fluorophenyl)(4-(5-methyl-1*H*-pyrazol-3-ylamino)quinazolin-2-yl)methanol (18 mg, 30%); $^1$H NMR (300 MHz, DMSO-d6) δ 2.25 (s, 3H), 5.67 (s, 1H), 5.83 (bs, 1H), 6.40 (bs, 1H), 7.13 (m, 2H), 7.55-7.53 (m, 3H), 7.79 (s, 2H), 8.57 (bs, 1H), 10.43 (s, 1H), 12.12 (bs, 1H); LC-MS (ESI) m/z 350 $(M+H)^+$.

**[00748]** To a suspension of (4-fluorophenyl)(4-(5-methyl-1*H*-pyrazol-3-ylamino)quinazolin-2-yl)methanone (2.3 g) in 30% MeOH/DCM (60 mL) at 0 °C was added dropwise 4M HCl/1,4-dioxane (10 mL). After all solid material had dissolved, the mixture was concentrated under reduced pressure, and to the residue was added 30% $CH_3CN/H_2O$ (80 mL) and the mixture was sonicated until all solid material had dissolved. The mixture was frozen and lyophilized overnight to afford (4-fluorophenyl)(4-(5-methyl-1*H*-pyrazol-3-ylamino)quinazolin-2-yl)methanol hydrochloride (100%). $^1$H NMR (300 MHz, DMSO-d6) δ 2.25 (s, 3H), 6.02 (s, 1H), 6.20 (s, 1H), 7.27 (t, 2H), 7.60 (qt, 2H), 7.80 (t, 1H), 8.08 (t, 1H), 8.23 (d, 1H), 8.83 (d, 1H), 12.16 (s, 1H), 14.51 (b, 1H); LC-MS (ESI) m/z 350 $(M+H)^+$. The compound of Formula (LVI), (*S*)-(4-fluorophenyl)(4-((5-methyl-1*H*-pyrazol-3-yl)amino)quinazolin-2-yl)methanol, may be obtained from this preparation by chiral liquid chromatographic separation of the enantiomers, or by other well known techniques for resolution of enantiomers, such as those described in: Eliel et al., *Stereochemistry of Organic Compounds*, Wiley-Interscience, New York, 1994.

**[00749]** In a preferred embodiment, the JAK-2 inhibitor is (*R*)-(4-fluorophenyl)(4-((5-methyl-1*H*-pyrazol-3-yl)amino)quinazolin-2-yl)methanol, which is also known in the art to be active as a JAK-2 inhibitor. In a preferred embodiment, the JAK-2 inhibitor is racemic (4-fluorophenyl)(4-((5-methyl-1*H*-pyrazol-3-yl)amino)quinazolin-2-yl)methanol, which is also known in the art to be active as a JAK-2 inhibitor.

**[00750]** In some preferred embodiments, JAK-2 inhibitors having Formula (LV) or Formula (LVI) can be prepared, isolated, or obtained by any method known to one of skill in the art, including, but not limited to, synthesis from a suitable optically pure precursor, asymmetric synthesis from an achiral starting material, or resolution of a racemic or enantiomeric mixture, for example, chiral chromatography, recrystallization,

resolution, diastereomeric salt formation, or derivatization into diastereomeric adducts followed by separation.

[00751] A method for preparation of the compound of Formula (LVI)comprises resolving racemic (4-fluorophenyl)(4-(5-methyl-1*H*-pyrazol-3-ylamino)quinazolin-2-yl)methanol with chiral chromatography. In certain embodiments, the two individual enantiomers are separated using a chiral column, wherein the stationary phase is silica gel coated with a chiral selector such as tris-(3,5-dimethylphenyl)carbamoyl cellulose.

[00752] A method for preparation of the compound of Formula (LVI) comprises the step of reducing the achiral ketone (4-fluorophenyl)(4-(5-methyl-1*H*-pyrazol-3-ylamino)quinazolin-2-yl)methanone, prepared as described above or by other methods known to one of skill in the art, with hydrogen in the present of a chiral catalyst. The achiral ketone (4-fluorophenyl)(4-(5-methyl-1*H*-pyrazol-3-ylamino)quinazolin-2-yl)methanone may be reduced to predominantly a single enantiomeric product with a chiral reducing system of "type A" or "type B," wherein type A and type B differ from each other solely by having chiral auxiliaries of opposite chiralities. In certain embodiments, the chiral catalyst is [(S)—P-Phos $RuCl_2$ (S)-DAIPEN].

**[00753]** The reduction of the achiral ketone (4-fluorophenyl)(4-(5-methyl-1*H*-pyrazol-3-ylamino)quinazolin-2-yl)methanone in presence of a chiral catalyst may be carried out in isopropyl alcohol as a solvent. The reduction of achiral ketone (4-fluorophenyl)(4-(5-methyl-1*H*-pyrazol-3-ylamino)quinazolin-2-yl)methanone in the presence of a chiral catalyst is carried out in isopropyl alcohol and water mixture as a solvent. Isopropyl alcohol and water are used in a ratio of 1:1, 8:1 or 9:1. DMSO is used as a cosolvent in the reaction. Alternatively, DMSO is used in amounts of 10, 20 or 30% based on the total amount of isopropyl alcohol and water mixture. Alternatively, isopropyl alcohol, DMSO and water are used in a ratio of 1:1:1, 4:4:0.5, 8:1:1, 47:47:6, 41:58:1, 44:50:6, or 18:79:3. Alternatively, isopropyl alcohol, DMSO and water are used in a ratio of 41:58:1. Alternatively, isopropyl alcohol, and DMSO are used in a ratio of 1:1. Alternatively, the reduction is carried out in presence of a base, such as potassium hydroxide, potassium tert butoxide and others. Alternatively, the base is used in 2-15 mol %, in one embodiment, 2 mol %, 5 mol %, 10 mol %, 12.5 mol % or 15 mol %. Alternatively, the reduction is

carried out at a temperature of 40-80 °C, in one embodiment, 40 °C, 50 °C, 60 °C, 70 °C or 80 °C. Alternatively, the reduction is carried out at a temperature of 70 °C. Alternatively, the reduction is carried out at a pressure of 4 bar to 30 bar, in one embodiment, 4, 5, 10, 15, 20, 25 or 30 bar. Alternatively, the reduction is carried out at a pressure of 4 bar. Alternatively, the catalyst loading in the reaction is 100/1, 250/1, 500/1, 1000/1, 2000/1, 3000/1, 4000/1, 5000/1, 7000/1, 10,0000/1 or 20,000/1. In certain embodiments, the catalyst loading in the reaction is 2000/1 or 4000/1.

**[00754]** A method for preparation of the compound of Formula (LVI)comprises the step of reducing the achiral ketone (4-fluorophenyl)(4-(5-methyl-1*H*-pyrazol-3-ylamino)quinazolin-2-yl)methanone with a ketoreductase (*e.g.*, alcohol dehydrogenase). *See* Moore, *et al.*, *Acc. Chem. Res.* **2007,** *40,* 1412-1419; Daussmann, *et al.*, *Engineering in Life Sciences* **2006,** *6,* 125-129; Schlummer, *et al.*, *Specialty Chemicals Magazine* **2008,** *28,* 48-49; Osswald, *et al.*, *Chimica Oggi* **2007,** *25*(Suppl.), 16-18; and Kambourakis, *et al.*, *PharmaChem* **2006,** *5*(9), 2-5.

**[00755]** An alternative method for preparation of the compound of Formula (LVI) comprises the step of reducing the achiral ketone (4-fluorophenyl)(4-(5-methyl-1*H*-pyrazol-3-ylamino)quinazolin-2-yl)methanone with a reducing reagent (e.g., borane or borohydride reagents) in the presence of a chiral catalyst. In certain embodiments, the reducing agent is borane or a borohydride reagent. In certain embodiments, the chiral catalyst is a chiral oxazaborolidine. Cory, *et al.*, *Tetrahedron Letters* **1996,** *37,* 5675; Cho, *Chem. Soc. Rev.* **2009,** *38,* 443.

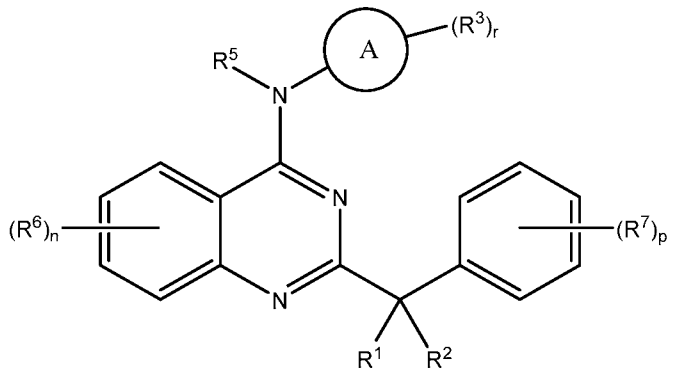
**[00756]** Another method for preparation of the compound of Formula (LVI) comprises the step of reducing the achiral ketone (4-fluorophenyl)(4-(5-methyl-1*H*-pyrazol-3-ylamino)quinazolin-2-yl)methanone via asymmetric hydrosilylation, as described in U.S. Patent Application Publication No. 2008/0269490, the disclosure of which is specifically incorporated herein by reference.

**[00757]** Another method for preparation of the compound of Formula (LVI) comprises the step of reducing the achiral ketone (4-fluorophenyl)(4-(5-methyl-1*H*-pyrazol-3-ylamino)quinazolin-2-yl)methanone via transfer hydrogenation catalyzed by an iridium complex, as described in Malacea, *et al.*, *Coord. Chem. Rev.* **2010,** *254,* 729-752.

**[00758]** The starting materials used in the synthesis of the compound of Formula (LVI) provided herein are either commercially available or can be prepared by a method known to one of skill in the art. For example, the achiral ketone (4-fluorophenyl)(4-(5-methyl-1*H*-pyrazol-3-ylamino)quinazolin-2-yl)methanone can be prepared according to the methods described in U.S. Patent Nos. 8,349,851, issued January 8, 2013, and 8,703,943, issued April 22, 2014, the disclosures of which are incorporated herein by reference in their entireties.

**[00759]** In an embodiment, the JAK-2 inhibitor is a JAK-2 inhibitor described in U.S. Patent Application Publication No. US 2013/0225614 A1, the disclosure of which are specifically incorporated herein by reference. In an embodiment, the JAK-2 inhibitor is a compound of Formula (LV-A):

Formula (LV-A)




or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein

A is azolyl other than pyrazolyl;

$R^1$ and $R^2$ are selected from (i), (ii), (iii), (iv) and (v) as follows:

(i) $R^1$ and $R^2$ together form =O, =S, $=NR^9$ or $=CR^{10}R^n$;

(ii) $R^1$ and $R^2$ are both $-OR^8$, or $R^1$ and $R^2$, together with the carbon atom to which they are attached, form cycloalkyl or heterocyclyl wherein the cycloalkyl is substituted with one to four substituents selected from halo, deutero, alkyl, haloalkyl, -OR , $-N(R)_2$, and $-S(O)_qR$ and wherein the heterocyclyl contains one to two heteroatoms wherein each heteroatom is independently selected from O, $NR^{24}$, S, S(O) and $S(O)_2$;

(iii) $R^1$ is hydrogen or halo; and $R^2$ is halo;

(iv) $R^1$ is alkyl, alkenyl, alkynyl, cycloalkyl or aryl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl and aryl are each optionally substituted with one to four substitutents selected from halo, deutero, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, cyano, =O, =N-$OR^{21}$, -$R^X OR^{21}$, -$R^X N(R^{22})_2$, -$R^X S(O)_q R^{23}$, -$C(O)R^{21}$, - $C(O)OR^{21}$ and - $C(O)N(R^{22})_2$ ; and

(v) $R^1$ is halo, deutero, -$OR^{12}$, -$NR^{13}R^{14}$, or -$S(O)_q R^{15}$; and $R^2$ is hydrogen, deutero, alkyl, alkenyl, alkynyl, cycloalkyl or aryl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl and aryl are each optionally substituted with one to four substitutents selected from halo, cyano, alkyl, -$R^X OR^W$, -$R^X S(O)_q R^V$ and -$R^X NR^Y R^Z$;

$R^3$ is hydrogen, deutero,halo, alkyl, cyano, haloalkyl, deuteroalkyl, cycloalkyl, cycloalkylalkyl, hydroxy or alkoxy;

$R^5$ is hydrogen or alkyl; each $R^6$ is independently selected from halo, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, -$R^X OR^{18}$, -$R^X NR^{19}R^{20}$, and -$R^X S(O)_q R^V$;

each $R^7$ is independently halo, alkyl, haloalkyl or -$R^X OR^W$;

R is alkyl, alkenyl or alkynyl;

$R^9$ is hydrogen, alkyl, haloalkyl, hydroxy, alkoxy or amino;

$R^{10}$ is hydrogen or alkyl;

$R^{11}$ is hydrogen, alkyl, haloalkyl or -$C(O)OR^8$;

$R^{12}$ is selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, -$C(O)R^V$, - $C(O)OR^W$ and -$C(O)NR^Y R^Z$, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl are each optionally substituted with one or more, in one embodiment, one to four, in one embodiment, one to three, in one embodiment, one, two or three, substituents independently selected from halo, oxo, alkyl, hydroxy, alkoxy, amino and alkylthio;

$R^{13}$ and $R^{14}$ are selected as follows:

(i) $R^{13}$ is hydrogen or alkyl; and $R^{14}$ is selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, alkoxy, -$C(O)R^V$, -$C(O)OR^W$, -$C(O)NR^Y R^Z$ and -$S(O)_q R^V$,

wherein the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl are each optionally substituted with one or more, in one embodiment, one to four, in one embodiment, one to three, in one embodiment, one, two or three, substituents independently selected from halo, oxo, alkyl, hydroxy, alkoxy, amino and alkylthio; or

(ii) $R^{13}$ and $R^{14}$, together with the nitrogen atom to which they are attached, form heterocyclyl or heteroaryl wherein the heterocyclyl or heteroaryl are substituted with one or more, in one embodiment, one to four, in one embodiment, one to three, in one embodiment, one, two or three, substituents independently selected from halo, alkyl, hydroxy, alkoxy, amino and alkylthio and wherein the heterocyclyl is optionally substituted with oxo; $R^{15}$ is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-C(O)NR^yR^z$ or $-NR^yR^z$, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl are each optionally substituted with one or more, in one embodiment, one to four, in one embodiment, one to three, in one embodiment, one, two or three, substituents independently selected from halo, oxo, alkyl, hydroxy, alkoxy, amino and alkylthio;

$R^{18}$ is hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroarylalkyl; wherein $R^{18}$ is optionally substituted with 1 to 3 groups $Q^1$, each $Q^1$ independently selected from alkyl, hydroxyl, halo, oxo, haloalkyl, alkoxy, aryloxy, alkoxyalkyl, alkoxycarbonyl, alkoxysulfonyl, carboxyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloaryl and amino;

$R^{19}$ and $R^{20}$ are selected as follows:

(i) $R^{19}$ and $R^{20}$ are each independently hydrogen or alkyl; or

(ii) $R^{19}$ and $R^{20}$, together with the nitrogen atom to which they are attached, form a heterocyclyl or heteroaryl which are each optionally substituted with 1 to 2 groups each independently selected from halo, oxo, alkyl, haloalkyl, hydroxyl and alkoxy;

$R^{21}$ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl or cycloalkyl;

each $R^{22}$ is independently hydrogen, alkyl, alkenyl, alkynyl, haloalkyl or cycloalkyl; or both $R^{22}$, together with the nitrogen atom to which they are attached, form a

heterocyclyl optionally substituted with oxo;

$R^{23}$ is alkyl, alkenyl, alkynyl or haloalkyl;

$R^{24}$ is hydrogen or alkyl;

each $R^x$ is independently alkylene or a direct bond;

$R^y$ is hydrogen, alkyl, alkenyl or alkynyl;

$R^w$ is independently hydrogen, alkyl, alkenyl, alkynyl or haloalkyl;

$R^y$ and $R^z$ are selected as follows:

(i) $R^y$ and $R^z$ are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or haloalkyl; or

(ii) $R^y$ and $R^z$, together with the nitrogen atom to which they are attached, form a heterocyclyl or heteroaryl which are optionally substituted with 1 to 2 groups each independently selected from halo, alkyl, haloalkyl, hydroxyl and alkoxy;

n is 0-4;

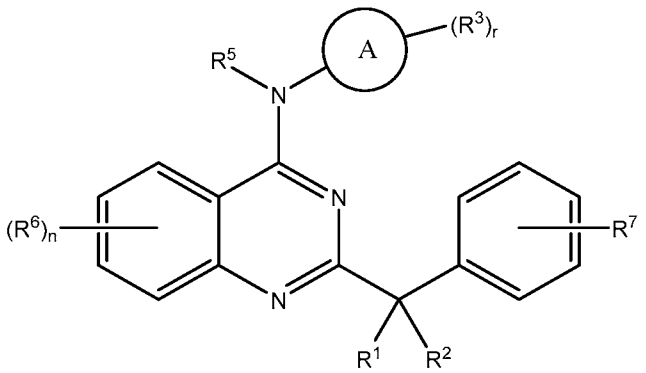
p is 0-5;

each q is independently 0, 1 or 2; and

r is 1-3.

**[00760]** In an embodiment, the JAK-2 inhibitor of Formula (LV-A) is a compound of Formula (LV-B):

Formula (LV-B)




or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein

A is imidazolyl, oxazolyl, thiazolyl, thiadiazolyl, or triazolyl;

$R^3$ is hydrogen, alkyl, haloalkyl or cycloalkyl;

each $R^6$ is independently selected from halo, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, $-R^xOR^{18}$, $-R^XNR^{19}R^{20}$, and $-R^xS(O)_qR^v$;

$R^7$ is halo;

$R^{18}$ is hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroarylalkyl; wherein $R^{18}$ is optionally substituted with 1 to 3 groups $Q^1$, each $Q^1$ independently selected from alkyl, hydroxyl, halo, oxo, haloalkyl, alkoxy, aryloxy, alkoxyalkyl, alkoxycarbonyl, alkoxysulfonyl, carboxyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloaryl and amino;

$R^{19}$ and $R^{20}$ are selected as follows:

(i) $R^{19}$ and $R^{20}$ are each independently hydrogen or alkyl; or

(ii) $R^{19}$ and $R^{20}$, together with the nitrogen atom to which they are attached, form a heterocyclyl or heteroaryl which are each optionally substituted with 1 to 2 groups each independently selected from halo, oxo, alkyl, haloalkyl, hydroxyl and alkoxy;

each $R^x$ is independently alkylene or a direct bond;

$R^v$ is hydrogen, alkyl, alkenyl or alkynyl;

$R^y$ and $R^z$ are selected as follows:

(i) $R^y$ and $R^z$ are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or haloalkyl; or

(ii) $R^y$ and $R^z$, together with the nitrogen atom to which they are attached, form a heterocyclyl or heteroaryl which are optionally substituted with 1 to 2 groups each independently selected from halo, alkyl, haloalkyl, hydroxyl and alkoxy;

n is 0-3;

each q is independently 0, 1 or 2; and

r is 1-3.

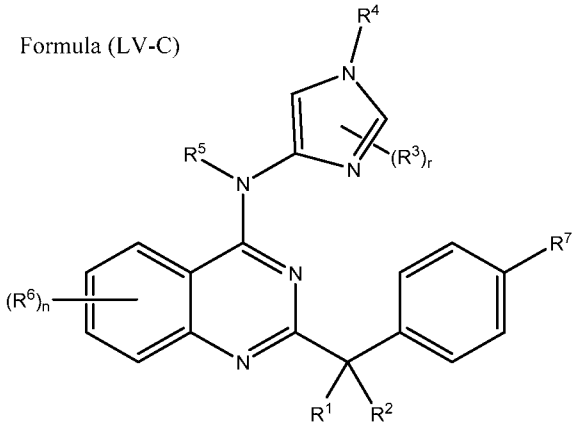
**[00761]** In a preferred embodiment of the JAK-2 inhibitor of Formula (LV-A) or (LV-B), $R^3$ is hydrogen or alkyl.

**[00762]** In a preferred embodiment of the JAK-2 inhibitor of Formula (LV-A) or (LV-B), A is imidazolyl, oxazolyl, thiazolyl, thiadiazolyl, or triazolyl.

**[00763]** In a preferred embodiment of the JAK-2 inhibitor of Formula (LV-A) or (LV-B), $R^7$ is fluro.

**[00764]** In a preferred embodiment, the JAK-2 inhibitor of Formula (LV-A) is a compound of Formula (LV-C):

Formula (LV-C)



or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, where

$R^1$ and $R^2$ are selected as follows:

(i) $R^1$ and $R^2$ together form =0;

(ii) $R^1$ and $R^2$, together with the carbon atom to which they are attached, form dioxacycloalkyl or cycloalkyl wherein the cycloalkyl is substituted with one to four substituents selected from halo, deutero, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, cyano, =0, and hydroxy;

(iii) $R^1$ is hydrogen or halo; and $R^2$ is halo;

(iv) $R^1$ is alkyl, and $R^2$ is hydrogen, alkyl, halo, hydroxy or alkoxy; or

(v) $R^1$ is halo, hydroxy or alkoxy; and $R^2$ is hydrogen or alkyl;

$R^3$ is hydrogen, alkyl or cycloalkyl,

$R^4$ is hydrogen or alkyl;

$R^5$ is hydrogen or alkyl;

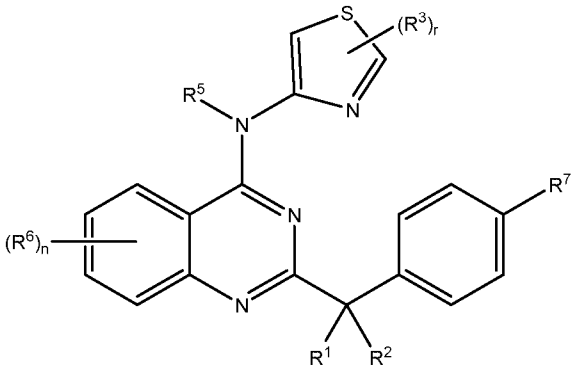
$R^7$ is halo; and

n is 0-3.

**[00765]** In a preferred embodiment of the JAK-2 inhibitor of Formula (LV-C), n is 0.

**[00766]** In an embodiment, JAK-2 inhibitor of Formula (LV-A) has the structure of Formula (LV-D):

Formula (LV-D)




or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof,

where

$R^1$ and $R^2$ are selected as follows:

(i) $R^1$ and $R^2$ together form =0;

(ii) $R^1$ and $R^2$, together with the carbon atom to which they are attached, form dioxacycloalkyl or cycloalkyl wherein the cycloalkyl is substituted with one to four substituents selected from halo, deutero, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, cyano, =0, and hydroxy;

(iii) $R^1$ is hydrogen or halo; and $R^2$ is halo;

(iv) $R^1$ is alkyl, and $R^2$ is hydrogen, alkyl, halo, hydroxy or alkoxy; or

(v) $R^1$ is halo, hydroxy or alkoxy; and $R^2$ is hydrogen or alkyl; $R^3$ is hydrogen, alkyl or cycloalkyl,

$R^5$ is hydrogen or alkyl;

$R^7$ is halo; and

n is 0-3.

**[00767]** In a preferred embodiment of the JAK-2 inhibitor of Formula (LV-D), n is 0.

**[00768]** In a preferred embodiment, JAK-2 inhibitor of Formula (LV-D) is selected from the group consisting of:

(4-fluorophenyl)(4-((1-methyl-1*H*-imidazol-4-yl)amino)quinazolin-2-yl)methanol;

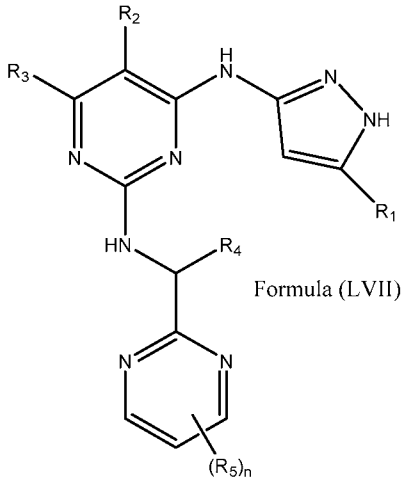
(4-((1*H*-imidazol-4-yl)amino)quinazolin-2-yl)(4-fluorophenyl)methanol;

(4-fluorophenyl)(4-(thiazol-4-ylamino)quinazolin-2-yl)methanol;

(4-fluorophenyl)(4-((5-methylthiazol-2-yl)amino)quinazolin-2-yl)methanol; and 2-(difluoro(4-fluorophenyl)methyl)-N-(1-methyl-1*H*-imidazol-4-yl)quinazolin-4-amine,

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

**[00769]** In an embodiment, the JAK-2 inhibitor is a compound of Formula (LVII):



Formula (LVII)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein:

$R^1$ is selected from hydrogen, hydroxy, amino, mercapto, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyloxy, N—($C_{1-6}$alkyl)amino, N,N—($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, $C_{1-6}$alkylsulphonylamino, 3-5-membered carbocyclyl or 3-5-membered heterocyclyl; wherein $R^1$ may be optionally substituted on carbon by one or more $R^6$; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from $R^7$;

$R^2$ and $R^3$ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, $C_{1-6}$alkanoyloxy, N—($C_{1-6}$alkyl)amino, N,N—($C_{1-6}$alkyl)$_2$-amino, $C_{1-6}$alkanoylamino, N—($C_{1-6}$alkyl)carbamoyl, N,N—($C_{1-6}$alkyl)$_2$carbamoyl, $C_{1-6}$alkyl$S(O)_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, N—($C_{1-6}$alkyl)sulphamoyl, N,N—($C_{1-6}$alkyl)$_2$sulphamoyl, ($C_{1-6}$alkyl)$_2$N—$S(O)_2$—NH—, ($C_{1-6}$alkyl)NH—$S(O)_2$—NH—, $NH_2$—$S(O)_2$—NH—, ($C_{1-6}$alkyl)$_2$N—$S(O)_2$—N($C_{1-6}$alkyl)-, ($C_{1-}$

$_{6}$alkyl)NH—S(O)$_2$—N($C_{1-6}$alkyl)-, $NH_2$—S(O)$_2$—N($C_{1-6}$alkyl)-, N—($C_{1-6}$alkyl)-N—($C_{1-6}$alkylsulphonyl)amino, $C_{1-6}$alkylsulphonylamino, carbocyclyl-$R^{19}$— or heterocyclyl-$R^{21}$; wherein $R^2$ and $R^3$ independently of each other may be optionally substituted on carbon by one or more $R^8$; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from $R^9$;

$R^4$ is selected from cyano, carboxy, carbamoyl, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkanoyl, N—($C_{1-6}$alkyl)carbamoyl, N,N—($C_{1-6}$alkyl)$_2$carbamoyl, $C_{1-6}$alkoxycarbonyl, carbocyclyl or heterocyclyl; wherein $R^4$ may be optionally substituted on carbon by one or more $R^{10}$; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from $R^{11}$;

$R^5$ is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, $C_{1-6}$alkanoyloxy, N—($C_{1-6}$alkyl)amino, N,N—($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, N—($C_{1-6}$alkyl)carbamoyl, N,N—($C_{1-6}$alkyl)$_2$carbamoyl, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, N—($C_{1-6}$alkyl)sulphamoyl, N,N—($C_{1-6}$alkyl)$_2$sulphamoyl, $C_{1-6}$alkylsulphonylamino, carbocyclyl or heterocyclyl; wherein $R^5$ may be optionally substituted on carbon by one or more $R^{12}$; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from $R^{13}$;

n=0, 1, 2 or 3; wherein the values of $R^5$ may be the same or different;

$R^6$, $R^8$, $R^{10}$ and $R^{12}$ are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, $C_{1-6}$alkanoyloxy, N—($C_{1-6}$alkyl)amino, N,N—($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, N—($C_{1-6}$alkyl)carbamoyl, N,N—($C_{1-6}$alkyl)$_2$carbamoyl, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, N—($C_{1-6}$alkyl)sulphamoyl, N,N—($C_{1-6}$alkyl)$_2$sulphamoyl, $C_{1-6}$alkylsulphonylamino, carbocyclyl or heterocyclyl; wherein $R^6$, $R^8$, $R^{10}$ and $R^{12}$ independently of each other may be optionally substituted on carbon by one or more $R^{14}$; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted

by a group selected from $R^{15}$;

$R^7$, $R^9$, $R^{11}$, $R^{13}$ and $R^{15}$ are independently selected from $C_{1-6}$alkyl, $C_{1-6}$alkanoyl, $C_{1-6}$alkylsulphonyl, $C_{1-6}$alkoxycarbonyl, carbamoyl, N—($C_{1-6}$alkyl)carbamoyl, N,N—($C_{1-6}$alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl; wherein $R^7$, $R^9$, $R^{11}$, $R^{13}$ and $R^{15}$ independently of each other may be optionally substituted on carbon by on or more $R^{16}$;

$R^{14}$ and $R^{16}$ are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, $C_{1-6}$alkanoyloxy, N—($C_{1-6}$alkyl)amino, N,N—($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, N—($C_{1-6}$alkyl)carbamoyl, N,N—($C_{1-6}$alkyl)$_2$carbamoyl, $C_{1-6}$alkyl$S(O)_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, N—($C_{1-6}$alkyl)sulphamoyl, N,N—($C_{1-6}$alkyl)$_2$sulphamoyl, $C_{1-6}$alkylsulphonylamino, carbocyclyl or heterocyclyl; wherein $R^{14}$ and $R^{16}$ independently of each other may be optionally substituted on carbon by one or more $R^{17}$; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from $R^{18}$;

$R^{17}$ is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulphamoyl, N-ethylsulphamoyl, N,N-dimethylsulphamoyl, N,N-diethylsulphamoyl or N-methyl-N-ethylsulphamoyl; and

$R^{19}$ and $R^{21}$ are independently selected from a direct bond, —O—, —N($R^{22}$)—, —C(O)—, —N($R^{23}$)C(O)—, —C(O)N($R^{24}$)—, —$S(O)_s$—, —$SO_2$N($R^{25}$)— or —N($R^{26}$)$SO_2$—; wherein $R^{22}$, $R^{23}$, $R^{24}$, $R^{25}$ and $R^{26}$ are independently selected from hydrogen or $C_{1-6}$alkyl and s is 0-2;

$R^{18}$ is selected from $C_{1-6}$alkyl, $C_{1-6}$alkanoyl, $C_{1-6}$alkylsulphonyl, $C_{1-6}$alkoxycarbonyl, carbamoyl, N—($C_{1-6}$alkyl)carbamoyl, N,N—($C_{1-6}$alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

**[00770]** In an embodiment, the JAK-2 inhibitor is a compound of Formula (LVII), wherein:

$R^1$ is selected from hydrogen, hydroxy, amino, mercapto, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyloxy, N—($C_{1-6}$alkyl)amino, N,N—($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, $C_{1-6}$alkylsulphonylamino, 3-5-membered carbocyclyl or 3-5-membered heterocyclyl; wherein $R^1$ may be optionally substituted on carbon by one or more $R^6$; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from $R^7$;

$R^2$ and $R^3$ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, $C_{1-6}$alkanoyloxy, N—($C_{1-6}$alkyl)amino, N,N—($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, N—($C_{1-6}$alkyl)carbamoyl, N,N—($C_{1-6}$alkyl)$_2$carbamoyl, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, N—($C_{1-6}$alkyl)sulphamoyl, N,N—($C_{1-6}$alkyl)$_2$sulphamoyl, $C_{1-6}$alkylsulphonylamino, carbocyclyl-$R^{19}$— or heterocyclyl-$R^{21}$—; wherein $R^2$ and $R^3$ independently of each other may be optionally substituted on carbon by one or more $R^8$; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from $R^9$;

$R^4$ is selected from cyano, carboxy, carbamoyl, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkanoyl, N—($C_{1-6}$alkyl)carbamoyl, N,N—($C_{1-6}$alkyl)$_2$carbamoyl, $C_{1-6}$alkoxycarbonyl, carbocyclyl or heterocyclyl; wherein $R^4$ may be optionally substituted on carbon by one or more $R^{10}$; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from $R^{11}$;

$R^5$ is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, $C_{1-6}$alkanoyloxy, N—($C_{1-6}$alkyl)amino, N,N—($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, N—($C_{1-6}$alkyl)carbamoyl, N,N—($C_{1-6}$alkyl)$_2$carbamoyl, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, N—($C_{1-6}$alkyl)sulphamoyl, N,N—($C_{1-6}$alkyl)$_2$sulphamoyl, $C_{1-6}$alkylsulphonylamino, carbocyclyl or heterocyclyl; wherein $R^5$ may be optionally substituted on carbon by one or more $R^2$; and wherein if said heterocyclyl contains an

—NH— moiety that nitrogen may be optionally substituted by a group selected from $R^{13}$;

n=0, 1, 2 or 3; wherein the values of $R^5$ may be the same or different;

$R^6$, $R^8$, $R^{10}$ and $R^{12}$ are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, $C_{1-6}$alkanoyloxy, N—($C_{1-6}$alkyl)amino, N,N—($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, N—($C_{1-6}$alkyl)carbamoyl, N,N—($C_{1-6}$alkyl)$_2$carbamoyl, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, N—($C_{1-6}$alkyl)sulphamoyl, N,N—($C_{1-6}$alkyl)$_2$sulphamoyl, $C_{1-6}$alkylsulphonylamino, carbocyclyl or heterocyclyl; wherein $R^6$, $R^8$, $R^{10}$ and $R^{12}$ independently of each other may be optionally substituted on carbon by one or more $R^{14}$; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from $R^{15}$;

$R^7$, $R^9$, $R^{11}$, $R^{13}$ and $R^{15}$ are independently selected from $C_{1-6}$alkyl, $C_{1-6}$alkanoyl, $C_{1-6}$alkylsulphonyl, $C_{1-6}$alkoxycarbonyl, carbamoyl, N—($C_{1-6}$alkyl)carbamoyl, N,N—($C_{1-6}$alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl; wherein $R^7$, $R^9$, $R^{11}$, $R^{13}$ and $R^{15}$ independently of each other may be optionally substituted on carbon by on or more $R^{16}$;

$R^{14}$ and $R^{16}$ are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, $C_{1-6}$alkanoyloxy, N—($C_{1-6}$alkyl)amino, N,N—($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, N—($C_{1-6}$alkyl)carbamoyl, N,N—($C_{1-6}$alkyl)$_2$carbamoyl, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, N—($C_{1-6}$alkyl)sulphamoyl, N,N—($C_{1-6}$alkyl)$_2$sulphamoyl, $C_{1-6}$alkylsulphonylamino, carbocyclyl or heterocyclyl; wherein $R^{14}$ and $R^{16}$ independently of each other may be optionally substituted on carbon by one or more $R^{17}$; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from $R^{18}$;

$R^{17}$ is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-

dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulphamoyl, N-ethylsulphamoyl, N,N-dimethylsulphamoyl, N,N-diethylsulphamoyl or N-methyl-N-ethylsulphamoyl; and

$R^{19}$ and $R^{21}$ are independently selected from —O—, —N($R^{22}$)—, —C(O)—, —N($R^{23}$)C(O)—, —C(O)N($R^{24}$)—, —S(O)$_s$—, —$SO_2$N($R^{25}$)— or —N($R^{26}$)$SO_2$—; wherein $R^{22}$, $R^{23}$, $R^{24}$, $R^{25}$ and $R^{26}$ are independently selected from hydrogen or $C_{1-6}$alkyl and s is 0-2;

$R^{18}$ is selected from $C_{1-6}$alkyl, $C_{1-6}$alkanoyl, $C_{1-6}$alkylsulphonyl, $C_{1-6}$alkoxycarbonyl, carbamoyl, N—($C_{1-6}$alkyl)carbamoyl, N,N—($C_{1-6}$alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

**[00771]** In an embodiment, the JAK-2 inhibitor is a compound of Formula (LVII), wherein:

$R^1$ is selected from hydrogen, hydroxy, amino, mercapto, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyloxy, N—($C_{1-6}$alkyl)amino, N,N—($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, $C_{1-6}$alkylsulphonylamino, 3-5-membered carbocyclyl or 3-5-membered heterocyclyl; wherein $R^1$ may be optionally substituted on carbon by one or more $R^6$; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from $R^7$;

$R^2$ and $R^3$ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, $C_{1-6}$alkanoyloxy, N—($C_{1-6}$alkyl)amino, N,N—($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, N—($C_{1-6}$alkyl)carbamoyl, N,N—($C_{1-6}$alkyl)$_2$carbamoyl, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, N—($C_{1-6}$alkyl)sulphamoyl, N,N—($C_{1-6}$alkyl)$_2$sulphamoyl, N—($C_{1-6}$alkyl)-N—($C_{1-6}$alkylsulphonyl)amino, $C_{1-6}$alkylsulphonylamino, carbocyclyl-$R^{19}$— or heterocyclyl-$R^{21}$—; wherein $R^2$ and $R^3$ independently of each other may be optionally substituted on carbon by one or more $R^8$; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from $R^9$;

$R^4$ is selected from cyano, carboxy, carbamoyl, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-}$

$_{6}$alkanoyl, N—($C_{1-6}$alkyl)carbamoyl, N,N—($C_{1-6}$alkyl)$_2$carbamoyl, $C_{1-6}$alkoxycarbonyl, carbocyclyl or heterocyclyl; wherein $R^4$ may be optionally substituted on carbon by one or more $R^{10}$; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from $R^{11}$;

$R^5$ is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, $C_{1-6}$alkanoyloxy, N—($C_{1-6}$alkyl)amino, N,N—($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, N—($C_{1-6}$alkyl)carbamoyl, N,N—($C_{1-6}$alkyl)$_2$carbamoyl, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, N—($C_{1-6}$alkyl)sulphamoyl, N,N—($C_{1-6}$alkyl)$_2$sulphamoyl, $C_{1-6}$alkylsulphonylamino, carbocyclyl or heterocyclyl; wherein $R^5$ may be optionally substituted on carbon by one or more $R^{12}$; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from $R^{13}$;

n=0, 1, 2 or 3; wherein the values of $R^5$ may be the same or different;

$R^6$, $R^8$, $R^{10}$ and $R^{12}$ are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, $C_{1-6}$alkanoyloxy, N—($C_{1-6}$alkyl)amino, N,N—($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, N—($C_{1-6}$alkyl)carbamoyl, N,N—($C_{1-6}$alkyl)$_2$carbamoyl, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, N—($C_{1-6}$alkyl)sulphamoyl, N,N—($C_{1-6}$alkyl)$_2$sulphamoyl, $C_{1-6}$alkylsulphonylamino, carbocyclyl or heterocyclyl; wherein $R^6$, $R^8$, $R^{10}$ and $R^{12}$ independently of each other may be optionally substituted on carbon by one or more $R^{14}$; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from $R^{15}$;

$R^7$, $R^9$, $R^{11}$, $R^{13}$ and $R^{15}$ are independently selected from ($C_{1-6}$)alkyl, ($C_{1-6}$)alkanoyl, ($C_{1-6}$)alkylsulphonyl, ($C_{1-6}$)alkoxycarbonyl, carbamoyl, N—(($C_{1-6}$)alkyl)carbamoyl, N,N—(($C_{1-6}$)alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl; wherein $R^7$, $R^9$, $R^{11}$, $R^{13}$ and $R^{15}$ independently of each other may be optionally substituted on carbon by on or more $R^{16}$;

$R^{14}$ and $R^{16}$ are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy,

carbamoyl, mercapto, sulphamoyl, $(C_{1-6})$alkyl, $(C_{2-6})$alkenyl, $(C_{2-6})$alkynyl, $(C_{1-6})$alkoxy, $(C_{1-6})$alkanoyl, $(C_{1-6})$alkanoyloxy, N—$((C_{1-6})$alkyl)amino, N,N—$((C_{1-6})$alkyl)$_2$amino, $(C_{1-6})$alkanoylamino, N—$((C_{1-6})$alkyl)carbamoyl, N,N—$((C_{1-6})$alkyl)$_2$carbamoyl, $(C_{1-6})$alkylS(O)$_a$ wherein a is 0 to 2, $(C_{1-6})$alkoxycarbonyl, N—$((C_{1-6})$alkyl)sulphamoyl, N,N—$((C_{1-6})$alkyl)$_2$sulphamoyl, $(C_{1-6})$alkylsulphonylamino, carbocyclyl or heterocyclyl; wherein $R^{14}$ and $R^{16}$ independently of each other may be optionally substituted on carbon by one or more $R^{17}$; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from $R^{18}$;

$R^{17}$ is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulphamoyl, N-ethylsulphamoyl, N,N-dimethylsulphamoyl, N,N-diethylsulphamoyl or N-methyl-N-ethylsulphamoyl; and

$R^{19}$ and $R^{21}$ are independently selected from a direct bond, —O—, —N($R^{22}$)—, —C(O)—, —N($R^{23}$)C(O)—, —C(O)N($R^{24}$)—, —S(O)$_s$—, —$SO_2$N($R^{25}$)— or —N($R^{26}$)$SO_2$—; wherein $R^{22}$, $R^{23}$, $R^{24}$, $R^{25}$ and $R^{26}$ are independently selected from hydrogen or $(C_{1-6})$alkyl and s is 0-2;

$R^{18}$ is selected from $(C_{1-6})$alkyl, $(C_{1-6})$alkanoyl, $(C_{1-6})$alkylsulphonyl, $(C_{1-6})$alkoxycarbonyl, carbamoyl, N—$((C_{1-6})$alkyl)carbamoyl, N,N—$((C_{1-6})$alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

**[00772]** Particular values of the variable groups contained in Formula (LVII) are as follows. Such values may be used, where appropriate, with any of the definitions, claims or embodiments defined hereinbefore or hereinafter in relation to compounds of Formula (LVII).

$R^1$ is selected from $(C_{1-6})$alkyl, $(C_{1-6})$alkoxy, 3-5-membered carbocyclyl, and N,N—$((C_{1-6})$alkyl)$_2$amino, wherein $R^1$ may be optionally substituted on carbon by one or more

$R^6$; and wherein $R^6$ is halo,

$R^1$ is $(C_{1-6})$alkoxy or 3-5-membered carbocyclyl.

$R^1$ is selected from $(C_{1-6})$alkyl, $(C_{1-6})$alkoxy or 3-5-membered carbocyclyl.

$R^1$ is $(C_{1-6})$alkyl or $(C_{1-6})$alkoxy.

$R^1$ is 3-5 membered carbocyclyl.

$R^1$ is N,N($(C_{1-6})$alkyl)$_2$amino.

$R^1$ is $(C_{1-6})$alkyl.

$R^1$ is $(C_{1-4})$alkyl.

$R^1$ is $(C_{1-6})$alkoxy.

$R^1$ is selected from methyl, methoxy, trifluoroethoxy, isopropoxy, cyclopropyl, and N,N-dimethylamino;

$R^1$ is isopropoxy or cyclopropyl.

$R^1$ is methyl, methoxy, isopropoxy or cyclopropyl.

$R^1$ is selected from methyl, methoxy, isopropoxy, N,N-dimethylamino, and cyclopropyl.

$R^1$ is isopropoxy.

$R^1$ is methyl.

$R^1$ is ethyl.

$R^1$ is selected from methyl, ethyl, propyl, and butyl.

$R^1$ is selected from $(C_{1-4})$alkyl, $(C_{1-4})$alkoxy, and cyclopropyl.

$R^1$ is methoxy.

$R^1$ is cyclopropyl. $R^1$ is N,N-dimethylamino.

$R^2$ is selected from hydrogen, halo, nitro, and $(C_{1-6})$alkyl, wherein $R^2$ may be optionally substituted on carbon by one or more $R^8$; and wherein $R^8$ is halo.

$R^2$ is selected from hydrogen, chloro, fluoro, bromo, nitro, and trifluoromethyl.

$R^2$ is halo.

$R^2$ is $(C_{1-6})$alkyl, wherein $R^2$ may be optionally substituted on carbon by one or more $R^8$; and wherein $R^8$ is halo.

$R^2$ and $R^3$ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $(C_{1-6})$alkyl, $(C_{2-6})$alkenyl, $(C_{2-6})$alkynyl, $(C_{1-6})$alkoxy, $(C_{1-6})$alkanoyl, $(C_{1-6})$alkanoyloxy, N—($(C_{1-6})$alkyl)amino, N,N—($(C_{1-6})$alkyl)$_2$amino, $(C_{1-6})$alkanoylamino, N—($(C_{1-6})$alkyl)carbamoyl, N,N—($(C_{1-}$

$_{6}$)alkyl)$_2$carbamoyl, ($C_{1-6}$)alkylS(O)$_a$ wherein a is 0 to 2, ($C_{1-6}$)alkoxycarbonyl, N—(($C_{1-6}$)alkyl)sulphamoyl, N,N—(($C_{1-6}$)alkyl)$_2$sulphamoyl, ($C_{1-6}$)alkylsulphonylamino, carbocyclyl-$R^{19}$— or heterocyclyl-$R^{21}$—; wherein $R^2$ and $R^3$ independently of each other may be optionally substituted on carbon by one or more $R^8$; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from $R^9$.

$R^2$ and $R^3$ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ($C_{1-6}$)alkyl, ($C_{2-6}$)alkenyl, ($C_{2-6}$)alkynyl, ($C_{1-6}$)alkoxy, ($C_{1-6}$)alkanoyl, ($C_{1-6}$)alkanoyloxy, N—(($C_{1-6}$)alkyl)amino, N,N—(($C_{1-6}$)alkyl)$_2$amino, ($C_{1-6}$)alkanoylamino, N—(($C_{1-6}$)alkyl)carbamoyl, N,N—(($C_{1-6}$)alkyl)$_2$carbamoyl, ($C_{1-6}$)alkylS(O)$_a$ wherein a is 0 to 2, ($C_{1-6}$)alkoxycarbonyl, N—()$C_{1-6}$)alkyl)sulphamoyl, N,N—(($C_{1-6}$)alkyl)$_2$sulphamoyl, N—(($C_{1-6}$)alkyl)-N—(($C_{1-6}$)alkylsulphonyl)amino, ($C_{1-6}$)alkylsulphonylamino, carbocyclyl-$R^{19}$— or heterocyclyl-$R^{21}$—; wherein $R^2$ and $R^3$ independently of each other may be optionally substituted on carbon by one or more $R^8$; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from $R^9$.

$R^2$ and $R^3$ are independently selected from hydrogen, halo, N—(($C_{1-6}$)alkyl)-N—(($C_{1-6}$)alkylsulphonyl)amino, or heterocyclyl-$R^{21}$—; wherein $R^{21}$ is a direct bond.

$R^2$ and $R^3$ are independently selected from hydrogen and halo.

$R^2$ and $R^3$ are independently selected from hydrogen and chloro.

$R^2$ and $R^3$ are independently selected from hydrogen, fluoro, chloro, bromo, N-methyl-N-mesylamino and morpholino.

$R^2$ is halo and $R^3$ is hydrogen.

$R^2$ is chloro and $R^3$ is hydrogen.

$R^2$ is chloro or fluoro and $R^3$ is hydrogen. $R^3$ is selected from hydrogen, halo, cyano, N—(($C_{1-6}$)alkyl)-N—(($C_{1-6}$)alkylsulphonyl)amino, ($C_{1-6}$)alkyl, (($C_{1-6}$)alkyl)$_2$N—S(O)$_2$—N(($C_{1-6}$)alkyl)-, and heterocyclyl-$R^{21}$—, wherein $R^3$ may be optionally substituted on carbon by one or more $R^8$; wherein $R^8$ is halo; and wherein $R^{21}$ is a bond.

$R^3$ is hydrogen.

$R^3$ is halo.

$R^3$ is selected from N—($(C_{1-6})$alkyl)-N—($(C_{1-6})$alkylsulphonyl)amino and ($(C_{1-6})$alkyl)$_2$N—S(O)$_2$—N($(C_{1-6})$alkyl)-.

$R^3$ is selected from heterocyclyl-$R^{21}$—, wherein $R^3$ may be optionally substituted on carbon by one or more $R^5$; wherein $R^5$ is halo; and wherein $R^{21}$ is a bond.

$R^3$ is selected from hydrogen, chloro, cyano, trifluoromethyl, $(CH_3)_2N$—S(O)$_2$—N($CH_3$)—, N-methyl-N-mesylamino, and morpholino.

$R^3$ is $(CH_3)_2N$—S(O)$_2$—N($CH_3$)—.

$R^3$ is N-methyl-N-mesylamino,

$R^3$ is morpholino.

$R^4$ is $(C_{1-6})$alkyl.

$R^4$ is methyl.

$R^5$ is halo.

$R^5$ is fluoro.

n=1.

$R^{19}$ and $R^{21}$ are independently selected from —O—, —N($R^{22}$)—, —C(O)—, —N($l^{23}$)C(O)—, —C(O)N($R^{24}$)—, —S(O)$_s$—, —SO$_2$N($R^{25}$)— or —N($R^{26}$)SO$_2$—; wherein $R^{22}$, $R^{23}$, $R^{24}$, $R^{25}$ and $R^{26}$ are independently selected from hydrogen or ($C_{1-6}$)alkyl and s is 0-2.

Therefore in a further aspect of the invention there is provided a compound of Formula (LVII) (as depicted herein above) wherein:

$R^1$ is selected from $(C_{1-6})$alkyl, $(C_{1-6})$alkoxy or 3-5-membered carbocyclyl;

$R^1$ and $R^3$ are independently selected from hydrogen, halo, N—($(C_{1-6})$alkyl)-N—($(C_{1-6})$alkylsulphonyl)amino, or heterocyclyl-$R^{21}$—;

$R^4$ is $(C_{1-6})$alkyl;

$R^5$ is halo;

n=1;

$R^{21}$ is a direct bond;

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

**[00773]** Therefore, in an embodiment of the invention, the JAK-2 inhibitor is a compound of Formula (LVII) wherein:

$R^1$ is $(C_{1-6})$alkoxy;

$R^2$ and $R^3$ are independently selected from hydrogen and halo;

$R^4$ is $(C_{1-6})$alkyl;

$R^5$ is halo;

n=1;

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

**[00774]** In an embodiment of the invention, the JAK-2 inhibitor is a compound of Formula (LVII) wherein:

$R^1$ is methyl, methoxy, isopropoxy or cyclopropyl;

$R^2$ and $R^3$ are independently selected from hydrogen, fluoro, chloro, bromo, N-methyl-N-mesylamino and morpholino;

$R^4$ is methyl;

$R^5$ is fluoro; and

n=1;

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

**[00775]** In an embodiment of the invention, the JAK-2 inhibitor is a compound of Formula (LVII) wherein:

$R^1$ is selected from $(C_{1-6})$alkyl, $(C_{1-6})$alkoxy, 3-5-membered carbocyclyl, and N,N—$((C_{1-6})$alkyl$)_2$amino, wherein $R^1$ may be optionally substituted on carbon by one or more $R^6$;

$R^2$ is selected from hydrogen, halo, nitro, and $(C_{1-6})$alkyl, wherein $R^2$ may be optionally substituted on carbon by one or more $R^8$;

$R^3$ is selected from hydrogen, halo, cyano, N—$((C_{1-6})$alkyl$)$-N—$((C_{1-6})$alkylsulphonyl)amino, $(C_{1-6})$alkyl, $((C_{1-6})$alkyl$)_2$N—$S(O)_2$—N$((C_{1-6})$alkyl$)$-, and heterocyclyl-$R^{21}$—, wherein $R^3$ may be optionally substituted on carbon by one or more $R^8$;

$R^4$ is $(C_{1-6})$alkyl;

$R^5$ is halo;

$R^6$ is halo;

$R^8$ is halo;

$R^{21}$ is a bond; and

n=1;

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

**[00776]** In an embodiment of the invention, the JAK-2 inhibitor is a compound of Formula (LVII) wherein:

$R^1$ is selected from methyl, methoxy, trifluoroethoxy, isopropoxy, cyclopropyl, and N,N-dimethylamino;

$R^2$ is selected from hydrogen, chloro, fluoro, bromo, nitro, and trifluoromethyl;

$R^3$ is selected from hydrogen, chloro, cyano, trifluoromethyl, $(CH_3)_2N—S(O)_2—N(CH_3)—$, N-methyl-N-mesylamino, and morpholino;

$R^4$ is methyl;

$R^5$ is fluoro; and

n is 1;

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

**[00777]** In an embodiment of the invention, the JAK-2 inhibitor is a compound of Formula (LVII) wherein:

$R^1$ is selected from $(C_{1-6})$alkoxy, wherein $R^1$ may be optionally substituted on carbon by one or more $R^6$;

$R^2$ is selected from hydrogen and halo;

$R^3$ is selected from hydrogen, halo, and heterocyclyl-$R^{21}$—;

$R^4$ is $(C_{1-6})$alkyl;

$R^5$ is halo;

$R^6$ is halo;

$R^{21}$ is a bond;

n is 1;

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

**[00778]** In an embodiment of the invention, the JAK-2 inhibitor is a compound of Formula (LVII) wherein:

$R^1$ is selected from $(C_{1-4})$alkyl, $(C_{1-4})$alkoxy, and cyclopropyl;

$R^2$ is selected from hydrogen, halo, nitro, and $(C_{1-6})$alkyl, wherein $R^2$ may be optionally substituted on carbon by one or more $R^8$;

$R^3$ is selected from hydrogen, halo, cyano, N—((C1-6)alkyl)-N—((C1-

$_{6}$)alkylsulphonyl)amino, ($C_{1-6}$)alkyl, (($C_{1-6}$)alkyl)$_2$N—S(O)$_2$—N(($C_{1-6}$)alkyl)-, and heterocyclyl-$R^{21}$—, wherein $R^3$ may be optionally substituted on carbon by one or more $R^8$;

$R^4$ is ($C_{1-6}$)alkyl;

$R^5$ is halo;

$R^6$ is halo;

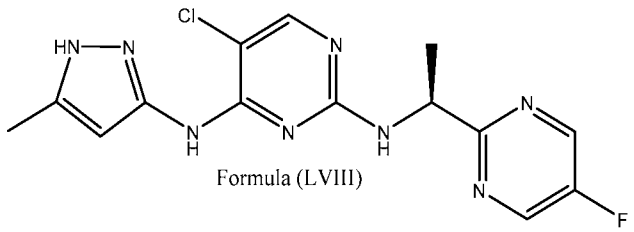
$R^8$ is halo;

$R^{21}$ is a bond; and

n=1;

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

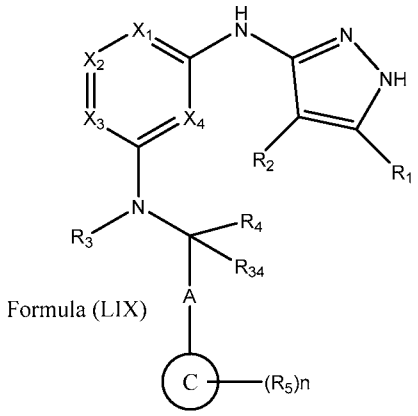
**[00779]** In a preferred embodiment, the JAK-2 inhibitor is AZD-1480. In a preferred embodiment, the JAK-2 inhibitor is (*S*)-5-chloro-$N^2$-(1-(5-fluoropyrimidin-2-yl)ethyl)-$N^4$-(5-methyl-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine. In a preferred embodiment, the JAK-2 inhibitor has the chemical structure shown in Formula (LVIII):




Formula (LVIII)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of this compound is described in U.S. Patent No. 8,088,784 and U.S. Patent Application Publication Nos. 2008/0287475 A1; 2010/0160325 A1; and, 2012/0071480 A1, the disclosures of which are incorporated by reference herein. In an embodiment, the JAK-2 inhibitor is selected from the compounds described in U.S. Patent No. 8,088,784 and U.S. Patent Application Publication Nos. 2008/0287475 A1; 2010/0160325 A1; and, 2012/0071480 A1, the disclosures of which are incorporated by reference herein.

**[00780]** In an embodiment, the JAK-2 inhibitor is a compound of Formula (LIX):



Formula (LIX)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein:

$R^1$ and $R^2$ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkanoyl, $C_{1-6}$ alkanoyloxy, N—($C_{1-6}$alkyl)amino, N,N—($C_{1-6}$ alkyl)$_2$-amino, $C_{1-6}$ alkanoylamino, N—($C_{1-6}$ alkyl)carbamoyl, N,N—($C_{1-6}$ alkyl)$_2$-carbamoyl, $C_{1-6}$ alkyl$S(O)_a$ wherein a is 0 to 2, $C_{1-6}$ alkoxycarbonyl, N—($C_{1-6}$ alkyl)sulphamoyl, N,N—($C_{1-6}$ alkyl)$_2$sulphamoyl, $C_{1-6}$ alkylsulphonylamino, carbocyclyl or heterocyclyl; wherein $R^1$ and $R^2$ independently of each other may be optionally substituted on carbon by one or more $R^6$; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from $R^7$;

one of $X^1$, $X^2$, $X^3$ and $X^4$ is =N—, the other three are independently selected from =$CR^8$—, =$CR^9$— and =$CR^{10}$—;

$R^3$ is hydrogen or optionally substituted $C_{1-6}$ alkyl; wherein said optional substituents are selected from one or more $R^{11}$;

$R^4$ and $R^{34}$ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkanoyl, $C_{1-6}$ alkanoyloxy, N—($C_{1-6}$ alkyl)amino, N,N—($C_{1-6}$ alkyl)$_2$amino, $C_{1-6}$ alkanoylamino, N—($C_{1-6}$ alkyl)carbamoyl, N,N—($C_{1-6}$ alkyl)$_2$carbamoyl, $C_{1-6}$ alkyl$S(O)_a$ wherein a is 0 to 2, $C_{1-6}$ alkoxycarbonyl, N—($C_{1-6}$ alkyl)sulphamoyl, N,N—($C_{1-6}$ alkyl)$_2$sulphamoyl, $C_{1-6}$ alkylsulphonylamino, carbocyclyl or heterocyclyl; wherein $R^4$ and $R^{34}$ may be independently optionally

substituted on carbon by one or more $R^{12}$; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from $R^{13}$;

A is a direct bond or $C_{1-2}$alkylene; wherein said $C_{1-2}$alkylene may be optionally substituted by one or more $R^{14}$;

Ring C is carbocyclyl or heterocyclyl; wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from $R^{15}$;

$R^5$ is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, $C_{1-6}$alkanoyloxy, N—($C_{1-6}$alkyl)amino, N,N—($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, N—($C_{1-6}$alkyl)carbamoyl, N,N—($C_{1-6}$alkyl)$_2$carbamoyl, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, N—($C_{1-6}$alkyl)sulphamoyl, N,N—($C_{1-6}$alkyl)$_2$sulphamoyl, $C_{1-6}$alkylsulphonylamino, carbocyclyl-$R^{37}$— or heterocyclyl-$R^{38}$—; wherein $R^5$ may be optionally substituted on carbon by one or more $R^{16}$; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from $R^{17}$;

n is 0, 1, 2 or 3; wherein the values of $R^5$ may be the same or different;

$R^8$, $R^9$ and $R^{10}$ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, $C_{1-6}$alkanoyloxy, N—($C_{1-6}$alkyl)amino, N,N—($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, N—($C_{1-6}$alkyl)carbamoyl, N,N—($C_{1-6}$alkyl)$_2$carbamoyl, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, N—($C_{1-6}$alkyl)sulphamoyl, N,N—($C_{1-6}$alkyl)$_2$sulphamoyl, $C_{1-6}$alkylsulphonylamino, carbocyclyl-$R^{25}$— or heterocyclyl-$R^{26}$—; wherein $R^8$, $R^9$ and $R^{10}$ independently of each other may be optionally substituted on carbon by one or more $R^{18}$; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from $R^{19}$;

$R^6$, $R^{11}$, $R^{12}$, $R^{14}$, $R^{16}$ and $R^{18}$ are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, $C_{1-6}$alkanoyloxy, N—($C_{1-6}$alkyl)amino, N,N—($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, N—($C_{1-6}$alkyl)carbamoyl,

N,N—($C_{1-6}$alkyl)$_2$carbamoyl, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, N—($C_{1-6}$alkyl)sulphamoyl, N,N—($C_{1-6}$alkyl)$_2$sulphamoyl, $C_{1-6}$alkylsulphonylamino, carbocyclyl-$R^{27}$— or heterocyclyl-$R^{28}$—; wherein $R^6$, $R^{11}$, $R^{12}$, $R^{14}$, $R^{16}$ and $R^{18}$ independently of each other may be optionally substituted on carbon by one or more $R^{20}$; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from $R^{21}$;

$R^7$, $R^{13}$, $R^{15}$, $R^{17}$, $R^{19}$ and $R^{21}$ are independently selected from $C_{1-6}$alkyl, $C_{1-6}$alkanoyl, $C_{1-6}$alkylsulphonyl, $C_{1-6}$alkoxycarbonyl, carbamoyl, N—($C_{1-6}$alkyl)carbamoyl, N,N—($C_{1-6}$alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl; wherein $R^7$, $R^{13}$, $R^{15}$, $R^{17}$, $R^{19}$ and $R^{21}$ independently of each other may be optionally substituted on carbon by on or more $R^{22}$;

$R^{20}$ and $R^{22}$ are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, $C_{1-6}$alkanoyloxy, N—($C_{1-6}$alkyl)amino, N,N—($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, N—($C_{1-6}$alkyl)carbamoyl, N,N—($C_{1-6}$alkyl)$_2$carbamoyl, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, N—($C_{1-6}$alkyl)sulphamoyl, N,N—($C_{1-6}$alkyl)$_2$sulphamoyl, $C_{1-6}$alkylsulphonylamino, $C_{1-6}$alkylsulphonyl-N—($C_{1-6}$alkyl)amino, carbocyclyl-$R^{35}$— or heterocyclyl-$R^{36}$—; wherein $R^{20}$ and $R^{22}$ independently of each other may be optionally substituted on carbon by one or more $R^{23}$; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from $R^{24}$;

$R^{25}$, $R^{26}$, $R^{27}$, $R^{28}$, $R^{35}$, $R^{36}$, $R^{37}$ and $R^{38}$ are independently selected from a direct bond, —O—, —N($R^{29}$)—, —C(O)—, —N($R^{30}$)C(O)—, —C(O)N($R^{31}$)—, —S(O)$_s$—, —NH═CH—, —$SO_2$N($R^{32}$)— or —N($R^{33}$)$SO_2$—; wherein $R^{29}$, $R^{30}$, $R^{31}$, $R^{32}$ and $R^{33}$ are independently selected from hydrogen or $C_{1-6}$alkyl and s is 0-2;

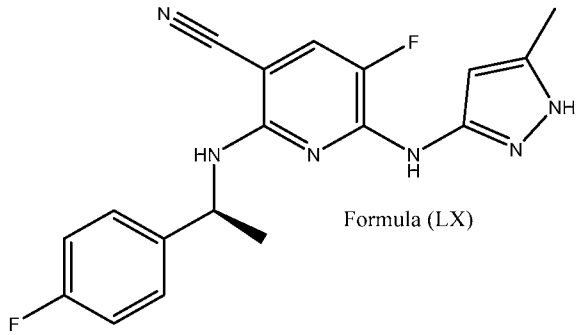
$R^{23}$ is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl,

ethoxycarbonyl, N-methylsulphamoyl, N-ethylsulphamoyl, N,N-dimethylsulphamoyl, N,N-diethylsulphamoyl, N-methyl-N-ethylsulphamoyl or phenyl; and

$R^{24}$ is selected from $C_{1-6}$ alkyl, $C_{1-6}$ alkanoyl, $C_{1-6}$ alkylsulphonyl, $C_{1-6}$ alkoxycarbonyl, carbamoyl, N—($C_{1-6}$ alkyl)carbamoyl, N,N—($C_{1-6}$ alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

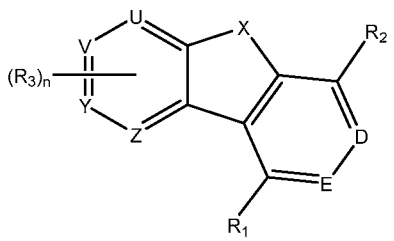
**[00781]** In a preferred embodiment, the JAK-2 inhibitor is (*S*)-5-fluoro-2-((1-(4-fluorophenyl)ethyl)amino)-6-((5-methyl-1*H*-pyrazol-3-yl)amino)nicotinonitrile. In a preferred embodiment, the JAK-2 inhibitor is a compound of Formula (LX):



Formula (LX)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of this compound is described in U.S. Patent No. 8,324,252 and U.S. Patent Application Publication Nos. 2008/0139561 A1 and 2013/0090358 A1, the disclosures of which are incorporated by reference herein. In an embodiment, the JAK-2 inhibitor is selected from the compounds described in U.S. Patent No. 8,324,252 and U.S. Patent Application Publication Nos. 2008/0139561 A1 and 2013/0090358 A1, the disclosures of which are incorporated by reference herein.

**[00782]** In an embodiment, the JAK-2 inhibitor is a compound of Formula (LXII):



Formula (LXII)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, or a stereoisomer thereof, wherein:

D is CH or N;

E is CH or N;

X is $CH_2$, $NR_4$, O or S;

U is CH or N;

V is CH or N;

Y is CH or N;

Z is CH or N;

R1 is $NR_5R_6$, $CR5R_6R_7$, $SR_5$ or $OR_5$;

$R_2$ is (C=O)OH, $(C=O)NH_2$, $(C=O)NHR_4$ or heterocyclyl;

$R_3$ is

(a) hydrogen;

(b) $C_{1-6}$ alkyl, which is optionally substituted with halo, hydroxyl, amino, phenyl, heterocyclyl, $C_{1-6}$ alkyl or $R_{10}$;

(c) $C_{2-6}$ alkenyl, which is optionally substituted with halo, hydroxyl, amino, phenyl, heterocyclyl, $C_{1-6}$ alkyl or $R_4$;

(d) $C_{3-10}$ cycloalkyl, which is optionally substituted with $C_{1-6}$ alkyl, $OR_4$, $NR_8R_4$, phenyl (which is optionally substituted with $C_{1-6}$ alkyl, $OR_4$ or $NR_8R_4$), halo, $R_{10}$ or heterocyclyl;

(e) —(CO)$R_8$;

(f) —(CO)—$NR_8R_9$;

(g) $C_{4-10}$ heterocyclyl, which is optionally substituted on either the carbon or the heteroatom with C1-6 alkyl, halo, $R_{10}$, $OR_4$, $NR_8R_4$, phenyl (which is optionally substituted with C1-6 alkyl, $OR_4$ or $NR_8R_4$), —(CO)$R_8$ or —(CO)—$NR_8R_9$;

(h) $OR_4$;

(i) $NR_8R_4$;

(j) halo;

(k) Aryl, which is optionally substituted with one or more groups selected from $C_{1-6}$ alkyl (which is optionally substituted with one to three halo), halo or $R_{10}$;

(l) Heteroaryl, which is optionally substituted with one or more groups selected

from $C_{1-6}$ alkyl (which is optionally substituted with one to three halo), halo or $R_{10}$;

(m) O-aryl, which is optionally substituted with one or more groups selected from $C_{1-6}$ alkyl, halo or $R_{10}$;

(n) O—$C_{1-6}$ alkyl, which is optionally substituted with $C_{1-6}$ alky, halo or $R_{10}$; or

(o) L-A-$R_{10}$;

$R_4$ is

(a) hydrogen;

(b) $C_{1-6}$ alkyl, which is optionally substituted with halo, hydroxyl, amino, aryl or heterocyclyl;

(c) $C_{3-10}$ cycloalkyl, which is optionally substituted with $C_{1-6}$ alkyl, $OR_{11}$, $NR_8R_{11}$, phenyl (which is optionally substituted with $C_{1-6}$ alkyl, $OR_{11}$ or $NR_8R_{11}$), heterocyclyl, aryl or heteroaryl;

(d) —(CO)$R_8$;

(e) —(CO)—$NR_8R_9$;

(f) $C_{4-10}$ heterocyclyl, which is optionally substituted on either the carbon or the heteroatom with $C_{1-6}$ alkyl, $OR_{11}$, $NR_8R_{11}$, phenyl (which is optionally substituted with $C_{1-6}$ alkyl, $OR_{11}$ or $NR_8R_{11}$), heterocyclyl, —(CO)$R_8$ or —(CO)—$NR_8R_9$;

(g) $OR_{11}$;

(h) $NR_8R_{11}$;

(i) Aryl, which is optionally substituted with one to five halo or $R_{10}$;

(j) Heteroaryl (wherein the heteroaryl has 5 or 6 members in which 1, 2, 3, or 4 of the atoms is a heteroatom selected from N, S and O), which is optionally substituted with one to five halo or $R_{10}$;

$R_5$ is

(a) hydrogen;

(b) $C_{1-8}$ alkyl, which is optionally substituted with halo, hydroxyl, amino, aryl, cycloalkyl or heterocyclyl;

(c) $C_{3-10}$ cycloalkyl, which is optionally substituted with $C_{1-6}$ alkyl, ($C_{1-6}$ alkyl)aryl, ($C_{1-6}$ alkyl)$OR_9$, $OR_4$, $NR_8R_4$, phenyl (which is optionally substituted with $C_{1-6}$ alkyl, $OR_4$, $NR_8R_4$, heterocyclyl, —(CO)R8 or —(CO)—$NR_8R_9$);

(d) —(CO)$R_8$;

(e) —(CO)—$NR_8R_9$;

(f) $C_{1-6}$ alkyl(C═O)$NR_8CR_9$(C═O)$NR_8R_9$;

(g) $C_{4-10}$ heterocyclyl which is optionally substituted on either the carbon or the heteroatom with one to three substituents selected from $C_{1-6}$ alkyl, halo, $OR_4$, $NR_8R_4$, —(CO)$R_8$, (CO)—$NR_8R_9$ or phenyl (which is optionally substituted with $C_{1-6}$ alkyl, $OR_4$, $NR_8R_4$, heterocyclyl, —(CO)$R_8$ or —(CO)—$NR_8R_9$);

$R_6$ is

(a) hydrogen;

(b) $C_{1-8}$ alkyl, which is optionally substituted with halo, hydroxyl, amino, aryl, cycloalkyl or heterocyclyl;

(c) $C_{3-10}$ cycloalkyl, which is optionally substituted with $C_{1-6}$ alkyl, ($C_{1-6}$ alkyl)aryl, ($C_{1-6}$ alkyl)$OR_9$, $OR_4$, $NR_8R_4$, phenyl (which is optionally substituted with $C_{1-6}$ alkyl, $OR_4$, $NR_8R_4$, heterocyclyl, —(CO)$R_8$ or —(CO)—$NR_8R_9$;

(d) —(CO)$R_8$;

(e) —(CO)—$NR_8R_9$;

(f) $C_{1-6}$ alkyl(C═O)$NR_8CR_9$(C═O)$NR_8R_9$;

(g) $C_{4-10}$ heterocyclyl which is optionally substituted on either the carbon or the heteroatom with one to three substituents selected from $C_{1-6}$ alkyl, halo, $OR_4$, $NR_8R_4$, —(CO)$R_8$, (CO)—$NR_8R_9$ or phenyl (which is optionally substituted with $C_{1-6}$ alkyl, $OR_4$, $NR_8R_4$, heterocyclyl, —(CO)$R_8$ or —(CO)—$NR_8R_9$);

$R_7$ is

(a) hydrogen;

(b) $C_{1-6}$ alkyl, which is optionally substituted with halo, hydroxyl, amino, phenyl or heterocyclyl;

(c) $C_{3-10}$ cycloalkyl, which is optionally substituted with $C_{1-6}$ alkyl, $OR_4$, $NR_8R_4$, phenyl (which is optionally substituted with $C_{1-6}$ alkyl, $OR_4$, $NR_8R_4$, heterocyclyl, —(CO)$R_8$ or —(CO)—$NR_8R_9$);

(d) $C_{4-10}$ heterocyclyl which is optionally substituted on either the carbon or the heteroatom with $C_{1-6}$ alkyl, $OR_4$, $NR_8R_4$, phenyl (which is optionally substituted with $C_{1-6}$ alkyl, $OR_4$, $NR_8R_4$, heterocyclyl, —(CO)$R_8$ or —(CO)—$NR_8R_9$);

Or $R_5$ and $R_6$, together with the atoms between them, can form a three to ten membered heterocyclic or heteroaryl ring which is optionally substituted with $C_{1-6}$ alkyl, ($C_{1-6}$ alkyl)aryl, ($C_{1-6}$ alkenyl)aryl, ($C_{1-6}$ alkyl)$OR_9$, $OR_4$, $NR_8R_4$, phenyl (which is optionally substituted with $C_{1-6}$ alkyl, $OR_4$, $NR_8R_4$, heterocyclyl, —(CO)$R_8$ or —(CO)—$NR_8R_9$), —(CO)$R_8$; —(CO)—NR8R9, or heterocyclyl;

$R_8$ is hydrogen or $C_{1-6}$ alkyl, —(CO)$R_{11}$, —(CO)$N(R_{11})_2$;

$R_9$ is hydrogen or $C_{1-6}$ alkyl;

$R_{10}$ is:

(a) hydrogen;

(b) $CO_2R_{11}$;

(c) $C(O)R_{11}$;

(d) $NHR_{11}$;

(e) $NR_{11}R_{12}$;

(f) $NHS(O)_2R_{11}$;

(g) $NHC(O)R_{11}$;

(h) $NHC(O)OR_{11}$;

(i) NH—C═$(NH)NH_2$;

(j) $NHC(O)NH_2$;

(k) $NHC(O)NHR_{11}$;

(l) $NHC(O)NR_{11}R_{12}$;

(m) NC3-6cycloalkyl;

(n) $C(O)NHR_{11}$;

(o) $C(O)NR_{11}R_{12}$;

(p) $SO_2NHR_{11}$;

(q) $SO_2NHC(O)R_{12}$; or

(r) $SO_2R_{11}$;

$R_{11}$ is selected from the group consisting of:

(a) hydrogen,

(b) $C_{3-6}$cycloalkyl, which is optionally substituted with aryl, heteroaryl or one to five halo;

(c) $C_{1-6}$ alkyl, which is optionally substituted with aryl, heteroaryl, or one to five

halo;

(d) Aryl, which is optionally substituted with one to five halo;

(e) Heteroaryl (wherein the heteroaryl has 5 or 6 members in which 1, 2, 3, or 4 of the atoms is a heteroatom selected from N, S and O), which is optionally substituted with one to five halo;

$R_{12}$ is selected from the group consisting of:

(a) hydrogen,

(b) $C_{1-6}$alkyl, which is optionally substituted with aryl, heteroaryl or one to five halo;

(c) $C_{3-6}$cycloalkyl, which is optionally substituted with aryl, heteroaryl or one to five halo;

(d) Aryl, which is optionally substituted with one to five halo;

(e) Heteroaryl (wherein the heteroaryl has 5 or 6 members in which 1, 2, 3, or 4 of the atoms is a heteroatom selected from N, S and O), which is optionally substituted with one to five halo;

A is absent or is selected from the group consisting of: aryl or heteroaryl (wherein the heteroaryl is a monocyclic ring of 5 or 6 atoms or a bicyclic ring of 9 or 10 atoms in which 1, 2, 3, or 4 of the atoms is a heteroatom selected from N, S and O), wherein said aryl or heteroaryl is optionally substituted with one or more substituents selected from halo, $(C_{1-3})$alkyl, ---C(O)OH, $CF_3$, ---$SO_2(C_{1-3})$alkyl, $SO_2N(C_{1-3})$alkyl, $SO_2NHC(O)$---$(C_{1-3})$alkyl or $N(CH_3)_2$;

L is absent or is selected from the group consisting of: ---$(CH_2)k$---W---, ---Z---$(CH_2)k$---, ---C≡C---, ---$C_{1-6}$alkyl-, ---$C_{3-6}$cycloalkyl- and ---$C_{2-5}$alkene-, wherein the alkene is optionally substituted with one or more groups selected from $C_{1-6}$alkyl or $C_{1-6}$cycloalkyl;

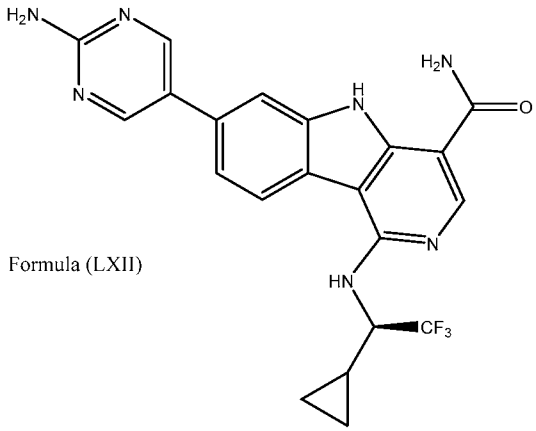
W is selected from the group consisting of: O, NH, $NC_{1-6}$alkyl and S(O)m, with the proviso that when W is O, S(O)m, NH or $NC_{1-6}$alkyl and simultaneously A is absent then $R_{10}$ is $CO_2R_{11}$, $COR_{11}$, $CONHR_{11}$ or $CONR_{11}R_{12}$;

k=0, 1, 2, 3, 4, or 5;

m=0, 1, or 2; and

n=0, 1, 2, or 3.

**[00783]** In a preferred embodiment, the JAK-2 inhibitor is ((*R*)-7-(2-aminopyrimidin-5-yl)-1-((1-cyclopropyl-2,2,2-trifluoroethyl)amino)-5*H*-pyrido[4,3-*b*]indole-4-carboxamide, which is also named 7-(2-aminopyrimidin-5-yl)-1-{[(1*R*)-1-cyclopropyl-2,2,2-trifluoroethyl]amino}-5*H*-pyrido[4,3-*b*]indole-4-carboxamide. In a preferred embodiment, the JAK-2 inhibitor is a compound of Formula (LXII):




Formula (LXII)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of this compound is known to those of ordinary skill in the art, and is described in Lim, *et al.*, Discovery of 1-amino-5*H*-pyrido[4,3-*b*]indol-4-carboxamide inhibitors of Janus kinase-2 (JAK2) for the treatment of myeloproliferative disorders, *J. Med. Chem.* **2011,** *54,* 7334-7349, the disclosure of which is incorporated by reference herein.

**[00784]** In an embodiment, the JAK-2 inhibitor is a compound selected from the JAK-2 inhibitors disclosed in U.S. Patent No. U.S. 8,518,964 or U.S. Patent Application Publication Nos. 2010/0048551 A1, the disclosures of which are incorporated by reference herein.

PD-1 Inhibitors

**[00785]** The PD-1 inhibitor may be any PD-1 inhibitor or PD-1 blocker known in the art. In particular, it is one of the PD-1 inhibitors or blockers described in more detail in the following paragraphs. The terms "inhibitor" and "blocker" are used interchangeably herein in reference to PD-1 inhibitors. For avoidance of doubt, references herein to a PD-1 inhibitor that is an antibody may refer to a compound or antigen-binding fragments, variants, conjugates, or biosimilars thereof. For avoidance of doubt, references herein to

a PD-1 inhibitor may also refer to a compound or a pharmaceutically acceptable salt, ester, solvate, hydrate, cocrystal, or prodrug thereof.

**[00786]** In some embodiments, the compositions and methods described include a PD-1 inhibitor. In some embodiments, the PD-1 inhibitor is a small molecule. In a preferred embodiment, the PD-1 inhibitor is an antibody, a fragment thereof, including Fab fragments, or a single-chain variable fragment (scFv). In some embodiments the PD-1 inhibitor is a polyclonal antibody. In a preferred embodiment, the PD-1 inhibitor is a monoclonal antibody. In some embodiments, the PD-1 inhibitor competes for binding with PD-1, and/or binds to an epitope on PD-1. In an embodiment, the antibody competes for binding with PD-1, and/or binds to an epitope on PD-1. In some embodiments, the PD-1 inhibitor is included in a composition or a method and is further combined with a BTK inhibitor, a PI3K inhibitor, and/or a JAK-2 inhibitor. In some embodiments, an anti-PD-1 monoclonal antibody is included in a composition or a method and is further combined with a BTK inhibitor, a PI3K inhibitor, and/or a JAK-2 inhibitor. In some embodiments, an anti-PD-1 monoclonal antibody is included in a composition or a method and is further combined with a BTK inhibitor and/or a JAK-2 inhibitor. In some embodiments, a PD-1 inhibitor is included in a composition or a method and is further combined with a BTK inhibitor. In some embodiments, an anti-PD-1 monoclonal antibody is included in a composition or a method and is further combined with a BTK inhibitor. In some embodiments, a PD-1 inhibitor is included in a composition or a method and is further combined with a PI3K inhibitor. In some embodiments, an anti-PD-1 monoclonal antibody is included in a composition or a method and is further combined with a PI3K inhibitor. In some embodiments, a PD-1 inhibitor is included in a composition or a method and is further combined with a JAK-2 inhibitor. In some embodiments, an anti-PD-1 monoclonal antibody is included in a composition or a method and is further combined with a JAK-2 inhibitor. In preferred embodiments, the compositions described herein provide a combination of a PD-1 inhibitor with a BTK inhibitor, or methods of using a combination of a PD-1 inhibitor with a BTK inhibitor. In some embodiments, the PD-1 inhibitors provided herein are selective for PD-1, in that the compounds bind or interact with PD-1 at substantially lower concentrations than they bind or interact with other receptors.

**[00787]** In some embodiments, the compositions and methods described include a PD-1 inhibitor that binds human PD-1 with a $K_D$ of about 100 pM or lower, binds human PD-1 with a $K_D$ of about 90 pM or lower, binds human PD-1 with a $K_D$ of about 80 pM or lower, binds human PD-1 with a $K_D$ of about 70 pM or lower, binds human PD-1 with a $K_D$ of about 60 pM or lower, binds human PD-1 with a $K_D$ of about 50 pM or lower, binds human PD-1 with a $K_D$ of about 40 pM or lower, or binds human PD-1 with a $K_D$ of about 30 pM or lower.

**[00788]** In some embodiments, the compositions and methods described include a PD-1 inhibitor that binds to human PD-1 with a $k_{assoc}$ of about $7.5 \times 10^5$ l/M·s or faster, binds to human PD-1 with a $k_{assoc}$ of about $7.5 \times 10^5$ l/M·s or faster, binds to human PD-1 with a $k_{assoc}$ of about $8 \times 10^5$ l/M·s or faster, binds to human PD-1 with a $k_{assoc}$ of about $8.5 \times 10^5$ l/M·s or faster, binds to human PD-1 with a $k_{assoc}$ of about $9 \times 10^5$ l/M·s or faster, binds to human PD-1 with a $k_{assoc}$ of about $9.5 \times 10^5$ l/M·s or faster, or binds to human PD-1 with a $k_{assoc}$ of about $1 \times 10^6$ l/M·s or faster.

**[00789]** In some embodiments, the compositions and methods described include a PD-1 inhibitor that binds to human PD-1 with a $k_{dissoc}$ of about $2 \times 10^{-5}$ l/s or slower, binds to human PD-1 with a $k_{dissoc}$ of about $2.1 \times 10^{-5}$ l/s or slower , binds to human PD-1 with a $k_{dissoc}$ of about $2.2 \times 10^{-5}$ l/s or slower, binds to human PD-1 with a $k_{dissoc}$ of about $2.3 \times 10^{-5}$ l/s or slower, binds to human PD-1 with a $k_{dissoc}$ of about $2.4 \times 10^{-5}$ l/s or slower, binds to human PD-1 with a $k_{dissoc}$ of about $2.5 \times 10^{-5}$ l/s or slower, binds to human PD-1 with a $k_{dissoc}$ of about $2.6 \times 10^{-5}$ l/s or slower or binds to human PD-1 with a $k_{dissoc}$ of about $2.7 \times 10^{-5}$ l/s or slower, binds to human PD-1 with a $k_{dissoc}$ of about $2.8 \times 10^{-5}$ l/s or slower, binds to human PD-1 with a $k_{dissoc}$ of about $2.9 \times 10^{-5}$ l/s or slower, or binds to human PD-1 with a $k_{dissoc}$ of about $3 \times 10^{-5}$ l/s or slower.

**[00790]** In some embodiments, the compositions and methods described include a PD-1 inhibitor that blocks or inhibits binding of human PD-Ll or human PD-L2 to human PD-1 with an $IC_{50}$ of about 10 nM or lower, blocks or inhibits binding of human PD-Ll or human PD-L2 to human PD-1 with an $IC_{50}$ of about 9 nM or lower, blocks or inhibits binding of human PD-Ll or human PD-L2 to human PD-1 with an $IC_{50}$ of about 8 nM or lower, blocks or inhibits binding of human PD-Ll or human PD-L2 to human PD-1 with

an $IC_{50}$ of about 7 nM or lower, blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an $IC_{50}$ of about 6 nM or lower, blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an $IC_{50}$ of about 5 nM or lower, blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an $IC_{50}$ of about 4 nM or lower, blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an $IC_{50}$ of about 3 nM or lower, blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an $IC_{50}$ of about 2 nM or lower, or blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an $IC_{50}$ of about 1 nM or lower.

**[00791]** In an embodiment, an anti-PD-1 antibody comprises nivolumab, produced by Bristol-Myers Squibb Co., or antigen-binding fragments, conjugates, or variants thereof. Nivolumab is referred to as 5C4 in International Patent Publication No. WO 2006/121168. Nivolumab is assigned CAS registry number 946414-94-4 and is also known to those of ordinary skill in the art as BMS-936558, MDX-1106 or ONO-4538. Nivolumab is a fully human IgG4 antibody blocking the PD-1 receptor. The clinical safety and efficacy of nivolumab in various forms of cancer has been described in Wang *et al.*, *Cancer Immunol Res.* **2014,** 2, 846-56; Page *et al.*, *Ann. Rev. Med.*, **2014,** *65,* 185-202; and Weber, *et al.*, *J. Clin. Oncology*, **2013,** *31,* 4311-4318. The nivolumab monoclonal antibody includes a heavy chain given by SEQ ID NO:1 and a light chain given by SEQ ID NO:2. Nivolumab has intra-heavy chain disulfide linkages at 22-96,140-196, 254-314, 360-418, 22"-96", 140"-196", 254"-314", and 360"-418"; intra-light chain disulfide linkages at 23'-88', 134'-194', 23'"-88'", and 134'"-194'"; inter-heavy-light chain disulfide linkages at 127-214', 127"-214'", inter-heavy-heavy chain disulfide linkages at 219-219" and 222-222"; and N-glycosylation sites (H $CH_2$ 84.4) at 290, 290". In an embodiment, the anti-PD-1 antibody is an immunoglobulin G4 kappa, anti-(human CD274) antibody. In an embodiment, an anti-PD-1 antibody comprises heavy and light chains having the sequences shown in SEQ ID NO:1 and SEQ ID NO:2, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, an anti-PD-1 antibody comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:1 and SEQ ID NO:2, respectively. In an embodiment, an anti-PD-1 antibody

comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:1 and SEQ ID NO:2, respectively. In an embodiment, an anti-PD-1 antibody comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:1 and SEQ ID NO:2, respectively. In an embodiment, an anti-PD-1 antibody comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:1 and SEQ ID NO:2, respectively. In an embodiment, an anti-PD-1 antibody comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:1 and SEQ ID NO:2, respectively.

**[00792]** In other embodiments, the anti-PD-1 antibody comprises the heavy and light chain CDRs or VRs of nivolumab. In one embodiment, the antibody $V_H$ region comprises the sequence shown in SEQ ID NO: 3, and the antibody $V_L$ region comprises the sequence shown in SEQ ID NO:4. In an embodiment, an anti-PD-1 antibody comprises $V_H$ and $V_L$ regions that are each at least 99% identical to the sequences shown in SEQ ID NO:3 and SEQ ID NO:4, respectively. In an embodiment, an anti-PD-1 antibody comprises $V_H$ and $V_L$ regions that are each at least 98% identical to the sequences shown in SEQ ID NO:3 and SEQ ID NO:4, respectively. In an embodiment, an anti-PD-1 antibody comprises $V_H$ and $V_L$ regions that are each at least 97% identical to the sequences shown in SEQ ID NO:3 and SEQ ID NO:4, respectively. In an embodiment, an anti-PD-1 antibody comprises $V_H$ and $V_L$ regions that are each at least 96% identical to the sequences shown in SEQ ID NO:3 and SEQ ID NO:4, respectively. In an embodiment, an anti-PD-1 antibody comprises $V_H$ and $V_L$ regions that are each at least 95% identical to the sequences shown in SEQ ID NO:3 and SEQ ID NO:4, respectively. In an alternative embodiment, the antibody comprises $V_H$ and/or $V_L$ regions having the amino acid sequences set forth in SEQ ID NO:3 and/or SEQ ID NO:4, respectively.

**[00793]** In another embodiment, the anti-PD-1 antibody comprises the heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7, respectively, and the light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:8, SEQ ID NO:9, and SEQ ID NO:10, respectively.

**[00794]** In an embodiment, an anti-PD-1 antibody comprises CDR1, CDR2 and CDR3 domains that are each at least 95% identical to the sequences shown in SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7, respectively. In an embodiment, an anti-PD-1 antibody comprises CDR1, CDR2 and CDR3 domains that are each at least 94% identical to the sequences shown in SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7, respectively. In an embodiment, an anti-PD-1 antibody comprises CDR1, CDR2 and CDR3 domains that are each at least 90% identical to the sequences shown in SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7, respectively. In an embodiment, an anti-PD-1 antibody comprises CDR1, CDR2 and CDR3 domains that are each at least 88% identical to the sequences shown in SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7, respectively. In another embodiment, the antibody competes for binding with, and/or binds to the same epitope on PD-1 as the aforementioned antibodies.

**[00795]** In an embodiment, an anti-PD-1 antibody comprises CDR1, CDR2 and CDR3 domains that are each at least 95% identical to the sequences shown in SEQ ID NO:8, SEQ ID NO:9, and SEQ ID NO:10, respectively. In an embodiment, an anti-PD-1 antibody comprises CDR1, CDR2 and CDR3 domains that are each at least 91% identical to the sequences shown in SEQ ID NO:8, SEQ ID NO:9, and SEQ ID NO:10, respectively. In an embodiment, an anti-PD-1 antibody comprises CDR1, CDR2 and CDR3 domains that are each at least 90% identical to the sequences shown in SEQ ID NO:8, SEQ ID NO:9, and SEQ ID NO:10, respectively. In an embodiment, an anti-PD-1 antibody comprises CDR1, CDR2 and CDR3 domains that are each at least 85% identical to the sequences shown in SEQ ID NO:8, SEQ ID NO:9, and SEQ ID NO:10, respectively. In another embodiment, the antibody competes for binding with, and/or binds to the same epitope on PD-1 as the aforementioned antibodies.

**[00796]** In an embodiment, the anti-PD-1 antibody is an antibody disclosed and/or prepared according to U.S. Patent No. 8,008,449 or U.S. Patent Application Publication Nos. 2009/0217401 A1 or 2013/0133091 A1, the disclosures of which are specifically incorporated by reference herein. For example, in an embodiment, the monoclonal antibody includes 5C4 (referred to herein as nivolumab), 17D8, 2D3, 4H1, 4A11, 7D3, and 5F4, described in U.S. Patent No. 8,008,449, the disclosures of which are hereby incorporated by reference. The PD-1 antibodies 17D8, 2D3, 4H1, 5C4, and 4A11, are all

directed against human PD-1, bind specifically to PD-1 and do not bind to other members of the CD28 family. The sequences and CDR regions for these antibodies are provided in U.S. Patent No. 8,008,449, in particular Figure 1 through Figure 12; all of which are incorporated by reference herein in their entireties.

**[00797]** The anti-PD-1 antibody nivolumab may be prepared by the following procedure, as described in U.S. Patent No. 8,008,449. Immunization protocols utilized as antigen both (i) a recombinant fusion protein comprising the extracellular portion of PD-1 and (ii) membrane bound full-length PD-1. Both antigens were generated by recombinant transfection methods in a CHO cell line. Fully human monoclonal antibodies to PD-1 were prepared using the HCo7 strain of HuMab transgenic mice and the KM strain of transgenic transchromosomic mice, each of which express human antibody genes. In each of these mouse strains, the endogenous mouse kappa light chain gene has been homozygously disrupted as described in Chen et al. *EMBO J.* **1993,** *12,* 811-820 and the endogenous mouse heavy chain gene has been homozygously disrupted as described in Example 1 of International Patent Publication No. WO 01/09187. Each of these mouse strains carries a human kappa light chain transgene, KCo5, as described in Fishwild, et al. *Nat. Biotechnology* **1996,** *14,* 845-851. The HCo7 strain carries the HCo7 human heavy chain transgene as described in U.S. Patent Nos. 5,545,806; 5,625,825; and 5,545,807. The KM strain contains the SC20 transchromosome as described in International Patent Publication No. WO 02/43478. To generate fully human monoclonal antibodies to PD-1, HuMab mice and KM Mice™ were immunized with purified recombinant PD-1 fusion protein and PD-1-transfected CHO cells as antigen. General immunization schemes for HuMab mice are described in Lonberg, et al. *Nature* **1994,** *368,* 856-859; Fishwild, et al. *Nat. Biotechnology* **1996,** *14,* 845-851, and International Patent Publication No. WO 98/24884. The mice were 6-16 weeks of age upon the first infusion of antigen. A purified recombinant preparation (5-50 μg) of PD-1 fusion protein antigen and 5-10×$10^6$ cells were used to immunize the HuMab mice and KM Mice™ intraperitonealy, subcutaneously (Sc) or via footpad injection. Transgenic mice were immunized twice with antigen in complete Freund's adjuvant or Ribi adjuvant IP, followed by 3-21 days IP (up to a total of 11 immunizations) with the antigen in incomplete Freund's or Ribi adjuvant. The immune response was monitored by

retroorbital bleeds. The plasma was screened by ELISA (as described below), and mice with sufficient titers of anti-PD-1 human immunoglobulin were used for fusions. Mice were boosted intravenously with antigen 3 days before sacrifice and removal of the spleen. Typically, 10-35 fusions for each antigen were performed. Several dozen mice were immunized for each antigen. To select HuMab or KM Mice™ producing antibodies that bound PD-1, sera from immunized mice were tested by ELISA as described by Fishwild, et al. *Nat. Biotechnology* **1996,** *14,* 845-851. Briefly, microtiter plates were coated with purified recombinant PD-1 fusion protein from transfected CHO cells at 1-2 μg/ml in PBS, 100 μL/wells incubated at 4° C overnight then blocked with 200 μL/well of 5% fetal bovine serum in PBS/Tween (0.05%). Dilutions of sera from PD-1-immunized mice were added to each well and incubated for 1-2 hours at ambient temperature. The plates were washed with PBS/Tween and then incubated with a goat-anti-human IgG polyclonal antibody conjugated with horseradish peroxidase (HRP) for 1 hour at room temperature. After washing, the plates were developed with ABTS substrate (Sigma, A-1888, 0.22 mg/ml) and analyzed by spectrophotometer at OD 415-495. Mice that developed the highest titers of anti-PD-1 antibodies were used for fusions. Fusions were performed as described below and hybridoma supernatants were tested for anti-PD-1 activity by ELISA. The mouse splenocytes, isolated from the HuMab or KM mice, were fused to a mouse myeloma cell line either using PEG based upon standard protocols or electric field based electrofusion using a Cyto Pulse large chamber cell fusion electroporator (Cyto Pulse Sciences, Inc., Glen Burnie, Md.). The resulting hybridomas were then screened for the production of antigen-specific antibodies. Single cell suspensions of splenocytes from immunized mice were fused to one-fourth the number of SP2/0 nonsecreting mouse myeloma cells (ATCC, CRL 1581) with 50% PEG (Sigma). Cells were plated at approximately 1×105/well in flat bottom microtiter plate, followed by about two week incubation in selective medium containing 10% fetal bovine serum, 10% P388D1 (ATCC, CRL TIB-63) conditioned medium, 3-5% origen (IGEN) in DMEM (Mediatech, CRL 10013, with high glucose, L-glutamine and sodium pyruvate) plus 5 mM HEPES, 0.055 mM 2-mercaptoethanol, 50 mg/ml gentamycin and 1×HAT (Sigma, CRL P-7185). After 1-2 weeks, cells were cultured in medium in which the HAT was replaced with HT. Individual wells were then screened by ELISA (described above)

for human anti-PD-1 monoclonal IgG antibodies. Once extensive hybridoma growth occurred, medium was monitored usually after 10-14 days. The antibody-secreting hybridomas were replated, screened again and, if still positive for human IgG, anti-PD-1 monoclonal antibodies were subcloned at least twice by limiting dilution. The stable subclones were then cultured in vitro to generate small amounts of antibody in tissue culture medium for further characterization. The antibody nivolumab may be produced in this manner, or by other known means given the disclosure of the amino acid sequences herein.

**[00798]** In another embodiment, the anti-PD-1 antibody comprises pembrolizumab, which is commercially available from Merck, or antigen-binding fragments, conjugates, or variants thereof. Pembrolizumab is referred to as h409A11 in International Patent Publication No. WO 2008/156712 A1, U.S. Patent No. 8,354,509 and U.S. Patent Application Publication Nos. US 2010/0266617 A1, US 2013/0108651 A1, and US 2013/0109843 A2. Pembrolizumab has an immunoglobulin G4, anti-(human protein PDCD1 (programmed cell death 1)) (human-Mus musculus monoclonal heavy chain), disulfide with human-Mus musculus monoclonal light chain, dimer structure. The structure of pembrolizumab may also be described as immunoglobulin G4, anti-(human programmed cell death 1); humanized mouse monoclonal [228-L-proline(H10-S>P)]γ4 heavy chain (134-218')-disulfide with humanized mouse monoclonal κ light chain dimer (226-226":229-229")-bisdisulfide. Pembrolizumab is assigned CAS registry number 1374853-91-4 and is also known as lambrolizumab, MK-3475, and SCH-900475. The clinical safety and efficacy of pembrolizumab in various forms of cancer is described in Fuerst, *Oncology Times*, **2014,** *36,* 35-36; Robert, *et al.*, *Lancet,* **2014,** *384,* 1109-17; and Thomas *et al.*, *Exp. Opin. Biol. Ther.*, **2014,** *14,* 1061-1064. In an embodiment, the pembrolizumab monoclonal antibody includes a heavy chain given by SEQ ID NO:12 and a light chain given by SEQ ID NO:14, and also shown below with disulfide and glycosylation information:

```
Heavy chain
QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGG     50
INPSNGGTNFNEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRD     100
YRFDMGFDYWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVK     150
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DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKT     200
YTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDT     250
LMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTY     300
RVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYT     350
LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS     400
DGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK        447

Light chain
EIVLTQSPATLSLSPGERATLSCRASKGVSTSGYSYLHWYQQKPGQAPRL     50'
LIYLASYLESGVPARFSGSGSGTDFTLTISSLEPEDFAVYYCQHSRDLPL     100'
TFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV     150'
QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEV     200'
THQGLSSPVTKSFNRGEC                                      218'

Disulfide bridges
22-96      22''-96''       23'-92'         23'''-92'''
134-218'   134''-218'''    138'-198'       138'''-198'''
147-203    147''-203''     226-226''       229-229''
261-321    261''-321''     367-425         367''-425''

Glycosylation sites (N)
Asn-297    Asn-297''
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**[00799]** In an embodiment, an anti-PD-1 antibody comprises heavy and light chains having the sequences shown in SEQ ID NO:12 and SEQ ID NO:14, respectively, or antigen binding fragments and variants thereof. In an embodiment, an anti-PD-1 antibody comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:12 and SEQ ID NO:14, respectively, or antigen binding fragments and variants thereof. In an embodiment, an anti-PD-1 antibody comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:12 and SEQ ID NO:14, respectively, or antigen binding fragments and variants thereof. In an embodiment, an anti-PD-1 antibody comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:12 and SEQ ID

NO:14, respectively, or antigen binding fragments and variants thereof. In an embodiment, an anti-PD-1 antibody comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:12 and SEQ ID NO:14, respectively, or antigen binding fragments and variants thereof. In an embodiment, an anti-PD-1 antibody comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:12 and SEQ ID NO:14, respectively, or antigen binding fragments and variants thereof.

**[00800]** In other embodiments, the anti-PD-1 antibody comprises the heavy and light chain CDRs or VRs of pembrolizumab. In an embodiment, the antibody $V_H$ region comprises the sequence of residues 20 to 446 of SEQ ID NO:11, and the antibody $V_L$ region comprises the sequence shown in SEQ ID NO:14. In an embodiment, an anti-PD-1 antibody comprises $V_H$ and $V_L$ regions that are each at least 99% identical to the sequences of residues 20 to 446 of SEQ ID NO:11 and the sequence shown in SEQ ID NO:14, respectively. In an embodiment, an anti-PD-1 antibody comprises $V_H$ and $V_L$ regions that are each at least 98% identical to the sequences of residues 20 to 446 of SEQ ID NO:11 and the sequence shown in SEQ ID NO:14, respectively. In an embodiment, an anti-PD-1 antibody comprises $V_H$ and $V_L$ regions that are each at least 97% identical to the sequences of residues 20 to 446 of SEQ ID NO:11 and the sequence shown in SEQ ID NO:14, respectively. In an embodiment, an anti-PD-1 antibody comprises $V_H$ and $V_L$ regions that are each at least 96% identical to the sequences of residues 20 to 446 of SEQ ID NO:11 and the sequence shown in SEQ ID NO:14, respectively. In an embodiment, an anti-PD-1 antibody comprises $V_H$ and $V_L$ regions that are each at least 95% identical to the sequences of residues 20 to 446 of SEQ ID NO:11 and the sequence shown in SEQ ID NO:14, respectively.

**[00801]** In an embodiment, the anti-PD-1 antibody comprises a heavy chain comprising amino acid residues 20 to 446 of SEQ ID NO:11 and a light chain comprising amino acid residues of 20-237 of SEQ ID NO:13.

**[00802]** In an embodiment, the anti-PD-1 antibody is an isolated antibody or antibody fragment which binds to human PD-1 comprising three light chain CDRs of SEQ ID NO:15, SEQ ID NO:16, and SEQ ID NO:17, and three heavy chain CDRs of SEQ ID

NO:18, SEQ ID NO:19 and SEQ ID NO:20.

**[00803]** In an embodiment, the anti-PD-1 antibody is an antibody disclosed in U.S. Patent No. 8,354,509 or U.S. Patent Application Publication Nos. 2010/0266617 A1, 2013/0108651 A1, 2013/0109843 A2, the disclosures of which are specifically incorporated by reference herein.

**[00804]** In an embodiment, the anti-PD-1 antibody is pidilizumab, which is also known as CT-011 (CureTech Ltd.), and which is disclosed in U.S. Patent No. 8,686,119 B2, the disclosures of which are specifically incorporated by reference herein. The efficacy of pidilizumab in the treatment of cancers, such as hematological malignancies, is described in Berger, *et al.*, *Clin. Cancer Res.* **2008,** *14,* 3044-51. The pidilizumab monoclonal antibody includes a heavy chain given by SEQ ID NO:21 and a light chain given by SEQ ID NO:22. Pidilizumab has intra-heavy chain disulfide linkages at 22-96, 144-200, 261-321, 367-425, 22"-96", 144"-200", 261"-321", and 367"-425"; intra-light chain disulfide linkages at 23'-87', 133'-193', 23'"-87'", and 133'"-193'"; inter-heavy-light chain disulfide linkages at 220-213' and 220"-213'", inter-heavy-heavy chain disulfide linkages at 226-226" 229-229"; and N-glycosylation sites (H $CH_2$ 84.4) at 297, 297".

**[00805]** In an embodiment, the anti-PD-1 antibody is an immunoglobulin G1 kappa, anti-(human CD274) humanized monoclonal antibody. In an embodiment, an anti-PD-1 antibody comprises heavy and light chains having the sequences shown in SEQ ID NO:21 and SEQ ID NO:22, respectively, or antigen binding fragments, variants, or conjugates thereof. In an embodiment, an anti-PD-1 antibody comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:21 and SEQ ID NO:22, respectively. In an embodiment, an anti-PD-1 antibody comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:21 and SEQ ID NO:22, respectively. In an embodiment, an anti-PD-1 antibody comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:21 and SEQ ID NO:22, respectively. In an embodiment, an anti-PD-1 antibody comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:21 and SEQ ID NO:22, respectively. In an embodiment, an anti-PD-1 antibody comprises heavy and light chains that are each at

least 95% identical to the sequences shown in SEQ ID NO:21 and SEQ ID NO:22, respectively.

**[00806]** In an embodiment, an anti-PD-L1 antibody comprises $V_H$ and $V_L$ regions that are each at least 99% identical to the sequences shown in SEQ ID NO:23 and SEQ ID NO:24, respectively. In an embodiment, an anti-PD-L1 antibody comprises $V_H$ and $V_L$ regions that are each at least 98% identical to the sequences shown in SEQ ID NO:23 and SEQ ID NO:24, respectively. In an embodiment, an anti-PD-L1 antibody comprises $V_H$ and $V_L$ regions that are each at least 97% identical to the sequences shown in SEQ ID NO:23 and SEQ ID NO:24, respectively. In an embodiment, an anti-PD-L1 antibody comprises $V_H$ and $V_L$ regions that are each at least 96% identical to the sequences shown in SEQ ID NO:23 and SEQ ID NO:24, respectively. In an embodiment, an anti-PD-L1 antibody comprises $V_H$ and $V_L$ regions that are each at least 95% identical to the sequences shown in SEQ ID NO:23 and SEQ ID NO:24, respectively.

**[00807]** In another embodiment, anti-PD-1 antibodies and other PD-1 inhibitors include those described in U.S. Patent Nos. 8,287,856, 8,580,247, and 8,168,757 and U.S. Patent Application Publication Nos. 2009/0028857 A1, 2010/0285013 A1, 2013/0022600 A1, and 2011/0008369 A1, the teachings of which are hereby incorporated by reference. In another embodiment, antibodies that compete with any of these antibodies for binding to PD-1 are also included. In another embodiment, the anti-PD-1 antibody is an antibody disclosed in U.S. Patent No. 8,735,553 B1, the disclosures of which are incorporated herein by reference.

**[00808]** In an embodiment, the anti-PD-1 antibody is a commercially-available monoclonal antibody, such as anti-m-PD-1 clones J43 (Cat # BE0033-2) and RMP1-14 (Cat # BE0146) (Bio X Cell, Inc., West Lebanon, NH, USA). A number of commercially-available anti-PD-1 antibodies are known to one of ordinary skill in the art.

**[00809]** Monoclonal antibodies that inhibit or block PD-1 can be prepared by procedures known to those of ordinary knowledge and skill in the art, *e.g.*, by injecting test subjects with PD-1 antigen and then isolating hybridomas expressing antibodies having the desired sequence or functional characteristics. DNA encoding the monoclonal antibodies is readily isolated and sequenced using conventional procedures (*e.g.*, by using

oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the monoclonal antibodies). The hybridoma cells serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as *E. coli* cells, simian COS cells, Chinese hamster ovary (CHO) cells, myeloma cells, or other suitable cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. The details of recombinant production of specific antibodies may be found in the references cited in the foregoing, the disclosures of which are incorporated by reference herein. Monoclonal antibodies that inhibit PD-1 can be prepared by standard molecular biology methods using the sequences provided herein by reverse translation and insertion into appropriate DNA or RNA vectors.

**[00810]** The anti-PD-1 antibody sequences discussed and referenced in the foregoing embodiments are summarized in Table 1.

TABLE 1. Anti-PD-1 antibody amino acid sequences.

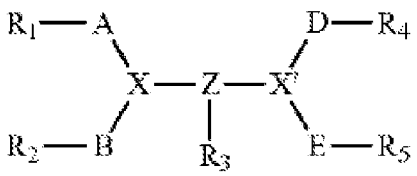
| Identifier | Sequence (One-Letter Amino Acid Symbols) | |
|---|---|---|
| SEQ ID NO:1 nivolumab heavy chain | QVQLVESGGG VVQPGRSLRL DCKASGITFS NSGMHWVRQA PGKGLEWVAV IWYDGSKRYY<br>ADSVKGRFTI SRDNSKNTLF LQMNSLRAED TAVYYCATND DYWGQGTLVT VSSASTKGPS<br>VFPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS<br>VVTVPSSSLG TKTYTCNVDH KPSNTKVDKR VESKYGPPCP PCPAPEFLGG PSVFLFPPKP<br>KDTLMISRTP EVTCVVVDVS QEDPEVQFNW YVDGVEVHNA KTKPREEQFN STYRVVSVLT<br>VLHQDWLNGK EYKCKVSNKG LPSSIEKTIS KAKGQPREPQ VYTLPPSQEE MTKNQVSLTC<br>LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SRLTVDKSRW QEGNVFSCSV<br>MHEALHNHYT QKSLSLSLGK | 60<br>120<br>180<br>240<br>300<br>360<br>420<br>440 |
| SEQ ID NO:2 nivolumab light chain | EIVLTQSPAT LSLSPGERAT LSCRASQSVS SYLAWYQQKP GQAPRLLIYD ASNRATGIPA<br>RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ SSNWPRTFGQ GTKVEIKRTV AAPSVFIFPP<br>SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT<br>LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC | 60<br>120<br>180<br>214 |
| SEQ ID NO:3 nivolumab variable heavy chain | QVQLVESGGG VVQPGRSLRL DCKASGITFS NSGMHWVRQA PGKGLEWVAV IWYDGSKRYY<br>ADSVKGRFTI SRDNSKNTLF LQMNSLRAED TAVYYCATND DYWGQGTLVT VSS | 60<br>113 |
| SEQ ID NO:4 nivolumab variable light chain | EIVLTQSPAT LSLSPGERAT LSCRASQSVS SYLAWYQQKP GQAPRLLIYD ASNRATGIPA<br>RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ SSNWPRTFGQ GTKVEIK | 60<br>107 |
| SEQ ID NO:5 nivolumab heavy chain CDR1 | NSGMH | 5 |
| SEQ ID NO:6 nivolumab heavy chain CDR2 | VIWYDGSKRY YADSVKG | 17 |
| SEQ ID NO:7 nivolumab heavy chain CDR3 | NDDY | 4 |
| SEQ ID NO:8 | RASQSVSSYL A | 11 |

| Identifier | Sequence (One-Letter Amino Acid Symbols) | |
|---|---|---|
| nivolumab light chain CDR1 | | |
| SEQ ID NO:9 nivolumab light chain CDR2 | DASNRAT | 7 |
| SEQ ID NO:10 nivolumab light chain CDR3 | QQSSNWPRT | 9 |
| SEQ ID NO:11 pembrolizumab heavy chain | MAVLGLLFCL VTFPSCVLSQ VQLVQSGVEV KKPGASVKVS CKASGYTFTN YYMYWVRQAP<br>GQGLEWMGGI NPSNGGTNFN EKFKNRVTLT TDSSTTTAYM ELKSLQFDDT AVYYCARRDY<br>RFDMGFDYWG QGTTVTVSSA STKGPSVFPL APCSRSTSES TAALGCLVKD YFPEPVTVSW<br>NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTKTY TCNVDHKPSN TKVDKRVESK<br>YGPPCPPCPA PEFLGGPSVF LFPPKPKDTL MISRTPEVTC VVVDVSQEDP EVQFNWYVDG<br>VEVHNAKTKP REEQFNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKGLPSS IEKTISKAKG<br>QPREPQVYTL PPSQEEMTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPVLDSD<br>GSFFLYSRLT VDKSRWQEGN VFSCSVMHEA LHNHYTQKSL SLSLGK | 60<br>120<br>180<br>240<br>300<br>360<br>420<br>466 |
| SEQ ID NO:12 pembrolizumab heavy chain | QVQLVQSGVE VKKPGASVKV SCKASGYTFT NYYMYWVRQA PGQGLEWMGG INPSNGGTNF<br>NEKFKNRVTL TTDSSTTTAY MELKSLQFDD TAVYYCARRD YRFDMGFDYW GQGTTVTVSS<br>ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS<br>GLYSLSSVVT VPSSSLGTKT YTCNVDHKPS NTKVDKRVES KYGPPCPPCP APEFLGGPSV<br>FLFPPKPKDT LMISRTPEVT CVVVDVSQED PEVQFNWYVD GVEVHNAKTK PREEQFNSTY<br>RVVSVLTVLH QDWLNGKEYK CKVSNKGLPS SIEKTISKAK GQPREPQVYT LPPSQEEMTK<br>NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS DGSFFLYSRL TVDKSRWQEG<br>NVFSCSVMHE ALHNHYTQKS LSLSLGK | 60<br>120<br>180<br>240<br>300<br>360<br>420<br>447 |
| SEQ ID NO:13 pembrolizumab variable light chainamino acid | MAPVQLLGLL VLFLPAMRCE IVLTQSPATL SLSPGERATL SCRASKGVST SGYSYLHWYQ<br>QKPGQAPRLL IYLASYLESG VPARFSGSGS GTDFTLTISS LEPEDFAVYY CQHSRDLPLT<br>FGGGTKVEIK | 60<br>120<br>130 |
| SEQ ID NO:14 pembrolizumab light chain | MAPVQLLGLL VLFLPAMRCE IVLTQSPATL SLSPGERATL SCRASKGVST SGYSYLHWYQ<br>QKPGQAPRLL IYLASYLESG VPARFSGSGS GTDFTLTISS LEPEDFAVYY CQHSRDLPLT<br>FGGGTKVEIK RTVAAPSVFI FPPSDEQLKS GTASVVCLLN NFYPREAKVQ WKVDNALQSG<br>NSQESVTEQD SKDSTYSLSS TLTLSKADYE KHKVYACEVT HQGLSSPVTK SFNRGEC | 60<br>120<br>180<br>237 |
| SEQ ID NO:15 pembrolizumab light chain CDR1 | RASKGVSTSG YSYLH | 15 |
| SEQ ID NO:16 pembrolizumab light chain CDR2 | LASYLES | 7 |
| SEQ ID NO:17 pembrolizumab light chain CDR3 | QHSRDLPLT | 9 |
| SEQ ID NO:18 pembrolizumab heavy chain CDR1 | NYYMY | 5 |
| SEQ ID NO:19 pembrolizumab heavy chain CDR2 | GINPSNGGTN FNEKFK | 16 |
| SEQ ID NO:20 pembrolizumab heavy chain CDR3 | RDYRFDMGFD Y | 11 |
| SEQ ID NO:21 pidilizumab heavy chain | QVQLVQSGSE LKKPGASVKI SCKASGYTFT NYGMNWVRQA PGQGLQWMGW INTDSGESTY<br>AEEFKGRFVF SLDTSVNTAY LQITSLTAED TGMYFCVRVG YDALDYWGQG TLVTVSSAST<br>KGPSVFPLAP SSKSTSGGTA ALGCLVKDYF PEPVTVSWNS GALTSGVHTF PAVLQSSGLY<br>SLSSVVTVPS SSLGTQTYIC NVNHKPSNTK VDKRVEPKSC DKTHTCPPCP APELLGGPSV<br>FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQYNSTY | 60<br>120<br>180<br>240<br>300 |

| Identifier | Sequence (One-Letter Amino Acid Symbols) | |
|---|---|---|
| | RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK GQPREPQVYT LPPSREEMTK<br>NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS DGSFFLYSKL TVDKSRWQQG<br>NVFSCSVMHE ALHNHYTQKS LSLSPGK | 360<br>420<br>447 |
| SEQ ID NO:22 pidilizumab light chain | EIVLTQSPSS LSASVGDRVT ITCSARSSVS YMHWFQQKPG KAPKLWIYRT SNLASGVPSR<br>FSGSGSGTSY CLTINSLQPE DFATYYCQQR SSFPLTFGGG TKLEIKRTVA APSVFIFPPS<br>DEQLKSGTAS VVCLLNNFYP REAKVQWKVD NALQSGNSQE SVTEQDSKDS TYSLSSTLTL<br>SKADYEKHKV YACEVTHQGL SSPVTKSFNR GEC | 60<br>120<br>180<br>213 |
| SEQ ID NO:23 pidilizumab variable heavy chain | QVQLVQSGSE LKKPGASVKI SCKASGYTFT NYGMNWVRQA PGQGLQWMGW INTDSGESTY<br>AEEFKGRFVF SLDTSVNTAY LQITSLTAED TGMYFCVRVG YDALDYWGQG TLVTVSS | 60<br>117 |
| SEQ ID NO:24 pidilizumab variable light chain | EIVLTQSPSS LSASVGDRVT ITCSARSSVS YMHWFQQKPG KAPKLWIYRT SNLASGVPSR<br>FSGSGSGTSY CLTINSLQPE DFATYYCQQR SSFPLTFGGG TKLEIK | 60<br>106 |

**[00811]** The PD-1 inhibitor may also be a small molecule or peptide, or a peptide derivative, such as those described in U.S. Patent Nos. 8,907,053; 9,096,642; and 9,044,442 and U.S. Patent Application Publication No. 2015/0087581; 1,2,4 oxadiazole compounds and derivatives such as those described in U.S. Patent Application Publication No. 2015/0073024; cyclic peptidomimetic compounds and derivatives such as those described in U.S. Patent Application Publication No. 2015/0073042; cyclic compounds and derivatives such as those described in U.S. Patent Application Publication No. 2015/0125491; 1,3,4 oxadiazole and 1,3,4 thiadiazole compounds and derivatives such as those described in International Patent Application Publication No. WO 2015/033301; peptide-based compounds and derivatives such as those described in International Patent Application Publication Nos. WO 2015/036927 and WO 2015/04490, or a macrocyclic peptide-based compounds and derivatives such as those described in U.S. Patent Application Publication No. 2014/0294898; the disclosures of each of which are hereby incorporated by reference in their entireties.

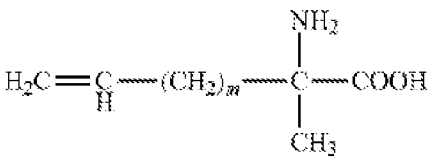
**[00812]** In an embodiment, the PD-1 inhibitor may also be a compound of Formula (LXIII):




(LXIII)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof,

wherein A is an amino acid sequence SNTSESF; B is an amino acid sequence SNTSESF;
Z is:
(i) from one to four peptide sequences arranged in any order each being of from three amino acids up to the full length of a mammalian PD1 ectodomain fragment selected from BC loop, D strand, FG loop, G strand, C strand, F strand, C' strand, C" strand, C"-D loop, C' strand to C' C" loop, C' strand to C" strand or D strand to DE loop;
(ii) G-L-Z', G is an amino acid sequence of from three amino acids to the full length of a peptide sequence of mammalian PD1 ectodomain fragments from D-strand or is absent; L is selected from $CO(CH_2)_n$-NH-, or PEG 2-20 KD; n is an integer selected from 2 to 10, both inclusive; and Z' is one to three peptide sequences arranged in any order each being of from three amino acids up to the full length of a mammalian PD1 ectodomain fragment selected from FG loop and G-strand; or
(iii) from one to four peptide sequences arranged in any order each being of from three amino acids up to the full length of a mammalian PD1 ectodomain fragment selected from D-strand, FG loop and G strand, wherein two or more amino acids of the peptide sequence combine together to form a lactam bond between any of the two fragments or within the fragment;
D is up to two peptide sequences arranged in any order each being of from three amino acids up to the full length of a mammalian PD1 ectodomain fragment selected from BC loop, FG loop, C C' loop to C' strand or is absent;
E is up to four peptide sequences arranged in any order each being of from three amino acids up to the full length of a mammalian PD1 ectodomain fragment selected from BC loop, D strand, FG loop, C C' loop to C' strand, G strand, FG loop to G strand or is absent;
X is lysine;
X' is selected from lysine, ornithine, diaminopropionic acid, diaminobutyric acid or olefinic amino acid of formula



which is optionally linked with an additional lysine; or X' is absent;

m is an integer selected from 1 to 6, both inclusive;

$R_1$ is selected from group consisting of $C_2$-$C_{20}$ acyl, polyethylene glycol (PEG) 2-20 kilodalton moiety; or absent;

$R_2$ and $R_3$ are independently selected from group consisting of $C_2$-$C_{20}$ acyl, PEG 2-20 kilodalton , absent or Ra-L'; Ra is selected from biotin or maleimido propionic acid; L' is selected from linkers $CO(CH_2)_n$, NH , $CO(CH_2\ CH_2\text{-}O\text{-})_nNH$ or $COCH_2(\text{-}OCH_2\text{-}CH_2)_nNH$-; and n is an integer selected from 2 to 10, both inclusive;

$R_4$ and $R_5$ are independently $NH_2$, or one or both of $R_4$ or $R_5$ are absent with the proviso to the compound of Formula (LXIII), that in a compound of Formula (I) as above defined:

a) up to 5 but not more than 25% of the amino acids may be substituted with other natural or unnatural amino acids;

b) not more than 30% of the amino acids may be omitted;

c) in each said peptide sequence up to 2 amino acids may be added individually at any position;

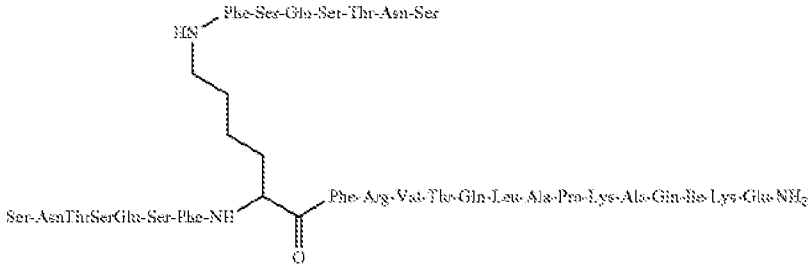
d) up to 5 but not more than 25% of the peptide bonds may instead be replaced by reduced amide bond ($\text{-}CH_2NH$-);

e) up to 100% of the amino acids may be D-amino acids;

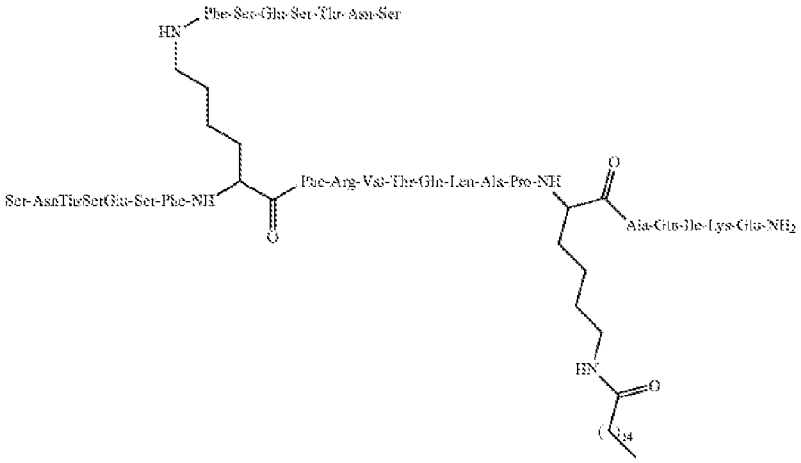
f) up to 100% of the amino acids may be in reverse order.

**[00813]** In an embodiment, the PD-1 inhibitor is AUNP-12.

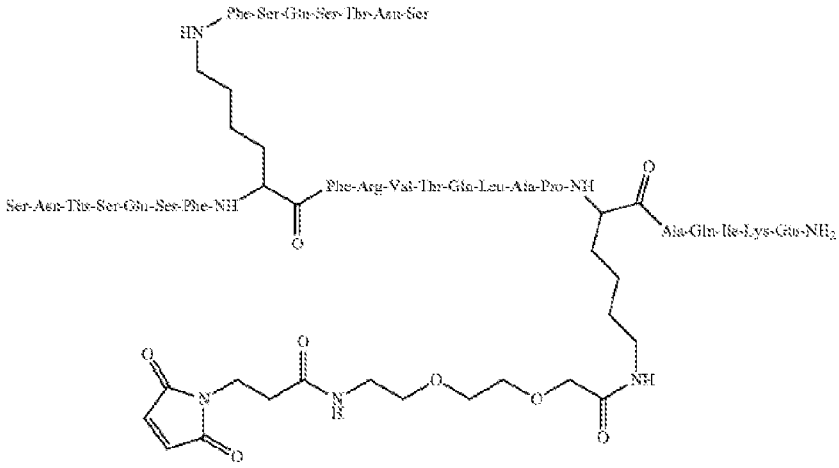
**[00814]** In an embodiment, the PD-1 inhibitor is a compound selected from the group consisting of:



(SEQ ID NO:26),



(SEQ ID NO:27),



(SEQ ID NO:28),

and

SNTSESFK(SNTSESF)FRVTQLAPKAQIK($CH_3(CH_2)_{14}CO$)E-$NH_2$ (SEQ ID NO:29),

wherein the branched groups are given by SEQ ID NO:25,

and pharmaceutically acceptable salts, solvates, hydrates, cocrystals, or prodrugs thereof.

PD-L1 and PD-L2 Inhibitors

**[00815]** The PD-L1 or PD-L2 inhibitor may be any PD-L1 or PD-L2 inhibitor or blocker known in the art. In particular, it is one of the PD-L1 or PD-L2 inhibitors or blockers described in more detail in the following paragraphs. The terms "inhibitor" and "blocker" are used interchangeably herein in reference to PD-L1 and PD-L2 inhibitors. For avoidance of doubt, references herein to a PD-L1 or PD-L2 inhibitor that is an antibody may refer to a compound or antigen-binding fragments, variants, conjugates, or biosimilars thereof. For avoidance of doubt, references herein to a PD-L1 or PD-L2 inhibitor may refer to a compound or a pharmaceutically acceptable salt, ester, solvate, hydrate, cocrystal, or prodrug thereof.

**[00816]** In some embodiments, the compositions and methods include a PD-L1 or PD-L2 inhibitor. In some embodiments, the PD-L1 and PD-L2 inhibitor is a small molecule. In some embodiments, the PD-L1 or PD-L2 inhibitor is an anti-PD-L1 or anti-PD-L2 antibody, a fragment thereof, including Fab fragments or single-chain variable fragments (scFv). In an aspect of the invention, the anti-PD-1 antibody or fragment thereof in any of the aforementioned embodiments is replaced by, or combined with, an anti-PD-L1 or anti-PD-L2 antibody or fragment thereof. In an embodiment, the antibody competes for binding with, and/or binds to an epitope on PD-L1 and/or PD-L2. In some embodiments, the PD-L1 or PD-L2 inhibitor is a monoclonal antibody. In some embodiments the PD-L1 or PD-L2 inhibitor is a polyclonal antibody. In some embodiments, a PD-L1 inhibitor is included in a composition or a method and is further combined with a BTK inhibitor, a PI3K inhibitor, and/or a JAK-2 inhibitor. In some embodiments, an anti-PD-L1 monoclonal antibody is included in a composition or a method and is further combined with a BTK inhibitor, a PI3K inhibitor, and/or a JAK-2 inhibitor. In some embodiments, a PD-L2 inhibitor is included in a composition or a method and is further combined with a BTK inhibitor, a PI3K inhibitor, and/or a JAK-2 inhibitor. In some embodiments, an anti-PD-L2 monoclonal antibody is included in a composition or a method and is further combined with a BTK inhibitor, a PI3K inhibitor, and/or a JAK-2 inhibitor. In some embodiments, a PD-L1 inhibitor is included in a composition or a method and is further combined with a BTK inhibitor. In some embodiments, an anti-PD-L1 monoclonal antibody is included in a composition or a method and is further combined with a BTK

inhibitor. In some embodiments, a PD-L2 inhibitor is included in a composition or a method and is further combined with a BTK inhibitor. In some embodiments, an anti-PD-L2 monoclonal antibody is included in a composition or a method and is further combined with a BTK inhibitor. In some embodiments, a PD-L1 inhibitor is included in a composition or a method and is further combined with a PI3K inhibitor. In some embodiments, an anti-PD-L1 monoclonal antibody is included in a composition or a method and is further combined with a PI3K inhibitor. In some embodiments, a PD-L2 inhibitor is included in a composition or a method and is further combined with a PI3K inhibitor. In some embodiments, an anti-PD-L2 monoclonal antibody is included in a composition or a method and is further combined with a PI3K inhibitor. In some embodiments, a PD-L1 inhibitor is included in a composition or a method and is further combined with a JAK-2 inhibitor. In some embodiments, an anti-PD-L1 monoclonal antibody is included in a composition or a method and is further combined with a JAK-2 inhibitor. In some embodiments, a PD-L2 inhibitor is included in a composition or a method and is further combined with a JAK-2 inhibitor. In some embodiments, an anti-PD-L2 monoclonal antibody is included in a composition or a method and is further combined with a JAK-2 inhibitor. In some embodiments, both a PD-1 inhibitor and a PD-L1 inhibitor are included in a composition or method and are further combined with a BTK inhibitor, a PI3K inhibitor, and/or a JAK-2 inhibitor. In some embodiments, both an anti-PD-1 monoclonal antibody and an anti-PD-L1 monoclonal antibody are included in a composition or method and are further combined with a BTK inhibitor, a PI3K inhibitor, and/or a JAK-2 inhibitor. In some embodiments, both a PD-1 inhibitor and a PD-L2 inhibitor are included in a composition or method and are further combined with a BTK inhibitor, a PI3K inhibitor, and/or a JAK-2 inhibitor. In some embodiments, both an anti-PD-1 monoclonal antibody and an anti-PD-L2 monoclonal antibody are included in a composition or method and are further combined with a BTK inhibitor, a PI3K inhibitor, and/or a JAK-2 inhibitor.

**[00817]** In preferred embodiments, the compositions described herein provide a combination of a PD-L1 and/or PD-L2 inhibitor with a BTK inhibitor, or methods of using a combination of a PD-L1 and/or PD-L2 inhibitor with a BTK inhibitor. In some embodiments, the PD-L1 inhibitors provided herein are selective for PD-L1, in that the

compounds bind or interact with PD-L1 at substantially lower concentrations than they bind or interact with other receptors, including the PD-L2 receptor. In certain embodiments, the compounds bind to the PD-L2 receptor at a binding constant that is at least about a 2-fold higher concentration, about a 3-fold higher concentration, about a 5-fold higher concentration, about a 10-fold higher concentration, about a 20-fold higher concentration, about a 30-fold higher concentration, about a 50-fold higher concentration, about a 100-fold higher concentration, about a 200-fold higher concentration, about a 300-fold higher concentration, or about a 500-fold higher concentration than to the PD-L1 receptor.

**[00818]** Without being bound by any theory, it is believed that tumor cells express PD-L1, and that T cells express PD-1. However, PD-L1 expression by tumor cells is not required for efficacy of PD-1 or PD-L1 inhibitors or blockers. In an embodiment, the tumor cells express PD-L1. In another embodiment, the tumor cells do not express PD-L1. In some embodiments, the methods and compositions described herein include a combination of a PD-1 and a PD-L1 antibody, such as those described herein, in combination with a BTK inhibitor. The administration of a combination of a PD-1 and a PD-L1 antibody and a BTK inhibitor may be simultaneous or sequential.

**[00819]** In some embodiments, the compositions and methods described include a PD-L1 and/or PD-L2 inhibitor that binds human PD-L1 and/or PD-L2 with a $K_D$ of about 100 pM or lower, binds human PD-L1 and/or PD-L2 with a $K_D$ of about 90 pM or lower, binds human PD-L1 and/or PD-L2 with a $K_D$ of about 80 pM or lower, binds human PD-L1 and/or PD-L2 with a $K_D$ of about 70 pM or lower, binds human PD-L1 and/or PD-L2 with a $K_D$ of about 60 pM or lower, a $K_D$ of about 50 pM or lower, binds human PD-L1 and/or PD-L2 with a $K_D$ of about 40 pM or lower, or binds human PD-L1 and/or PD-L2 with a KD of about 30 pM or lower,

**[00820]** In some embodiments, the compositions and methods described include a PD-L1 and/or PD-L2 inhibitor that binds to human PD-L1 and/or PD-L2 with a $k_{assoc}$ of about $7.5 \times 10^5$ l/M·s or faster, binds to human PD-L1 and/or PD-L2 with a $k_{assoc}$ of about $8 \times 10^5$ l/M·s or faster, binds to human PD-L1and/ or PD-L2 with a $k_{assoc}$ of about $8.5 \times 10^5$ l/M·s or faster, binds to human PD-L1 and/or PD-L2 with a $k_{assoc}$ of about $9 \times 10^5$ l/M·s

or faster, binds to human PD-L1 and/or PD-L2 with a $k_{assoc}$ of about $9.5 \times 10^5$ l/M·s and/or faster, or binds to human PD-L1 and/or PD-L2 with a $k_{assoc}$ of about $1 \times 10^6$ l/M·s or faster.

**[00821]** In some embodiments, the compositions and methods described include a PD-L1 and/or PD-L2 inhibitor that binds to human PD-L1 or PD-L2 with a $k_{dissoc}$ of about $2 \times 10^{-5}$ l/s or slower, binds to human PD-1 with a $k_{dissoc}$ of about $2.1 \times 10^{-5}$ l/s or slower , binds to human PD-1 with a $k_{dissoc}$ of about $2.2 \times 10^{-5}$ l/s or slower, binds to human PD-1 with a $k_{dissoc}$ of about $2.3 \times 10^{-5}$ l/s or slower, binds to human PD-1 with a $k_{dissoc}$ of about $2.4 \times 10^{-5}$ l/s or slower, binds to human PD-1 with a $k_{dissoc}$ of about $2.5 \times 10^{-5}$ l/s or slower, binds to human PD-1 with a $k_{dissoc}$ of about $2.6 \times 10^{-5}$ l/s or slower, binds to human PD-L1 or PD-L2 with a $k_{dissoc}$ of about $2.7 \times 10^{-5}$ l/s or slower, or binds to human PD-L1 or PD-L2 with a $k_{dissoc}$ of about $3 \times 10^{-5}$ l/s or slower.

**[00822]** In some embodiments, the compositions and methods described include a PD-L1 and/or PD-L2 inhibitor that blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an $IC_{50}$ of about 10 nM or lower; blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an $IC_{50}$ of about 9 nM or lower; blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an $IC_{50}$ of about 8 nM or lower; blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an $IC_{50}$ of about 7 nM or lower; blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an $IC_{50}$ of about 6 nM or lower; blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an $IC_{50}$ of about 5 nM or lower; blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an $IC_{50}$ of about 4 nM or lower; blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an $IC_{50}$ of about 3 nM or lower; blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an $IC_{50}$ of about 2 nM or lower; or blocks human PD-1, or blocks binding of human PD-L1 or human PD-L2 to human PD-1 with an $IC_{50}$ of about 1 nM or lower.

**[00823]** In an embodiment, the anti-PD-L1 antibody is durvalumab, which is also known as MEDI4736, produced by Medimmune, LLC, Gaithersburg, Maryland, a subsidiary of AstraZeneca plc., or antigen-binding fragments, conjugates, or variants thereof. In an

embodiment, the anti-PD-L1 antibody is an antibody disclosed in U.S. Patent No. 8,779,108 or U.S. Patent Application Publication No. 2013/0034559, the disclosures of which are specifically incorporated by reference herein. The clinical efficacy of durvalumab (MEDI4736, SEQ ID NO:30 and SEQ ID NO:31) has been described in: Page et al., *Ann. Rev. Med.*, **2014,** *65,* 185-202; Brahmer, et al., *J. Clin. Oncol.* **2014,** *32,* 5s (supplement, abstract 8021); and McDermott, et al., *Cancer Treatment Rev.*, **2014,** *40,* 1056-64. The durvalumab (MEDI4736) monoclonal antibody includes a $V_H$ region given by SEQ ID NO:32 (corresponding to SEQ ID NO:72 in U.S. Patent No. 8,779,108) and a $V_L$ region given by SEQ ID NO:33 (corresponding to SEQ ID NO:77 in U.S. Patent No. 8,779,108). The durvalumab monoclonal antibody includes disulfide linkages at 22-96, 22"-96", 23'-89', 23'"-89'", 135'-195', 135'"-195'", 148-204, 148"-204", 215'-224, 215'"-224", 230-230", 233-233", 265-325, 265"-325", 371-429, and 371"-429'; and N-glycosylation sites at Asn-301 and Asn-301".

**[00824]** In an embodiment, the anti-PD-L1 antibody is an immunoglobulin G1, anti-(human CD antigen CD274) (human monoclonal heavy chain), disulfide with human monoclonal κ-chain, dimer. In an embodiment, the anti-PD-L1 antibody comprises the heavy and light chains of durvalumab (MEDI4736). In an embodiment, an anti-PD-L1 antibody comprises heavy and light chains having the sequences shown in SEQ ID NO:30 and SEQ ID NO:31, respectively, or antigen binding fragments, variants, or conjugates thereof. In an embodiment, an anti-PD-L1 antibody comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:30 and SEQ ID NO:31, respectively. In an embodiment, an anti-PD-L1 antibody comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:30 and SEQ ID NO:31, respectively. In an embodiment, an anti-PD-L1 antibody comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:30 and SEQ ID NO:31, respectively. In an embodiment, an anti-PD-L1 antibody comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:30 and SEQ ID NO:31, respectively. In an embodiment, an anti-PD-L1 antibody comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:30 and SEQ ID NO:31, respectively.

**[00825]** In an embodiment, the anti-PD-L1 antibody comprises $V_H$ and $V_L$ regions having the sequences shown in SEQ ID NO:32 (corresponding to SEQ ID NO:72 in U.S. Patent No. 8,779,108) and SEQ ID NO:33 (corresponding to SEQ ID NO:77 in U.S. Patent No. 8,779,108), respectively, as described in U.S. Patent No. 8,779,108 or U.S. Patent Application Publication No. 2013/0034559, the disclosures of which are specifically incorporated by reference herein, including antigen binding fragments, conjugates, and variants thereof. In an embodiment, an anti-PD-L1 antibody comprises $V_H$ and $V_L$ regions that are each at least 99% identical to the sequences shown in SEQ ID NO:32 and SEQ ID NO:33, respectively. In an embodiment, an anti-PD-L1 antibody comprises $V_H$ and $V_L$ regions that are each at least 98% identical to the sequences shown in SEQ ID NO:32 and SEQ ID NO:33, respectively. In an embodiment, an anti-PD-L1 antibody comprises $V_H$ and $V_L$ regions that are each at least 97% identical to the sequences shown in SEQ ID NO:32 and SEQ ID NO:33, respectively. In an embodiment, an anti-PD-L1 antibody comprises $V_H$ and $V_L$ regions that are each at least 96% identical to the sequences shown in SEQ ID NO:32 and SEQ ID NO:33, respectively. In an embodiment, an anti-PD-L1 antibody comprises $V_H$ and $V_L$ regions that are each at least 95% identical to the sequences shown in SEQ ID NO:32 and SEQ ID NO:33, respectively. In an embodiment, an anti-PD-L1 antibody comprises $V_H$ and $V_L$ regions that are each at least 90% identical to the sequences shown in SEQ ID NO:32 and SEQ ID NO:33, respectively.

**[00826]** In another embodiment, the anti-PD-L1 antibody comprises an amino acid sequence comprising a $V_H$ CDR1 having the amino acid sequence of SEQ ID NO:34 (corresponding to SEQ ID NO:23 in U.S. Patent No. 8,779,108), a $V_H$ CDR2 having the amino acid sequence of SEQ ID NO:35 (corresponding to SEQ ID NO:24 in U.S. Patent No. 8,779,108), a $V_H$ CDR3 having the amino acid sequence of SEQ ID NO:36 (corresponding to SEQ ID NO:25 in U.S. Patent No. 8,779,108), a $V_L$ CDR1 having the amino acid sequence of SEQ ID NO:37 (corresponding to SEQ ID NO:28 in U.S. Patent No. 8,779,108), a $V_L$ CDR2 having the amino acid sequence of SEQ ID NO:38 (corresponding to SEQ ID NO:29 in U.S. Patent No. 8,779,108), and a $V_L$ CDR3 having the amino acid sequence of SEQ ID NO:39 (corresponding to SEQ ID NO:30 in U.S. Patent No. 8,779,108), as described in U.S. Patent No. 8,779,108 or U.S. Patent

Application Publication No. 2013/0034559, the disclosures of which are specifically incorporated by reference herein.

**[00827]** In another embodiment, the anti-PD-L1 antibody comprises an amino acid sequence comprising a $V_H$ CDR1 having the amino acid sequence of SEQ ID NO:40 (corresponding to SEQ ID NO:3 in U.S. Patent No. 8,779,108), a $V_H$ CDR2 having the amino acid sequence of SEQ ID NO:41 (corresponding to SEQ ID NO:4 in U.S. Patent No. 8,779,108), a $V_H$ CDR3 having the amino acid sequence of SEQ ID NO:42 (corresponding to SEQ ID NO:5 in U.S. Patent No. 8,779,108), a $V_L$ CDR1 having the amino acid sequence of SEQ ID NO:43 (corresponding to SEQ ID NO:8 in U.S. Patent No. 8,779,108), a $V_L$ CDR2 having the amino acid sequence of SEQ ID NO:44 (corresponding to SEQ ID NO:9 in U.S. Patent No. 8,779,108), and a $V_L$ CDR3 having the amino acid sequence of SEQ ID NO:45 (corresponding to SEQ ID NO:10 in U.S. Patent No. 8,779,108), as described in U.S. Patent No. 8,779,108 or U.S. Patent Application Publication No. 2013/0034559 A1, the disclosures of which are specifically incorporated by reference herein.

**[00828]** In another embodiment, the anti-PD-L1 antibody comprises an amino acid sequence comprising a $V_H$ CDR1 having the amino acid sequence of SEQ ID NO:46 (corresponding to SEQ ID NO:13 in U.S. Patent No. 8,779,108), a $V_H$ CDR2 having the amino acid sequence of SEQ ID NO:47 (corresponding to SEQ ID NO:14 in U.S. Patent No. 8,779,108), a $V_H$ CDR3 having the amino acid sequence of SEQ ID NO:48 (corresponding to SEQ ID NO:15 in U.S. Patent No. 8,779,108), a $V_L$ CDR1 having the amino acid sequence of SEQ ID NO:49 (corresponding to SEQ ID NO:18 in U.S. Patent No. 8,779,108), a $V_L$ CDR2 having the amino acid sequence of SEQ ID NO:50 (corresponding to SEQ ID NO:19 in U.S. Patent No. 8,779,108), and a $V_L$ CDR3 having the amino acid sequence of SEQ ID NO:51 (corresponding to SEQ ID NO:20 in U.S. Patent No. 8,779,108), as described in U.S. Patent No. 8,779,108 or U.S. Patent Application Publication No. 2013/0034559, the disclosures of which are specifically incorporated by reference herein.

**[00829]** In another embodiment, the anti-PD-L1 antibody comprises an amino acid sequence comprising a $V_H$ CDR1 having the amino acid sequence of SEQ ID NO:52

(corresponding to SEQ ID NO:63 in U.S. Patent No. 8,779,108), a $V_H$ CDR2 having the amino acid sequence of SEQ ID NO:53 (corresponding to SEQ ID NO:64 in U.S. Patent No. 8,779,108), a $V_H$ CDR3 having the amino acid sequence of SEQ ID NO:54 (corresponding to SEQ ID NO:65 in U.S. Patent No. 8,779,108), a $V_L$ CDR1 having the amino acid sequence of SEQ ID NO:55 (corresponding to SEQ ID NO:68 in U.S. Patent No. 8,779,108), a $V_L$ CDR2 having the amino acid sequence of SEQ ID NO:56 (corresponding to SEQ ID NO:69 in U.S. Patent No. 8,779,108), and a $V_L$ CDR3 having the amino acid sequence of SEQ ID NO:57 (corresponding to SEQ ID NO:70 in U.S. Patent No. 8,779,108), as described in U.S. Patent No. 8,779,108 or U.S. Patent Application Publication No. 2013/0034559, the disclosures of which are specifically incorporated by reference herein.

**[00830]** In another embodiment, the anti-PD-L1 antibody comprises an amino acid sequence comprising a $V_H$ CDR1 having the amino acid sequence of SEQ ID NO:58 (corresponding to SEQ ID NO:73 in U.S. Patent No. 8,779,108), a $V_H$ CDR2 having the amino acid sequence of SEQ ID NO:59 (corresponding to SEQ ID NO:74 in U.S. Patent No. 8,779,108), a $V_H$ CDR3 having the amino acid sequence of SEQ ID NO:60 (corresponding to SEQ ID NO:75 in U.S. Patent No. 8,779,108), a $V_L$ CDR1 having the amino acid sequence of SEQ ID NO:61 (corresponding to SEQ ID NO:78 in U.S. Patent No. 8,779,108), a $V_L$ CDR2 having the amino acid sequence of SEQ ID NO:62 (corresponding to SEQ ID NO:79 in U.S. Patent No. 8,779,108), and a $V_L$ CDR3 having the amino acid sequence of SEQ ID NO:63 (corresponding to SEQ ID NO:80 in U.S. Patent No. 8,779,108), as described in U.S. Patent No. 8,779,108 or U.S. Patent Application Publication No. 2013/0034559, the disclosures of which are specifically incorporated by reference herein.

**[00831]** In an embodiment, the anti-PD-L1 antibody is atezolizumab, also known as MPDL3280A or RG7446, produced by Genentech, Inc., a subsidiary of Roche, or antigen-binding fragments, conjugates, or variants thereof. In an embodiment, the anti-PD-L1 antibody is an antibody disclosed in U.S. Patent No. 8,217,149, the disclosure of which is specifically incorporated by reference herein. In an embodiment, the anti-PD-L1 antibody is an antibody disclosed in U.S. Patent Application Publication Nos. 2010/0203056 A1, 2013/0045200 A1, 2013/0045201 A1, 2013/0045202 A1, or

2014/0065135 A1, the disclosures of which are specifically incorporated by reference herein. The atezolizumab monoclonal antibody includes a heavy chain given by SEQ ID NO:64 and a light chain given by SEQ ID NO:65. Atezolizumab has intra-heavy chain disulfide linkages (C23-C104) at 22-96, 145-201, 262-322, 368-426, 22"-96", 145"-201", 262"-322", and 368"-426"; intra-light chain disulfide linkages (C23-C104) at 23'-88', 134'-194', 23'"-88'", and 134'"-194'"; intra-heavy-light chain disulfide linkages (h 5-CL 126) at 221-214' and 221"-214'"; intra-heavy-heavy chain disulfide linkages (h 11, h 14) at 227-227" and 230-230"; and N-glycosylation sites (H $CH_2$ N84.4>A) at 298 and 298'.

**[00832]** In an embodiment, the anti-PD-L1 antibody is an immunoglobulin G1 kappa, anti-(human PD-L1) humanized monoclonal antibody. In an embodiment, the anti-PD-L1 antibody comprises the heavy and light chains of atezolizumab (MPDL3280A). In an embodiment, an anti-PD-L1 antibody comprises heavy and light chains having the sequences shown in SEQ ID NO:64 and SEQ ID NO:65, respectively, or antigen binding fragments, variants, or conjugates thereof. In an embodiment, an anti-PD-L1 antibody comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:64 and SEQ ID NO:65, respectively. In an embodiment, an anti-PD-L1 antibody comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:64 and SEQ ID NO:65, respectively. In an embodiment, an anti-PD-L1 antibody comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:64 and SEQ ID NO:65, respectively. In an embodiment, an anti-PD-L1 antibody comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:64 and SEQ ID NO:65, respectively. In an embodiment, an anti-PD-L1 antibody comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:64 and SEQ ID NO:65, respectively.

**[00833]** In an embodiment, the anti-PD-L1 antibody comprises the heavy and light chain CDRs or VRs of atezolizumab (MPDL3280A). In an embodiment, the anti-PD-L1 antibody $V_H$ region comprises the sequence shown in SEQ ID NO:66 (corresponding to SEQ ID NO:20 in U.S. Patent No. 8,217,149), and the anti-PD-L1 antibody $V_L$ region comprises the sequence shown in SEQ ID NO:67 (corresponding to SEQ ID NO:21 in U.S. Patent No. 8,217,149). In an embodiment, an anti-PD-L1 antibody comprises $V_H$

and $V_L$ regions that are each at least 99% identical to the sequences shown in SEQ ID NO:66 and SEQ ID NO:67, respectively. In an embodiment, an anti-PD-L1 antibody comprises $V_H$ and $V_L$ regions that are each at least 98% identical to the sequences shown in SEQ ID NO:66 and SEQ ID NO:67, respectively. In an embodiment, an anti-PD-L1 antibody comprises $V_H$ and $V_L$ regions that are each at least 97% identical to the sequences shown in SEQ ID NO:66 and SEQ ID NO:67, respectively. In an embodiment, an anti-PD-L1 antibody comprises $V_H$ and $V_L$ regions that are each at least 96% identical to the sequences shown in SEQ ID NO:66 and SEQ ID NO:67, respectively. In an embodiment, an anti-PD-L1 antibody comprises $V_H$ and $V_L$ regions that are each at least 95% identical to the sequences shown in SEQ ID NO:66 and SEQ ID NO:67, respectively.

**[00834]** In an embodiment, the anti-PD-L1 antibody comprises a heavy chain variable region ($V_H$) polypeptide that comprises an HVR-H1, HVR-H2 and HVR-H3 sequence, wherein the HVR-H1 sequence is given by SEQ ID NO:68 ($GFTFSX_1SWIH$) (corresponding to SEQ ID NO:1 in U.S. Patent No. 8,217,149), the HVR-H2 sequence is SEQ ID NO:69 ($AWIX_2PYGGSX_3YYADSVKG$) (corresponding to SEQ ID NO:2 in U.S. Patent No. 8,217,149), and the HVR-H3 sequence is SEQ ID NO:70 (RHWPGGFDY) (corresponding to SEQ ID NO:3 in U.S. Patent No. 8,217,149), further wherein $X_1$ is D or G, $X_2$ is S or L, and $X_3$ is T or S, and the anti-PD-L1 antibody also comprises a light chain variable region ($V_L$) polypeptide that comprises an HVR-L1, HVR-L2 and HVR-L3 sequence wherein the HVR-L1 sequence is given by SEQ ID NO:71 ($RASQX_4X_5X_6TX_7X_8A$) (corresponding to SEQ ID NO:8 in U.S. Patent No. 8,217,149), the HVR-L2 sequence is given by SEQ ID NO:72 ($SASX_9LX_{10}S$) (corresponding to SEQ ID NO:9 in U.S. Patent No. 8,217,149), and the HVR-L3 sequence is SEQ ID NO:73 ($QQX_{11}X_{12}X_{13}X_{14}PX_{15}T$) (corresponding to SEQ ID NO:10 in U.S. Patent No. 8,217,149), further wherein further wherein: $X_4$ is D or V; $X_5$ is V or I; $X_6$ is S or N; $X_7$ is A or F; $X_8$ isV or L; $X_9$ is F or T; $X_{10}$ is Y or A; $X_{11}$ is Y, G, F, or S; $X_{12}$ is L, Y, F or W; $X_{13}$ is Y, N, A, T, G, F or I; $X_{14}$ is H, V, P, T or I; and $X_{15}$ is A, W, R, P or T.

**[00835]** In an embodiment, the anti-PD-L1 antibody is avelumab, also known as MSB0010718C, produced by Merck KGaA/EMD Serono, or antigen-binding fragments,

conjugates, or variants thereof. In an embodiment, the anti-PD-L1 antibody is an antibody disclosed in U.S. Patent Application Publication No. US 2014/0341917 A1, the disclosure of which is specifically incorporated by reference herein. The avelumab monoclonal antibody includes a heavy chain given by SEQ ID NO:74 and a light chain given by SEQ ID NO:75. Avelumab has intra-heavy chain disulfide linkages (C23-C104) at 22-96, 147-203, 264-324, 370-428, 22"-96", 147"-203", 264"-324", and 370"-428"; intra-light chain disulfide linkages (C23-C104) at 22'-90', 138'-197', 22'"-90'", and 138'"-197'"; intra-heavy-light chain disulfide linkages (h 5-CL 126) at 223-215' and 223"-215'"; intra-heavy-heavy chain disulfide linkages (h 11, h 14) at 229-229" and 232-232"; N-glycosylation sites (H $CH_2$ N84.4) at 300, 300"; fucosylated complex bi-antennary CHO-type glycans; and H CHS K2 C-terminal lysine clipping at 450 and 450'.

**[00836]** In an embodiment, the anti-PD-L1 antibody is an immunoglobulin G1 lambda-1, anti-(human PD-L1) human monoclonal antibody. In an embodiment, the anti-PD-L1 antibody comprises the heavy and light chains of avelumab (MSB0010718C). In an embodiment, an anti-PD-L1 antibody comprises heavy and light chains having the sequences shown in SEQ ID NO:74 and SEQ ID NO:75, respectively, or antigen binding fragments, variants, or conjugates thereof. In an embodiment, an anti-PD-L1 antibody comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:74 and SEQ ID NO:75, respectively. In an embodiment, an anti-PD-L1 antibody comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:74 and SEQ ID NO:75, respectively. In an embodiment, an anti-PD-L1 antibody comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:74 and SEQ ID NO:75, respectively. In an embodiment, an anti-PD-L1 antibody comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:74 and SEQ ID NO:75, respectively. In an embodiment, an anti-PD-L1 antibody comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:74 and SEQ ID NO:75, respectively.

**[00837]** In an embodiment, the anti-PD-L1 antibody $V_H$ region comprises the sequence given in SEQ ID NO:76 (corresponding to SEQ ID NO:24 in U.S. Patent Application Publication No. US 2014/0341917 A1), and the anti-PD-L1 antibody $V_L$ region

comprises the sequence given in SEQ ID NO:77 (corresponding to SEQ ID NO:25 in U.S. Patent Application Publication No. US 2014/0341917 A1). In an embodiment, an anti-PD-L1 antibody comprises $V_H$ and $V_L$ regions that are each at least 99% identical to the sequences shown in SEQ ID NO:76 and SEQ ID NO:77, respectively. In an embodiment, an anti-PD-L1 antibody comprises $V_H$ and $V_L$ regions that are each at least 98% identical to the sequences shown in SEQ ID NO:76 and SEQ ID NO:77, respectively. In an embodiment, an anti-PD-L1 antibody comprises $V_H$ and $V_L$ regions that are each at least 97% identical to the sequences shown in SEQ ID NO:76 and SEQ ID NO:77, respectively. In an embodiment, an anti-PD-L1 antibody comprises $V_H$ and $V_L$ regions that are each at least 96% identical to the sequences shown in SEQ ID NO:76 and SEQ ID NO:77, respectively. In an embodiment, an anti-PD-L1 antibody comprises $V_H$ and $V_L$ regions that are each at least 95% identical to the sequences shown in SEQ ID NO:76 and SEQ ID NO:77, respectively.

**[00838]** In an embodiment, the anti-PD-L1 antibody comprises a heavy chain variable region ($V_H$) polypeptide that comprises an HVR-H1, HVR-H2 and HVR-H3 sequence, wherein the HVR-H1 sequence is given by SEQ ID NO:78 (corresponding to SEQ ID NO:15 in U.S. Patent Application Publication No. US 2014/0341917 A1), the HVR-H2 sequence is given by SEQ ID NO:79 (corresponding to SEQ ID NO:16 in U.S. Patent Application Publication No. US 2014/0341917 A1), and the HVR-H3 sequence is given by SEQ ID NO:80 (corresponding to SEQ ID NO:17 in U.S. Patent Application Publication No. US 2014/0341917 A1), and the anti-PD-L1 antibody also comprises a light chain variable region ($V_L$) polypeptide that comprises an HVR-L1, HVR-L2 and HVR-L3 sequence wherein the HVR-L1 sequence is given by SEQ ID NO:81 (corresponding to SEQ ID NO:18 in U.S. Patent Application Publication No. US 2014/0341917 A1), the HVR-L2 sequence is given by SEQ ID NO:82 (corresponding to SEQ ID NO:19 in U.S. Patent Application Publication No. US 2014/0341917 A1), and the HVR-L3 sequence is SEQ ID NO:83 (corresponding to SEQ ID NO:20 in U.S. Patent Application Publication No. US 2014/0341917 A1).

**[00839]** In an embodiment, the anti-PD-L1 antibody is MDX-1105, also known as BMS-935559, which is disclosed in U.S. Patent No. US 7,943,743 B2, the disclosures of which are specifically incorporated by reference herein. In an embodiment, the anti-PD-L1

antibody is selected from the anti-PD-L1 antibodies disclosed in U.S. Patent No. US 7,943,743 B2, which are specifically incorporated by reference herein.

**[00840]** In an embodiment, the anti-PD-L1 antibody is a commercially-available monoclonal antibody, such as INVIVOMAB anti-m-PD-L1 clone 10F.9G2 (Catalog # BE0101, Bio X Cell, Inc., West Lebanon, NH, USA). In an embodiment, the anti-PD-L1 antibody is a commercially-available monoclonal antibody, such as AFFYMETRIX EBIOSCIENCE (MIH1). A number of commercially-available anti-PD-L1 antibodies are known to one of ordinary skill in the art.

**[00841]** In an embodiment, the anti-PD-L2 antibody is a commercially-available monoclonal antibody, such as BIOLEGEND 24F.10C12 Mouse IgG2a, κ isotype (catalog # 329602 Biolegend, Inc., San Diego, CA), SIGMA anti-PD-L2 antibody (catalog # SAB3500395, Sigma-Aldrich Co., St. Louis, MO), or other commercially-available anti-PD-L2 antibodies known to one of ordinary skill in the art.

**[00842]** Monoclonal antibodies that inhibit PD-L1 and/or PD-L2 can be prepared by procedures known to those of ordinary knowledge and skill in the art, e.g. by injecting test subjects with PD-L1 or PD-L2 antigen and then isolating hybridomas expressing antibodies having the desired sequence or functional characteristics. DNA encoding the monoclonal antibodies is readily isolated and sequenced using conventional procedures (*e.g.*, by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the monoclonal antibodies). The hybridoma cells serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as *E. coli* cells, simian COS cells, Chinese hamster ovary (CHO) cells, myeloma cells, or other suitable cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. The details of recombinant production of specific antibodies may be found in the references cited in the foregoing, the disclosures of which are incorporated by reference herein. Monoclonal antibodies that inhibit PD-1 can be prepared by standard molecular biology methods using the sequences provided herein by reverse translation and insertion into appropriate DNA or RNA vectors.

**[00843]** The anti-PD-L1 antibody sequences referenced in the foregoing embodiments

are summarized in Table 2.

TABLE 2. Anti-PD-L1 antibody amino acid sequences.

| Identifier | Sequence (One-Letter Amino Acid Symbols) | |
|---|---|---|
| SEQ ID NO:30 durvalumab (MEDI4736) heavy chain | EVQLVESGGG LVQPGGSLRL SCAASGFTFS RYWMSWVRQA PGKGLEWVAN IKQDGSEKYY<br>VDSVKGRFTI SRDNAKNSLY LQMNSLRAED TAVYYCAREG GWFGELAFDY WGQGTLVTVS<br>SASTKGPSVF PLAPSSKSTS GGTAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPAVLQS<br>SGLYSLSSVV TVPSSSLGTQ TYICNVNHKP SNTKVDKRVE PKSCDKTHTC PPCPAPEFEG<br>GPSVFLFPPK PKDTLMISRT PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN AKTKPREEQY<br>NSTYRVVSVL TVLHQDWLNG KEYKCKVSNK ALPASIEKTI SKAKGQPREP QVYTLPPSRE<br>EMTKNQVSLT CLVKGFYPSD IAVEWESNGQ PENNYKTTPP VLDSDGSFFL YSKLTVDKSR<br>WQQGNVFSCS VMHEALHNHY TQKSLSLSPG K | 60<br>120<br>180<br>240<br>300<br>360<br>420<br>451 |
| SEQ ID NO:31 durvalumab (MEDI4736) light chain | EVQLVESGGG LVQPGGSLRL SCAASGFTFS RYWMSWVRQA PGKGLEWVAN EIVLTQSPGT<br>LSLSPGERAT LSCRASQRVS SSYLAWYQQK PGQAPRLLIY DASSRATGIP DRFSGSGSGT<br>DFTLTISRLE PEDFAVYYCQ QYGSLPWTFG QGTKVEIKRT VAAPSVFIFP PSDEQLKSGT<br>ASVVCLLNNF YPREAKVQWK VDNALQSGNS QESVTEQDSK DSTYSLSSTL TLSKADYEKH<br>KVYACEVTHQ GLSSPVTKSF NRGEC | 60<br>120<br>180<br>240<br>265 |
| SEQ ID NO:32 durvalumab (MEDI4736) variable heavy chain | EVQLVESGGG LVQPGGSLRL SCAASGFTFS RYWMSWVRQA PGKGLEWVAN IKQDGSEKYY<br>VDSVKGRFTI SRDNAKNSLY LQMNSLRAED TAVYYCAREG GWFGELAFDY WGQGTLVTVS<br>S | 60<br>120<br>121 |
| SEQ ID NO:33 durvalumab (MEDI4736) variable light chain | EIVLTQSPGT LSLSPGERAT LSCRASQRVS SSYLAWYQQK PGQAPRLLIY DASSRATGIP<br>DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ QYGSLPWTFG QGTKVEIK | 60<br>108 |
| SEQ ID NO:34 durvalumab (MEDI4736) heavy chain CDR1 | RYWMS | 5 |
| SEQ ID NO:35 durvalumab (MEDI4736) heavy chain CDR2 | NIKQDGSEKY YVDSVKG | 17 |
| SEQ ID NO:36 durvalumab (MEDI4736) heavy chain CDR3 | EGGWFGELAF DY | 12 |
| SEQ ID NO:37 durvalumab (MEDI4736) light chain CDR1 | RASQRVSSSY LA | 12 |
| SEQ ID NO:38 durvalumab (MEDI4736) light chain CDR2 | DASSRAT | 7 |
| SEQ ID NO:39 durvalumab (MEDI4736) light chain CDR3 | QQYGSLPWT | 9 |
| SEQ ID NO:40 durvalumab alternative heavy chain CDR1 | TYSMN | 5 |
| SEQ ID NO:41 durvalumab alternative | SISSSGDYIY YADSVKG | 17 |

| Identifier | Sequence (One-Letter Amino Acid Symbols) | |
|---|---|---|
| heavy chain CDR2 | | |
| SEQ ID NO:42 durvalumab alternative heavy chain CDR3 | DLVTSMVAFD Y | 11 |
| SEQ ID NO:43 durvalumab alternative light chain CDR1 | SGDALPQKYV F | 11 |
| SEQ ID NO:44 durvalumab alternative light chain CDR2 | EDSKRPS | 7 |
| SEQ ID NO:45 durvalumab alternative light chain CDR3 | YSTDRSGNHR V | 11 |
| SEQ ID NO:46 durvalumab alternative heavy chain CDR1 | SYWMS | 5 |
| SEQ ID NO:47 durvalumab alternative heavy chain CDR2 | NIKQDGGEQY YVDSVKG | 17 |
| SEQ ID NO:48 durvalumab alternative heavy chain CDR3 | DWNYGYYDMD V | 11 |
| SEQ ID NO:49 durvalumab alternative light chain CDR1 | RASQSVSSNY LA | 12 |
| SEQ ID NO:50 durvalumab alternative light chain CDR2 | GTSSRAT | 7 |
| SEQ ID NO:51 durvalumab alternative light chain CDR3 | QQYGSSIFT | 9 |
| SEQ ID NO:52 durvalumab alternative heavy chain CDR1 | TYSMN | 5 |
| SEQ ID NO:53 durvalumab alternative heavy chain CDR2 | SISSSGDYIY YADSVKG | 17 |
| SEQ ID NO:54 durvalumab alternative heavy chain | DLVTSMVAFD Y | 11 |

| Identifier | Sequence (One-Letter Amino Acid Symbols) | |
|---|---|---|
| CDR3 | | |
| SEQ ID NO:55 durvalumab alternative light chain CDR1 | SGDALPQKYV F | 11 |
| SEQ ID NO:56 durvalumab alternative light chain CDR2 | EDSKRPS | 7 |
| SEQ ID NO:57 durvalumab alternative light chain CDR3 | YSTDRSGNHR V | 11 |
| SEQ ID NO:58 durvalumab alternative heavy chain CDR1 | RYWMS | 5 |
| SEQ ID NO:59 durvalumab alternative heavy chain CDR2 | NIKQDGSEKY YVDSVKG | 17 |
| SEQ ID NO:60 durvalumab alternative heavy chain CDR3 | EGGWFGELAF DY | 12 |
| SEQ ID NO:61 durvalumab alternative light chain CDR1 | RASQRVSSSY LA | 12 |
| SEQ ID NO:62 durvalumab alternative light chain CDR2 | DASSRAT | 7 |
| SEQ ID NO:63 durvalumab alternative light chain CDR3 | QQYGSLPWT | 9 |
| SEQ ID NO:64 atezolizumab (MPDL3280A) heavy chain | EVQLVESGGG LVQPGGSLRL SCAASGFTFS DSWIHWVRQA PGKGLEWVAW ISPYGGSTYY<br>ADSVKGRFTI SADTSKNTAY LQMNSLRAED TAVYYCARRH WPGGFDYWGQ GTLVTVSSAS<br>TKGPSVFPLA PSSKSTSGGT AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL<br>YSLSSVVTVP SSSLGTQTYI CNVNHKPSNT KVDKKVEPKS CDKTHTCPPC PAPELLGGPS<br>VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYAST<br>YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSREEMT<br>KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ<br>GNVFSCSVMH EALHNHYTQK SLSLSPGK | 60<br>120<br>180<br>240<br>300<br>360<br>420<br>448 |
| SEQ ID NO:65 atezolizumab (MPDL3280A) light chain | DIQMTQSPSS LSASVGDRVT ITCRASQDVS TAVAWYQQKP GKAPKLLIYS ASFLYSGVPS<br>RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YLYHPATFGQ GTKVEIKRTV AAPSVFIFPP<br>SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT<br>LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC | 60<br>120<br>180<br>214 |
| SEQ ID NO:66 atezolizumab (MPDL3280A) variable heavy chain | EVQLVESGGG LVQPGGSLRL SCAASGFTFS DSWIHWVRQA PGKGLEWVAW ISPYGGSTYY<br>ADSVKGRFTI SADTSKNTAY LQMNSLRAED TAVYYCARRH WPGGFDYWGQ GTLVTVSA | 60<br>118 |
| SEQ ID NO:67 atezolizumab (MPDL3280A) | DIQMTQSPSS LSASVGDRVT ITCRASQDVS TAVAWYQQKP GKAPKLLIYS ASFLYSGVPS<br>RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YLYHPATFGQ GTKVEIKR | 60<br>108 |

| Identifier | Sequence (One-Letter Amino Acid Symbols) | |
|---|---|---|
| variable light chain | | |
| SEQ ID NO:68 atezolizumab (MPDL3280A) heavy chain HVR-H1 | GFTFSXSWIH | 10 |
| SEQ ID NO:69 atezolizumab (MPDL3280A) heavy chain HVR-H2 | AWIXPYGGSX YYADSVKG | 18 |
| SEQ ID NO:70 atezolizumab (MPDL3280A) heavy chain HVR-H3 | RHWPGGFDY | 9 |
| SEQ ID NO:71 atezolizumab (MPDL3280A) heavy chain HVR-L1 | RASQXXXTXX A | 11 |
| SEQ ID NO:72 atezolizumab (MPDL3280A) heavy chain HVR-L2 | SASXLXS | 7 |
| SEQ ID NO:73 atezolizumab (MPDL3280A) heavy chain HVR-L3 | QQXXXXPXT | 9 |
| SEQ ID NO:74 avelumab (MSB0010718C) heavy chain | EVQLLESGGG LVQPGGSLRL SCAASGFTFS SYIMMWVRQA PGKGLEWVSS IYPSGGITFY<br>ADTVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARIK LGTVTTVDYW GQGTLVTVSS<br>ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS<br>GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG<br>PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN<br>STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE<br>LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW<br>QQGNVFSCSV MHEALHNHYT QKSLSLSPGK | 60<br>120<br>180<br>240<br>300<br>360<br>420<br>450 |
| SEQ ID NO:75 avelumab (MSB0010718C) light chain | QSALTQPASV SGSPGQSITI SCTGTSSDVG GYNYVSWYQQ HPGKAPKLMI YDVSNRPSGV<br>SNRFSGSKSG NTASLTISGL QAEDEADYYC SSYTSSSTRV FGTGTKVTVL GQPKANPTVT<br>LFPPSSEELQ ANKATLVCLI SDFYPGAVTV AWKADGSPVK AGVETTKPSK QSNNKYAASS<br>YLSLTPEQWK SHRSYSCQVT HEGSTVEKTV APTECS | 60<br>120<br>180<br>216 |
| SEQ ID NO:76 avelumab (MSB0010718C) variable heavy chain | EVQLLESGGG LVQPGGSLRL SCAASGFTFS SYIMMWVRQA PGKGLEWVSS IYPSGGITFY<br>ADTVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARIK LGTVTTVDYW GQGTLVTVSS | 60<br>120 |
| SEQ ID NO:77 avelumab (MSB0010718C) variable light chain | QSALTQPASV SGSPGQSITI SCTGTSSDVG GYNYVSWYQQ HPGKAPKLMI YDVSNRPSGV<br>SNRFSGSKSG NTASLTISGL QAEDEADYYC SSYTSSSTRV FGTGTKVTVL | 60<br>110 |
| SEQ ID NO:78 avelumab (MSB0010718C) heavy chain HVR-H1 | SYIMM | 5 |
| SEQ ID NO:79 avelumab (MSB0010718C) heavy chain HVR-H2 | SIYPSGGITF YADTVKG | 17 |
| SEQ ID NO:80 avelumab | IKLGTVTTVD Y | 11 |

| Identifier | Sequence (One-Letter Amino Acid Symbols) | |
|---|---|---|
| (MSB0010718C) heavy chain HVR-H3 | | |
| SEQ ID NO:81 avelumab (MSB0010718C) heavy chain HVR-L1 | TGTSSDVGGY NYVS | 14 |
| SEQ ID NO:82 avelumab (MSB0010718C) heavy chain HVR-L2 | DVSNRPS | 7 |
| SEQ ID NO:83 avelumab (MSB0010718C) heavy chain HVR-L3 | SSYTSSSTRV | 10 |

Pharmaceutical Compositions

**[00844]** In some embodiments, the invention provides pharmaceutical compositions for treating solid tumor cancers, lymphomas and leukemia.

**[00845]** The pharmaceutical compositions are typically formulated to provide a therapeutically effective amount of a combination of a PI3K inhibitor, including a PI3K-γ or PI3K-δ inhibitor, a JAK-2 inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, and/or a BTK inhibitor as the active ingredients, or a pharmaceutically acceptable salt, ester, prodrug, solvate, hydrate or derivative thereof. Where desired, the pharmaceutical compositions contain a pharmaceutically acceptable salt and/or coordination complex thereof, and one or more pharmaceutically acceptable excipients, carriers, including inert solid diluents and fillers, diluents, including sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers and adjuvants.

**[00846]** The pharmaceutical compositions are administered as a combination of a PI3K inhibitor, including a PI3K-γ or PI3K-δ inhibitor, a JAK-2 inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, and/or a BTK inhibitor. Where desired, other active pharmaceutical ingredient(s) may be mixed into a preparation or both components may be formulated into separate preparations for use in combination separately or at the same time.

**[00847]** In some embodiments, the concentration of each of the PI3K, PD-1, and BTK inhibitors provided in the pharmaceutical compositions of the invention is independently less than, for example, 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19%, 18%,

17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002% or 0.0001% w/w, w/v or v/v, relative to the total mass or volume of the pharmaceutical composition.

**[00848]** In some embodiments, the concentration of each of the PI3K, JAK-2, PD-1, PD-L1, and BTK inhibitors provided in the pharmaceutical compositions of the invention is independently greater than 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19.75%, 19.50%, 19.25% 19%, 18.75%, 18.50%, 18.25% 18%, 17.75%, 17.50%, 17.25% 17%, 16.75%, 16.50%, 16.25% 16%, 15.75%, 15.50%, 15.25% 15%, 14.75%, 14.50%, 14.25% 14%, 13.75%, 13.50%, 13.25% 13%, 12.75%, 12.50%, 12.25% 12%, 11.75%, 11.50%, 11.25% 11%, 10.75%, 10.50%, 10.25% 10%, 9.75%, 9.50%, 9.25% 9%, 8.75%, 8.50%, 8.25% 8%, 7.75%, 7.50%, 7.25% 7%, 6.75%, 6.50%, 6.25% 6%, 5.75%, 5.50%, 5.25% 5%, 4.75%, 4.50%, 4.25%, 4%, 3.75%, 3.50%, 3.25%, 3%, 2.75%, 2.50%, 2.25%, 2%, 1.75%, 1.50%, 125%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002% or 0.0001% w/w, w/v, or v/v, relative to the total mass or volume of the pharmaceutical composition.

**[00849]** In some embodiments, the concentration of each of the PI3K, JAK-2, PD-1, PD-L1, and BTK inhibitors of the invention is independently in the range from approximately 0.0001% to approximately 50%, approximately 0.001% to approximately 40%, approximately 0.01% to approximately 30%, approximately 0.02% to approximately 29%, approximately 0.03% to approximately 28%, approximately 0.04% to approximately 27%, approximately 0.05% to approximately 26%, approximately 0.06% to approximately 25%, approximately 0.07% to approximately 24%, approximately 0.08% to approximately 23%, approximately 0.09% to approximately 22%, approximately 0.1% to approximately 21%, approximately 0.2% to approximately 20%, approximately 0.3% to approximately 19%, approximately 0.4% to approximately 18%, approximately 0.5% to approximately 17%, approximately 0.6% to approximately 16%,

approximately 0.7% to approximately 15%, approximately 0.8% to approximately 14%, approximately 0.9% to approximately 12% or approximately 1% to approximately 10% w/w, w/v or v/v, relative to the total mass or volume of the pharmaceutical composition.

**[00850]** In some embodiments, the concentration of each of the PI3K, JAK-2, PD-1, PD-L1, and BTK inhibitors of the invention is independently in the range from approximately 0.001% to approximately 10%, approximately 0.01% to approximately 5%, approximately 0.02% to approximately 4.5%, approximately 0.03% to approximately 4%, approximately 0.04% to approximately 3.5%, approximately 0.05% to approximately 3%, approximately 0.06% to approximately 2.5%, approximately 0.07% to approximately 2%, approximately 0.08% to approximately 1.5%, approximately 0.09% to approximately 1%, approximately 0.1% to approximately 0.9% w/w, w/v or v/v, relative to the total mass or volume of the pharmaceutical composition.

**[00851]** In some embodiments, the amount of each of the PI3K, JAK-2, PD-1, PD-L1, and BTK inhibitors of the invention is independently equal to or less than 3.0 g, 2.5 g, 2.0 g, 1.5 g, 1.0 g, 0.95 g, 0.9 g, 0.85 g, 0.8 g, 0.75 g, 0.7 g, 0.65 g, 0.6 g, 0.55 g, 0.5 g, 0.45 g, 0.4 g, 0.35 g, 0.3 g, 0.25 g, 0.2 g, 0.15 g, 0.1 g, 0.09 g, 0.08 g, 0.07 g, 0.06 g, 0.05 g, 0.04 g, 0.03 g, 0.02 g, 0.01 g, 0.009 g, 0.008 g, 0.007 g, 0.006 g, 0.005 g, 0.004 g, 0.003 g, 0.002 g, 0.001 g, 0.0009 g, 0.0008 g, 0.0007 g, 0.0006 g, 0.0005 g, 0.0004 g, 0.0003 g, 0.0002 g or 0.0001 g.

**[00852]** In some embodiments, the amount of each of the PI3K, JAK-2, PD-1, PD-L1, and BTK inhibitors of the invention is independently more than 0.0001 g, 0.0002 g, 0.0003 g, 0.0004 g, 0.0005 g, 0.0006 g, 0.0007 g, 0.0008 g, 0.0009 g, 0.001 g, 0.0015 g, 0.002 g, 0.0025 g, 0.003 g, 0.0035 g, 0.004 g, 0.0045 g, 0.005 g, 0.0055 g, 0.006 g, 0.0065 g, 0.007 g, 0.0075 g, 0.008 g, 0.0085 g, 0.009 g, 0.0095 g, 0.01 g, 0.015 g, 0.02 g, 0.025 g, 0.03 g, 0.035 g, 0.04 g, 0.045 g, 0.05 g, 0.055 g, 0.06 g, 0.065 g, 0.07 g, 0.075 g, 0.08 g, 0.085 g, 0.09 g, 0.095 g, 0.1 g, 0.15 g, 0.2 g, 0.25 g, 0.3 g, 0.35 g, 0.4 g, 0.45 g, 0.5 g, 0.55 g, 0.6 g, 0.65 g, 0.7 g, 0.75 g, 0.8 g, 0.85 g, 0.9 g, 0.95 g, 1 g, 1.5 g, 2 g, 2.5, or 3 g.

**[00853]** Each of the PI3K, JAK-2, PD-1, PD-L1, and BTK inhibitors according to the invention is effective over a wide dosage range. For example, in the treatment of adult

humans, dosages independently range from 0.01 to 1000 mg, from 0.5 to 100 mg, from 1 to 50 mg per day, and from 5 to 40 mg per day are examples of dosages that may be used. The exact dosage will depend upon the route of administration, the form in which the compound is administered, the gender and age of the subject to be treated, the body weight of the subject to be treated, and the preference and experience of the attending physician.

**[00854]** Described below are non-limiting pharmaceutical compositions and methods for preparing the same.

Pharmaceutical Compositions for Oral Administration

**[00855]** In some embodiments, the invention provides a pharmaceutical composition for oral administration containing the combination of a PI3K, JAK-2, PD-1, PD-L1, and/or BTK inhibitor, and a pharmaceutical excipient suitable for oral administration.

**[00856]** In some embodiments, the invention provides a solid pharmaceutical composition for oral administration containing: (i) an effective amount of each of a PI3K, JAK-2, PD-1, PD-L1, and/or BTK inhibitor in combination and (ii) a pharmaceutical excipient suitable for oral administration. In some embodiments, the composition further contains (iii) an effective amount of a fourth compound.

**[00857]** In some embodiments, the pharmaceutical composition may be a liquid pharmaceutical composition suitable for oral consumption. Pharmaceutical compositions of the invention suitable for oral administration can be presented as discrete dosage forms, such as capsules, sachets, or tablets, or liquids or aerosol sprays each containing a predetermined amount of an active ingredient as a powder or in granules, a solution, or a suspension in an aqueous or non-aqueous liquid, an oil-in-water emulsion, a water-in-oil liquid emulsion, powders for reconstitution, powders for oral consumptions, bottles (including powders or liquids in a bottle), orally dissolving films, lozenges, pastes, tubes, gums, and packs. Such dosage forms can be prepared by any of the methods of pharmacy, but all methods include the step of bringing the active ingredient(s) into association with the carrier, which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient(s) with liquid carriers or finely divided solid carriers or both, and then, if

necessary, shaping the product into the desired presentation. For example, a tablet can be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with an excipient such as, but not limited to, a binder, a lubricant, an inert diluent, and/or a surface active or dispersing agent. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

**[00858]** The invention further encompasses anhydrous pharmaceutical compositions and dosage forms since water can facilitate the degradation of some compounds. For example, water may be added (*e.g.*, 5%) in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms of the invention which contain lactose can be made anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected. An anhydrous pharmaceutical composition may be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions may be packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastic or the like, unit dose containers, blister packs, and strip packs.

**[00859]** Each of the PI3K, JAK-2, PD-1, PD-L1, and/or BTK inhibitors as active ingredients can be combined in an intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier can take a wide variety of forms depending on the form of preparation desired for administration. In preparing the compositions for an oral dosage form, any of the usual pharmaceutical media can be employed as carriers, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like in the case of oral liquid preparations (such as suspensions, solutions, and elixirs) or aerosols; or carriers such as starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants,

binders, and disintegrating agents can be used in the case of oral solid preparations, in some embodiments without employing the use of lactose. For example, suitable carriers include powders, capsules, and tablets, with the solid oral preparations. If desired, tablets can be coated by standard aqueous or nonaqueous techniques.

**[00860]** Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (*e.g.*, ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, microcrystalline cellulose, and mixtures thereof.

**[00861]** Examples of suitable fillers for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (*e.g.*, granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof.

**[00862]** Disintegrants may be used in the compositions of the invention to provide tablets that disintegrate when exposed to an aqueous environment. Too much of a disintegrant may produce tablets which disintegrate in the bottle. Too little may be insufficient for disintegration to occur, thus altering the rate and extent of release of the active ingredients from the dosage form. Thus, a sufficient amount of disintegrant that is neither too little nor too much to detrimentally alter the release of the active ingredient(s) may be used to form the dosage forms of the compounds disclosed herein. The amount of disintegrant used may vary based upon the type of formulation and mode of administration, and may be readily discernible to those of ordinary skill in the art. About 0.5 to about 15 weight percent of disintegrant, or about 1 to about 5 weight percent of disintegrant, may be used in the pharmaceutical composition. Disintegrants that can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, other starches, clays, other

algins, other celluloses, gums or mixtures thereof.

**[00863]** Lubricants which can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, calcium stearate, magnesium stearate, sodium stearyl fumarate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethylaureate, agar, or mixtures thereof. Additional lubricants include, for example, a syloid silica gel, a coagulated aerosol of synthetic silica, silicified microcrystalline cellulose, or mixtures thereof. A lubricant can optionally be added in an amount of less than about 0.5% or less than about 1% (by weight) of the pharmaceutical composition.

**[00864]** When aqueous suspensions and/or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if so desired, emulsifying and/or suspending agents, together with such diluents as water, ethanol, propylene glycol, glycerin and various combinations thereof.

**[00865]** The tablets can be uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed. Formulations for oral use can also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

**[00866]** Surfactants which can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, hydrophilic surfactants, lipophilic surfactants, and mixtures thereof. That is, a mixture of hydrophilic surfactants may be employed, a mixture of lipophilic surfactants may be employed, or a mixture of at least one hydrophilic surfactant and at least one lipophilic surfactant may be employed.

**[00867]** A suitable hydrophilic surfactant may generally have an HLB value of at least

10, while suitable lipophilic surfactants may generally have an HLB value of or less than about 10. An empirical parameter used to characterize the relative hydrophilicity and hydrophobicity of non-ionic amphiphilic compounds is the hydrophilic-lipophilic balance ("HLB" value). Surfactants with lower HLB values are more lipophilic or hydrophobic, and have greater solubility in oils, while surfactants with higher HLB values are more hydrophilic, and have greater solubility in aqueous solutions. Hydrophilic surfactants are generally considered to be those compounds having an HLB value greater than about 10, as well as anionic, cationic, or zwitterionic compounds for which the HLB scale is not generally applicable. Similarly, lipophilic (*i.e.*, hydrophobic) surfactants are compounds having an HLB value equal to or less than about 10. However, HLB value of a surfactant is merely a rough guide generally used to enable formulation of industrial, pharmaceutical and cosmetic emulsions.

**[00868]** Hydrophilic surfactants may be either ionic or non-ionic. Suitable ionic surfactants include, but are not limited to, alkylammonium salts; fusidic acid salts; fatty acid derivatives of amino acids, oligopeptides, and polypeptides; glyceride derivatives of amino acids, oligopeptides, and polypeptides; lecithins and hydrogenated lecithins; lysolecithins and hydrogenated lysolecithins; phospholipids and derivatives thereof; lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; fatty acid salts; sodium docusate; acylactylates; mono- and di-acetylated tartaric acid esters of mono- and di-glycerides; succinylated mono- and di-glycerides; citric acid esters of mono- and di-glycerides; and mixtures thereof.

**[00869]** Within the aforementioned group, ionic surfactants include, by way of example: lecithins, lysolecithin, phospholipids, lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; fatty acid salts; sodium docusate; acylactylates; mono- and di-acetylated tartaric acid esters of mono- and di-glycerides; succinylated mono- and di-glycerides; citric acid esters of mono- and di-glycerides; and mixtures thereof.

**[00870]** Ionic surfactants may be the ionized forms of lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidic acid, phosphatidylserine, lysophosphatidylcholine, lysophosphatidylethanolamine,

lysophosphatidylglycerol, lysophosphatidic acid, lysophosphatidylserine, PEG-phosphatidylethanolamine, PVP-phosphatidylethanolamine, lactylic esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid esters of mono/diglycerides, cholylsarcosine, caproate, caprylate, caprate, laurate, myristate, palmitate, oleate, ricinoleate, linoleate, linolenate, stearate, lauryl sulfate, teracecyl sulfate, docusate, lauroyl carnitines, palmitoyl carnitines, myristoyl carnitines, and salts and mixtures thereof.

**[00871]** Hydrophilic non-ionic surfactants may include, but not limited to, alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; polyoxyalkylene alkyl ethers such as polyethylene glycol alkyl ethers; polyoxyalkylene alkylphenols such as polyethylene glycol alkyl phenols; polyoxyalkylene alkyl phenol fatty acid esters such as polyethylene glycol fatty acids monoesters and polyethylene glycol fatty acids diesters; polyethylene glycol glycerol fatty acid esters; polyglycerol fatty acid esters; polyoxyalkylene sorbitan fatty acid esters such as polyethylene glycol sorbitan fatty acid esters; hydrophilic transesterification products of a polyol with at least one member of the group consisting of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids, and sterols; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylated vitamins and derivatives thereof; polyoxyethylene-polyoxypropylene block copolymers; and mixtures thereof; polyethylene glycol sorbitan fatty acid esters and hydrophilic transesterification products of a polyol with at least one member of the group consisting of triglycerides, vegetable oils, and hydrogenated vegetable oils. The polyol may be glycerol, ethylene glycol, polyethylene glycol, sorbitol, propylene glycol, pentaerythritol, or a saccharide.

**[00872]** Other hydrophilic-non-ionic surfactants include, without limitation, PEG-10 laurate, PEG-12 laurate, PEG-20 laurate, PEG-32 laurate, PEG-32 dilaurate, PEG-12 oleate, PEG-15 oleate, PEG-20 oleate, PEG-20 dioleate, PEG-32 oleate, PEG-200 oleate, PEG-400 oleate, PEG-15 stearate, PEG-32 distearate, PEG-40 stearate, PEG-100 stearate, PEG-20 dilaurate, PEG-25 glyceryl trioleate, PEG-32 dioleate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-20 glyceryl stearate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-40 palm kernel

oil, PEG-50 hydrogenated castor oil, PEG-40 castor oil, PEG-35 castor oil, PEG-60 castor oil, PEG-40 hydrogenated castor oil, PEG-60 hydrogenated castor oil, PEG-60 corn oil, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polyglyceryl-10 laurate, PEG-30 cholesterol, PEG-25 phyto sterol, PEG-30 soya sterol, PEG-20 trioleate, PEG-40 sorbitan oleate, PEG-80 sorbitan laurate, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, POE-20 oleyl ether, POE-20 stearyl ether, tocopheryl PEG-100 succinate, PEG-24 cholesterol, polyglyceryl-10oleate, Tween 40, Tween 60, sucrose monostearate, sucrose monolaurate, sucrose monopalmitate, PEG 10-100 nonyl phenol series, PEG 15-100 octyl phenol series, and poloxamers.

**[00873]** Suitable lipophilic surfactants include, by way of example only: fatty alcohols; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; propylene glycol fatty acid esters; sorbitan fatty acid esters; polyethylene glycol sorbitan fatty acid esters; sterols and sterol derivatives; polyoxyethylated sterols and sterol derivatives; polyethylene glycol alkyl ethers; sugar esters; sugar ethers; lactic acid derivatives of mono- and di-glycerides; hydrophobic transesterification products of a polyol with at least one member of the group consisting of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids and sterols; oil-soluble vitamins/vitamin derivatives; and mixtures thereof. Within this group, preferred lipophilic surfactants include glycerol fatty acid esters, propylene glycol fatty acid esters, and mixtures thereof, or are hydrophobic transesterification products of a polyol with at least one member of the group consisting of vegetable oils, hydrogenated vegetable oils, and triglycerides.

**[00874]** In an embodiment, the composition may include a solubilizer to ensure good solubilization and/or dissolution of the compound of the present invention and to minimize precipitation of the compound of the present invention. This can be especially important for compositions for non-oral use - *e.g.*, compositions for injection. A solubilizer may also be added to increase the solubility of the hydrophilic drug and/or other components, such as surfactants, or to maintain the composition as a stable or homogeneous solution or dispersion.

**[00875]** Examples of suitable solubilizers include, but are not limited to, the following:

alcohols and polyols, such as ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediols and isomers thereof, glycerol, pentaerythritol, sorbitol, mannitol, transcutol, dimethyl isosorbide, polyethylene glycol, polypropylene glycol, polyvinylalcohol, hydroxypropyl methylcellulose and other cellulose derivatives, cyclodextrins and cyclodextrin derivatives; ethers of polyethylene glycols having an average molecular weight of about 200 to about 6000, such as tetrahydrofurfuryl alcohol PEG ether (glycofurol) or methoxy PEG; amides and other nitrogen-containing compounds such as 2-pyrrolidone, 2-piperidone, Ɛ-caprolactam, N-alkylpyrrolidone, N-hydroxyalkylpyrrolidone, N-alkylpiperidone, N-alkylcaprolactam, dimethylacetamide and polyvinylpyrrolidone; esters such as ethyl propionate, tributylcitrate, acetyl triethylcitrate, acetyl tributyl citrate, triethylcitrate, ethyl oleate, ethyl caprylate, ethyl butyrate, triacetin, propylene glycol monoacetate, propylene glycol diacetate, .epsilon.-caprolactone and isomers thereof, δ-valerolactone and isomers thereof, β-butyrolactone and isomers thereof; and other solubilizers known in the art, such as dimethyl acetamide, dimethyl isosorbide, N-methyl pyrrolidones, monooctanoin, diethylene glycol monoethyl ether, and water.

**[00876]** Mixtures of solubilizers may also be used. Examples include, but not limited to, triacetin, triethylcitrate, ethyl oleate, ethyl caprylate, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cyclodextrins, ethanol, polyethylene glycol 200-100, glycofurol, transcutol, propylene glycol, and dimethyl isosorbide. Particularly preferred solubilizers include sorbitol, glycerol, triacetin, ethyl alcohol, PEG-400, glycofurol and propylene glycol.

**[00877]** The amount of solubilizer that can be included is not particularly limited. The amount of a given solubilizer may be limited to a bioacceptable amount, which may be readily determined by one of skill in the art. In some circumstances, it may be advantageous to include amounts of solubilizers far in excess of bioacceptable amounts, for example to maximize the concentration of the drug, with excess solubilizer removed prior to providing the composition to a patient using conventional techniques, such as distillation or evaporation. Thus, if present, the solubilizer can be in a weight ratio of 10%, 25%, 50%, 100%, or up to about 200% by weight, based on the combined weight of

the drug, and other excipients. If desired, very small amounts of solubilizer may also be used, such as 5%, 2%, 1% or even less. Typically, the solubilizer may be present in an amount of about 1% to about 100%, more typically about 5% to about 25% by weight.

**[00878]** The composition can further include one or more pharmaceutically acceptable additives and excipients. Such additives and excipients include, without limitation, detackifiers, anti-foaming agents, buffering agents, polymers, antioxidants, preservatives, chelating agents, viscomodulators, tonicifiers, flavorants, colorants, odorants, opacifiers, suspending agents, binders, fillers, plasticizers, lubricants, and mixtures thereof.

**[00879]** In addition, an acid or a base may be incorporated into the composition to facilitate processing, to enhance stability, or for other reasons. Examples of pharmaceutically acceptable bases include amino acids, amino acid esters, ammonium hydroxide, potassium hydroxide, sodium hydroxide, sodium hydrogen carbonate, aluminum hydroxide, calcium carbonate, magnesium hydroxide, magnesium aluminum silicate, synthetic aluminum silicate, synthetic hydrocalcite, magnesium aluminum hydroxide, diisopropylethylamine, ethanolamine, ethylenediamine, triethanolamine, triethylamine, triisopropanolamine, trimethylamine, tris(hydroxymethyl)aminomethane (TRIS) and the like. Also suitable are bases that are salts of a pharmaceutically acceptable acid, such as acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acid, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, uric acid, and the like. Salts of polyprotic acids, such as sodium phosphate, disodium hydrogen phosphate, and sodium dihydrogen phosphate can also be used. When the base is a salt, the cation can be any convenient and pharmaceutically acceptable cation, such as ammonium, alkali metals and alkaline earth metals. Example may include, but not limited to, sodium, potassium, lithium, magnesium, calcium and ammonium.

**[00880]** Suitable acids are pharmaceutically acceptable organic or inorganic acids. Examples of suitable inorganic acids include hydrochloric acid, hydrobromic acid,

hydriodic acid, sulfuric acid, nitric acid, boric acid, phosphoric acid, and the like. Examples of suitable organic acids include acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acids, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, methanesulfonic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid and uric acid.

Pharmaceutical Compositions for Injection

**[00881]** In some embodiments, the invention provides a pharmaceutical composition for injection containing the combination of the PI3K, JAK-2, PD-1, PD-L1, and/or BTK inhibitors and a pharmaceutical excipient suitable for injection. Components and amounts of active pharmaceutical ingredients in the compositions are as described herein.

**[00882]** The forms in which the compositions of the present invention may be incorporated for administration by injection include aqueous or oil suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, or peanut oil, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles.

**[00883]** Aqueous solutions in saline are also conventionally used for injection. Ethanol, glycerol, propylene glycol and liquid polyethylene glycol (and suitable mixtures thereof), cyclodextrin derivatives, and vegetable oils may also be employed. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, for the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid and thimerosal.

**[00884]** Sterile injectable solutions are prepared by incorporating the combination of the PI3K, PD-1, and/or BTK inhibitors in the required amounts in the appropriate solvent with various other ingredients as enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and

the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, certain desirable methods of preparation are spray-drying, vacuum-drying and freeze-drying (lyophilization) techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. Other lyophilized or spray-dried antibody formulations known to those of skill in the art may also be employed with the present invention. Such formulations include those disclosed in U.S. Patent Nos. 5,908,826, 6,267,958, 7,682,609, 7,592,004, and 8,298,530, and U.S. Patent Application Publication No. 2010/0158925, the teachings of which are specifically incorporated by reference herein.

Pharmaceutical Compositions for Topical Delivery

**[00885]** In some embodiments, the invention provides a pharmaceutical composition for transdermal delivery containing the combination of the PI3K, JAK-2, PD-1, PD-L1, and/or BTK inhibitors and a pharmaceutical excipient suitable for transdermal delivery.

**[00886]** Compositions of the present invention can be formulated into preparations in solid, semi-solid, or liquid forms suitable for local or topical administration, such as gels, water soluble jellies, creams, lotions, suspensions, foams, powders, slurries, ointments, solutions, oils, pastes, suppositories, sprays, emulsions, saline solutions, dimethylsulfoxide (DMSO)-based solutions. In general, carriers with higher densities are capable of providing an area with a prolonged exposure to the active ingredients. In contrast, a solution formulation may provide more immediate exposure of the active ingredient to the chosen area.

**[00887]** The pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients, which are compounds that allow increased penetration of, or assist in the delivery of, therapeutic molecules across the stratum corneum permeability barrier of the skin. There are many of these penetration-enhancing molecules known to those trained in the art of topical formulation. Examples of such carriers and excipients include, but are not limited to, humectants (*e.g.*, urea), glycols (*e.g.*, propylene glycol), alcohols (*e.g.*, ethanol), fatty acids (*e.g.*, oleic acid), surfactants (*e.g.*, isopropyl myristate and sodium lauryl sulfate), pyrrolidones, glycerol monolaurate, sulfoxides, terpenes (*e.g.*,

menthol), amines, amides, alkanes, alkanols, water, calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

**[00888]** Another formulation for use in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the combination of the PI3K, PD-1, and BTK inhibitors in controlled amounts, either with or without another active pharmaceutical ingredient.

**[00889]** The construction and use of transdermal patches for the delivery of active pharmaceutical ingredients is well known in the art. See, *e.g.*, U.S. Patent Nos. 5,023,252; 4,992,445 and 5,001,139. Such patches may be constructed for continuous, pulsatile, or on demand delivery of active pharmaceutical ingredients.

Other Pharmaceutical Compositions

**[00890]** Pharmaceutical compositions may also be prepared from compositions described herein and one or more pharmaceutically acceptable excipients suitable for sublingual, buccal, rectal, intraosseous, intraocular, intranasal, epidural, or intraspinal administration. Preparations for such pharmaceutical compositions are well-known in the art. See, *e.g.*, Anderson, *et al.*, *Handbook of Clinical Drug Data*, Tenth Edition, McGraw-Hill, 2002; and Pratt and Taylor, eds., *Principles of Drug Action,* Third Edition, Churchill Livingston, N.Y., 1990, each of which is incorporated by reference herein in its entirety.

**[00891]** Administration of the combination of the PI3K, JAK-2, PD-1, PD-L1, and BTK inhibitors or pharmaceutical composition of these compounds can be effected by any method that enables delivery of the compounds to the site of action. These methods include oral routes, intraduodenal routes, parenteral injection (including intravenous, intraarterial, subcutaneous, intramuscular, intravascular, intraperitoneal or infusion), topical (*e.g.*, transdermal application), rectal administration, via local delivery by catheter or stent or through inhalation. The combination of compounds can also be administered intraadiposally or intrathecally.

**[00892]** Parenteral administration forms include solutions or suspensions of active

compound in sterile aqueous solutions, for example, aqueous propylene glycol or dextrose solutions. Such dosage forms can be suitably buffered, if desired.

**[00893]** The invention also provides kits. The kits include each of the PI3K, PD-1, and BTK inhibitors, either alone or in combination in suitable packaging, and written material that can include instructions for use, discussion of clinical studies and listing of side effects. 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 active pharmaceutical ingredient. In some embodiments, the PI3K, PD-1, and BTK inhibitors and the active pharmaceutical ingredient are provided as separate compositions in separate containers within the kit. In some embodiments, the PI3K, PD-1, and BTK inhibitors and the active pharmaceutical ingredient 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.

Dosages and Dosing Regimens

**[00894]** The amounts of the combination of the BTK, PI3K, PD-1, PD-L1, and/or JAK-2 inhibitors administered will be dependent on the mammal being treated, the severity of the disorder or condition, the rate of administration, the disposition of the compounds and the discretion of the prescribing physician. However, an effective dosage is in the range of about 0.001 to about 100 mg per kg body weight per day, such as about 1 to about 35 mg/kg/day, in single or divided doses. For a 70 kg human, this would amount to about 0.05 to 7 g/day, such as about 0.05 to about 2.5 g/day. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other

cases still larger doses may be employed without causing any harmful side effect, for example by dividing such larger doses into several small doses for administration throughout the day.

**[00895]** In some embodiments, the combination of the BTK, PI3K, PD-1, PD-L1, and/or JAK-2 inhibitors is administered in a single dose. Typically, such administration will be by injection, for example by intravenous injection, in order to introduce the active pharmaceutical ingredients quickly. However, other routes may be used as appropriate. A single dose of the combination of the BTK, PI3K, PD-1, PD-L1, and/or JAK-2 inhibitors may also be used for treatment of an acute condition.

**[00896]** In some embodiments, the combination of the BTK, PI3K, PD-1, PD-L1, and/or JAK-2 inhibitors is administered in multiple doses. Dosing may be about once, twice, three times, four times, five times, six times, or more than six times per day. Dosing may be about once a month, once every two weeks, once a week, or once every other day. In other embodiments, the combination of the BTK, PI3K, PD-1, PD-L1, and/or JAK-2 inhibitors is administered about once per day to about 6 times per day. In another embodiment the administration of the combination of the BTK, PI3K, PD-1, PD-L1, and/or JAK-2 inhibitors continues for less than about 7 days. In yet another embodiment the administration continues for more than about 6, 10, 14, 28 days, two months, six months, or one year. In some cases, continuous dosing is achieved and maintained as long as necessary.

**[00897]** Administration of the active pharmaceutical ingredients of the invention may continue as long as necessary. In some embodiments, the combination of the BTK, PI3K, PD-1, PD-L1, and/or JAK-2 inhibitors is administered for more than 1, 2, 3, 4, 5, 6, 7, 14, or 28 days. In some embodiments, the combination of the PI3K, PD-1, PD-L1, and BTK inhibitors is administered for less than 28, 14, 7, 6, 5, 4, 3, 2, or 1 day. In some embodiments, the combination of the BTK, PI3K, PD-1, PD-L1, and/or JAK-2 inhibitors is administered chronically on an ongoing basis - *e.g.*, for the treatment of chronic effects.

**[00898]** In some embodiments, an effective dosage of each of the BTK, PI3K, PD-1, PD-L1, or JAK-2 inhibitors is in the range of about 1 mg to about 500 mg, about 10 mg to about 300 mg, about 20 mg to about 250 mg, about 25 mg to about 200 mg, about 10

mg to about 200 mg, about 20 mg to about 150 mg, about 30 mg to about 120 mg, about 10 mg to about 90 mg, about 20 mg to about 80 mg, about 30 mg to about 70 mg, about 40 mg to about 60 mg, about 45 mg to about 55 mg, about 48 mg to about 52 mg, about 50 mg to about 150 mg, about 60 mg to about 140 mg, about 70 mg to about 130 mg, about 80 mg to about 120 mg, about 90 mg to about 110 mg, about 95 mg to about 105 mg, about 150 mg to about 250 mg, about 160 mg to about 240 mg, about 170 mg to about 230 mg, about 180 mg to about 220 mg, about 190 mg to about 210 mg, about 195 mg to about 205 mg, or about 198 to about 202 mg. In some embodiments, an effective dosage of each of the BTK, PI3K, PD-1, PD-L1, or JAK-2 inhibitors is about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, or about 500 mg. In some embodiments, an effective dosage of each of the BTK, PI3K, PD-1, PD-L1, or JAK-2 inhibitors is 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 375 mg, 400 mg, 425 mg, 450 mg, 475 mg, or 500 mg.

**[00899]** In some embodiments, an effective dosage of each of the BTK, PI3K, PD-1, PD-L1, or JAK-2 inhibitors is in the range of about 0.01 mg/kg to about 4.3 mg/kg, about 0.15 mg/kg to about 3.6 mg/kg, about 0.3 mg/kg to about 3.2 mg/kg, about 0.35 mg/kg to about 2.85 mg/kg, about 0.15 mg/kg to about 2.85 mg/kg, about 0.3 mg to about 2.15 mg/kg, about 0.45 mg/kg to about 1.7 mg/kg, about 0.15 mg/kg to about 1.3 mg/kg, about 0.3 mg/kg to about 1.15 mg/kg, about 0.45 mg/kg to about 1 mg/kg, about 0.55 mg/kg to about 0.85 mg/kg, about 0.65 mg/kg to about 0.8 mg/kg, about 0.7 mg/kg to about 0.75 mg/kg, about 0.7 mg/kg to about 2.15 mg/kg, about 0.85 mg/kg to about 2 mg/kg, about 1 mg/kg to about 1.85 mg/kg, about 1.15 mg/kg to about 1.7 mg/kg, about 1.3 mg/kg mg to about 1.6 mg/kg, about 1.35 mg/kg to about 1.5 mg/kg, about 2.15 mg/kg to about 3.6 mg/kg, about 2.3 mg/kg to about 3.4 mg/kg, about 2.4 mg/kg to about 3.3 mg/kg, about 2.6 mg/kg to about 3.15 mg/kg, about 2.7 mg/kg to about 3 mg/kg, about 2.8 mg/kg to about 3 mg/kg, or about 2.85 mg/kg to about 2.95 mg/kg. In some embodiments, an effective dosage of each of the BTK, PI3K, PD-1, PD-L1, or JAK-2 inhibitors is about

0.35 mg/kg, about 0.7 mg/kg, about 1 mg/kg, about 1.4 mg/kg, about 1.8 mg/kg, about 2.1 mg/kg, about 2.5 mg/kg, about 2.85 mg/kg, about 3.2 mg/kg, or about 3.6 mg/kg.

**[00900]** In some embodiments, an inhibitor of each of the BTK, PI3K, PD-1, PD-L1, or JAK-2 inhibitors is adminstered at a dosage of 10 to 400 mg BID, including a dosage of 5 mg, 10 mg, 12.5 mg, 25 mg, 40 mg, 50 mg, 75 mg, 100 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 375 mg, 400 mg, 425 mg, 450 mg, 475 mg, and 500 mg BID.

**[00901]** In some embodiments, a dose of the PD-1 or PD-L1 inhibitors is administered at a concentration of 10 mg/mL, 25 mg/mL, 40 mg/mL, 50 mg/mL, 60 mg/mL, 75 mg/mL, 100 mg/mL, and 200 mg/mL.

**[00902]** An effective amount of the combination of the BTK, PI3K, PD-1, PD-L1, and JAK-2 inhibitors may be administered in either single or multiple doses by any of the accepted modes of administration of active pharmaceutical ingredients having similar utilities, including rectal, buccal, intranasal and transdermal routes, by intra-arterial injection, intravenously, intraperitoneally, parenterally, intramuscularly, subcutaneously, orally, topically, or as an inhalant.

Methods of Treating Solid Tumor Cancers

**[00903]** In some embodiments, the invention relates to a method of treating a hyperproliferative disorder in a mammal that comprises administering to said mammal a therapeutically effective amount of a PD-1 inhibitor (and/or a PD-L1 inhibitor) and a BTK inhibitor, or a pharmaceutically acceptable salt or ester, prodrug, solvate or hydrate of the BTK inhibitor, or a variant or a fragment of the PD-1 inhibitor (and/or the PD-L1 inhibitor). In some embodiments, the invention relates to a method of treating a hyperproliferative disorder in a mammal that comprises administering to said mammal a therapeutically effective amount of a PD-1 inhibitor (and/or a PD-L1 inhibitor), a BTK inhibitor, and a PI3K inhibitor (or a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) or a pharmaceutically acceptable salt or ester, prodrug, solvate or hydrate of either or both of the PI3K inhibitor and BTK inhibitor, or a variant or a fragment of the PD-1 inhibitor. In some embodiments, the invention relates to a method of treating a

hyperproliferative disorder in a mammal that comprises administering to said mammal a therapeutically effective amount of a PD-1 inhibitor (and/or a PD-L1 inhibitor), a BTK inhibitor, a JAK-2 inhibitor, and a PI3K inhibitor (or a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) or a pharmaceutically acceptable salt or ester, prodrug, solvate or hydrate of either or both of the PI3K inhibitor and BTK inhibitor, or a variant or a fragment of the PD-1 inhibitor. In some embodiments, the invention relates to a method of treating a hyperproliferative disorder in a mammal, wherein the hyperproliferative disorder is a solid tumor cancer.

**[00904]** In some embodiments, the invention relates to a method of treating, with a combination of a PI3K inhibitor, including a PI3K-γ or PI3K-δ inhibitor, a JAK-2 inhibitor, a BTK inhibitor, a PD-1 inhibitor, and/or a PD-L1 inhibitor, a solid tumor cancer in a mammal selected from the group consisting of bladder cancer, squamous cell carcinoma, head and neck cancer, pancreatic ductal adenocarcinoma (PDA), pancreatic cancer, colon carcinoma, mammary carcinoma, breast cancer, fibrosarcoma, mesothelioma, renal cell carcinoma, lung carcinoma, thyoma, prostate cancer, colorectal cancer, ovarian cancer, acute myeloid leukemia, thymus cancer, brain cancer, squamous cell cancer, skin cancer, eye cancer, retinoblastoma, melanoma, intraocular melanoma, oral cavity cancer, oropharyngeal cancer, gastric cancer, stomach cancer, cervical cancer, renal cancer, kidney cancer, liver cancer, ovarian cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, acquired immune deficiency syndrome (AIDS)-related cancers (*e.g.*, lymphoma and Kaposi's sarcoma), viral-induced cancers such as cervical carcinoma (human papillomavirus), B-cell lymphoproliferative disease, nasopharyngeal carcinoma (Epstein-Barr virus), Kaposi's sarcoma and primary effusion lymphomas (Kaposi's sarcoma herpesvirus), hepatocellular carcinoma (hepatitis B and hepatitis C viruses), and T-cell leukemias (Human T-cell leukemia virus-1), glioblastoma, glioma, esophogeal tumors, head and neck tumor, metastatic colon cancer, head and neck squamous cell carcinoma, ovary tumor, pancreas tumor, renal cell carcinoma, hematological neoplasms, small-cell lung cancer, non-small-cell lung cancer, stage IV melanoma, and glioma.

**[00905]** In some embodiments, the invention relates to a method of treating a solid tumor cancer with a composition including a combination of a PI3K inhibitor, including a

PI3K-γ or PI3K-δ inhibitor, a JAK-2 inhibitor, a BTK inhibitor, a PD-1 inhibitor, and/or a PD-L1 inhibitor, wherein the dose is effective to inhibit signaling between the solid tumor cells and at least one microenvironment selected from the group consisting of macrophages, monocytes, mast cells, helper T cells, cytotoxic T cells, regulatory T cells, natural killer cells, myeloid-derived suppressor cells, regulatory B cells, neutrophils, dendritic cells, and fibroblasts. In some embodiments, the invention relates to a method of treating pancreatic cancer, breast cancer, ovarian cancer, melanoma, lung cancer, squamous cell carcinoma including head and neck cancer, and colorectal cancer using a combination of a BTK inhibitor, a PI3K inhibitor, a JAK-2 inhibitor, a PD-1 inhibitor, and/or a PD-L1 inhibitor, wherein the dose is effective to inhibit signaling between the solid tumor cells and at least one microenvironment selected from the group consisting of macrophages, monocytes, mast cells, helper T cells, cytotoxic T cells, regulatory T cells, natural killer cells, myeloid-derived suppressor cells, regulatory B cells, neutrophils, dendritic cells, and fibroblasts. In an embodiment, the invention provides a method for treating pancreatic cancer, breast cancer, ovarian cancer, melanoma, lung cancer, head and neck cancer, and colorectal cancer using a combination of a BTK inhibitor and gemcitabine, or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof. In an embodiment, the invention provides a method for treating pancreatic cancer, breast cancer, ovarian cancer, melanoma, lung cancer, head and neck cancer, and colorectal cancer using a combination of a BTK inhibitor and gemcitabine, or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof, wherein the BTK inhibitor is a compound of Formula (XVIII). In some embodiments, the invention provides a method of treating a hyperproliferative disorder selected from the group consisting of myeloproliferative proliferative neoplasm, chronic myelogenous leukemia, chronic neutrophilic leukemia, polycythemia vera, primary myelofibrosis, essential thrombocythemia, chronic eosinophilic leukemia, mastocytosis, and myelodysplastic syndrome. In some embodiments, the invention provides a method of treating a glioma, wherein the glioma is selected from the group consisting of fibrillary astrocytoma, anaplastic astrocytoma, pilocytic astrocytoma, astrocytoma, pleomorphic xanthoastrocytoma, subependymal giant cell astrocytoma, glioblastoma multiforme, oligodendroglioma, ependymoma, subependymoma, choroid plexus tumor, choroid

plexus papilloma, choroid plexus carcinoma, oligoastrocytoma, gliomatosis cerebri, and gliosarcoma. In some embodiments, the invention provides a method of treating a cancer, wherein the cancer is selected from primary central nervous system lymphoma, reticulum cell sarcoma, diffuse histiocytic lymphoma, and microglioma.

**[00906]** In some embodiments, the invention relates to a BTK inhibitor, for example a compound of Formula (XVII) and particularly a compound of Formula (XVIII) to Formula (XVIII-D), or a pharmaceutically acceptable salt or ester, prodrug, solvate or hydrate thereof, for use in the treatment of a glioma. In some embodiments, the invention relates to a BTK inhibitor, for example a compound of Formula (I) and particularly a compound of Formula (II) to Formula (VII), or a pharmaceutically acceptable salt or ester, prodrug, solvate or hydrate thereof, for use in the treatment of a glioma, wherein the glioma is selected from the group consisting of fibrillary astrocytoma, anaplastic astrocytoma, pilocytic astrocytoma, astrocytoma, pleomorphic xanthoastrocytoma, subependymal giant cell astrocytoma, glioblastoma multiforme, oligodendroglioma, ependymoma, subependymoma, choroid plexus tumor, choroid plexus papilloma, choroid plexus carcinoma, oligoastrocytoma, gliomatosis cerebri, and gliosarcoma.

**[00907]** Efficacy of the compounds and combinations of compounds described herein in treating, preventing, ameliorating, and/or managing the indicated diseases or disorders can be tested using various models known in the art. For example, models for determining efficacy of treatments for pancreatic cancer are described in Herreros-Villanueva, *et al.*, *World J. Gastroenterol.* **2012,** *18,* 1286-1294. Models for determining efficacy of treatments for breast cancer are described, *e.g.*, in Fantozzi, *Breast Cancer Res.* **2006,** *8,* 212. Models for determining efficacy of treatments for ovarian cancer are described, for example, in Mullany, *et al.*, *Endocrinology* **2012,** *153,* 1585-92; and Fong, *et al.*, *J. Ovarian Res.* **2009,** *2,* 12. Models for determining efficacy of treatments for melanoma are described, for example, in Damsky, *et al.*, *Pigment Cell & Melanoma Res.* **2010,** *23,* 853–859. Models for determining efficacy of treatments for lung cancer are described, for example, in Meuwissen, *et al.*, *Genes & Development*, **2005,** *19,* 643-664. Models for determining efficacy of treatments for lung cancer are described, for example, in Kim, *Clin. Exp. Otorhinolaryngol.* **2009,** *2,* 55-60; and Sano, *Head Neck Oncol.* **2009,** *1,* 32. Models for determining efficacy of treatments for colorectal cancer, including the

CT26 model, are described below in the examples.

**[00908]** Efficacy of the compounds and combinations of compounds described herein in treating, preventing, ameliorating, and/or managing other indicated diseases or disorders described here can also be tested using other models known in the art. Efficacy in treating, preventing and/or managing asthma can be assessed using the ova induced asthma model described, for example, in Lee, *et al.*, *J. Allergy Clin. Immunol.* **2006,** *118,* 403-9. Efficacy in treating, preventing and/or managing arthritis (*e.g.*, rheumatoid or psoriatic arthritis) can be assessed using the autoimmune animal models described in, for example, Williams, *et al.*, *Chem. Biol.* **2010,** *17,* 123-34, WO 2009/088986, WO 2009/088880, and WO 2011/008302. Efficacy in treating, preventing and/or managing psoriasis can be assessed using transgenic or knockout mouse model with targeted mutations in epidermis, vasculature or immune cells, mouse model resulting from spontaneous mutations, and immuno-deficient mouse model with xenotransplantation of human skin or immune cells, all of which are described, for example, in Boehncke, *et al.*, *Clinics in Dermatology*, **2007,** *25,* 596-605. Efficacy in treating, preventing and/or managing fibrosis or fibrotic conditions can be assessed using the unilateral ureteral obstruction model of renal fibrosis, which is described, for example, in Chevalier, *et al.*, *Kidney International* **2009,** *75,* 1145-1152; the bleomycin induced model of pulmonary fibrosis described in, for example, Moore, *et al.*, *Am. J. Physiol. Lung. Cell. Mol. Physiol.* **2008,** *294,* L152-L160; a variety of liver/biliary fibrosis models described in, for example, Chuang et al., *Clin. Liver Dis.* **2008,** *12,* 333-347 and Omenetti, *et al.*, *Laboratory Investigation*, **2007,** *87,* 499-514 (biliary duct-ligated model); or any of a number of myelofibrosis mouse models such as those described in Varicchio, *et al.*, *Expert Rev. Hematol.* **2009,** *2,* 315-334. Efficacy in treating, preventing and/or managing scleroderma can be assessed using a mouse model induced by repeated local injections of bleomycin described, for example, in Yamamoto, *et al.*, *J. Invest. Dermatol.* **1999,** *112,* 456-462. Efficacy in treating, preventing and/or managing dermatomyositis can be assessed using a myositis mouse model induced by immunization with rabbit myosin as described, for example, in Phyanagi, *et al.*, *Arthritis & Rheumatism,* **2009,** *60(10),* 3118-3127. Efficacy in treating, preventing and/or managing lupus can be assessed using various animal models described, for example, in Ghoreishi, *et al.*, *Lupus*, **2009,** *19,*

1029-1035; Ohl, *et al.*, *J. Biomed. & Biotechnol.*, Article ID 432595 (2011); Xia, *et al.*, *Rheumatology*, **2011,** *50,* 2187-2196; Pau, *et al.*, *PLoS ONE,* **2012,** *7(5)*, e36761; Mustafa, *et al.*, *Toxicology*, **2011,** *90,* 156-168; Ichikawa, *et al.*, *Arthritis & Rheumatism*, **2012,** *62(2)*, 493-503; Rankin, *et al.*, *J. Immunology*, **2012,** *188,* 1656-1667. Efficacy in treating, preventing and/or managing Sjögren's syndrome can be assessed using various mouse models described, for example, in Chiorini, *et al.*, *J. Autoimmunity*, **2009,** *33,* 190-196.

Methods of Treating Hematological Malignancies

**[00909]** In an embodiment, the invention relates to a method of treating a cancer in a mammal, wherein the cancer is a B cell hematological malignancy selected from the group consisting of chronic lymphocytic leukemia (CLL), small lymphocytic leukemia (SLL), non-Hodgkin's lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Hodgkin's lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Burkitt's lymphoma, Waldenström's macroglobulinemia (WM), Burkitt's lymphoma, multiple myeloma, myelodysplatic syndromes, or myelofibrosis. In an embodiment, the invention relates to a method of treating a cancer in a mammal, wherein the cancer is chronic myelocytic leukemia, acute myeloid leukemia, DLBCL (including activated B-cell (ABC) and germinal center B-cell (GCB) subtypes), follicle center lymphoma, Hodgkin's disease, multiple myeloma, indolent non-Hodgkin's lymphoma, and mature B-cell ALL.

**[00910]** In an embodiment, the invention relates to a method of treating CLL in a human that comprises the step of administering to said human a therapeutically effective amount of a BTK inhibitor, including a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In some embodiments for treatment of CLL, a therapeutically effective amount of a PD-1 inhibitor, a PD-L1 inhibitor, and/or a PD-L2 inhibitor or an antigen-binding fragment, variant, conjugate, or biosimilar thereof is also administered before, after or concurrently with a BTK inhibitor. In some embodiments for treatment of CLL, a therapeutically effective amount of a PD-L1 inhibitor, and/or a PD-L2 inhibitor is co-administered with a BTK inhibitor. In some embodiments for treatment of CLL, a therapeutically effective amount of a PI3K inhibitor, including a PI3K inhibitor of Formula (IX) or a

pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, is also administered before, after or concurrently with a BTK inhibitor. In some embodiments, a PI3K inhibitor is co-administered with a BTK inhibitor. In some embodiments for treatment of CLL, a therapeutically effective amount of Formula (XVIII) or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof is co-administered with a therapeutically effective amount of Formula (IX) or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In an embodiment, the invention relates to a method of treating SLL in a human that comprises the step of administering to said human a therapeutically effective amount of a BTK inhibitor of a BTK inhibitor, including a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In some embodiments for treatment of SLL, a therapeutically effective amount of a PD-1 inhibitor, a PD-L1 inhibitor, and/or a PD-L2 inhibitor or an antigen-binding fragment, variant, conjugate, or biosimilar thereof is also administered before, after or concurrently with a BTK inhibitor. In some embodiments for treatment of SLL, a therapeutically effective amount of a PD-L1 inhibitor, and/or a PD-L2 inhibitor is co-administered with a BTK inhibitor. In some embodiments for treatment of SLL, a therapeutically effective amount of a PI3K inhibitor, including a PI3K inhibitor of Formula (IX) or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, is also administered before, after or concurrently with a BTK inhibitor. In some embodiments for treatment of SLL, a therapeutically effective amount of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, is co-administered with a therapeutically effective amount of Formula (IX), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In an embodiment, the invention relates to a method of treating CLL in a human that comprises the step of administering to said human a BTK inhibitor, including a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, in a dosing regimen selected from the group consisting of 100 mg QD, 175 mg QD, 250 mg QD, 400 mg QD, and 100 mg BID. In an embodiment, the invention relates to a method of treating CLL in a human that comprises the step of administering to said human a BTK inhibitor, including a BTK inhibitor of

Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, in a dosing regimen selected from the group consisting of 100 mg QD, 175 mg QD, 250 mg QD, 400 mg QD, and 100 mg BID.

**[00911]** In an embodiment, the invention relates to a use of a composition of a BTK inhibitor, including a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, in the manufacture of a medicament for treating CLL or SLL, wherein the treating comprises the step of administering one or more doses of a BTK inhibitor, including a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In some embodiments, the composition further comprises a PD-L1 inhibitor, and/or a PD-L2 inhibitor or an antigen-binding fragment, variant, conjugate, or biosimilar thereof. In some embodiments, the composition further comprises a PI3K inhibitor, including a PI3K inhibitor of Formula (IX) or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In some embodiments, the composition comprises Formula (XVIII) or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and Formula (IX) or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof.

**[00912]** In an embodiment, the invention relates to a method of treating CLL in a mammal which comprises the step of administering to said mammal a therapeutically effective amount of a BTK inhibitor, including a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In an embodiment, the invention relates to a method of treating SLL in a mammal that comprises the step of administering to said mammal a therapeutically effective amount of a BTK inhibitor, including a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In some embodiments, the method further comprises administering a therapeutically effective amount of a PD-L1 inhibitor, and/or a PD-L2 inhibitor or an antigen-binding fragment, variant, conjugate, or biosimilar thereof before, after, or concurrently with a therapeutically effective amount of a BTK inhibitor. In some embodiments, the method further comprises administering a therapeutically effective amount of a PI3K inhibitor,

including a PI3K inhibitor of Formula (IX) or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof before, after, or concurrently with a therapeutically effective amount of a BTK inhibitor. In some embodiments the method further comprises administering a therapeutically effective amount of Formula (XVIII) or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, before, after, or concurrently with a therapeutically effective amount of Formula (IX) or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof.

**[00913]** In an embodiment, the mammal in any of the foregoing embodiments is selected from the group consisting of a human, a canine, a feline, or an equine. In an embodiment, the mammal in any of the foregoing embodiments is a companion animal.

**[00914]** In an embodiment, the invention relates to a method of treating a subtype of CLL in a human that comprises the step of administering to said mammal a therapeutically effective amount of a BTK inhibitor, including a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. A number of subtypes of CLL have been characterized. CLL is often classified for immunoglobulin heavy-chain variable-region ($IgV_H$) mutational status in leukemic cells. R. N. Damle, *et al.*, *Blood* **1999,** *94,* 1840-47; T. J. Hamblin, *et al.*, *Blood* **1999**, *94,* 1848-54. Patients with $IgV_H$ mutations generally survive longer than patients without $IgV_H$ mutations. ZAP70 expression (positive or negative) is also used to characterize CLL. L. Z. Rassenti, *et al.*, *N. Engl. J. Med.* **2004,** *351,* 893-901. The methylation of ZAP-70 at CpG3 is also used to characterize CLL, for example by pyrosequencing. R. Claus, *et al.*, *J. Clin. Oncol.* **2012,** *30,* 2483-91; J. A. Woyach, *et al.*, *Blood* **2014,** *123,* 1810-17. CLL is also classified by stage of disease under the Binet or Rai criteria. J. L. Binet, *et al.*, *Cancer* **1977,** *40,* 855-64; K. R. Rai, T. Han, *Hematol. Oncol. Clin. North Am.* **1990,** *4,* 447-56. Other common mutations, such as 11p deletion, 13q deletion, and 17p deletion can be assessed using well-known techniques such as fluorescence *in situ* hybridization (FISH). In an embodiment, the invention relates to a method of treating a CLL in a human that comprises the step of administering to said mammal a therapeutically effective amount of a BTK inhibitor, including a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, wherein the CLL is selected from the group

consisting of $IgV_H$ mutation negative CLL, ZAP-70 positive CLL, ZAP-70 methylated at CpG3 CLL, CD38 positive CLL, chronic lymphocytic leukemia characterized by a 17p13.1 (17p) deletion, and CLL characterized by a 11q22.3 (11q) deletion.

**[00915]** In an embodiment, the invention relates to a method of treating a CLL in a human that comprises the step of administering to said mammal a therapeutically effective amount of a BTK inhibitor, including a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, wherein the CLL has undergone a Richter's transformation. Methods of assessing Richter's transformation, which is also known as Richter's syndrome, are described in P. Jain and S. O'Brien, *Oncology*, **2012,** *26,* 1146–52. Richter's transformation is a subtype of CLL that is observed in 5-10% of patients. It involves the development of aggressive lymphoma from CLL and has a generally poor prognosis.

**[00916]** In an embodiment, the invention relates to a method of treating a subtype of CLL in a human, comprising the step of administering to said mammal a therapeutically effective amount of a BTK inhibitor, including a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, wherein the subtype of CLL is a subtype of CLL that increases monocytes and NK cells in peripheral blood when measured after a period of treatment with the BTK inhibitor selected from the group consisting of about 14 days, about 28 days, about 56 days, about 1 month, about 2 months, about 3 months, about 6 months, and about 1 year, and wherein the term "about" refers to a measurement interval of +/- 2 days. In some embodiments for treatment of a subtype of CLL, a therapeutically effective amount of a PD-1 inhibitor, a PD-L1 inhibitor, and/or a PD-L2 inhibitor or an antigen-binding fragment, variant, conjugate, or biosimilar thereof is also administered before, after or concurrently with a BTK inhibitor. In some embodiments for treatment of a subtype of CLL, a therapeutically effective amount of a PD-L1 inhibitor, and/or a PD-L2 inhibitor is co-administered with a BTK inhibitor. In some embodiments for treatment of SLL, a therapeutically effective amount of a PI3K inhibitor, including a PI3K inhibitor of Formula (IX) or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, is also administered before, after or concurrently with a BTK inhibitor. In some embodiments for treatment of a subtype of CLL, a therapeutically effective

amount of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, is co-administered with a therapeutically effective amount of Formula (IX), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof.

**[00917]** In an embodiment, the invention relates to a method of treating CLL or SLL in a patient, wherein the patient is sensitive to lymphocytosis. In an embodiment, the invention relates to a method of treating CLL or SLL in a patient, wherein the patient exhibits lymphocytosis caused by a disorder selected from the group consisting of a viral infection, a bacterial infection, a protozoal infection, or a post-splenectomy state. In an embodiment, the viral infection in any of the foregoing embodiments is selected from the group consisting of infectious mononucleosis, hepatitis, and cytomegalovirus. In an embodiment, the bacterial infection in any of the foregoing embodiments is selected from the group consisting of pertussis, tuberculosis, and brucellosis.

**[00918]** The methods described above may be used as first-line cancer therapy, or after treatment with conventional chemotherapic active pharmaceutical ingredients, including cyclophosphamide, fludarabine, cyclophosphamide and fludarabine (FC chemotherapy), and chlorambucil. The methods described above may also be supplemented with immunotherapeutic monoclonal antibodies such as the anti-CD52 monoclonal antibody alemtuzumab. In an embodiment, the invention relates to a method of treating CLL in a human that comprises the step of administering to said human a therapeutically effective amount of a BTK inhibitor, including a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt, ester, prodrug, cocrystal, solvate or hydrate thereof, and further comprises the step of administering to said human an active pharmaceutical ingredient selected from the group consisting of cyclophosphamide, fludarabine, cyclophosphamide, chlorambucil, salts, esters, prodrugs, cocrystals, solvates, or hydrates thereof, and combinations thereof, and alemtuzumab, antigen-binding fragments, derivatives, conjugates, variants, and radioisotope-labeled complexes thereof.

**[00919]** In an embodiment, the invention relates to a method of treating hematological malignancies in a human comprising the step of administering to said human a therapeutically effective amount of a BTK inhibitor, including a BTK inhibitor of

Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. Hematological malignancies include CLL and SLL, as well as other cancers of the blood, including B cell malignancies. In an embodiment, the invention relates to a method of treating a hematological malignancy selected from the group consisting of non-Hodgkin's lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Hodgkin's lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Waldenström's macroglobulinemia (WM), Burkitt's lymphoma, multiple myeloma, or myelofibrosis in a human that comprises the step of administering a therapeutically effective amount of a BTK inhibitor, including a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In some embodiments for treatment of hematological malignancies, a therapeutically effective amount of a PD-1 inhibitor, a PD-L1 inhibitor, and/or a PD-L2 inhibitor or an antigen-binding fragment, variant, conjugate, or biosimilar thereof is also administered before, after or concurrently with a BTK inhibitor. In some embodiments for treatment of hematological malignancies, a therapeutically effective amount of a PD-L1 inhibitor, and/or a PD-L2 inhibitor is co-administered with a BTK inhibitor. In some embodiments for treatment of hematological malignancies, a therapeutically effective amount of a PI3K inhibitor, including a PI3K inhibitor of Formula (IX) or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, is also administered before, after or concurrently with a BTK inhibitor. In some embodiments for treatment of hematological malignancies, a therapeutically effective amount of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, is co-administered with a therapeutically effective amount of Formula (IX), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof.

**[00920]** In an embodiment, the invention relates to a method of treating a NHL selected from the group consisting of indolent NHL and aggressive NHL comprising the step of administering a therapeutically effective amount of a BTK inhibitor, including a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In some embodiments for treatment of a NHL, a therapeutically effective amount of a PD-1 inhibitor, a PD-L1 inhibitor, and/or a PD-L2

inhibitor or an antigen-binding fragment, variant, conjugate, or biosimilar thereof is also administered before, after or concurrently with a BTK inhibitor. In some embodiments for treatment of a NHL, a therapeutically effective amount of a PD-L1 inhibitor, and/or a PD-L2 inhibitor is co-administered with a BTK inhibitor. In some embodiments for treatment of a NHL, a therapeutically effective amount of a PI3K inhibitor, including a PI3K inhibitor of Formula (IX) or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, is also administered before, after or concurrently with a BTK inhibitor. In some embodiments for treatment of a NHL, a therapeutically effective amount of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, is co-administered with a therapeutically effective amount of Formula (IX), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof.

**[00921]** In an embodiment, the invention relates to a method of treating a DLBCL selected from the group consisting of activated B-cell like diffuse large B-cell lymphoma (DLBCL-ABC) and germinal center B-cell like diffuse large B-cell lymphoma (DLBCL-GCB), comprising the step of administering a therapeutically effective amount of a BTK inhibitor, including a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In some embodiments for treatment of a DLBCL, a therapeutically effective amount of a PD-1 inhibitor, a PD-L1 inhibitor, and/or a PD-L2 inhibitor or an antigen-binding fragment, variant, conjugate, or biosimilar thereof is also administered before, after or concurrently with a BTK inhibitor. In some embodiments for treatment of a DLBCL, a therapeutically effective amount of a PD-L1 inhibitor, and/or a PD-L2 inhibitor is co-administered with a BTK inhibitor. In some embodiments for treatment of a DLBCL, a therapeutically effective amount of a PI3K inhibitor, including a PI3K inhibitor of Formula (IX) or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, is also administered before, after or concurrently with a BTK inhibitor. In some embodiments for treatment of a DLBCL, a therapeutically effective amount of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, is co-administered with a therapeutically effective amount of Formula (IX), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate

thereof.

**[00922]** In an embodiment, the invention relates to a method of treating an MCL selected from the group consisting of mantle zone MCL, nodular MCL, diffuse MCL, and blastoid MCL (also known as blastic variant MCL), comprising the step of administering a therapeutically effective amount of a BTK inhibitor, including a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In some embodiments for treatment of an MCL, a therapeutically effective amount of a PD-1 inhibitor, a PD-L1 inhibitor, and/or a PD-L2 inhibitor or an antigen-binding fragment, variant, conjugate, or biosimilar thereof is also administered before, after or concurrently with a BTK inhibitor. In some embodiments for treatment of an MCL, a therapeutically effective amount of a PD-L1 inhibitor, and/or a PD-L2 inhibitor is co-administered with a BTK inhibitor. In some embodiments for treatment of an MCL, a therapeutically effective amount of a PI3K inhibitor, including a PI3K inhibitor of Formula (IX) or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, is also administered before, after or concurrently with a BTK inhibitor. In some embodiments for treatment of an MCL, a therapeutically effective amount of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, is co-administered with a therapeutically effective amount of Formula (IX), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof.

**[00923]**

**[00924]** In an embodiment, the invention relates to a method of treating a B-ALL selected from the group consisting of early pre-B cell B-ALL, pre-B cell B-ALL, and mature B cell B-ALL (also known as Burkitt's leukemia), comprising the step of administering a therapeutically effective amount of a BTK inhibitor, including a BTK inhibitor, including a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In some embodiments for treatment of a B-ALL, a therapeutically effective amount of a PD-1 inhibitor, a PD-L1 inhibitor, and/or a PD-L2 inhibitor or an antigen-binding fragment, variant, conjugate, or biosimilar thereof is also administered before, after or concurrently

with a BTK inhibitor. In some embodiments for treatment of a B-ALL, a therapeutically effective amount of a PD-L1 inhibitor, and/or a PD-L2 inhibitor is co-administered with a BTK inhibitor. In some embodiments for treatment of a B-ALL, a therapeutically effective amount of a PI3K inhibitor, including a PI3K inhibitor of Formula (IX) or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, is also administered before, after or concurrently with a BTK inhibitor. In some embodiments for treatment of a B-ALL, a therapeutically effective amount of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, is co-administered with a therapeutically effective amount of Formula (IX), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof.

**[00925]** In an embodiment, the invention relates to a method of treating a Burkitt's lymphoma selected from the group consisting of sporadic Burkitt's lymphoma, endemic Burkitt's lymphoma, and human immunodeficiency virus-associated Burkitt's lymphoma, comprising the step of administering a therapeutically effective amount of a BTK inhibitor, including a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In some embodiments for treatment of a Burkitt's lymphoma, a therapeutically effective amount of a PD-1 inhibitor, a PD-L1 inhibitor, and/or a PD-L2 inhibitor or an antigen-binding fragment, variant, conjugate, or biosimilar thereof is also administered before, after or concurrently with a BTK inhibitor. In some embodiments for treatment of a Burkitt's lymphoma, a therapeutically effective amount of a PD-L1 inhibitor, and/or a PD-L2 inhibitor is co-administered with a BTK inhibitor. In some embodiments for treatment of a Burkitt's lymphoma, a therapeutically effective amount of a PI3K inhibitor, including a PI3K inhibitor of Formula (IX) or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, is also administered before, after or concurrently with a BTK inhibitor. In some embodiments for treatment of a Burkitt's lymphoma, a therapeutically effective amount of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, is co-administered with a therapeutically effective amount of Formula (IX), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof.

**[00926]** In an embodiment, the invention relates to a method of treating a multiple myeloma selected from the group consisting of hyperdiploid multiple myeloma and non-hyperdiploid multiple myeloma, comprising the step of administering a therapeutically effective amount of a BTK inhibitor, including a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In some embodiments for treatment of a multiple myeloma, a therapeutically effective amount of a PD-1 inhibitor, a PD-L1 inhibitor, and/or a PD-L2 inhibitor or an antigen-binding fragment, variant, conjugate, or biosimilar thereof is also administered before, after or concurrently with a BTK inhibitor. In some embodiments for treatment of a multiple myeloma, a therapeutically effective amount of a PD-L1 inhibitor, and/or a PD-L2 inhibitor is co-administered with a BTK inhibitor. In some embodiments for treatment of a multiple myeloma, a therapeutically effective amount of a PI3K inhibitor, including a PI3K inhibitor of Formula (IX) or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, is also administered before, after or concurrently with a BTK inhibitor. In some embodiments for treatment of a multiple myeloma, a therapeutically effective amount of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, is co-administered with a therapeutically effective amount of Formula (IX), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof.

**[00927]** In an embodiment, the invention relates to a method of treating a myelofibrosis selected from the group consisting of primary myelofibrosis (also known as chronic idiopathic myelofibrosis) and myelofibrosis secondary to polycythemia vera or essential thrombocythaemia, comprising the step of administering a therapeutically effective amount of a BTK inhibitor, including a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In some embodiments, the invention provides a method of treating disorders such as myeloproliferative disorders (MPDs), myeloproliferative neoplasms, polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), myelodysplastic syndrome, chronic myelogenous leukemia (BCR-ABL1-positive), chronic neutrophilic leukemia, chronic eosinophilic leukemia, or mastocytosis. In some embodiments for treatment of a myelofibrosis, a therapeutically effective amount of a PD-1 inhibitor, a

PD-L1 inhibitor, and/or a PD-L2 inhibitor or an antigen-binding fragment, variant, conjugate, or biosimilar thereof is also administered before, after or concurrently with a BTK inhibitor. In some embodiments for treatment of a myelofibrosis, a therapeutically effective amount of a PD-L1 inhibitor, and/or a PD-L2 inhibitor is co-administered with a BTK inhibitor. In some embodiments for treatment of a myelofibrosis, a therapeutically effective amount of a PI3K inhibitor, including a PI3K inhibitor of Formula (IX) or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, is also administered before, after or concurrently with a BTK inhibitor. In some embodiments for treatment of a myelofibrosis, a therapeutically effective amount of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, is co-administered with a therapeutically effective amount of Formula (IX), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof.

**[00928]** In an embodiment, the invention relates to a method of treating a subtype of a hematological malignancy in a human, comprising the step of administering to said human a therapeutically effective amount of a BTK inhibitor, including a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, wherein the subtype of a hematological malignancy is a subtype of a hematological malignancy that increases monocytes and NK cells in peripheral blood when measured after a period of treatment with the BTK inhibitor selected from the group consisting of about 14 days, about 28 days, about 56 days, about 1 month, about 2 months, about 3 months, about 6 months, and about 1 year, wherein the term "about" refers to a measurement interval of +/- 2 days, and wherein the hematological malignancy is selected from the group consisting of non-Hodgkin's lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Hodgkin's lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Waldenström's macroglobulinemia (WM), Burkitt's lymphoma, multiple myeloma, or myelofibrosis. In some embodiments for treatment of a subtype of a hematological malignancy, a therapeutically effective amount of a PD-1 inhibitor, a PD-L1 inhibitor, and/or a PD-L2 inhibitor or an antigen-binding fragment, variant, conjugate, or biosimilar thereof is also administered before, after or concurrently with a

BTK inhibitor. In some embodiments for treatment of a subtype of a hematological malignancy, a therapeutically effective amount of a PD-L1 inhibitor, and/or a PD-L2 inhibitor is co-administered with a BTK inhibitor. In some embodiments for treatment of a subtype of a hematological malignancy, a therapeutically effective amount of a PI3K inhibitor, including a PI3K inhibitor of Formula (IX) or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, is also administered before, after or concurrently with a BTK inhibitor. In some embodiments for treatment of a subtype of a hematological malignancy, a therapeutically effective amount of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, is co-administered with a therapeutically effective amount of Formula (IX), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof.

Methods of Treating Other Disorders

**[00929]** In some embodiments, the invention relates to a method of treating an inflammatory, immune, or autoimmune disorder in a mammal with a combination of a PI3K inhibitor, including a PI3K-γ or PI3K-δ inhibitor, a JAK-2 inhibitor, a BTK inhibitor, a PD-1 inhibitor, and/or a PD-L1 inhibitor. In some embodiments, the invention also relates to a method of treating a disease with a combination of a PI3K inhibitor, including a PI3K-γ or PI3K-δ inhibitor, a JAK-2 inhibitor, a BTK inhibitor, a PD-1 inhibitor, and/or a PD-L1 inhibitor, wherein the disease is selected from the group consisting of tumor angiogenesis, chronic inflammatory disease, rheumatoid arthritis, atherosclerosis, inflammatory bowel disease, skin diseases such as psoriasis, eczema, and scleroderma, diabetes, diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, ulcerative colitis, atopic dermatitis, pouchitis, spondylarthritis, uveitis, Behcet's disease, polymyalgia rheumatica, giant-cell arteritis, sarcoidosis, Kawasaki disease, juvenile idiopathic arthritis, hidratenitis suppurativa, Sjögren's syndrome, psoriatic arthritis, juvenile rheumatoid arthritis, ankylosing spoldylitis, Crohn's Disease, lupus, lupus nephritis, hepatitis C virus infection, non-cancerous hyperproliferative disorders, benign hyperplasia of the skin (e.g., psoriasis), restenosis, and prostate hyperproliferative disorders (e.g., benign prostatic hypertrophy (BPH)). In some embodiments for treatment of an inflammatory, immune, or

autoimmune disorder, a therapeutically effective amount of a PD-1 inhibitor, a PD-L1 inhibitor, and/or a PD-L2 inhibitor or an antigen-binding fragment, variant, conjugate, or biosimilar thereof is also administered before, after or concurrently with a BTK inhibitor. In some embodiments for treatment of an inflammatory, immune, or autoimmune disorder, a therapeutically effective amount of a PD-L1 inhibitor, and/or a PD-L2 inhibitor is co-administered with a BTK inhibitor. In some embodiments for treatment of an inflammatory, immune, or autoimmune disorder, a therapeutically effective amount of a PI3K inhibitor, including a PI3K inhibitor of Formula (IX) or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, is also administered before, after or concurrently with a BTK inhibitor. In some embodiments for treatment of an inflammatory, immune, or autoimmune disorder, a therapeutically effective amount of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, is co-administered with a therapeutically effective amount of Formula (IX), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof.

Methods of Treating Patients Sensitive to Bleeding Events

**[00930]** In some embodiments, the invention provides a method of treating a cancer in a human sensitive to bleeding events, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof, and a PD-1 inhibitor or a PD-L1 inhibitor, or antigen-binding fragments, variants, or conjugates thereof. In a preferred embodiment, the invention provides a method of treating a cancer in a human sensitive to bleeding events, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is Formula (XVIII), or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof. In some embodiments for treatment of a cancer in a human sensitive to bleeding, a therapeutically effective amount of a PD-1 inhibitor, a PD-L1 inhibitor, and/or a PD-L2 inhibitor or an antigen-binding fragment, variant, conjugate, or biosimilar thereof is also administered before, after or concurrently with a BTK inhibitor. In some embodiments for treatment of a cancer in a human sensitive to bleeding, a therapeutically effective amount of a PD-L1 inhibitor, and/or a PD-L2 inhibitor is co-administered with a BTK inhibitor. In some

embodiments for treatment of a cancer in a human sensitive to bleeding, a therapeutically effective amount of a PI3K inhibitor, including a PI3K inhibitor of Formula (IX) or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, is also administered before, after or concurrently with a BTK inhibitor. In some embodiments, a PI3K inhibitor is co-administered with a BTK inhibitor. In some embodiments for treatment of a cancer in a human sensitive to bleeding, a therapeutically effective amount of Formula (XVIII) or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof is co-administered with a therapeutically effective amount of Formula (IX) or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In some embodiments, the invention provides a method of treating a hyperproliferative disorder, such as a cancer or an inflammatory, immune, or autoimmune disease, in a human intolerant to ibrutinib.

**[00931]** In some embodiments, the invention provides a method of treating a cancer in a human sensitive to bleeding events, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is Formula (XVIII), or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof, and a PD-1 inhibitor or a PD-L1 inhibitor, or antigen-binding fragments, variants, or conjugates thereof, further comprising the step of administering a therapeutically effective dose of an anticoagulent or antiplatelet active pharmaceutical ingredient.

**[00932]** In some embodiments, the invention provides a method of treating a cancer in a human sensitive to bleeding events, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is Formula (XVIII), and wherein the cancer is selected from the group consisting of bladder cancer, squamous cell carcinoma including head and neck cancer, pancreatic ductal adenocarcinoma (PDA), pancreatic cancer, colon carcinoma, mammary carcinoma, breast cancer, fibrosarcoma, mesothelioma, renal cell carcinoma, lung carcinoma, thyoma, prostate cancer, colorectal cancer, ovarian cancer, acute myeloid leukemia, thymus cancer, brain cancer, squamous cell cancer, skin cancer, eye cancer, retinoblastoma, melanoma, intraocular melanoma, oral cavity and oropharyngeal cancers, gastric cancer, stomach cancer, cervical cancer, head, neck, renal cancer, kidney cancer, liver cancer,

ovarian cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, acquired immune deficiency syndrome (AIDS)-related cancers (e.g., lymphoma and Kaposi's sarcoma), viral-induced cancer, glioblastoma, esophogeal tumors, hematological neoplasms, non-small-cell lung cancer, chronic myelocytic leukemia, diffuse large B-cell lymphoma, esophagus tumor, follicle center lymphoma, head and neck tumor, hepatitis C virus infection, hepatocellular carcinoma, Hodgkin's disease, metastatic colon cancer, multiple myeloma, non-Hodgkin's lymphoma, indolent non-Hodgkin's lymphoma, ovary tumor, pancreas tumor, renal cell carcinoma, small-cell lung cancer, stage IV melanoma, chronic lymphocytic leukemia, B-cell acute lymphoblastic leukemia (ALL), mature B-cell ALL, follicular lymphoma, mantle cell lymphoma, and Burkitt's lymphoma.

**[00933]** In some embodiments, the invention provides a method of treating a disease in a human sensitive to or intolerant to ibrutinib.

**[00934]** In some embodiments, the invention provides a method of treating a cancer in a human sensitive to platelet-mediated thrombosis comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is Formula (XVIII), or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof, and a PD-1 inhibitor or a PD-L1 inhibitor, or antigen-binding fragments, variants, or conjugates thereof.

**[00935]** In some embodiments, the BTK inhibitor and the anticoagulent or the antiplatelet active pharmaceutical ingredient are administered sequentially. In some embodiments, the BTK inhibitor and the anticoagulent or the antiplatelet active pharmaceutical ingredient are administered concomittently. In some embodiments, the BTK inhibitor is administered before the anticoagulent or the antiplatelet active pharmaceutical ingredient. In some embodiments, the BTK inhibitor is administered after the anticoagulent or the antiplatelet active pharmaceutical ingredient. In some embodiments, a PD-1 or PD-L1 inhibitor is co-administered with the BTK inhibitor and the anticoagulent or the antiplatelet active pharmaceutical ingredient at the same time or at different times.

**[00936]** Selected anti-platelet and anticoagulent active pharmaceutical ingredients for

use in the methods of the present invention include, but are not limited to, cyclooxygenase inhibitors (e.g., aspirin), adenosine diphosphate (ADP) receptor inhibitors (e.g., clopidogrel and ticlopidine), phosphodiesterase inhibitors (e.g., cilostazol), glycoprotein IIb/IIIa inhibitors (e.g., abciximab, eptifibatide, and tirofiban), adenosine reuptake inhibitors (e.g., dipyridamole), and acetylsalicylic acid (aspirin). In other embodiments, examples of anti-platelet active pharmaceutical ingredients for use in the methods of the present invention include anagrelide, aspirin/extended-release dipyridamole, cilostazol, clopidogrel, dipyridamole, prasugrel, ticagrelor, ticlopidine, vorapaxar, tirofiban HCl, eptifibatide, abciximab, argatroban, bivalirudin, dalteparin, desirudin, enoxaparin, fondaparinux, heparin, lepirudin, apixaban, dabigatran etexilate mesylate, rivaroxaban, and warfarin.

**[00937]** In an embodiment, the invention includes a method of treating a cancer, comprising the step of orally administering, to a human in need thereof, a Bruton's tyrosine kinase (BTK) inhibitor, wherein the BTK inhibitor is (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and a PD-1 inhibitor or a PD-L1 inhibitor, or antigen-binding fragments, variants, or conjugates thereof, further comprising the step of administering a therapeutically effective dose of an anticoagulant or antiplatelet active pharmaceutical ingredient, wherein the anticoagulant or antiplatelet active pharmaceutical ingredient is selected from the group consisting of acenocoumarol, anagrelide, anagrelide hydrochloride, abciximab, aloxiprin, antithrombin, apixaban, argatroban, aspirin, aspirin with extended-release dipyridamole, beraprost, betrixaban, bivalirudin, carbasalate calcium, cilostazol, clopidogrel, clopidogrel bisulfate, cloricromen, dabigatran etexilate, darexaban, dalteparin, dalteparin sodium, defibrotide, dicumarol, diphenadione, dipyridamole, ditazole, desirudin, edoxaban, enoxaparin, enoxaparin sodium, eptifibatide, fondaparinux, fondaparinux sodium, heparin, heparin sodium, heparin calcium, idraparinux, idraparinux sodium, iloprost, indobufen, lepirudin, low molecular weight heparin, melagatran, nadroparin, otamixaban, parnaparin, phenindione, phenprocoumon, prasugrel, picotamide, prostacyclin, ramatroban, reviparin, rivaroxaban, sulodexide, terutroban, terutroban sodium, ticagrelor, ticlopidine, ticlopidine hydrochloride, tinzaparin, tinzaparin sodium, tirofiban, tirofiban hydrochloride,

treprostinil, treprostinil sodium, triflusal, vorapaxar, warfarin, warfarin sodium, ximelagatran, salts thereof, solvates thereof, hydrates thereof, and combinations thereof.

Combinations of BTK Inhibitors, PI3K Inhibitors, JAK-2 Inhibitors, PD-1 Inhibitors, and/or PD-L1 and PD-L2 Inhibitors with Anti-CD20 Antibodies

**[00938]** The BTK inhibitors of the present invention and combinations of the BTK inhibitors with PI3K inhibitors, JAK-2 inhibitors, PD-1 inhibitors, and/or PD-L1 inhibitors may also be safely co-administered with immunotherapeutic antibodies such as the anti-CD20 antibodies rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, and ibritumomab, and or antigen-binding fragments, derivatives, conjugates, variants, and radioisotope-labeled complexes thereof, which may be given alone or with conventional chemotherapeutic active pharmaceutical ingredients such as those described herein. The CD20 antigen also called human B-lymphocyte-restricted differentiation antigen, Bp35, or B1) is found on the surface of normal "pre-B" and mature B lymphocytes, including malignant B lymphocytes. Nadler, *et al.*, *J. Clin. Invest.* **1981,** *67,* 134-40; Stashenko, *et al.*, *J. Immunol.* **1980,** *139,* 3260-85. The CD20 antigen is a glycosylated integral membrane protein with a molecular weight of approximately 35 kD. Tedder, *et al.*, *Proc. Natl. Acad. Sci. USA,* **1988,** *85,* 208-12. CD20 is also expressed on most B cell non-Hodgkin's lymphoma cells, but is not found on hematopoietic stem cells, pro-B cells, normal plasma cells, or other normal tissues. Anti-CD20 antibodies are currently used as therapies for many hematological malignancies, including indolent NHL, aggressive NHL, and CLL/SLL. Lim, *et. al.*, *Haematologica* **2010,** *95,* 135-43; Beers, *et. al.*, *Sem. Hematol.* **2010,** *47,* 107-14; and Klein, *et al.*, *mAbs* **2013,** *5,* 22-33. In an embodiment, the foregoing combinations exhibit synergistic effects that result in greater efficacy, less side effects, the use of less active pharmaceutical ingredient to achieve a given clinical result, and/or other synergistic effects.

**[00939]** In an embodiment, the invention relates to a method of treating a hematological malignancy, solid tumor cancer, or immune, autoimmune, or inflammatory disorder in a human comprising the step of administering to said human a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and further comprising the step of administering an anti-CD20 antibody,

wherein the anti-CD20 antibody is a monoclonal antibody or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof. In an embodiment, the invention relates to a method of treating a hematological malignancy, solid tumor cancer, or immune, autoimmune, or inflammatory disorder in a human comprising the step of administering to said human a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and further comprising the step of administering an anti-CD20 antibody, wherein the anti-CD20 antibody is an anti-CD20 monoclonal antibody or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof, and wherein the anti-CD20 antibody specifically binds to human CD20 with a $K_D$ selected from the group consisting of $1\times10^{-7}$ M or less, $5\times10^{-8}$ M or less, $1\times10^{-8}$ M or less, and $5\times10^{-9}$ M or less. Anti-CD20 monoclonal antibodies are classified as Type I or Type II, as described in Klein, *et al.*, *mAbs* **2013,** *5,* 22-33. Type I anti-CD20 monoclonal antibodies are characterized by binding to the Class I epitope, localization of CD20 to lipid rafts, high complement-dependent cytotoxicity, full binding capacity, weak homotypic aggregation, and moderate cell death induction. Type II anti-CD20 monoclonal antibodies are characterized by binding to the Class I epitope, a lack of localization of CD20 to lipid rafts, low complement-dependent cytotoxicity, half binding capacity, homotypic aggregation, and strong cell death induction. Both Type I and Type II anti-CD20 monoclonal antibodies exhibit antibody-dependent cytotoxiticy (ADCC) and are thus useful with BTK inhibitors described herein. Type I anti-CD20 monoclonal antibodies include but are not limited to rituximab, ocrelizumab, and ofatumumab. Type II anti-CD20 monoclonal antibodies include but are not limited to obinutuzumab and tositumomab. In some embodiments for treatment of a hematological malignancy, solid tumor cancer, or immune, autoimmune, or inflammatory disorder, a therapeutically effective amount of a PD-1 inhibitor, a PD-L1 inhibitor, and/or a PD-L2 inhibitor or an antigen-binding fragment, variant, conjugate, or biosimilar thereof is also administered before, after or concurrently with a BTK inhibitor. In some embodiments for treatment of a hematological malignancy, solid tumor cancer, or immune, autoimmune, or inflammatory disorder , a therapeutically effective amount of a PD-L1 inhibitor, and/or a PD-L2 inhibitor is co-administered with a BTK inhibitor. In some embodiments for

treatment of a hematological malignancy, solid tumor cancer, or immune, autoimmune, or inflammatory disorder, a therapeutically effective amount of a PI3K inhibitor, including a PI3K inhibitor of Formula (IX) or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, is also administered before, after or concurrently with a BTK inhibitor. In some embodiments for treatment of a hematological malignancy, solid tumor cancer, or immune, autoimmune, or inflammatory disorder, a therapeutically effective amount of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, is co-administered with a therapeutically effective amount of Formula (IX), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof.

**[00940]** In an embodiment, the invention relates to a method of treating a hematological malignancy, solid tumor cancer, or immune, autoimmune, or inflammatory disorder in a human comprising the step of administering to said human a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and further comprising the step of administering an anti-CD20 antibody, wherein the anti-CD20 antibody is a monoclonal antibody or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof. In an embodiment, the invention relates to a method of treating a hematological malignancy, solid tumor cancer, or immune, autoimmune, or inflammatory disorder in a human comprising the step of administering to said human a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and further comprising the step of administering an anti-CD20 antibody, wherein the anti-CD20 antibody is an anti-CD20 monoclonal antibody or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof, and wherein the anti-CD20 antibody specifically binds to human CD20 with a $K_D$ selected from the group consisting of $1\times10^{-7}$ M or less, $5\times10^{-8}$ M or less, $1\times10^{-8}$ M or less, and $5\times10^{-9}$ M or less.

**[00941]** In an embodiment, the invention relates to a method of treating a hematological malignancy, solid tumor cancer, or immune, autoimmune, or inflammatory disorder in a human comprising the step of administering to said human a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or

hydrate thereof, and further comprising the step of administering an Type I anti-CD20 antibody, or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof. In an embodiment, the invention relates to a method of treating a hematological malignancy, solid tumor cancer, or immune, autoimmune, or inflammatory disorder in a human comprising the step of administering to said human a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and further comprising the step of administering an Type II anti-CD20 antibody, or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof. In an embodiment, the invention relates to a method of treating a hematological malignancy, solid tumor cancer, or immune, autoimmune, or inflammatory disorder in a human comprising the step of administering to said human a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and a PD-1 or PD-L1 inhibitor, or an antigen-binding fragment, derivative, conjugate, or variant thereof, and further comprising the step of administering an Type I anti-CD20 antibody, or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof. In an embodiment, the invention relates to a method of treating a hematological malignancy, solid tumor cancer, or immune, autoimmune, or inflammatory disorder in a human comprising the step of administering to said human a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and a PD-1 or PD-L1 inhibitor, or an antigen-binding fragment, derivative, conjugate, or variant thereof, and further comprising the step of administering an Type II anti-CD20 antibody, or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof.

**[00942]** In some embodiments, the BTK inhibitors of the present invention and combinations of the BTK inhibitors with PI3K inhibitors, JAK-2 inhibitors, PD-1 inhibitors, and/or PD-L1 inhibitors and the anti-CD20 monoclonal antibody are administered sequentially. In some embodiments, the BTK inhibitors of the present invention and combinations of the BTK inhibitors with PI3K inhibitors, JAK-2 inhibitors, PD-1 inhibitors, and/or PD-L1 inhibitors and the anti-CD20 monoclonal antibody are administered concomitantly. In some embodiments, the BTK inhibitors of the present

invention and combinations of the BTK inhibitors with PI3K inhibitors, JAK-2 inhibitors, PD-1 inhibitors, and/or PD-L1 inhibitors is administered before the anti-CD20 monoclonal antibody. In some embodiments, the BTK inhibitors of the present invention and combinations of the BTK inhibitors with PI3K inhibitors, JAK-2 inhibitors, PD-1 inhibitors, and/or PD-L1 inhibitors is administered after the anticoagulant or the antiplatelet active pharmaceutical ingredient. In some embodiments, the BTK inhibitors of the present invention and combinations of the BTK inhibitors with PI3K inhibitors, JAK-2 inhibitors, PD-1 inhibitors, and/or PD-L1 inhibitors and the anti-CD20 monoclonal antibody are administered over the same time period, and the BTK inhibitor administration continues after the anti-CD20 monoclonal antibody administration is completed.

**[00943]** In an embodiment, the anti-CD20 monoclonal antibody is rituximab, or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof. Rituximab is a chimeric murine-human monoclonal antibody directed against CD20, and its structure comprises an IgG1 kappa immunoglobulin containing murine light- and heavy-chain variable region sequences and human constant region sequences. Rituximab is composed of two heavy chains of 451 amino acids and two light chains of 213 amino acids. The amino acid sequence for the heavy chains of rituximab is set forth in SEQ ID NO:84. The amino acid sequence for the light chains of rituximab is set forth in SEQ ID NO:85. Rituximab is commercially available, and its properties and use in cancer and other diseases is described in more detail in Rastetter, *et al.*, *Ann. Rev. Med.* **2004,** *55,* 477-503, and in Plosker and Figgett, *Drugs*, **2003,** *63,* 803-43. In an embodiment, the anti-CD20 monoclonal antibody is an anti-CD20 biosimilar monoclonal antibody approved by drug regulatory authorities with reference to rituximab. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 90% to SEQ ID NO:84. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 90% to SEQ ID NO:85. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 95% to SEQ ID NO:84. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 95% to SEQ ID NO:85. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of

greater than 98% to SEQ ID NO:84. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 98% to SEQ ID NO:85. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 99% to SEQ ID NO:84. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 99% to SEQ ID NO:85.

**[00944]** In an embodiment, the anti-CD20 monoclonal antibody is obinutuzumab, or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof. Obinutuzumab is also known as afutuzumab or GA-101. Obinutuzumab is a humanized monoclonal antibody directed against CD20. The amino acid sequence for the heavy chains of obinutuzumab is set forth in SEQ ID NO:86. The amino acid sequence for the light chains of obinutuzumab is set forth in SEQ ID NO:87. Obinutuzumab is commercially available, and its properties and use in cancer and other diseases is described in more detail in Robak, *Curr. Opin. Investig. Drugs* **2009,** *10,* 588-96. In an embodiment, the anti-CD20 monoclonal antibody is an anti-CD20 biosimilar monoclonal antibody approved by drug regulatory authorities with reference to obinutuzumab. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 90% to SEQ ID NO:86. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 90% to SEQ ID NO:87. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 95% to SEQ ID NO:86. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 95% to SEQ ID NO:87. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 98% to SEQ ID NO:86. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 98% to SEQ ID NO:87. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 99% to SEQ ID NO:86. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 99% to SEQ ID NO:87. In an embodiment, the anti-CD20 monoclonal antibody obinutuzumab is an immunoglobulin G1, anti-(human B-lymphocyte antigen CD20 (membrane-spanning 4-domains subfamily A member 1, B-lymphocyte surface antigen B1, Leu-16 or Bp35)), humanized mouse monoclonal obinutuzumab des-CH3107-K-γ1

heavy chain (222-219')-disulfide with humanized mouse monoclonal obinutuzumab κ light chain dimer (228-228":231- 231")-bisdisulfide antibody.

**[00945]** In an embodiment, the anti-CD20 monoclonal antibody is ofatumumab, or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof. Ofatumumab is described in Cheson, *J. Clin. Oncol.* **2010,** *28,* 3525-30. The crystal structure of the Fab fragment of ofatumumab has been reported in Protein Data Bank reference 3GIZ and in Du, *et al.*, *Mol. Immunol.* **2009,** *46,* 2419-2423. Ofatumumab is commercially available, and its preparation, properties, and use in cancer and other diseases are described in more detail in U.S. Patent No. 8,529,202 B2, the disclosure of which is incorporated herein by reference. In an embodiment, the anti-CD20 monoclonal antibody is an anti-CD20 biosimilar monoclonal antibody approved by drug regulatory authorities with reference to ofatumumab. In an embodiment, the anti-CD20 monoclonal antibody has a variable heavy chain sequence identity of greater than 90% to SEQ ID NO:88. In an embodiment, the anti-CD20 monoclonal antibody has a variable light chain sequence identity of greater than 90% to SEQ ID NO:89. In an embodiment, the anti-CD20 monoclonal antibody has a variable heavy chain sequence identity of greater than 95% to SEQ ID NO:88. In an embodiment, the anti-CD20 monoclonal antibody has a variable light chain sequence identity of greater than 95% to SEQ ID NO:89. In an embodiment, the anti-CD20 monoclonal antibody has a variable heavy chain sequence identity of greater than 98% to SEQ ID NO:88. In an embodiment, the anti-CD20 monoclonal antibody has a variable light chain sequence identity of greater than 98% to SEQ ID NO:89. In an embodiment, the anti-CD20 monoclonal antibody has a variable heavy chain sequence identity of greater than 99% to SEQ ID NO:88. In an embodiment, the anti-CD20 monoclonal antibody has a variable light chain sequence identity of greater than 99% to SEQ ID NO:89. In an embodiment, the anti-CD20 monoclonal antibody has a Fab fragment heavy chain sequence identity of greater than 90% to SEQ ID NO:90. In an embodiment, the anti-CD20 monoclonal antibody has a Fab fragment light chain sequence identity of greater than 90% to SEQ ID NO:91. In an embodiment, the anti-CD20 monoclonal antibody has a Fab fragment heavy chain sequence identity of greater than 95% to SEQ ID NO:90. In an embodiment, the anti-CD20 monoclonal antibody has a Fab fragment light chain sequence identity of greater

than 95% to SEQ ID NO:91. In an embodiment, the anti-CD20 monoclonal antibody has a Fab fragment heavy chain sequence identity of greater than 98% to SEQ ID NO:90. In an embodiment, the anti-CD20 monoclonal antibody has a Fab fragment light chain sequence identity of greater than 98% to SEQ ID NO:91. In an embodiment, the anti-CD20 monoclonal antibody has a Fab fragment heavy chain sequence identity of greater than 99% to SEQ ID NO:90. In an embodiment, the anti-CD20 monoclonal antibody has a Fab fragment light chain sequence identity of greater than 99% to SEQ ID NO:91. In an embodiment, the anti-CD20 monoclonal antibody ofatumumab is an immunoglobulin G1, anti-(human B-lymphocyte antigen CD20 (membrane-spanning 4-domains subfamily A member 1, B-lymphocyte surface antigen B1, Leu-16 or Bp35)); human monoclonal ofatumumab-CD20 γ1 heavy chain (225-214')-disulfide with human monoclonal ofatumumab-CD20 κ light chain, dimer (231-231":234-234")-bisdisulfide antibody.

**[00946]** In an embodiment, the anti-CD20 monoclonal antibody is veltuzumab, or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof. Veltuzumab is also known as hA20. Veltuzumab is described in Goldenberg, *et al.*, *Leuk. Lymphoma* **2010**, *51*, 747-55. In an embodiment, the anti-CD20 monoclonal antibody is an anti-CD20 biosimilar monoclonal antibody approved by drug regulatory authorities with reference to veltuzumab. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 90% to SEQ ID NO:92. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 90% to SEQ ID NO:93. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 95% to SEQ ID NO:92. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 95% to SEQ ID NO:93. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 98% to SEQ ID NO:92. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 98% to SEQ ID NO:93. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 99% to SEQ ID NO:92. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 99% to SEQ ID NO:93. In an embodiment, the anti-CD20 monoclonal antibody ofatumumab is an immunoglobulin G1, anti-(human B-lymphocyte antigen

CD20 (membrane-spanning 4-domains subfamily A member 1, Leu-16, Bp35)); [218-arginine,360-glutamic acid,362-methionine]humanized mouse monoclonal hA20 γ1 heavy chain (224-213')-disulfide with humanized mouse monoclonal hA20 κ light chain (230-230":233-233")-bisdisulfide dimer

**[00947]** In an embodiment, the anti-CD20 monoclonal antibody is tositumomab, or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof. In an embodiment, the anti-CD20 monoclonal antibody is $^{131}$I-labeled tositumomab. In an embodiment, the anti-CD20 monoclonal antibody is an anti-CD20 biosimilar monoclonal antibody approved by drug regulatory authorities with reference to tositumomab. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 90% to SEQ ID NO:94. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 90% to SEQ ID NO:95. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 95% to SEQ ID NO:94. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 95% to SEQ ID NO:95. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 98% to SEQ ID NO:94. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 98% to SEQ ID NO:95. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 99% to SEQ ID NO:94. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 99% to SEQ ID NO:95.

**[00948]** In an embodiment, the anti-CD20 monoclonal antibody is ibritumomab, or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof. The active form of ibritumomab used in therapy is ibritumomab tiuxetan. When used with ibritumomab, the chelator tiuxetan (diethylene triamine pentaacetic acid) is complexed with a radioactive isotope such as $^{90}$Y or $^{111}$In. In an embodiment, the anti-CD20 monoclonal antibody is ibritumomab tiuxetan, or radioisotope-labeled complex thereof. In an embodiment, the anti-CD20 monoclonal antibody is an anti-CD20 biosimilar monoclonal antibody approved by drug regulatory authorities with reference to tositumomab. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain

sequence identity of greater than 90% to SEQ ID NO:96. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 90% to SEQ ID NO:97. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 95% to SEQ ID NO:96. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 95% to SEQ ID NO:97. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 98% to SEQ ID NO:96. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 98% to SEQ ID NO:97. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 99% to SEQ ID NO:96. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 99% to SEQ ID NO:97.

**[00949]** In an embodiment, an anti-CD20 antibody selected from the group consisting of obinutuzumab, ofatumumab, veltuzumab, tositumomab, and ibritumomab, and or antigen-binding fragments, derivatives, conjugates, variants, and radioisotope-labeled complexes thereof, is administered to a subject by infusion in a dose selected from the group consisting of about 10 mg, about 20 mg, about 25 mg, about 50 mg, about 75 mg, 100 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, about 1100 mg, about 1200 mg, about 1300 mg, about 1400 mg, about 1500 mg, about 1600 mg, about 1700 mg, about 1800 mg, about 1900 mg, and about 2000 mg. In an embodiment, the anti-CD20 antibody is administered weekly. In an embodiment, the anti-CD20 antibody is admininstered every two weeks. In an embodiment, the anti-CD20 antibody is admininstered every three weeks. In an embodiment, the anti-CD20 antibody is admininstered monthly. In an embodiment, the anti-CD20 antibody is administered at a lower initial dose, which is escalated when administered at subsequent intervals admininstered monthly. For example, the first infusion can deliver 300 mg of anti-CD20 antibody, and subsequent weekly doses could deliver 2,000 mg of anti-CD20 antibody for eight weeks, followed by monthly doses of 2,000 mg of anti-CD20 antibody. During any of the foregoing embodiments, the BTK inhibitors of the present invention and combinations of the BTK inhibitors with PI3K inhibitors, JAK-2 inhibitors, PD-1

inhibitors, and/or PD-L1 inhibitors may be administered daily, twice daily, or at different intervals as described above, at the dosages described above.

**[00950]** In an embodiment, the invention provides a kit comprising a composition comprising a BTK inhibitor of the present invention and combinations of the BTK inhibitors with PI3K inhibitors, JAK-2 inhibitors, PD-1 inhibitors, and/or PD-L1 inhibitors and a composition comprising an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, and ibritumomab, or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof, for use in the treatment of CLL or SLL, hematological malignancies, B cell malignancies, or, or any of the other diseases described herein. The compositions are typically both pharmaceutical compositions. The kit is for use in co-administration of the anti-CD20 antibody and the BTK inhibitor, either simultaneously or separately, in the treatment of CLL or SLL, hematological malignancies, B cell malignancies, or any of the other diseases described herein.

**[00951]** The anti-CD20 antibody amino acid sequences referenced in the foregoing are summarized in Table 1.

TABLE 1. Anti-CD20 antibody amino acid sequences.

| Identifier | Sequence (One-Letter Amino Acid Symbols) | |
|---|---|---|
| SEQ ID NO:84 rituximab heavy chain | QVQLQQPGAE LVKPGASVKM SCKASGYTFT SYNMHWVKQT PGRGLEWIGA IYPGNGDTSY<br>NQKFKGKATL TADKSSSTAY MQLSSLTSED SAVYYCARST YYGGDWYFNV WGAGTTVTVS<br>AASTKGPSVF PLAPSSKSTS GGTAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPAVLQS<br>SGLYSLSSVV TVPSSSLGTQ TYICNVNHKP SNTKVDKKVE PKSCDKTHTC PPCPAPELLG<br>GPSVFLFPPK PKDTLMISRT PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN AKTKPREEQY<br>NSTYRVVSVL TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP QVYTLPPSRD<br>ELTKNQVSLT CLVKGFYPSD IAVEWESNGQ PENNYKTTPP VLDSDGSFFL YSKLTVDKSR<br>WQQGNVFSCS VMHEALHNHY TQKSLSLSPG K | 60<br>120<br>180<br>240<br>300<br>360<br>420<br>451 |
| SEQ ID NO:85 rituximab light chain | QIVLSQSPAI LSASPGEKVT MTCRASSSVS YIHWFQQKPG SSPKPWIYAT SNLASGVPVR<br>FSGSGSGTSY SLTISRVEAE DAATYYCQQW TSNPPTFGGG TKLEIKRTVA APSVFIFPPS<br>DEQLKSGTAS VVCLLNNFYP REAKVQWKVD NALQSGNSQE SVTEQDSKDS TYSLSSTLTL<br>SKADYEKHKV YACEVTHQGL SSPVTKSFNR GEC | 60<br>120<br>180<br>213 |
| SEQ ID NO:86 obinutuzumab heavy chain | QVQLVQSGAE VKKPGSSVKV SCKASGYAFS YSWINWVRQA PGQGLEWMGR IFPGDGDTDY<br>NGKFKGRVTI TADKSTSTAY MELSSLRSED TAVYYCARNV FDGYWLVYWG QGTLVTVSSA<br>STKGPSVFPL APSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG<br>LYSLSSVVTV PSSSLGTQTY ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP<br>SVFLFPPKPK DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS<br>TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSRDEL<br>TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ<br>QGNVFSCSVM HEALHNHYTQ KSLSLSPGK | 60<br>120<br>180<br>240<br>300<br>360<br>420<br>449 |
| SEQ ID NO:87 obinutuzumab light chain | DIVMTQTPLS LPVTPGEPAS ISCRSSKSLL HSNGITYLYW YLQKPGQSPQ LLIYQMSNLV<br>SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCAQNLELP YTFGGGTKVE IKRTVAAPSV<br>FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL<br>SSTLTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC | 60<br>120<br>180<br>219 |
| SEQ ID NO:88 | EVQLVESGGG LVQPGRSLRL SCAASGFTFN DYAMHWVRQA PGKGLEWVST ISWNSGSIGY | 60 |

| Identifier | Sequence (One-Letter Amino Acid Symbols) | |
|---|---|---|
| ofatumumab variable heavy chain | ADSVKGRFTI SRDNAKKSLY LQMNSLRAED TALYYCAKDI QYGNYYYGMD VWGQGTTVTV SS | 120 122 |
| SEQ ID NO:89 ofatumumab variable light chain | EIVLTQSPAT LSLSPGERAT LSCRASQSVS SYLAWYQQKP GQAPRLLIYD ASNRATGIPA RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ RSNWPITFGQ GTRLEIK | 60 107 |
| SEQ ID NO:90 ofatumumab Fab fragment heavy chain | EVQLVESGGG LVQPGRSLRL SCAASGFTFN DYAMHWVRQA PGKGLEWVST ISWNSGSIGY ADSVKGRFTI SRDNAKKSLY LQMNSLRAED TALYYCAKDI QYGNYYYGMD VWGQGTTVTV SSASTKGPSV FPLAPGSSKS TSGTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSSLGT QTYICNVNHK PSNTKVDKKV EP | 60 120 180 222 |
| SEQ ID NO:91 ofatumumab Fab fragment light chain | EIVLTQSPAT LSLSPGERAT LSCRASQSVS SYLAWYQQKP GQAPRLLIYD ASNRATGIPA RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ RSNWPITFGQ GTRLEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN R | 60 120 180 211 |
| SEQ ID NO:92 veltuzumab heavy chain | QVQLQQSGAE VKKPGSSVKV SCKASGYTFT SYNMHWVKQA PGQGLEWIGA IYPGMGDTSY NQKFKGKATL TADESTNTAY MELSSLRSED TAFYYCARST YYGGDWYFDV WGQGTTVTVS SASTKGPSVF PLAPSSKSTS GGTAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV TVPSSSLGTQ TYICNVNHKP SNTKVDKRVE PKSCDKTHTC PPCPAPELLG GPSVFLFPPK PKDTLMISRT PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN AKTKPREEQY NSTYRVVSVL TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP QVYTLPPSRE EMTKNQVSLT CLVKGFYPSD IAVEWESNGQ PENNYKTTPP VLDSDGSFFL YSKLTVDKSR WQQGNVFSCS VMHEALHNHY TQKSLSLSPG K | 60 120 180 240 300 360 420 451 |
| SEQ ID NO:93 veltuzumab light chain | DIQLTQSPSS LSASVGDRVT MTCRASSSVS YIHWFQQKPG KAPKPWIYAT SNLASGVPVR FSGSGSGTDY TFTISSLQPE DIATYYCQQW TSNPPTFGGG TKLEIKRTVA APSVFIFPPS DEQLKSGTAS VVCLLNNFYP REAKVQWKVD NALQSGNSQE SVTEQDSKDS TYSLSSTLTL SKADYEKHKV YACEVTHQGL SSPVTKSFNR GEC | 60 120 180 213 |
| SEQ ID NO:94 tositumomab heavy chain | QAYLQQSGAE LVRPGASVKM SCKASGYTFT SYNMHWVKQT PRQGLEWIGA IYPGNGDTSY NQKFKGKATL TVDKSSSTAY MQLSSLTSED SAVYFCARVV YYSNSYWYFD VWGTGTTVTV SGPSVFPLAP SSKSTSGGTA ALGCLVKDYF PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTQTYIC NVNHKPSNTK VDKKAEPKSC DKTHTCPPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK GQPREPQVYT LPPSRDELTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGK | 60 120 180 240 300 360 420 447 |
| SEQ ID NO:95 tositumomab light chain | QIVLSQSPAI LSASPGEKVT MTCRASSSVS YMHWYQQKPG SSPKPWIYAP SNLASGVPAR FSGSGSGTSY SLTISRVEAE DAATYYCQQW SFNPPTFGAG TKLELKRTVA APSVFIFPPS DEQLKSGTAS VVCLLNNFYP REAKVQWKVD NALQSGNSQE SVTEQDSKDS TYSLSSTLTL SKADYEKHKV YACEVTHQGL SSPVTKSFNR | 60 120 180 210 |
| SEQ ID NO:96 ibritumomab heavy chain | QAYLQQSGAE LVRPGASVKM SCKASGYTFT SYNMHWVKQT PRQGLEWIGA IYPGNGDTSY NQKFKGKATL TVDKSSSTAY MQLSSLTSED SAVYFCARVV YYSNSYWYFD VWGTGTTVTV SAPSVYPLAP VCGDTTGSSV TLGCLVKGYF PEPVTLTWNS GSLSSGVHTF PAVLQSDLYT LSSSVTVTSS TWPSQSITCN VAHPASSTKV DKKIEPRGPT IKPCPPCKCP APNLLGGPSV FIFPPKIKDV LMISLSPIVT CVVVDVSEDD PDVQISWFVN NVEVHTAQTQ THREDYNSTL RVVSALPIQH QDWMSGKEFK CKVNNKDLPA PIERTISKPK GSVRAPQVYV LPPPEEEMTK KQVTLTCMVT DFMPEDIYVE WTNNGKTELN YKNTEPVLDS DGSYFMYSKL RVEKKNWVER NSYSCSVVHE GLHNHHTTKS FSR | 60 120 180 240 300 360 420 443 |
| SEQ ID NO:97 ibritumomab light chain | QIVLSQSPAI LSASPGEKVT MTCRASSSVS YMHWYQQKPG SSPKPWIYAP SNLASGVPAR FSGSGSGTSY SLTISRVEAE DAATYYCQQW SFNPPTFGAG TKLELKRADA APTVFIFPPS DEQLKSGTAS VVCLLNNFYP REAKVQWKVD NALQSGNSQE SVTEQDSKDS TYSLSSTLTL SKADYEKHKV YACEVTHQGL SSPVTKSFN | 60 120 180 209 |

Combinations of BTK Inhibitors, PI3K Inhibitors, JAK-2 Inhibitors, PD-1 Inhibitors, and/or PD-L1 and PD-L2 Inhibitors with Chemotherapeutic Active Pharmaceutical Ingredients

**[00952]** The combinations of the BTK inhibitors with PI3K inhibitors, JAK-2 inhibitors, PD-1 inhibitors, and/or PD-L1 inhibitors and/or PD-L2 inhibitors may also be safely co-administered with chemotherapeutic active pharmaceutical ingredients such as gemcitabine and albumin-bound paclitaxel (nab-paclitaxel). In an embodiment, the

invention relates to a method of treating a hematological malignancy, solid tumor cancer, or immune, autoimmune, or inflammatory disorder in a human comprising the step of administering to said human a BTK inhibitors, a PI3K inhibitor, a JAK-2 inhibitor, a PD-1 inhibitor, and/or a PD-L1 inhibitor and/or PD-L2 inhibitor, and further comprising the step of administering a therapeutically-effective amount of gemcitabine, or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In an embodiment, the invention relates to a method of treating a hematological malignancy, solid tumor cancer, or immune, autoimmune, or inflammatory disorder in a human comprising the step of administering to said human a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and further comprising the step of administering a therapeutically-effective amount of gemcitabine, or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In an embodiment, the solid tumor cancer in any of the foregoing embodiments is pancreatic cancer.

**[00953]** In an embodiment, the invention relates to a method of treating a hematological malignancy, solid tumor cancer, or immune, autoimmune, or inflammatory disorder in a human comprising the step of administering to said human a BTK inhibitors, a PI3K inhibitor, a JAK-2 inhibitor, a PD-1 inhibitor, and/or a PD-L1 inhibitor and/or PD-L2 inhibitor, and further comprising the step of administering a therapeutically-effective amount of nab-paclitaxel. In an embodiment, the invention relates to a method of treating a hematological malignancy, solid tumor cancer, or immune, autoimmune, or inflammatory disorder in a human comprising the step of administering to said human a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and further comprising the step of administering a therapeutically-effective amount of nab-paclitaxel. In an embodiment, the solid tumor cancer in any of the foregoing embodiments is pancreatic cancer.

**[00954]** In an embodiment, the invention provides a synergistic combination of a BTK inhibitor of Formula (XVIII), a PD-1 inhibitor and/or a PD-L1 inhibitor, and gemcitabine for the treatment of a hyperproliferative disorder.

**[00955]** In an embodiment, the invention provides a synergistic combination of a BTK

inhibitor of Formula (XVIII), a PD-1 inhibitor and/or a PD-L1 inhibitor, and gemcitabine for the treatment of a cancer.

**[00956]** In an embodiment, the invention provides a synergistic combination of a BTK inhibitor of Formula (XVIII), a PD-1 inhibitor and/or a PD-L1 inhibitor, and gemcitabine for the treatment of a cancer, wherein the cancer is selected from the group consisting of ovarian cancer, breast cancer, non-small cell lung cancer, and pancreatic cancer. In an embodiment, the invention provides a synergistic combination of a BTK inhibitor of Formula (XVIII), a PD-1 inhibitor and/or a PD-L1 inhibitor, nab-paclitaxel, and gemcitabine for the treatment of a cancer, wherein the cancer is selected from the group consisting of ovarian cancer, breast cancer, non-small cell lung cancer, and pancreatic cancer.

**[00957]** In an embodiment, the invention relates to a method of treating a hematological malignancy, solid tumor cancer, or immune, autoimmune, or inflammatory disorder in a human comprising the step of administering to said human a BTK inhibitors, a PI3K inhibitor, a JAK-2 inhibitor, a PD-1 inhibitor, and/or a PD-L1 inhibitor and/or PD-L2 inhibitor, and further comprising the step of administering a therapeutically-effective amount of a chemotherapeutic active pharmaceutical ingredient selected from the group consisting of thalidomide, pomalidomide, lenalidomide, bortezomib, and combinations thereof.

**[00958]** In an embodiment, the invention provides a method of treating a hematological malignancy or a solid tumor cancer in a human comprising the step of administering to said human a BTK inhibitor, a PI3K inhibitor, and/or a PD-1 and/or a PD-L1 inhibitor and/or PD-L2 inhibitor, and further comprising the step of administering a therapeutically-effective amount of bendamustine hydrochloride. In an embodiment, the invention provides a method of treating a hematological malignancy or a solid tumor cancer in a human comprising the step of administering to said human a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and/or a PD-1 and/or a PD-L1 inhibitor and/or PD-L2 inhibitor, and further comprising the step of administering a therapeutically-effective amount of bendamustine hydrochloride.

**[00959]** In an embodiment, the invention provides a method of treating a hematological malignancy or a solid tumor cancer in a human comprising the step of administering to said human a BTK inhibitor, a PI3K inhibitor, and/or a PD-1 and/or a PD-L1 inhibitor and/or PD-L2 inhibitor, and further comprising the step of administering a therapeutically-effective amount of a combination of fludarabine, cyclophosphamide, and rituximab (which collectively may be referred to as "FCR" or "FCR chemotherapy"). In an embodiment, the invention provides a method of treating a hematological malignancy or a solid tumor cancer in a human comprising the step of administering to said human a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and further comprising the step of administering a therapeutically-effective amount of FCR chemotherapy. In an embodiment, the invention provides a hematological malignancy or a solid tumor cancer comprising the step of administering to said human a BTK inhibitor and a PD-1 and/or PD-L1 inhibitor, and further comprising the step of administering a therapeutically-effective amount of FCR chemotherapy. FCR chemotherapy has been shown to improve survival in patients with cancer, as described in Hallek, *et al.*, *Lancet.* **2010,** *376,* 1164-1174.

**[00960]** In an embodiment, the invention provides a method of treating a hematological malignancy or a solid tumor cancer in a human comprising the step of administering to said human a BTK inhibitor, a PI3K inhibitor, and/or a PD-1 and/or a PD-L1 inhibitor and/or PD-L2 inhibitor, and further comprising the step of administering a therapeutically-effective amount of a combination of rituximab, cyclophosphamide, doxorubicin hydrochloride (also referred to as hydroxydaunomycin), vincristine sulfate (also referred to as oncovin), and prednisone (which collectively may be referred to as "R-CHOP" or "R-CHOP chemotherapy"). In an embodiment, the invention provides a method of treating a hematological malignancy or a solid tumor cancer in a human comprising the step of administering to said human a BTK inhibitor of Formula (XVIII), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and further comprising the step of administering a therapeutically-effective amount of R-CHOP chemotherapy. In an embodiment, the invention provides a hematological malignancy or a solid tumor cancer comprising the step of administering to

said human a BTK inhibitor and/or a PD-1 and/or a PD-L1 inhibitor and/or PD-L2 inhibitor, and further comprising the step of administering a therapeutically-effective amount of R-CHOP therapy. R-CHOP chemotherapy has been shown to improve the 10-year progression-free and overall survival rates for patients with cancer, as described in Sehn, *Blood*, **2010**, *116*, 2000-2001.

**[00961]** In any of the foregoing embodiments, the chemotherapeutic active pharmaceutical ingredient or combinations thereof may be administered before, concurrently, or after administration of the PD-1 and/or PD-L1 inhibitors and/or PD-L2 inhibitors and the BTK inhibitors.

**[00962]** While preferred embodiments of the invention are shown and described herein, such embodiments are provided by way of example only and are not intended to otherwise limit the scope of the invention. Various alternatives to the described embodiments of the invention may be employed in practicing the invention.

## EXAMPLES

**[00963]** The embodiments encompassed herein are now described with reference to the following examples. These examples are provided for the purpose of illustration only and the disclosure encompassed herein should in no way be construed as being limited to these examples, but rather should be construed to encompass any and all variations which become evident as a result of the teachings provided herein.

Example 1 – Synergistic Combination of a BTK Inhibitor and a PI3K-δ Inhibitor

**[00964]** Ficoll purified mantle cell lymphoma (MCL) cells ($2\times10^5$) isolated from bone marrow or peripheral blood were treated with each drug alone and with six equimolar concentrations of a BTK inhibitor (Formula (XVIII)) and a PI3K-δ inhibitor (Formula (IX)) ranging from 0.01 nM to 10 μM on 96-well plates in triplicate. Plated cells were then cultured in HS-5 conditioned media at 37 °C with 5% $CO_2$. After 72 hours of culture, cell viability was determined using an (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium) (MTS) assay (Cell Titer 96, Promega). Viability data were used to generate cell viability curves for each drug alone and in combination for each sample. The potential synergy of the combination of the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX) at a given

equimolar concentration was determined using the median effect model as described in Chou and Talalay, Quantitative analysis of dose-effect relationships: the combined effects of multiple drugs or enzyme inhibitors. *Adv Enzyme Regul.* **1984,** 22, 27-55. The statistical modeling was run in R using a script that utilizes the median effect model as described in Lee, *et al.*, Interaction index and different methods for determining drug interaction in combination therapy. *J. Biopharm. Stat.* **2007,** *17,* 461-80. A value of 1, less than 1, and greater than 1 using R defines an additive interaction, a synergistic interaction, and an antagonistic interaction, respectively. The Lee, *et al.*, method calculates a 95% confidence interval for each data point. For each viability curve, to be considered synergistic, a data point must have an interaction index below 1 and the upper confidence interval must also be below 1. In order to summarize and demonstrate collective synergy results, an interaction dot blot was generated for the primary patient samples.

**[00965]** A similar approach was utilized to study diffuse large B cell lymphoma (DLBCL) (TMD8) and MCL (MINO) cell lines. Cells were treated with each drug alone and with six equimolar concentrations of the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX) ranging from 0.003 nM to 1.0 μM (for TMD8) or 0.03 nM to 10 μM (for MINO) on 96-well plates in triplicate. Plated cells were then cultured in standard conditioned media plus FBS at 37°C with 5% $CO_2$. After 72 hours of culture, viability was determined using an MTS assay (Cell Titer 96, Promega). Viability data were used to generate cell viability curves for each drug alone and in combination for each sample. The results of the experiments described in this example are shown in FIGS 1, 2, 3, and 4.

Example 2 – Synergistic Combination of a BTK Inhibitor and a PI3K-δ Inhibitor

**[00966]** Combination experiments were performed to determine the synergistic, additive, or antagonistic behavior of drug combinations using the Chou/Talalay method/algorithm by defining combination indexes for drug combinations. Information about experimental design for evaluation of synergy is described in, *e.g.*, Chou and Talalay P. Quantitative analysis of dose-effect relationships: the combined effects of multiple drugs or enzyme inhibitors. *Adv. Enzyme Regul.* **1984,** *22,* 27-55 and more generally in, *e.g.*, Greco, *et al.*, The search for synergy: a critical review from a response

surface perspective. *Pharmacol. Rev.* **1995,** *47,* 331-385. The study was performed using the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX). Single active pharmaceutical ingredient activities were first determined in the various cell lines and subsequently, the combination indexes were established using equimolar ratios taking the single active pharmaceutical ingredient drug EC50s into consideration. For individual active pharmaceutical ingredients that displayed no single active pharmaceutical ingredient activity, equimolar ratios were used at fixed concentrations to establish combination indexes. The readout from 72 hour proliferation assays using Cell TiterGlo (ATP content of remaining cells) determined the fraction of cells that were effected as compared to untreated cells (Fa = fraction affected = (1- ((cells + inhibitor) – background signal) / ((cells + DMSO) – background signal)).

**[00967]** The combination index obtained was ranked according to Table 4.

TABLE 4. Combination Index (CI) Ranking Scheme

| **Range of CI** | **Description** |
|---|---|
| <0.1 | Very strong synergism |
| 0.1-0.3 | Strong synergism |
| 0.3-0.7 | Synergism |
| 0.7-0.85 | Moderate synergism |
| 0.85-0.9 | Slight synergism |
| 0.9-1.1 | Nearly additive |
| 1.1-1.2 | Slight antagonism |
| 1.2-1.45 | Moderate antagonism |
| 1.45-3.3 | Antagonism |
| 3.3-10 | Strong antagonism |
| >10 | Very strong antagonism |

**[00968]** The detailed results of the cell line studies for the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX) are given in FIG. 5 to FIG. 37. The results of the cell line studies are summarized in Table 5.

TABLE 5. Summary of results of the combination of a BTK inhibitor with a PI3K-δ inhibitor (S = synergistic, A = additive, X = no effect).

| Cell Line | Indication | ED25 | ED50 | ED75 | ED90 |
|---|---|---|---|---|---|
| Raji | Burkitt's | S | S | S | S |
| Ramos | Burkitt's | X | X | X | X |
| Daudi | Burkitt's | S | S | S | S |
| Mino | MCL | S | S | S | S |
| Pfeiffer | iNHL | S | S | S | S |
| DOHH | iNHL | S | S | S | S |
| REC-1 | iNHL | S | S | A | A |
| U937 | Myeloid | S | S | S | S |
| K562 | CML | X | X | X | X |
| SU-DHL-1 | ABC | S | A | X | X |
| SU-DHL-2 | ABC | S | S | S | S |
| HBL-1 | ABC | S | S | S | S |
| TMD8 | ABC | S | S | S | S |
| LY19 | GCB | X | X | X | X |
| LY7 | GCB | S | S | S | S |
| LY1 | GCB | X | X | X | X |
| SU-DHL-6 | GCB | S | S | S | S |
| SupB15 | B-ALL | S | S | S | S |
| CCRF | B-ALL | S | A/S | X | X |

Example 3 – Synergistic Combination of a BTK Inhibitor and the JAK-2 Inhibitor Ruxolitinib

**[00969]** Combination experiments were performed to determine the synergistic, additive, or antagonistic behavior of drug combinations using the methods described above in Example 2. The study was performed using the BTK inhibitor of Formula (XVIII) and the JAK-2 inhibitor of Formula XXX (ruxolitinib).

**[00970]** The detailed results of the cell line studies for the BTK inhibitor of Formula (XVIII) and the JAK-2 inhibitor of Formula XXX (ruxolitinib) are given in FIG. 38 to FIG. 65. The results of the cell line studies are summarized in Table 6.

TABLE 6. Summary of results of the combination of a BTK inhibitor with a JAK-2 inhibitor (S = synergistic, A = additive, X = no effect).

| Cell Line | Indication | ED25 | ED50 | ED75 | ED90 |
|---|---|---|---|---|---|
| Raji | Burkitt's | S | S | S | S |
| Ramos | Burkitt's | S | S | S | S |
| Daudi | Burkitt's | S | S | S | S |
| Mino | MCL | S | S | S | S |
| Pfeiffer | iNHL | S | S | S | S |
| DOHH | iNHL | S | S | S | S |
| REC-1 | iNHL | S | S | S | S |
| JVM-2 | CLL like | S | S | S | X |
| U937 | Myeloid | X | X | X | X |
| K562 | CML | X | X | X | X |
| SU-DHL-1 | ABC | S | S | S | S |
| SU-DHL-2 | ABC | S | S | S | X |
| HBL-1 | ABC | S | S | S | S |
| TMD8 | ABC | S | S | S | S |
| LY19 | GCB | X | X | X | X |
| LY7 | GCB | X | X | X | X |
| LY1 | GCB | X | X | X | X |
| SU-DHL-6 | GCB | S | S | X | X |
| SupB15 | B-ALL | X | X | X | X |
| CCRF | B-ALL | X | X | A | A |

Example 4 – Synergistic Combination of a BTK Inhibitor and the JAK-2 Inhibitor Pacritinib

**[00971]** Combination experiments were performed to determine the synergistic, additive, or antagonistic behavior of drug combinations using the methods described above in Example 2. The study was performed using the BTK inhibitor of Formula (XVIII) and the JAK-2 inhibitor of Formula LIV (pacritinib).

**[00972]** The detailed results of the cell line studies for the BTK inhibitor of Formula (XVIII) and the JAK-2 inhibitor of Formula LIV (pacritinib) are given in FIG. 66 to FIG. 94. The results of the cell line studies are summarized in Table 7.

TABLE 7. Summary of results of the combination of a BTK inhibitor with the JAK-2 inhibitor of Formula LIV (pacritinib) (S = synergistic, A = additive, X = no effect).

| Cell Line | Indication | ED25 | ED50 | ED75 | ED90 |
|---|---|---|---|---|---|
| Mino | MCL | S | S | S | S |
| JVM-2 | prolymphocytic leukemia | S | S | S | S |
| Maver-1 | B-ALL, MCL | S | S | S | S |
| Raji | B-ALL, Burkitt's | S | S | S | S |
| Daudi | Burkitt's | S | S | S | S |
| Rec-1 | FL | X | S | S | S |
| CCRF | B-ALL | S | S | S | S |
| Sup-B15 | B-ALL | S | S | A | A |
| SU-DHL-4 | DLBCL-ABC | S | S | S | S |
| EB3 | B-ALL, Burkitt's | S | S | S | S |
| CA46 | B-ALL, Burkitt's | S | S | S | S |
| Pfeiffer | FL | S | S | S | S |
| DB | B-ALL, MCL | S | S | S | S |
| DOHH2 | FL | S | S | S | S |
| Namalwa | B-ALL, Burkitt's | S | S | S | S |
| JVM-13 | B-ALL, MCL | S | S | S | S |
| SU-DHL-1 | DLBCL-ABC | S | S | S | S |
| SU-DHL-2 | DLBCL-ABC | S | S | S | X |
| Ramos | Burkitt's | S | S | S | S |
| SU-DHL-6 | DLBCL-GCB | S | S | S | A |
| TMD-8 | DLBCL-ABC | X | X | S | S |
| SU-DHL-10 | DLBCL-GCB | S | S | S | S |
| HBL-1 | DLBCL-ABC | S | S | S | X |
| OCI-Ly3 | DLBCL-ABC | S | S | S | S |
| OCI-Ly7 | DLBCL-ABC | S | S | S | S |
| Jeko | B-ALL, MCL | S | S | S | S |

Example 5 – Synergistic Combination of a BTK Inhibitor and a α-PD-L1 Inhibitor in the CT26 Colorectal Cancer Model

**[00973]** The CT26 (colon tumor #26) syngeneic mouse colorectal model was used to investigate the therapeutic efficacy of the combination of the BTK inhibitor of Formula (XVIII) and an anti-PD-L1 monoclonal antibody (BioXcell InVivoMAb anti-m-PD-L1, clone 10F.9G2). A syngeneic mouse colorectal model bears a tumor derived from the species of origin and allows for study of potential treatments in a human surrogate model with a functional immune system. CT cells were developed in 1975 by exposing Balb/c mice to *N*-nitroso-*N*-methylurethane, which lead to a rapid-growing grade IV carcinoma that may be readily implanted and easily metastasizes, as described in: Griswold et al.,

*Cancer* **1975,** *36,* 2441-2444. Further details of the CT26 syngeneic mouse colorectal model may be found in: Castle, *et al.*, *BMC Genomics,* **2013,** *15,* 190; Endo, *et al.*, *Cancer Gene Therapy*, **2002,** *9,* 142-148; Roth *et al.*, *Adv. Immunol.* **1994,** *57,* 281-351; Fearon, *et al.*, *Cancer Res.* **1988,** *48,* 2975-2980. CT26 cells share many molecular features with human cells and thus represent a model for aggressive, undifferentiated, refractory human colorectal carcinoma cells.

**[00974]** Tumor cells were cultured in complete Roswell Park Memorial Institute 1640 medium (cRPMI; Invitrogen) containing 10% fetal bovine serum (FBS; Thermo Scientific), 100 U/mL penicillin (Invitrogen), 100 µg/mL streptomycin (Invitrogen), and 50 µM 2-mercaptoethanol (2-ME) (Sigma-Aldrich). Tumor cells were implanted into mice while in the exponential growth phase (below $1.5 \times 10^6$ cells/mL). Six to eight week old female Babl/c mice were inoculated with $5 \times 10^6$ CT26 cells by subcutaneous injection into the right and left sides of their abdomen. Tumor growth was monitored with a digital caliper every 2 to 3 days and expressed as volume (length × width × height). The dosing scheme used with the Balb/c mice in the CT26 syngeneic mouse colorectal model is shown in FIG. 95.

**[00975]** FIG. 96 illustrates the effect of the vehicle on tumor volume, wherein tumor volumes (in $mm^3$) are observed to steadily increase in all nine animals used in the study over 15 days after innoculation. All nine animals showed tumor volumes that were greater than 1500 $mm^3$ after 14 days. FIG. 97 illustrates the effect of treatment with an α-PD-L1 inhibitor (BioXcell InVivoMAb anti-m-PD-L1, Clone 10F.9G2) on tumor volume. Compared to FIG. 96, FIG. 97 shows that two of nine animals maintained tumor sizes of less than 500 $mm^3$ while one of nine showed regression. FIG. 98 illustrates the effect of treatment with α-PD-L1 inhibitor (BioXcell InVivoMAb anti-m-PD-L1, Clone 10F.9G2) in combination with treatment with the BTK inhibitor of Formula (XVIII) on tumor volume. Compared to FIG. 96 and FIG. 97, FIG. 98 shows that six of nine animals maintained tumor sizes of less than 500 $mm^3$ while six of nine animals also showed tumor regression.

**[00976]** Overall, tumor volumes were reduced much more significantly in mice receiving the combination when compared to anti-PD-L1 treatment alone. The

combination with the BTK inhibitor of Formula (XVIII) resulted in a 66.6% tumor regression rate as compared to 11.1% in mice treated with antibody alone.

**[00977]** FIG. 99 illustrates additional synergistic effects of an α-PD-L1 antibody (BioXcell InVivoMAb anti-m-PD-L1, clone 10F.9G2) in combination with the BTK inhibitor of Formula (XVIII) as measured through modulation of circulating immature myeloid cells (myeloid-derived suppressor cells, or MDSCs) in a syngeneic CT26 colon cancer model in mice. The results show that BTK inhibition leads to modulation of circulating immature myeloid cells, which can limit the activity of PD-1 and PD-1L antibodies. The results further illustrate that BTK inhibition effects on the tumor microenvironment are synergistic when combined with an α-PD-1L inhibitor.

Example 6 – BTK Inhibitory Effects on Solid Tumor Microenvironment in the ID8 Ovarian Cancer Model

**[00978]** The ID8 syngeneic orthotropic ovarian cancer murine model was used to investigate the therapeutic efficacy of the BTK inhibitor of Formula (XVIII) through treatment of the solid tumor microenvironment. Human ovarian cancer models, including the ID8 syngeneic orthotropic ovarian cancer model and other animal models, are described in Fong and Kakar, *J. Ovarian Res.* **2009,** *2,* 12; Greenaway, *et al., Gynecol. Oncol.* **2008,** *108,* 385-94; Urzua, *et al., Tumour Biol.* **2005,** *26,* 236-44; Janat-Amsbury, *et al., Anticancer Res.* **2006,** *26,* 3223-28; Janat-Amsbury, *et al., Anticancer Res.* **2006,** *26,* 2785-89. Animals were treated with vehicle or Formula (XVIII), 15 mg/kg/BID given orally. The results of the study are shown in FIG. 100, FIG. 101, FIG. 102, FIG. 103, FIG. 104, FIG. 105, FIG. 106, and FIG. 107.

**[00979]** FIG. 100 and FIG. 101 demonstrate that the BTK inhibitor of Formula (XVIII) impairs ID8 ovarian cancer growth in the ID8 syngeneic murine model. FIG. 102 shows that tumor response to treatment with the BTK inhibitor of Formula (XVIII) correlates with a significant reduction in immunosuppressive tumor-associated lymphocytes in tumor-bearing mice. FIG. 103 shows treatment with the BTK inhibitor of Formula (XVIII) impairs ID8 ovarian cancer growth (through reduction in tumor volume) in the syngeneic murine model. FIG. 104 and FIG. 105 show that the tumor response induced by treatment with the BTK inhibitor of Formula (XVIII) correlates with a significant reduction in immunosuppressive B cells in tumor-bearing mice. FIG. 106 and FIG. 107

show that the tumor response induced by treatment with the BTK inhibitor of Formula (XVIII) correlates with a significant reduction in immunosuppressive tumor associated Tregs and an increase in cytolytic $CD8^+$ T cells.

**[00980]** The results shown in FIG. 100 to FIG. 107 illustrate the surprising efficacy of the BTK inhibitor of Formula (XVIII) in modulating tumor microenvironment in a model predictive of efficacy as a treatment for ovarian cancer in humans.

Example 7 – Synergistic Combination of a BTK Inhibitor and an α-PD-L1 Inhibitor in the ID8 Ovarian Cancer Model

**[00981]** The ID8 ovarian cancer model of Example 6 was also used to investigate potential synergistic effects between the BTK inhibitor of Formula (XVIII) and an α-PD-L1 inhibitor. Doses of 15 mg/kg BID of Formula (XVIII) and 150 μg of α-PD-L1 antibody (BioXcell InVivoMAb anti-m-PD-L1, clone 10F.9G2) were used. Each cohort consisted of 12 mice. Every two weeks mice are injected with luciferin, and tumor growth was monitored using the Xenogen system (Caliper Life Sciences, PerkinElmer, Hopkinton, MA, USA). Tumor size was measured by calculated flux.

**[00982]** Bioluminescence imaging of mice treated with vehicle, Formula (XVIII), alone, an α-PD-L1 inhibitor (BioXcell InVivoMAb anti-m-PD-L1, clone 10F.9G2), and a combination of Formula (XVIII) and the α-PD-L1 inhibitor are shown in FIG. 108. The imaging results after two weeks of imaging are summarized in FIG. 109. The results show that Formula (XVIII) alone or in combination with an anti-PD-L1 antibody impairs ID8 ovarian cancer growth in a syngeneic murine model. The results also show that the combination of Formula (XVIII) and the α-PD-L1 inhibitor exhibits synergy not obtained through treatment with only Formula (XVIII) or with only the anti-PD-L1 antibody.

Example 8 – Synergistic Combination of a BTK Inhibitor and a PI3K-δ Inhibitor in an Orthotopic Pancreatic Cancer Model and Effects on Solid Tumor Microenvironment

**[00983]** An orthotopic pancreatic cancer model was used to investigate the therapeutic efficacy of the combination of the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX) through treatment of the solid tumor microenvironment. Orthotopic pancreatic cancer models in mice are clinically relevant, benefit from tissue site-specific pathology, and allow for study of metastasis. Qiu and Su, *Methods Mol.*

*Biol.* **2013,** *980,* 215–223. A cell line derived from KrasG12D;Trp53R172H;Pdx1-Cre (KPC) mice was orthotopically implanted into the head of the pancreas after 35 passages. Based on the mice background from where the cell lines were generated, $1\times10^6$ cells were injected in C57BL/6 mice. Throughout the experiment, animals were provided with food and water *ad libitum* and subjected to a 12-h dark/light cycle. Animal studies were performed in accordance with the U.S. Public Health Service "Guidelines for the Care and Use of Laboratory Animals" (IACUC). After euthanization, pancreatic tumors were dissected out, weighed and single cell suspensions were prepared for flow cytometry analysis.

**[00984]** Mice were dosed orally with 15 mg/kg of Formula (XVIII), 15 mg/kg of Formula (IX), or a combination of 15 mg/kg of both drugs. Results of the experiments are shown in FIG. 110, which illustrates tumor growth suppression in the orthotopic pancreatic cancer model. The statistical p-value (presumption against null hypothesis) is shown for each tested single active pharmaceutical ingredient and for the combination against the vehicle. The results show that all three treatments provide statistically significant reductions in tumor volume in the pancreatic cancer model.

**[00985]** Additional results of the experiments relating to treatment of the tumor microenvironment are shown in FIG. 111 to FIG. 113. FIG. 111 shows the effects of oral dosing with 15 mg/kg of the BTK inhibitor of Formula (XVIII), 15 mg/kg of the PI3K inhibitor of Formula (IX), or a combination of both drugs on myeloid tumor-associated macrophages (TAMs) in pancreatic tumor-bearing mice. FIG. 112 illustrates the effects of oral dosing with 15 mg/kg of the BTK inhibitor of Formula (XVIII), 15 mg/kg of the PI3K inhibitor of Formula (IX), or a combination of both inhibitors on myeloid-derived suppressor cells (MDSCs) in pancreatic tumor-bearing mice. FIG. 113 illustrates the effects of oral dosing with 15 mg/kg of the BTK inhibitor of Formula (XVIII), 15 mg/kg of the PI3K inhibitor of Formula (IX), or a combination of both inhibitors on regulatory T cells (Tregs) in pancreatic tumor-bearing mice. The results shown in FIG. 111 to FIG. 113 demonstrate that of the BTK inhibitor of Formula (XVIII) and the combination of the BTK inhibitor of Formula (XVIII) and the PI3K inhibitor of Formula (IX) reduce immunosuppressive tumor associated myeloid cells and Tregs in pancreatic tumor-bearing mice. Overall, BTK inhibition with Formula (XVIII) or a combination of

Formula (XVIII) and Formula (IX), significantly reduced tumor burden in an aggressive orthotopic PDA model, decreased immature myeloid infiltrate, reduced the number of tumor associated macrophages, and reduced the number of immunosuppressive Tregs, demonstrating a strong effect on the tumor microenvironment.

Example 9 – Synergistic Combination of a BTK Inhibitor and Gemcitabine in an Orthotopic Pancreatic Cancer Model and Effects on Solid Tumor Microenvironment

**[00986]** An additional study using the orthotopic model described in Example 8 was performed to observe potential reduction in tumor burden through modulation of tumor infiltrating MDSCs and TAMs using the BTK inhibitor of Formula (XVIII) in combination with gemcitabine ("Gem"). In this study, KrasG12D;Trp53R172H;Pdx1-Cre (KPC) derived mouse pancreatic cancer cells (10,000 cells) were injected into the pancreases of 24 female mice. After one week of expansion, drug treatment was started in mice developing pancreatic tumors. Animals were treated with (1) vehicle (N=6); (2) Formula (XVIII), 15 mg/kg BID given orally (N=6); (3) gemcitabine 15 mg/kg intravenous administered every 4 days for 3 injections (N=6); or (4) Formula (XVIII), 15 mg/kg BID given orally together with gemcitabine, 50 mg/kg intravenous administered every 4 days for 3 injections (N=6). At 2 weeks after initiation of treatment, mice in the vehicle group showed signs of deteriorating health and all groups were euthanized.

**[00987]** Single cell suspensions from tumor samples were prepared as follows. Mouse tumor tissue was collected and stored in PBS/0.1% soybean trypsin inhibitor prior to enzymatic dissociation. Samples were finely minced with a scissors and mouse tissue was transferred into DMEM containing 1.0 mg/ml collagenase IV (Gibco), 0.1% soybean trypsin inhibitor, and 50 U/ml DNase (Roche) and incubated at 37 °C for 30 minutes with constant stirring while human tissue was digested in 2.0 mg/ml collagenase IV, 1.0 mg/ml hyluronidase, 0.1% soybean trypsin inhibitor, and 50 U/ml DNase for 45 minutes. Suspensions were filtered through a 100 micron filter and washed with FACS buffer (PBS/0.5% BSA/2.0 mM EDTA) prior to staining. Two million total cells were stained with antibodies as indicated. Intracellular detection of FoxP3 was achieved following permeabilization with BD Perm Buffer III (BD Biosciences) and eBioscience Fix/Perm respectively. Following surface staining, samples were acquired on a BD Fortessa and analyzed using FlowJo (Treestar) software.

**[00988]** Tumors were collected and measured; relative to the vehicle treatment, Formula (XVIII) monotherapy resulted in a 2-fold reduction in tumor growth, results which compared favorably with gemcitabine alone. The combination of Formula (XVIII) and gemcitabine resulted in a further reduction in tumor growth when compared to each single active pharmaceutical ingredient. In FIG. 114, the reduction in tumor size upon treatment is shown. The effects on particular cell subsets are shown in the flow cytometry data presented in FIG. 115, FIG. 116, FIG. 117, and FIG. 118.

**[00989]** The results shown in FIG. 114 to FIG. 118 illustrate synergistic reduction in tumor burden by modulation of the tumor infiltrating MDSCs and TAMs, which affects Treg and $CD8^+$ T cell levels, through inhibition of BTK using Formula (XVIII) and particularly with a synergistic combination of Formula (XVIII) and gemcitabine. The combination of Formula (XVIII) and gemcitabine resulted in a further reduction in tumor growth when compared to each single active pharmaceutical ingredient.

Example 10 – BTK Inhibitory Effects on Solid Tumor Microenvironment in the KPC Pancreatic Cancer Model

**[00990]** Given the potential for BTK inhibition to affect TAMs and MDSCs, single-active pharmaceutical ingredient Formula (XVIII) was evaluated in mice with advanced pancreatic cancer arising as the result of genetic modifications of oncogenes KRAS and p53, and the pancreatic differentiation promoter PDX-1 (KPC mice). The KPC mouse model recapitulates many of the molecular, histopathologic, and clinical features of human disease (Westphalen and Olive, *Cancer J.* **2012,** *18,* 502-510). Combination therapy with gemcitabine was also evaluated in this model. Mice were enrolled after identification of spontaneously appearing tumors in the pancreas that were $\geq$ 100 $mm^3$ (as assessed by high-resolution ultrasonography). Mice were treated with (1) vehicle (N=6); or (2) Formula (XVIII), 15 mg/kg BID given orally (N=6).

**[00991]** As shown in FIG. 119, treatment with single-active pharmaceutical ingredient Formula (XVIII) substantially slowed pancreatic cancer growth and increased animal survival. With vehicle, tumor volumes predose averaged 152 $mm^3$, and at day 28 averaged 525 $mm^3$. In the cohort treated with Formula (XVIII), tumor volumes predose averaged 165 $mm^3$, and at day 28 averaged 272 $mm^3$, indicating significant improvement. With vehicle, survival at day 14 was 5/6 animals, and at day 28 was 0/6 animals. With

Formula (XVIII), survival at day 14 was 6/6 animals, and at day 28 was 5/6 animals.

**[00992]** Analysis of tumor tissues showed that immunosuppressive TAMs ($CD11b^+Ly6ClowF4/80^+Csf1r^+$), MDSCs ($Gr1^+Ly6CHi$), and Tregs ($CD4^+CD25^+FoxP3^+$) were significantly reduced with Formula (XVIII) treatment (FIG. 120, FIG. 121, and FIG. 122). As expected, the decrease in these immunosuppressive cell subsets correlated with a significant increase in $CD8^+$ cells (FIG. 123).

Example 11 – Study of a BTK Inhibitor and a Combination of a BTK Inhibitor and a PI3K Inhibitor in Canine Lymphoma

**[00993]** Canine B cell lymphoma exists as a pathological entity that is characterized by large anaplastic, centroblastic or immunoblastic lymphocytes with high proliferative grade, significant peripheral lymphadenopathy and an aggressive clinical course. While some dogs respond initially to prednisone, most canine lymphomas progress quickly and must be treated with combination therapies, including cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP), or other cytotoxic agents. In their histopathologic features, clinical course, and high relapse rate after initial treatment, canine B cell lymphomas resemble diffuse large B cell lymphoma (DLBCL) in humans. Thus, responses of canine B cell lymphomas to experimental treatments are considered to provide proof of concept for therapeutic candidates in DLBCL.

**[00994]** In this example, companion dogs with newly diagnosed or relapsed/refractory B cell lymphoma were enrolled on a veterinary clinical trial of the BTK inhibitor of Formula (XVIII) ("Arm 1") or the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX) ("Arm 2"). Enrollment has completed for both arms. The results show that combined treatment with the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX) may have greater efficacy than treatment with the BTK inhibitor of Formula (XVIII) alone in aggressive lymphomas.

**[00995]** Twenty-one dogs were treated in Arm 1 with the BTK inhibitor of Formula (XVIII) at dosages of 2.5 mg/kg once daily to 20 mg/kg twice daily. Intra-subject dose escalation was allowed. Six of the 11 dogs that initiated at 2.5 or 5 mg/kg once daily were escalated and completed the study with dosages of 10 mg/kg twice daily. Among all the dose cohorts, 8 dogs had shrinkage of target lesions >20%; the best tumor

responses were between 45-49% reduction in the sum of target lesions in two dogs. Complete responses ("CR", disappearance of all evidence of disease per evaluator judgment; and absence of new lesions) were not observed in Arm 1. CR were defined as disappearance of all evidence of disease per evaluator judgment, and absence of new lesions. Vali, *et al.*, *Vet. Comp. Oncol.* **2010,** 8, 28-37.

**[00996]** In the combination phase of the study (Arm 2), 10 dogs were treated with 10 mg/kg the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX) at 2.5 or 3.5 mg/kg, on a twice daily schedule. Of these, 7 dogs had shrinkage of target lesions > 20%, providing evidence of biological activity for the combination; four of these dogs achieved a PR. The best tumor responses were between 58-65% reduction in the sum of target lesions, with one sustained CR observed among the 10 dogs treated. The initial reductions in the sum of target lesions continued to deepen during the course of therapy in 7 of the 10 dogs. A summary of the results is presented in Table 8.

TABLE 8. Summary of the results of the canine lymphoma study.

| **Response Metric** | **Formula (XVIII) and Formula (IX)** | **Formula (XVIII) monotherapy** |
|---|---|---|
| Sum LD[a] decreased by ≥20% | 7/10 (70 %) | 8/21 (38 %) |
| Sum LD[a] decreased by ≥30% (PR) | 4/10 (40 %) | 6/21 (28.6 %) |
| CR by investigator evaluation | 1/10 (10 %) | 0/21 (0 %) |
| Median time on study | 23 days | 24 days |
| Median time to best response | 18 days | 7 days |

[a] LD, longest diameter, sum of up to 5 target lesions.

**[00997]** These data suggest that in companion dogs with naturally occurring B cell lymphomas, treatment with the combination of the BTK inhibitor of Formula (XVIII) and the PI3K-δ inhibitor of Formula (IX) may provide increased biological activity (tumor shrinkage and stable disease) and may possibly lead to deeper responses than treatment with the BTK inhibitor of Formula (XVIII) alone. The higher rate of biological responses and extended response duration (median time to best response), along with the observation of a CR in this aggressive disease setting, provide evidence of synergy between Formula (XVIII) and Formula (IX).

Example 12 – Effects of BTK Inhibitors on Thrombosis

**[00998]** Clinical studies have shown that targeting the BCR signaling pathway by inhibiting BTK produces significant clinical benefit (Byrd, *et al.*, *N. Engl. J. Med.* **2013**, *369*, 32-42, Wang, *et al.*, *N. Engl. J. Med.* **2013**, *369(6)*, 507-16). However, in these studies, bleeding has been reported in up to 50% of ibrutinib-treated patients. Most bleeding events were of grade 1-2 (spontaneous bruising or petechiae) but, in 5% of patients, they were of grade 3 or higher after trauma. These results are reflected in the prescribing information for ibrutinib, where bleeding events of any grade, including bruising and petechiae, were reported in approximately half of patients treated with ibrutinib (IMBRUVICA package insert and prescribing information, revised July 2014, U.S. Food and Drug Administration).

**[00999]** Constitutive or aberrant activation of the BCR signaling cascade has been implicated in the propagation and maintenance of a variety of B cell malignancies. Small molecule inhibitors of BTK, a protein early in this cascade and specifically expressed in B cells, have emerged as a new class of targeted agents. There are several BTK inhibitors, including Formula XXVII (CC-292), and Formula (XX-A) (PCI-32765, ibrutinib), in clinical development. Importantly, early stage clinical trials have found ibrutinib to be particularly active in chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL), suggesting that this class of inhibitors may play a significant role in various types of cancers (Aalipour and Advani, *Br. J. Haematol.* **2013**, *163*, 436-43). However, their effects are not limited to leukemia or lymphomas as platelets also rely on the Tec kinases family members BTK and Tec for signal transduction in response to various thrombogenic stimuli (Oda, *et al.*, *Blood* **2000**, *95(5)*, 1663-70; Atkinson, et al. *Blood* **2003**, *102(10)*, 3592-99). In fact, both Tec and BTK play an important role in the regulation of phospholipase Cγ2 (PLCγ2) downstream of the collagen receptor glycoprotein VI (GPVI) in human platelets. In addition, BTK is activated and undergoes tyrosine phosphorylation upon challenge of the platelet thrombin receptor, which requires the engagement of αIIbβ3 integrin and PI3K activity (Laffargue, *et al.*, *FEBS Lett.* **1999**, *443(1)*, 66-70). It has also been implicated in GPIbα-dependent thrombus stability at sites of vascular injury (Liu, *et al.*, *Blood* **2006**, *108(8)*, 2596-603). Thus, BTK and Tec are involved in several processes important in supporting the formation of a stable

hemostatic plug, which is critical for preventing significant blood loss in response to vascular injury. Hence, the effects of the BTK inhibitor of Formula (XVIII) and ibrutinib were evaluated on human platelet-mediated thrombosis by utilizing the *in vivo* human thrombus formation in the VWF HA1 mice model described in Chen, *et al. Nat. Biotechnol.* **2008,** *26(1),* 114-19.

**[001000]** Administration of anesthesia, insertion of venous and arterial catheters, fluorescent labeling and administration of human platelets ($5 \times 10^8$/ml), and surgical preparation of the cremaster muscle in mice have been previously described (Chen, *et al. Nat Biotechnol.* **2008,** *26(1),* 114-19). Injury to the vessel wall of arterioles (~40–65 mm diameter) was performed using a pulsed nitrogen dye laser (440 nm, Photonic Instruments) applied through a 20× water-immersion Olympus objective (LUMPlanFl, 0.5 numerical aperature (NA)) of a Zeiss Axiotech vario microscope. Human platelet and wall interactions were visualized by fluorescence microscopy using a system equipped with a Yokogawa CSU-22 spinning disk confocal scanner, iXON EM camera, and 488 nm and 561 nm laser lines to detect BCECF-labeled and rhodamine-labeled platelets, respectively (Revolution XD, Andor Technology). The extent of thrombus formation was assessed for 2 minutes after injury and the area ($\mu m^2$) of coverage determined (Image IQ, Andor Technology). For the Formula (XVIII), Formula (XXVII) (CC-292), and Formula (XX-A) (ibrutinib) inhibition studies, the BTK inhibitors were added to purified human platelets for 30 minutes before administration.

**[001001]** The *in vivo* thrombus effects of the BTK inhibitors, Formula (XVIII), Formula (XXVII) (CC-292), and Formula (XX-A) (ibrutinib), were evaluated on human platelet-mediated thrombosis by utilizing the *in vivo* human thrombus formation in the VWF HA1 mice model, which has been previously described (Chen, *et al., Nat Biotechnol.* **2008,** *26(1),* 114-19). Purified human platelets were preincubated with various concentrations of the BTK inhibitors (0.1 μM, 0.5 μM, or 1 μM) or DMSO and then administered to VWF HA1 mice, followed by laser-induced thrombus formation. The BTK inhibitor-treated human platelets were fluorescently labeled and infused continuously through a catheter inserted into the femoral artery. Their behavior in response to laser-induced vascular injury was monitored in real time using two-channel confocal intravital microscopy (Furie and Furie, *J. Clin. Invest.* **2005,** *115(12),* 2255-62).

Upon induction of arteriole injury untreated platelets rapidly formed thrombi with an average thrombus size of 6,450 ± 292 $mm^2$ (mean ± s.e.m.), as shown in FIG. 124 and FIG. 125. Similarly, Formula (XVIII) (1 μM) treated platelets formed a slightly smaller but not significantly different thrombi with an average thrombus size of 5733 ± 393 $mm^2$ (mean ± s.e.m.). In contrast, a dramatic reduction in thrombus size occurred in platelets pretreated with 1 μM of Formula (XX-A) (ibrutinib), 2600 ± 246 $mm^2$ (mean ± s.e.m.), resulting in a reduction in maximal thrombus size by approximately 61% compared with control ($P > 0.001$) (FIG. 124 and FIG. 126). Similar results were obtained with platelets pretreated with 500 nM of Formula (XVIII) or ibrutinib: thrombus size of 5946 ± 283 $mm^2$, and 2710 ± 325 $mm^2$ respectively. These initial results may provide some mechanic background and explanation on the reported 44% bleeding related adverse event rates in the Phase III RESONATE™ study comparing ibrutinib with ofatumumab. The results obtained for Formula XXVII (CC-292) were similar to that for Formula (XX-A) (ibrutinib), as shown in FIG. 124, 125, and 126. The effect of the BTK inhibitor concentration is shown in FIG. 127. These results demonstrate the surprising advantage of the BTK inhibitor of Formula (XVIII), which does not interfere with thrombus formation, while the BTK inhibitors of Formula XXVII (CC-292) and Formula (XX-A) (ibrutinib) interfere with thrombus formation.

**[001002]** The objective of this study was to evaluate *in vivo* thrombus formation in the presence of BTK inhibitors. *In vivo* testing of novel antiplatelet active pharmaceutical ingredients requires informative biomarkers. By utilizing a genetic modified mouse von Willebrand factor (VWFR1326H) model that supports human but not mouse platelet-mediated thrombosis, we evaluated the effects of Formula (XVIII), Formula XXVII (CC-292), and Formula (XX-A) (ibrutinib) on thrombus formation. These results show that Formula (XVIII) had no significant effect on human platelet-mediated thrombus formation while Formula (XX-A) (ibrutinib) was able to limit this process, resulting in a reduction in maximal thrombus size by 61% compared with control. Formula XXVII (CC-292) showed an effect similar to Formula (XX-A) (ibrutinib). These results, which show reduced thrombus formation for ibrutinib at physiologically relevant concentrations, may provide some mechanistic background for the Grade ≥ 3 bleeding events (*e.g.*, subdural hematoma, gastrointestinal bleeding,

hematuria and postprocedural hemorrhage) that have been reported in ≤ 6% of patients treated with Formula (XX-A) (ibrutinib).

**[001003]** GPVI platelet aggregation was measured for Formula (XVIII) and Formula (XX-A) (ibrutinib). Blood was obtained from untreated humans, and platelets were purified from plasma-rich protein by centrifugation. Cells were resuspended to a final concentration of 350,000/μL in buffer containing 145 mmol/L NaCl, 10 mmol/L HEPES, 0.5 mmol/L $Na_2HPO_4$, 5 mmol/L KCl, 2 mmol/L $MgCl_2$, 1 mmol/L $CaCl_2$, and 0.1% glucose, at pH 7.4. Stock solutions of Convulxin (CVX) GPVI were prepared on the day of experimentation and added to platelet suspensions 5 minutes (37 °C, 1200 rpm) before the induction of aggregation. Aggregation was assessed with a Chronolog Lumi-Aggregometer (model 540 VS; Chronolog, Havertown, PA) and permitted to proceed for 6 minutes after the addition of agonist. The results are reported as maximum percent change in light transmittance from baseline with platelet buffer used as a reference. The results are shown in FIG. 128.

**[001004]** In FIG. 129, the results of CVX-induced (250 ng/mL) human platelet aggregation results before and 15 minutes after administration of the BTK inhibitors to 6 healthy individuals are shown.

**[001005]** The results depicted in FIG. 128 and FIG. 129 indicate that the BTK inhibitor of Formula (XX-A) (ibrutinib) significantly inhibits GPVI platelet aggregation, while the BTK inhibitor of Formula (XVIII) does not, further illustrating the surprising benefits of the latter compound.

Example 13 – Effects of BTK Inhibitors on Antibody-Dependent NK Cell Mediated Cytotoxicity using Rituximab

**[001006]** Rituximab-combination chemotherapy is today's standard of care in $CD20^+$ B-cell malignancies. Previous studies investigated and determined that ibrutinib antagonizes rituximab antibody-dependent cell mediated cytotoxicity (ADCC) mediated by NK cells. This may be due to ibrutinib's secondary irreversible binding to interleukin-2 inducible tyrosine kinase (ITK) which is required for FcR-stimulated NK cell function including calcium mobilization, granule release, and overall ADCC. Kohrt, *et al.*, *Blood* **2014,** *123*, 1957-60.

**[001007]** In this example, the effects of Formula (XVIII) and ibrutinib on NK cell function were evaluated in primary NK cells from healthy volunteers and CLL patients. The activation of NK cells co-cultured with antibody-coated target cells was strongly inhibited by ibrutinib. The secretion of IFN-γ was reduced by 48% ($p = 0.018$) and 72% ($p = 0.002$) in cultures treated with ibrutinib at 0.1 and 1.0 μM respectively and NK cell degranulation was significantly ($p = 0.002$) reduced, compared with control cultures. Formula (XVIII) treatment at 1 μM, a clinically relevant concentration, did not inhibit IFN-γ or NK cell degranulation. Rituximab-mediated ADCC was evaluated in NK cells from healthy volunteers as well as assays of NK cells from CLL patients targeting autologous CLL cells. In both cases, ADCC was not inhibited by Formula (XVIII) treatment at 1 μM. In contrast, addition of ibrutinib to the ADCC assays strongly inhibited the rituximab-mediated cytotoxicity of target cells, and no increase over natural cytotoxicity was observed at any rituximab concentration. This result indicates that the combination of rituximab and Formula (XVIII) provides an unexpected benefit in the treatment of CLL.

**[001008]** BTK is a non-receptor enzyme in the Tec kinase family that is expressed among cells of hematopoietic origin, including B cells, myeloid cells, mast cells and platelets, where it regulates multiple cellular processes including proliferation, differentiation, apoptosis, and cell migration. Khan, *Immunol Res.* **2001,** *23,* 147-56; Mohamed, *et al., Immunol Rev.* **2009,** *228,* 58-73; Bradshaw, *Cell Signal.* **2010,** *22,* 1175-84. Functional null mutations of BTK in humans cause the inherited disease, X linked agammaglobulinemia, which is characterized by a lack of mature peripheral B cells. Vihinen, *et al., Front Biosci.* **2000,** *5,* D917-28. Conversely, BTK activation is implicated in the pathogenesis of several B-cell malignancies. Herman, *et al., Blood* **2011,** *117,* 6287-96; Kil, *et al., Am. J. Blood Res.* **2013,** *3,* 71-83; Tai, *et al., Blood* **2012,** *120,* 1877-87; Buggy, and Elias, *Int. Rev. Immunol.* **2012,** *31,* 119-32 (Erratum in: *Int. Rev. Immunol.* **2012,** *31,* 428). In addition, BTK-dependent activation of mast cells and other immunocytes in peritumoral inflammatory stroma has been shown to sustain the complex microenvironment needed for lymphoid and solid tumor maintenance. Soucek, *et al., Neoplasia* **2011,** *13,* 1093-100; Ponader, *et al., Blood* **2012,** *119,* 1182-89; de Rooij, *et al., Blood* **2012,** *119,* 2590-94. Taken together, these findings have suggested

that inhibition of BTK may offer an attractive strategy for treating B-cell neoplasms, other hematologic malignancies, and solid tumors.

**[001009]** Ibrutinib (PCI-32765, IMBRUVICA), is a first-in-class therapeutic BTK inhibitor. This orally delivered, small-molecule drug is being developed by Pharmacyclics, Inc. for the therapy of B-cell malignancies. As described above, in patients with heavily pretreated indolent non-Hodgkin lymphoma (iNHL), mantle cell lymphoma (MCL), and CLL, ibrutinib showed substantial antitumor activity, inducing durable regressions of lymphadenopathy and splenomegaly in the majority of patients. Advani, *et al.*, *J. Clin. Oncol.* **2013,** *31,* 88-94; Byrd, *et al.*, *N. Engl. J. Med.* **2013**, *369,* 32-42; Wang, *et al.*, *N. Engl. J. Med.* **2013,** *369,* 507-16; O'Brien, *et al.*, *Blood* **2012,** *119,* 1182-89. The pattern of changes in CLL was notable. Inhibition of BTK with ibrutinib caused rapid and substantial mobilization of malignant CLL cells from tissues sites into the peripheral blood, as described in J. A. Woyach, *et al.*, *Blood* **2014,** *123,* 1810-17; this effect was consistent with decreased adherence of CLL to protective stromal cells. Ponader, *et al.*, *Blood* **2012,** *119,* 1182-89; de Rooij, *et al.*, *Blood* **2012**, *119,* 2590-94. Ibrutinib has been generally well tolerated. At dose levels associated with total BTK occupancy, not dose-limiting toxicities were identified and subjects found the drug tolerable over periods extending to >2.5 years.

**[001010]** Given the homology between BTK and interleukin-2 inducible tyrosine kinase (ITK), it has been recently confirmed that ibrutinib irreversibly binds ITK. Dubovsky, *et al.*, *Blood* **2013,** *122,* 2539-2549. ITK expression in Fc receptor (FcR)-stimulated NK cells leads to increased calcium mobilization, granule release, and cytotoxicity. Khurana, *et al.*, *J. Immunol.* **2007,** *178,* 3575-3582. As rituximab is a backbone of lymphoma therapy, with mechanisms of action including ADCC, as well as direct induction of apoptosis and complement-dependent cytotoxicity and FcR stimulation is requisite for ADCC, we investigated if ibrutinib or Formula (XVIII) (lacking ITK inhibition) influenced rituximab's anti-lymphoma activity *in vitro* by assessing NK cell IFN-γ secretion, degranulation by CD107a mobilization, and cytotoxicity by chromium release using $CD20^+$ cell lines and autologous patient samples with chronic lymphocytic leukemia (CLL).

**[001011]** Formula (XVIII) is a more selective inhibitor than ibrutinib, as shown previously. Formula (XVIII) is not a potent inhibitor of Itk kinase, in contrast to ibrutinib (see Table 9). Itk kinase is required for FcR-stimulated NK cell function including calcium mobilization, granule release, and overall ADCC. As anti-CD20 antibodies like rituximab are standard of care drugs, often as part of combination regimens, for the treatment of CD20+ B-cell malignancies, the potential of ibrutinib or Formula (XVIII) to antagonize ADCC was evaluated *in vitro*. We hypothesized that Btk inhibitor, Formula (XVIII) which does not have activity against Itk, may preserve NK cell function and therefore synergize rather than antagonize rituximab-mediated ADCC. Rituximab-dependent NK-cell mediated cytotoxicity was assessed using lymphoma cell lines as well as autologous CLL tumor cells.

**[001012]** Cell culture conditions were as follows. Cell lines Raji and DHL-4 were maintained in RPMI 1630 supplemented with fetal bovine serum, L-glutamine, 2-mercaptoethanol and penicillin-streptomycin at 37 °C in a humidified incubator. The HER18 cells were maintained in DEM supplemented with fetal bovine serum, penicillin-streptomycin and. Prior to assay, HER18 cells were harvested using trypsin-EDTA, washed with phosphate-buffered saline (PBS) containing 5% serum and viable cells were counted. For culture of primary target cells, peripheral blood from CLL patients was subject to density centrifugation to obtain peripheral blood mononuclear cells (PBMC). Cell preparations were washed and then subject to positive selection of $CD5^{+}CD19^{+}$ CLL cells using magnetic beads (MACS, Miltenyi Biotech). Cell preparations were used fresh after selection. NK cells from CLL patients and healthy volunteers were enriched from peripheral blood collected in sodium citrate anti-coagulant tubes and then subject to density centrifugation. Removal of non NK cells was performed using negative selection by MACS separation. Freshly isolated NK cells were washed three times, enumerated, and then used immediately for ADCC assays.

**[001013]** Cytokine secretion was determined as follows. Rituximab and trastuzumab-dependent NK-cell mediated degranulation and cytokine release were assessed using lymphoma and HER2+ breast cancer cell lines (DHL-4 and HER18, respectively). Target cells were cultured in flat-bottom plates containing 10 μg/mL of rituximab (DHL-4) or trastuzumab (HER18) and test articles (0.1 or 1 μM ibrutinib, 1

μM Formula (XVIII), or DMSO vehicle control). NK cells from healthy donors were enriched as described above and then added to the target cells and incubated for 4 hours at 37 °C. Triplicate cultures were performed on NK cells from donors. After incubation, supernatants were harvested, centrifuged briefly, and then analyzed for interferon-γ using an enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Minneapolis, MN, USA).

**[001014]** Lytic granule release was determined as follows. NK cells from healthy donors were enriched and cultured in the presence of target cells, monoclonal antibodies and test articles as described above. After 4 hours, the cultures were harvested and cells were pelleted, washed, and then stained for flow cytometry evaluation. Degranulation was evaluated via by flow cytometery by externalization of CD107a, a protein normally present on the inner leaflet of lytic granules, and gating on NK cells ($CD3^-CD16^+$ lymphocytes). The percentage of CD107a positive NK cells was quantified by comparison with a negative control (isotype control, unstained cells/FMO). Control cultures (NK cells cultured without target cells, or NK, target cell co-cultures in the absence of appropriate monoclonal antibody) were also evaluated; all experiments were performed in triplicate.

**[001015]** ADCC assays were performed as follows. Briefly, target cells (Raji or primary CLL) were labeled by incubation at 37 °C with 100 μCi $^{51}Cr$ for 4 hours prior to co-culture with NK cells. Cells were washed, enumerated, and then added in triplicate to prepared 96-well plates containing treated NK cells at an effector:target (E:T) ratio of 25:1. Rituximab (Genentech) was added to ADCC wells at concentrations of 0.1, 1.0 or 10 μg/mL and the assays were briefly mixed and then centrifuged to collect cells at the bottom of the wells. The effect of NK cell natural cytotoxicity was assessed in wells containing no rituximab. Cultures were incubated at 37 °C for 4 hours, and then centrifuged. Supernatants were harvested and $^{51}Cr$ release was measured by liquid scintillation counting. All experiments were performed in triplicate.

**[001016]** Ibrutinib inhibited rituximab-induced NK cell cytokine secretion in a dose-dependent manner (0.1 and 1 μM) (FIG. 130: 48% $p = 0.018$; 72% $p = 0.002$, respectively). At 1 μM, Formula (XVIII) did not significantly inhibit cytokine secretion

(FIG. 130: 3.5%). Similarly, Formula (XVIII) had no inhibitory effect on rituximab-stimulated NK cell degranulation (< 2%) while ibrutinib reduced degranulation by ~50% ($p = 0.24$, FIG. 131). Formula (XVIII) had no inhibitory effect while ibrutinib prevented trastuzumab-stimulated NK cell cytokine release and degranulation by ~92% and ~84% at 1μM, respectively (FIG. 130 and FIG. 131: ***$p = 0.004$, **$p = 0.002$).

**[001017]** In Raji cell samples, *ex vivo* NK cell activity against autologous tumor cells was not inhibited by addition of Formula (XVIII) at 1 μM, and increased cell lysis was observed with increasing concentrations of rituximab at a constant E:T ratio (FIG. 132). A plot highlighting the differences between Formula (XVIII) and ibrutinib at 10 μM is shown in FIG. 133. In primary CLL samples, *ex vivo* NK cell activity against autologous tumor cells was not inhibited by addition of Formula (XVIII) at 1 μM, and increased cell lysis was observed with increasing concentrations of rituximab at a constant E:T ratio (FIG. 134). In contrast, addition of 1 μM ibrutinib completely inhibited ADCC, with less than 10% cell lysis at any rituximab concentration and no increase in cell lysis in the presence of rituximab, compared with cultures without rituximab. The difference between Formula (XVIII) and ibrutinib was highly significant in this assay ($p = 0.001$).

**[001018]** In ADCC assays using healthy donor NK cells, antibody-dependent lysis of rituximab-coated Raji cells was not inhibited by addition of 1 μM Formula (XVIII) (FIG. 134). In these experiments, addition of rituximab stimulated a 5- to 8-fold increase in cell lysis at 0.1 and 1 μg/mL, compared with low (< 20%) natural cytotoxicity in the absence of rituximab. As previously reported, addition of 1 μM ibrutinib strongly inhibited the antibody-dependent lysis of target cells, with less than 20% cell lysis at all rituximab concentrations and no increase in ADCC with at higher rituximab concentrations.

**[001019]** Ibrutinib is clinically effective as monotherapy and in combination with rituximab, despite inhibition of ADCC *in vitro* and *in vivo* murine models due to ibrutinib's secondary irreversible binding to ITK. Preclinically, the efficacy of therapeutics which do not inhibit NK cell function, including Formula (XVIII), is superior to ibrutinib. Clinical investigation is needed to determine the impact of this finding on patients receiving rituximab as these results provide support for the

unexpected property of Formula (XVIII) as a better active pharmaceutical ingredient than ibrutinib to use in combination with antibodies that have ADCC as a mechanism of action. The improved performance of Formula (XVIII) in combination with anti-CD20 antibody therapies is expected to extend to its use in combination with PI3K inhibitors and PD-1/PD-L1 inhibitors in both hematological malignancies and solid tumors, as these combinations would also benefit from reduced inhibition of NK cell function.

Example 14 – Synergistic Combinations of a BTK Inhibitor, a PI3K-δ Inhibitor, and an α-PD-L1 Inhibitor in the 4T1 Orthotopic Breast Cancer Model

**[001020]** The 4T1 mouse breast cancer model was used to investigate the therapeutic efficacy of various combinations of the BTK inhibitor of Formula (XVIII), the BTK inhibitor ibrutinib (Formula (XX-A)), and the PI3K-δ inhibitor of Formula (IX), with an anti-PD-1L monoclonal antibody (αPD-L1, BioXcell InVivoMAb anti-m-PD-L1, clone 10F.9G2). This model features a tumor derived from the species of origin and allows for study of potential treatments in a human surrogate model with a functional immune system. The 4T1 mouse breast cancer model is described in Pulaski and Ostrand-Rosenberg, *Curr Protoc Immunol.* **2001,** Ch. 20, Unit 20.2, and Chen, *et al., Mol. Therapy* **2007,** *15,* 2194-202. The 4T1 model is an accepted experimental animal model for human breast cancer for at least two reasons: tumor cells are transplanted into the mammary gland so that the primary tumor grows in the correct anatomical location, and metastatic disease in this model develops spontaneously from the primary tumor. Also, the progressive spread of 4T1 metastases to lymph nodes and other organs occurs in a similar manner to the stages observed in human mammary cancer. This model also shares many molecular features with human disease and thus represents a model for advanced, resistant human breast cancers, including those resistant to 6-thioguanine and those refractory to most treatments based on stimulation of the immune system.

**[001021]** The treatment schema included the following arms: (1) IgG only; (2) the BTK inhibitor of Formula (XVIII) at 15 mg/kg, BID, on days 6 to 20; (3) the PI3K-δ inhibitor of Formula (IX) at 15 mg/kg, BID, on days 6 to 20; (4) the BTK inhibitor of Formula (XVIII) and the PI3K inhibitor of Formula (IX) each at 15 mg/kg, BID, on days 6 to 20; (5) the BTK inhibitor ibrutinib at 6 mg/kg, QD, on days 6 to 20; (6) α-PD-L1 antibody at 150 μg, on days 6, 9, 12, 15, and 18; (7) the BTK inhibitor of Formula (XVIII) at 15

mg/kg, BID, on days 6 to 20, combined with α-PD-L1 antibody at 150 μg, on days 6, 9, 12, 15, and 18; (8) the PI3K-δ inhibitor of Formula (IX) at 15 mg/kg, BID, on days 6 to 20, combined with α-PD-L1 antibody at 150 μg, on days 6, 9, 12, 15, and 18; (9) the PI3K-δ inhibitor ibrutinib at 6 mg/kg, QD, on days 6 to 20, combined with α-PD-L1 antibody at 150 μg, on days 6, 9, 12, 15, and 18; and (10) the BTK inhibitor of Formula (XVIII) and the PI3K inhibitor of Formula (IX) each at 15 mg/kg, BID, on days 6 to 20, further combined with α-PD-L1 antibody at 150 μg, on days 6, 9, 12, 15, and 18. The overall treatment and dosing schema used for the α-PD-L1 inhibitor in combination with the BTK inhibitor of Formula (XVIII), the PI3K inhibitor of Formula (IX), and the BTK inhibitor ibrutinib is depicted in FIG. 135.

**[001022]** The preparation of tumors and rodent species was performed as described in Example 4. A total of 12 mice were used in each arm of the study.

**[001023]** The results of the study are shown in FIG. 136 and FIG. 137. FIG. 136 illustrates the effects of the treatment schema arms on tumor volumes. FIG. 137 illustrates tumor infiltrating lymphocytes ("TILs").

Example 15 – Synergistic Combinations of a BTK Inhibitor, a PI3K-δ Inhibitor, and an α-PD-L1 inhibitor in the A20 Orthotopic Lymphoma Model

**[001024]** The A20 mouse orthotopic lymphoma cancer model was used to investigate the therapeutic efficacy of various combinations of the BTK inhibitor of Formula (XVIII), the BTK inhibitor ibrutinib (Formula (XX-A)), and the PI3K-δ inhibitor of Formula (IX), with an anti-PD-1L monoclonal antibody (αPD-L1, BioXcell InVivoMAb anti-m-PD-L1, clone 10F.9G2). The A20 lymphoma mouse model is described in Palmieri, *et al.*, *Blood* **2010,** *116,* 226-38; Kim, *et al.*, *J. Immunol.* **1979,** *122,* 549-54. A20 is poorly immunogenic, and A20 cells are injected into BALB/c mice lead to a disseminated leukemia with infiltration of lymph nodes, liver, and spleen and the presence of malignant cells in bone marrow and peripheral blood. This leukemia is highly resistant. Myeloablative doses of irradiation followed by syngeneic bone marrow transplant fail to cure A20 bearing mice. Graner, *et al.*, *Clin Cancer Res.* **2000,** *6,* 909-15.

**[001025]** The treatment schema included the following arms: (1) IgG only; (2) the BTK inhibitor of Formula (XVIII) at 15 mg/kg, BID, on days 6 to 20; (3) the PI3K-δ inhibitor

of Formula (IX) at 15 mg/kg, BID, on days 6 to 20; (4) the BTK inhibitor of Formula (XVIII) and the PI3K inhibitor of Formula (IX) each at 15 mg/kg, BID, on days 6 to 20; (5) the BTK inhibitor ibrutinib at 6 mg/kg, QD, on days 6 to 20; (6) α-PD-L1 antibody at 150 μg, on days 6, 9, 12, 15, and 18; (7) the BTK inhibitor of Formula (XVIII) at 15 mg/kg, BID, on days 6 to 20, combined with α-PD-L1 antibody at 150 μg, on days 6, 9, 12, 15, and 18; (8) the PI3K-δ inhibitor of Formula (IX) at 15 mg/kg, BID, on days 6 to 20, combined with α-PD-L1 antibody at 150 μg, on days 6, 9, 12, 15, and 18; (9) the PI3K-δ inhibitor ibrutinib at 6 mg/kg, QD, on days 6 to 20, combined with α-PD-L1 antibody at 150 μg, on days 6, 9, 12, 15, and 18; and (10) the BTK inhibitor of Formula (XVIII) and the PI3K inhibitor of Formula (IX) each at 15 mg/kg, BID, on days 6 to 20, further combined with α-PD-L1 antibody at 150 μg, on days 6, 9, 12, 15, and 18. The overall treatment and dosing schema used for the α-PD-L1 inhibitor in combination with the BTK inhibitor of Formula (XVIII), the PI3K inhibitor of Formula (IX), and the BTK inhibitor ibrutinib is depicted in FIG. 138.

**[001026]** The preparation of tumors and rodent species was performed as described in Example 4. A total of 12 mice were used in each arm of the study.

**[001027]** The results of the study are shown in FIG. 139 and FIG. 140. FIG. 139 illustrates the effects of the treatment schema arms on tumor volumes. FIG. 140 illustrates tumor infiltrating lymphocytes ("TILs").

Example 16 – Preclinical Characteristics of BTK Inhibitors

**[001028]** The BTK inhibitor ibrutinib ((1-[(3*R*)-3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidin-1-yl]prop-2-en-1-one) is a first-generation BTK inhibitor. In clinical testing as a monotherapy in subjects with hematologic malignancies, ibrutinib was generally well tolerated at dose levels through 840 mg (the highest dose tested). Advani, *et al.*, *J. Clin. Oncol.* **2013,** *31,* 88-94; Byrd, *et al.*, *N. Engl. J. Med.* **2013**, *369,* 32-42; Wang, *et al.*, *N. Engl. J. Med.* **2013,** *369,* 507-16. No maximum tolerated dose (MTD) was apparent within the tested dose range. Furthermore, subjects typically found the drug tolerable over periods extending to > 2 years. No subject had tumor lysis syndrome. No overt pattern of myelosuppression was associated with ibrutinib treatment. No drug-related reductions in circulating $CD4^+$ T cells or serum

immunoglobulins were noted. Adverse events with an apparent relationship to study drug included diarrhea and rash.

**[001029]** In subjects with heavily pretreated non-Hodgkin lymphoma (NHL), ibrutinib showed substantial antitumor activity, inducing durable regressions of lymphadenopathy and splenomegaly in most subjects. Improvements in disease-associated anemia and thrombocytopenia were observed. The pattern of changes in subjects with CLL was notable. Single-active pharmaceutical ingredient ibrutinib caused rapid and substantial reductions in lymph node size concomitant with a redistribution of malignant sites into the peripheral blood. An asymptomatic absolute lymphocyte count (ALC) increase was observed that was maximal during the first few months of treatment and generally decreased thereafter but could be persistent in some subjects or could be seen repeatedly in subjects who had interruption and resumption of drug therapy.

**[001030]** Collectively, these data with ibrutinib support the potential benefits of selective BTK inhibition in the treatment of subjects with relapsed lymphoid cancers. However, while highly potent in inhibiting BTK, ibrutinib has also shown *in vitro* activity against other kinases with a cysteine in the same position as Cys481 in BTK to which the drug covalently binds. For example, ibrutinib inhibits epidermal growth factor receptor (EGFR), which may be the cause of ibrutinib-related diarrhea and rash. In addition, it is a substrate for both cytochrome P450 (CYP) enzymes 3A4/5 and 2D6, which increases the possibility of drug-drug interactions. These liabilities support the development of alternative BTK inhibitors for use in the therapy of lymphoid cancer.

**[001031]** The preclinical selectivity and potency characteristics of the second-generation BTK inhibitor of Formula (XVIII) were compared to the first-generation BTK inhibitor ibrutinib. In Table 9, a kinome screen (performed Life Technologies or based on literature data) is shown that compares these compounds.

TABLE 9. Kinome Screen for BTK Inhibitors ($IC_{50}$, nM)

| 3F-Cys Kinase | Formula (XVIII) | Ibrutinib (Formula (XX-A)) |
|---|---|---|
| Btk | 3.1 | 0.5 |
| Tec | 29 | 78 |
| Bmx | 39 | 0.80 |
| Itk | >1000 | 10.7 |
| Txk | 291 | 2.0 |
| EGFR | >1000 | 5.6 |
| ErbB2 | 912 | 9.4 |
| ErbB4 | 13.2 | 2.7 |
| Blk | >1000 | 0.5 |
| JAK-3 | >1000 | 16.1 |

**[001032]** The results shown in Table 9 are obtained from a 10 point biochemical assay generated from 10 point concentration curves. The BTK inhibitor of Formula (XVIII) shows much greater selectivity for BTK compared to other kinases than ibrutinib.

**[001033]** A comparison of the *in vivo* potency results for the BTK inhibitors of Formula (XVIII) and ibrutinib is shown in FIG. 141. CD86 and CD69 are cell surface proteins that are BCR activation markers. To obtain the *in vivo* potency results, mice were gavaged at increasing drug concentration and sacrificed at one time point (3 h post-dose). BCR was stimulated with IgM and the expression of activation marker CD69 and CD86 are monitored by flow cytometry and to determine $EC_{50}$ values.

**[001034]** *In vitro* and *in vivo* safety pharmacology studies with Formula (XVIII) have demonstrated a favorable nonclinical safety profile. When screened at 10 μM in binding assays evaluating interactions with 80 known pharmacologic targets such as G-protein-coupled receptors, nuclear receptors, proteases, and ion channels, Formula (XVIII) shows significant activity only against the A3 adenosine receptor; follow-up dose-response experiments indicated a $IC_{50}$ of 2.7 μM, suggesting a low clinical risk of off-target effects. Formula (XVIII) at 10 μM showed no inhibition of *in vitro* EGFR phosphorylation in an A431 human epidermoid cancer cell line whereas ibrutinib had an $IC_{50}$ of 66 nM. The *in vitro* effect of Formula (XVIII) on human ether-à-go-go-related gene (hERG) channel activity was investigated *in vitro* in human embryonic kidney cells stably transfected with hERG. Formula (XVIII) inhibited hERG channel activity by 25%

at 10 μM, suggesting a low clinical risk that Formula (XVIII) would induce clinical QT prolongation as predicted by this assay. Formula (XVIII) was well tolerated in standard *in vivo* Good Laboratory Practices (GLP) studies of pharmacologic safety. A functional observation battery in rats at doses of through 300 mg/kg (the highest dose level) revealed no adverse effects on neurobehavioral effects or body temperature at any dose level. A study of respiratory function in rats also indicated no treatment-related adverse effects at doses through 300 mg/kg (the highest dose level). In a cardiovascular function study in awake telemeterized male beagle dogs, single doses of Formula (XVIII) at dose levels through 30 mg/kg (the highest dose level) induced no meaningful changes in body temperature, cardiovascular, or electrocardiographic (ECG) (including QT interval) parameters. The results suggest that Formula (XVIII) is unlikely to cause serious off-target effects or adverse effects on critical organ systems.

**[001035]** The drug-drug interaction potential of Formula (XVIII) was also evaluated. *In vitro* experiments evaluating loss of parent drug as catalyzed by CYPs indicated that Formula (XVIII) is metabolized by CYP3A4. *In vitro* metabolism studies using mouse, rat, dog, rabbit, monkey, and human hepatocytes incubated with $^{14}$C-labeled Formula (XVIII) indicated two mono-oxidized metabolites and a glutathione conjugate. No unique human metabolite was identified. Preliminary evaluations of metabolism in the plasma, bile, and urine of rats, dogs, and monkeys indicated metabolic processes of oxidation, glutathione binding, and hydrolysis. It was shown that Formula (XVIII) binds to glutathione but does not deplete glutathione *in vitro*. Nonclinical CYP interaction studies data indicate that Formula (XVIII) is very unlikely to cause clinical drug-drug interactions through alteration of the metabolism of drugs that are substrates for CYP enzymes.

Example 17 – Clinical Study of a BTK Inhibitor in Leukemia/Lymphoma and Effects on Bone Marrow and Lymphoid Microenvironments

**[001036]** Clinical studies have shown that targeting the BCR signaling pathway by inhibiting BTK produces significant clinical benefit in patients with non-Hodgkin's lymphoma (NHL). The second generation BTK inhibitor, Formula (XVIII), achieves significant oral bioavailability and potency, and has favorable preclinical characteristics, as described above. The purpose of this study is to evaluate the safety and efficacy of the

second generation BTK inhibitor of Formula (XVIII) in treating subjects with chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL).

**[001037]** The design and conduct of this study is supported by an understanding of the history and current therapies for subjects with lymphoid cancers; knowledge of the activity and safety of a first-generation BTK inhibitor, ibrutinib, in subjects with hematologic cancers; and the available nonclinical information regarding Formula (XVIII). The collective data support the following conclusions. BTK expression plays an important role in the biology of lymphoid neoplasms, which represent serious and life-threatening disorders with continuing unmet medical need. Clinical evaluation of Formula (XVIII) as a potential treatment for these disorders has sound scientific rationale based on observations that the compound selectively abrogates BTK activity and shows activity in nonclinical models of lymphoid cancers. These data are supported by clinical documentation that ibrutinib, a first-generation BTK inhibitor, is clinically active in these diseases. Ibrutinib clinical data and Formula (XVIII) nonclinical safety pharmacology and toxicology studies support the safety of testing Formula (XVIII) in subjects with B cell malignancies.

**[001038]** The primary objectives of the clinical study are as follows: (1) establish the safety and the MTD of orally administered Formula (XVIII) in subjects with CLL/SLL; (2) determine pharmacokinetics (PK) of orally administered Formula (XVIII) and identification of its major metabolite(s); and (3) measure pharmacodynamic (PD) parameters including drug occupancy of BTK, the target enzyme, and effect on biologic markers of B cell function.

**[001039]** The secondary objective of the clinical study is to evaluate tumor responses in patients treated with Formula (XVIII).

**[001040]** This study is a multicenter, open-label, nonrandomized, sequential group, dose escalation study. The following dose cohorts will be evaluated:

Cohort 1: 100 mg/day for 28 days (= 1 cycle)
Cohort 2: 175 mg/day for 28 days (= 1 cycle)
Cohort 3: 250 mg/day for 28 days (= 1 cycle)
Cohort 4: 350 mg/day for 28 days (= 1 cycle)

Cohort 5: 450 mg/day for 28 days (= 1 cycle)

Cohort 6: To be determined amount in mg/day for 28 days (= 1 cycle)

**[001041]** Each cohort will be enrolled sequentially with 6 subjects per cohort. If ≤ 1 dose-limiting toxicity (DLT) is observed in the cohort during Cycle 1, escalation to the next cohort will proceed. Subjects may be enrolled in the next cohort if 4 of the 6 subjects enrolled in the cohort completed Cycle 1 without experiencing a DLT, while the remaining 2 subjects are completing evaluation. If ≥ 2 DLTs are observed during Cycle 1, dosing at that dose and higher will be suspended and the MTD will be established as the previous cohort. The MTD is defined as the largest daily dose for which fewer than 33% of the subjects experience a DLT during Cycle 1. Dose escalation will end when either the MTD is achieved or at 3 dose levels above full BTK occupancy, whichever occurs first. Full BTK occupancy is defined as Formula (XVIII) active-site occupancy of > 80% (average of all subjects in cohort) at 24 hours postdose. Should escalation to Cohort 6 be necessary, the dose will be determined based on the aggregate data from Cohorts 1 to 5, which includes safety, efficacy, and PK/PD results. The dose for Cohort 6 will not exceed 900 mg/day.

**[001042]** Treatment with Formula (XVIII) may be continued for > 28 days until disease progression or an unacceptable drug-related toxicity occurs. Subjects with disease progression will be removed from the study. All subjects who discontinue study drug will have a safety follow-up visit 30 (±7) days after the last dose of study drug unless they have started another cancer therapy within that timeframe. Radiologic tumor assessment will be done at screening and at the end of Cycle 2, Cycle 4, and Cycle 12 and at investigator discretion. Confirmation of complete response (CR) will require bone marrow analysis and radiologic tumor assessment. For subjects who remain on study for > 11 months, a mandatory bone marrow aspirate and biopsy is required in Cycle 12 concurrent with the radiologic tumor assessment.

**[001043]** All subjects will have standard hematology, chemistry, and urinalysis safety panels done at screening. This study also includes pancreatic function assessment (serum amylase and serum lipase) due to the pancreatic findings in the 28-day GLP rat toxicity study. Once dosing commences, all subjects will be evaluated for safety once weekly for

the first 4 weeks, every other week for Cycle 2, and monthly thereafter. Blood samples will be collected during the first week of treatment for PK/PD assessments. ECGs will be done at screening, and on Day 1-2, 8, 15, 22, 28 of Cycle 1, Day 15 and 28 of Cycle 2, and monthly thereafter through Cycle 6. ECGs are done in triplicate for screening only. Thereafter, single ECG tests are done unless a repeat ECG testing is required.

**[001044]** Dose-limiting toxicity is defined as any of the following events (if not related to disease progression): (1) any Grade ≥ 3 non-hematologic toxicity (except alopecia) persisting despite receipt of a single course of standard outpatient symptomatic therapy (e.g., Grade 3 diarrhea that responds to a single, therapeutic dose of Imodium® would not be considered a DLT); (2) grade ≥ 3 prolongation of the corrected QT interval (QTc), as determined by a central ECG laboratory overread; (3) grade 4 neutropenia (absolute neutrophil count [ANC] < 500/μL) lasting > 7 days after discontinuation of therapy without growth factors or lasting > 5 days after discontinuation of therapy while on growth factors (i.e., Grade 4 neutropenia not lasting as long as specified will not be considered a DLT), (4) grade 4 thrombocytopenia (platelet count < 20,000/μL) lasting > 7 days after discontinuation of therapy or requiring transfusion (*i.e.*, Grade 4 thrombocytopenia not lasting as long as specified will not be considered a DLT), and (5) dosing delay due to toxicity for > 7 consecutive days.

**[001045]** The efficacy parameters for the study include overall response rate, duration of response, and progression-free survival (PFS). The safety parameters for the study include DLTs and MTD, frequency, severity, and attribution of adverse events (AEs) based on the Common Terminology Criteria for Adverse Events (CTCAE v4.03) for non-hematologic AEs. Hallek, *et al.*, *Blood* **2008,** *111,* 5446-5456.

**[001046]** The schedule of assessments is as follows, with all days stated in the following meaning the given day or +/- 2 days from the given day. A physical examination, including vital signs and weight, are performed at screening, during cycle 1 at 1, 8, 15, 22, and 28 days, during cycle 2 at 15 and 28 days, during cycles 3 to 24 at 28 days, and at follow up (after the last dose). The screening physical examination includes, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities,

musculoskeletal system, lymphatic system, and nervous system. Symptom-directed physical exams are done thereafter. Vital signs (blood pressure, pulse, respiratory rate, and temperature) are assessed after the subject has rested in the sitting position. Eastern Cooperative Oncology Group (ECOG) status is assessed at screening, during cycle 1 at 1, 8, 15, 22, and 28 days, during cycle 2 at 15 and 28 days, during cycles 3 to 24 at 28 days, and at follow up, using the published ECOG performance status indications described in Oken, *et al.*, *Am. J. Clin. Oncol.* **1982,** *5*, 649-655. ECG testing is performed at screening, during cycle 1 at 1, 2, 8, 15, 22, and 28 days, during cycle 2 at 15 and 28 days, during cycles 3 to 24 at 28 days, and at follow up. The 12-lead ECG test will be done in triplicate (≥ 1 minute apart) at screening. The calculated QTc average of the 3 ECGs must be <480 ms for eligibility. On cycle 1, day 1 and cycle 1, day 8, single ECGs are done predose and at 1, 2, 4, and 6 h postdose. The single ECG on Cycle 1 Day 2 is done predose. On cycle 1, day 15, day 22, and day 28, a single ECG is done 2 hours post-dose. Starting with cycle 2, a single ECG is done per visit. Subjects should be in supine position and resting for at least 10 minutes before study-related ECGs. Two consecutive machine-read QTc > 500 ms or > 60 ms above baseline require central ECG review. Hematology, including complete blood count with differential and platelet and reticulocyte counts, is assessed at screening, during cycle 1 at 1, 8, 15, 22, and 28 days, during cycle 2 at 15 and 28 days, during cycles 3 to 24 at 28 days, and at follow up. Serum chemistry is assesed at screening, during cycle 1 at 1, 8, 15, 22, and 28 days, during cycle 2 at 15 and 28 days, during cycles 3 to 24 at 28 days, and at follow up. Serum chemistry includes albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphate, potassium, sodium, total bilirubin, total protein, and uric acid. Cell counts and serum immunoglobulin are performed at screening, at cycle 2, day 28, and at every 6 months thereafter until last dose and include T/B/NK/monocyte cell counts (CD3, CD4, CD8, CD14, CD19, CD19, CD16/56, and others as needed) and serum immunoglobulin (IgG, IgM, IgA, and total immunoglobulin). Bone marrow aspirates are performed at cycle 12. Pharmacodynamics samples are drawn during cycle 1 at 1, 2, and 8 days, and at follow up. On days 1 and 8, pharmacodynamic samples are drawn pre-dose and 4 hours (±10 minutes) post-dose, and on day 2, pharmacodynamic

samples are drawn pre-dose. Pharmacokinetics samples are drawn during cycle 1 at 1, 2, 8, 15, 22, and 28 days. Pharmacokinetic samples for Cycle 1 Day 1 are drawn pre-dose and at 0.5, 1, 2, 4, 6 and 24 hours (before dose on Day 2) post-dose. Samples for Cycle 1 Day 8 are drawn pre-dose and at 0.5, 1, 2, 4, and 6 hours post-dose. On Cycle 1 Day 15, 22, and 28, a PK sample is drawn pre-dose and the second PK sample must be drawn before (up to 10 minutes before) the ECG acquisition, which is 2 hours postdose. Pretreatment radiologic tumor assessments are performed within 30 days before the first dose. A computed tomography (CT) scan (with contrast unless contraindicated) is required of the chest, abdomen, and pelvis. In addition, a positron emission tomography (PET) or PET/CT must done for subjects with SLL. Radiologic tumor assessments are mandatory at the end of Cycle 2 (-7 days), Cycle 4 (- 7days), and Cycle 12 (-7 days). Otherwise, radiologic tumor assessments are done at investigator discretion. A CT (with contrast unless contraindicated) scan of the chest, abdomen, and pelvis is required for subjects with CLL. In addition, a PET/CT is required in subjects with SLL. Bone marrow and radiologic assessments are both required for confirmation of a complete response (CR). Clinical assessments of tumor response should be done at the end of Cycle 6 and every 3 months thereafter. Molecular markers are measured at screening, and include interphase cytogenetics, stimulated karyotype, IgHV mutational status, Zap-70 methylation, and beta-2 microglobulin levels. Urinalysis is performed at screening, and includes pH, ketones, specific gravity, bilirubin, protein, blood, and glucose. Other assessments, including informed consent, eligibility, medical history, and pregnancy test are done at the time of screening.

**[001047]** The investigator rates the subject's response to treatment based on recent guidelines for CLL, as given in Hallek, *et al.*, *Blood* **2008,** *111,* 5446-56, and for SLL, as given in Cheson, *et al., J. Clin. Oncol.* **2007,** *25,* 579-586. The response assessment criteria for CLL are summarized in Table 10.

TABLE 10. Response Assessment Criteria for CLL. Abbreviations: ANC = absolute neutrophil count; CR = complete remission; CRi = CR with incomplete blood count recovery; PR = partial remission.

| Response | Peripheral Blood | Bone Marrow (if performed) | Nodes, Liver, and Spleen[a] |
|---|---|---|---|
| CR | Lymphocytes < 4 x $10^9$/L<br>ANC >1.5 x $10^9$/L[b]<br>Platelets > 100 x $10^9$/L[b]<br>Hemoglobin > 11.0 g/dL (untransfused)[b] | Normocellular<br><30% lymphocytes<br>No B-lymphoid nodules | Normal (e.g., no lymph nodes >1.5 cm) |
| CRi | Lymphocytes < 4 x $10^9$/L<br>Persistent anemia, thrombocytopenia, or neutropenia related to drug toxicity | Hypocellular<br><30% lymphocytes | Normal (*e.g.*, no lymph nodes >1.5 cm) |
| PR | Lymphocytes ≥ 50% decrease from baseline<br>ANC > 1.5 x $10^9$/L<br>or<br>Platelets > 100 x $10^9$/L<br>or<br>50% improvement over baseline[b]<br>or<br>Hemoglobin > 11.0 g/dL or<br>50% improvement over baseline (untransfused)[b] | Not assessed | ≥50% reduction in lymphadenopathy[c] and/or in spleen or liver enlargement |

a. Computed tomography (CT) scan of abdomen, pelvis, and chest is required for this evaluation

b. Without need for exogenous growth factors

c. In the sum products of ≤ 6 lymph nodes or in the largest diameter of the enlarged lymph node(s) detected before therapy and no increase in any lymph node or new enlarged lymph nodes

**[001048]** The response assessment criteria for SLL are summarized in Table 11.

TABLE 11. Response Assessment Criteria for SLL. Abbreviations: CR = complete remission, CT = computed tomography, FDG = [$^{18}$F]fluorodeoxyglucose, PET = positron-emission tomography, PR = partial remission, SD = stable disease, SPD = sum of the product of the diameters.

| Response | Definition | Nodal Masses | Spleen, Liver | Bone Marrow |
|---|---|---|---|---|
| CR | Disappearance of all evidence of disease | (a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative<br>(b) Variably FDG-avid or PET negative; regression to normal size on CT | Not palpable, nodules disappeared | If infiltrate present at screening, infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohisto-chemistry should be negative |
| PR | Regression of measurable disease and no new sites | ≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes<br>(a) FDG-avid or PET positive prior to therapy; ≥ 1 PET positive at previously involved site<br>(b) Variably FDG-avid or PET negative; regression on CT | ≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen | Irrelevant if positive prior to therapy; cell type should be specified |
| SD | Failure to attain CR/PR or progressive disease | (a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease, and no new sites on CT or PET<br>(b) Variably FDG avid or PET negative; no change in size of previous lesions on CT | | |

**[001049]** The PK parameters of the study are as follows. The plasma PK of Formula (XVIII) and a metabolite is characterized using noncompartmental analysis. The following PK parameters are calculated, whenever possible, from plasma concentrations of Formula (XVIII):

$AUC_{(0\text{-}t)}$: Area under the plasma concentration-time curve calculated using linear

trapezoidal summation from time 0 to time t, where t is the time of the last measurable concentration (Ct),

$AUC_{(0-24)}$: Area under the plasma concentration-time curve from 0 to 24 hours, calculated using linear trapezoidal summation,

$AUC_{(0-\infty)}$: Area under the plasma concentration-time curve from 0 to infinity, calculated using the formula: $AUC_{(0-\infty)} = AUC_{(0-t)} + Ct / \lambda z$, where $\lambda z$ is the apparent terminal elimination rate constant,

$C_{max}$: Maximum observed plasma concentration,

$T_{max}$: Time of the maximum plasma concentration (obtained without interpolation),

$t_{½}$: Terminal elimination half-life (whenever possible),

$\lambda_z$: Terminal elimination rate constant (whenever possible),

Cl/F: Oral clearance.

**[001050]** The PD parameters of the study are as follows. The occupancy of BTK by Formula (XVIII) are measured in peripheral blood mononuclear cells (PBMCs) with the aid of a biotin-tagged Formula (XVIII) analogue probe. The effect of Formula (XVIII) on biologic markers of B cell function will also be evaluated.

**[001051]** The statistical analysis used in the study is as follows. No formal statistical tests of hypotheses are performed. Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions for discrete variables) are used to summarize data as appropriate.

**[001052]** The following definitions are used for the safety and efficacy analysis sets: Safety analysis set: All enrolled subjects who receive ≥ 1 dose of study drug; Per-protocol (PP) analysis set: All enrolled subjects who receive ≥ 1 dose of study drug and with ≥ 1 tumor response assessment after treatment. The safety analysis set will be used for evaluating the safety parameters in this study. The PP analysis sets will be analyzed for efficacy parameters in this study.

**[001053]** No imputation of values for missing data is performed except for missing or partial start and end dates for adverse events and concomitant medication will be imputed

according to prespecified, conservative imputation rules. Subjects lost to follow-up (or drop out) will be included in statistical analyses to the point of their last evaluation.

**[001054]** The safety endpoint analysis was performed as follows. Safety summaries will include summaries in the form of tables and listings. The frequency (number and percentage) of treatment emergent adverse events will be reported in each treatment group by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term. Summaries will also be presented by the severity of the adverse event and by relationship to study drug. Laboratory shift tables containing counts and percentages will be prepared by treatment assignment, laboratory parameter, and time. Summary tables will be prepared for each laboratory parameter. Figures of changes in laboratory parameters over time will be generated. Vital signs, ECGs, and physical exams will be tabulated and summarized.

**[001055]** Additional analyses include summaries of subject demographics, baseline characteristics, compliance, and concurrent treatments. Concomitant medications will be coded according to the World Health Organization (WHO) Drug Dictionary and tabulated.

**[001056]** The analysis of efficacy parameters was performed as follows. The point estimate of the overall response rate will be calculated for the PP analysis set. The corresponding 95% confidence interval also will be derived. The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). Kaplan-Meier methodology will be used to estimate event-free curves and corresponding quantiles (including the median). Progression-free survival is measured from the time of first study drug administration until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). Kaplan-Meier methodology will be used to estimate the event-free curves and corresponding quantiles (including the median).

**[001057]** The study scheme is a sequential cohort escalation. Each cohort consists of six subjects. The sample size of the study is 24 to 36 subjects, depending on dose escalation into subsequent cohorts. Cohort 1 (N = 6) consists of Formula (XVIII), 100 mg QD for 28 days. Cohort 2 (N = 6) consists of Formula (XVIII), 175 mg QD for 28 days. Cohort 3 (N = 6) consists of Formula (XVIII), 250 mg QD for 28 days. Cohort 4 (N = 6) consists of Formula (XVIII), 350 mg QD for 28 days. Cohort 5 (N = 6) consists of Formula (XVIII), 450 mg QD for 28 days. Cohort 6 (N = 6) consists of Formula (XVIII), at a dose to be determined QD for 28 days. The dose level for Cohort 6 will be determined based on the safety and efficacy of Cohorts 1 to 5, and will not exceed 900 mg/day. Escalation will end with either the MTD cohort or three levels above full BTK occupancy, whichever is observed first. An additional arm of the study will explore 100 mg BID dosing. Treatment with oral Formula (XVIII) may be continued for greater than 28 days until disease progression or an unacceptable drug-related toxicity occurs.

**[001058]** The inclusion criteria for the study are as follows: (1) men and women ≥ 18 years of age with a confirmed diagnosis of CLL/SLL, which has relapsed after, or been refractory to, ≥ 2 previous treatments for CLL/SLL; however, subjects with 17p deletion are eligible if they have relapsed after, or been refractory to, 1 prior treatment for CLL/SLL; (2) body weight ≥ 60 kg, (3) ECOG performance status of ≤ 2; (4) agreement to use contraception during the study and for 30 days after the last dose of study drug if sexually active and able to bear children; (5) willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty; or (6) ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local subject privacy regulations).

**[001059]** The dosage form and strength of Formula (XVIII) used in the clinical study is a hard gelatin capsules prepared using standard pharmaceutical grade excipients (microcrystalline cellulose) and containing 25 mg of Formula (XVIII) each. The color of the capsules is Swedish orange. The route of administration is oral (*per os*, or PO). The dose regimen is once daily or twice daily, as defined by the cohort, on an empty stomach (defined as no food 2 hours before and 30 minutes after dosing).

**[001060]** The baseline characteristics for the patients enrolled in the clinical study are given in Table 12.

TABLE 12. Relapsed/refractory CLL baseline characteristics.

| **Characteristic** | **CLL (N=44)** |
|---|---|
| Patient Demographics | |
| Age (years), median (range) | 62 (45-84) |
| Sex, men (%) | 33 (75) |
| Prior therapies, median (range), n | 3 (1-10) |
| ≥3 prior therapies, n (%) | 26 (59) |
| Clinical Details | |
| ECOG performance status ≥1 (%) | 28 (63) |
| Rai stage III/IV | 16 (36) |
| Bulky disease ≥ 5 cm, n (%) | 15 (34) |
| Cytopenia at baseline | 33 (75) |
| Cytogenic Status | |
| Chromosome 11q22.3 deletion (Del 11q), n (%) | 18 (41) |
| Chromosome 17p13.1 (Del 17p), n (%) | 19 (34) |
| $IgV_H$ status (unmutated), n (%) | 28 (64) |

**[001061]** The results of the clinical study in relapsed/refractory CLL patients are summarized in Table 13.

TABLE 13. Activity of Formula (XVIII) in relapsed/refractory CLL. (PR = partial response; PR+L = partial response with lymphocytosis; SD = stable disease; PD = progressive disease.)

| **n (%)** | **All Cohorts (N=31)** | **100 mg QD (N=8)** | **175 mg QD (N=8)** | **250 mg QD (N=7)** | **100 mg BID (N=3)** | **400 mg QD (N=5)** |
|---|---|---|---|---|---|---|
| **PR** | 22 (71) | 7 (88) | 5 (63) | 5 (71) | 3 (100) | 2 (40) |
| **PR+L** | 7 (23) | 0 (0) | 3 (37) | 2 (29) | 0 (0) | 2 (40) |
| **SD** | 2 (6) | 1 (12) | 0 (0) | 0 (0) | 0 (0) | 1 (20) |
| **PD** | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Median (range) Cycles | | | | | | |
| | **7.3 (3.0-10.8)** | **10.0 (9.0-10.8)** | **8.6 (3.0-8.8)** | **7.0 (7.0-7.3)** | **5.2 (4.7-5.5)** | **5.0 (4.8-5.5)** |

**[001062]** FIG. 142 shows the median % change in ALC and SPD from baseline in the clinical study of Formula (XVIII), plotted in comparison to the results reported for ibrutinib in Figure 1A of Byrd, *et al.*, *N. Engl. J. Med.* **2013,** *369,* 32-42. The results show that Formula (XVIII) leads to a more rapid patient response in CLL than corresponding treatment with ibrutinib. This effect is illustrated, for example, by the median % change in SPD, which achieved the same status in the present study at 7 months of treatment with Formula (XVIII) as compared to 18 months for ibrutinib. The % change in SPD observed in the different cohorts (*i.e.* by dose and dosing regimen) is shown in FIG. 143, and in all cases shows significant responses.

**[001063]** A Kaplan-Meier curve showing PFS from the clinical CLL study of Formula (XVIII) is shown in FIG. 144. A comparison of survival curves was performed using the Log-Rank (Mantle-Cox) test, with a p-value of 0.0206 indicating that the survival curves are different. The number of patients at risk is shown in FIG. 145. Both FIG. 144 and FIG. 145 show the results for Formula (XVIII) in comparison to the results reported for ibrutinib in Byrd, *et al.*, *N. Engl. J. Med.* **2013,** *369,* 32-42. An improvement in survival and a reduction in risk are observed in CLL patients treated with Formula (XVIII) in comparison to patients treated with ibrutinib.

**[001064]** Based on the data and comparisons shown in FIG. 142 to FIG. 145, the CLL study with Formula (XVIII) showed that the efficacy of Formula (XVIII) was surprisingly superior to that of ibrutinib.

**[001065]** In the literature study of ibrutinib, increased disease progression was associated with patients with high-risk cytogenetic lesions (17p13.1 deletion or 11q22.3 deletion), as shown in Figure 3A in Byrd, *et al.*, *N. Engl. J. Med.* **2013,** *369,* 32-42, which shows ibrutinib PFS including PFS broken down by genetic abnormality. The 17p and 11q deletions are validated high-risk characteristics of CLL, and the 17p deletion is the highest risk. In FIG. 146, the PFS is shown for Formula (XVIII) in patients with the 17p deletion in comparison to the results obtained for ibrutinib in Byrd, *et al.*, *N. Engl. J. Med.* **2013,** *369,* 32-42. A p-value of 0.0696 was obtained. In FIG. 147, the number of

patients at risk with the 17p deletion is compared. To date, no 17p patients have progressed on Formula (XVIII).

**[001066]** The adverse events observed in the clinical study in relapsed/refractory CLL are given in Table 14. No DLTs were observed. The MTD was not reached. No treatment-related serious adverse events (SAEs) were observed. No prophylactic antivirals or antibiotics were needed.

TABLE 14. Treatment-related adverse events reported in the clinical study of Formula (XVIII) in relapsed/refractory CLL. (Reported in ≥ 5% of patients.)

| **Adverse Events (Treatment-Related), n (%)** | **Grade** | **All (N=44)** |
|---|---|---|
| Headache | 1/2 | 7 (16) |
| Increased tendency to bruise | 1 | 6 (14) |
| Diarrhea | 1 | 4 (9) |
| Petechiae | 1 | 3 (7) |

**[001067]** The clinical study of Formula (XVIII) thus showed other unexpectedly superior results compared to ibrutinib therapy. A lack of lymphocytosis was observed in the study. Furthermore, only grade 1 AEs were observed, and these AEs were attributable to the high BTK selectivity of Formula (XVIII).

**[001068]** BTK target occupancy was measured for relapsed/refractory CLL patients with the results shown in FIG. 148. For 200 mg QD dosing of the BTK inhibitor of Formula (XVIII), approximately 94% - 99% BTK occupancy was observed, with superior 24 hour coverage and less inter-patient variability also observed. For 420 mg and 840 mg QD of the BTK inhibitor ibrutinib, 80% - 90% BTK occupancy was observed, with more inter-patient variability and capped occupancy. These results indicate that the BTK inhibitor of Formula (XVIII) achieves superior BTK occupancy in CLL patients than ibrutinib.

**[001069]** The effects of Formula (XVIII) on cell subset percentages were also evaluated using flow cytometry analysis of peripheral blood, with the results shown in FIG. 149, FIG. 150, FIG. 151, FIG. 152, FIG. 153, and FIG. 154. PBMC samples from CLL patient samples drawn prior to (predose) and after 28 days of dosing with Formula

(XVIII) were compared for potential changes in cell subsets. PBMCs were stained with monoclonal antibodies conjugated to fluorescent tags (flourochromes) to identify cell subsets via flow cytometry. Non-viable cells were excluded from the analysis using the dye 7-aminoactinomycin D (7-AAD). To produce the metric of percent change, the following steps were taken. First, each cell subset was defined by hierarchical flow cytometry gating. Then, the change in frequency (between day 1 and day 28) was calculated for each cell subset. MDSC subsets were measured as a % of all myeloid cells. T cell subsets were measured as a % of all $CD3^+$ cells, and NK cells were measured as a % of all live $CD45^+$ cells. In FIG. 149 and FIG. 150, the results show the % change in MDSC (monocytic) level over 28 days versus % ALC change at cycle 1 day 28 (C1D28) and at cycle 2 day 28 (C2D28). A cycle is 28 days. A trend is observed wherein patients with decreasing ALC % had increasing MDSC (monocytic) %. This may include patients who had quickly resolving lymphocytosis and those with no initial lymphocytosis. This provides evidence that treatment with Formula (XVIII) mobilizes MDSCs and thus affects the CLL tumor microenvironment in marrow and lymph nodes, which is an unexpected indication of superior efficacy. In FIG. 151 and FIG. 152, the results show the % change in NK cell level over 28 days versus % ALC change, measured at C1D28 or C2D28, and similar trends are observed wherein patients with decreasing ALC % had increasing NK cell %. This may include patients who had quickly resolving lymphocytosis and those having no initial lymphocytosis. The effects in FIG. 149 to FIG. 152 are observed in multiple cohorts, at doses including 100 mg BID, 200 mg QD, and 400 mg QD. In FIG. 153 and FIG. 154, the effects on NK cells and MDSC cells are compared to a number of other markers versus % change in ALC at C1D28 and C2D28. These other markers include CD4+ T cells, CD8+ T cells, CD4+/CD8+ T cell ratio, NK-T cells, PD-1+ CD4+ T cells, and PD-1+ CD8+ T cells. The effects on NK cells and MDSC cells are observed to be much more pronounced than on any of these other markers.

**[001070]** These results suggest that after Formula (XVIII) administration, the CLL microenvironment undergoes a change wherein NK cells and monocytic MDSC subsets increase in frequency in the peripheral blood in patients with falling ALC counts, an important clinical parameter in CLL. The NK cell increase may reflect an overall

increase in cytolytic activity against B-CLL resulting in the ALC % to drop. The increase in MDSC % in the blood may be due to a movement of these cells out of the lymph nodes, spleen, and bone marrow, which are all possible sites of CLL proliferation. Fewer MDSCs at the CLL proliferation centers would likely result in a reduced immunosuppressive microenvironment leading to an increase in cell-mediated immunity against the tumor, decreased tumor proliferation, and eventually lower ALC% in the circulation.

**[001071]** Updated clinical results from the CLL study are shown in FIG. 155 to FIG. 160. FIG. 155 shows an update of the data presented in FIG. 142. FIG. 156 shows an update of the data presented in FIG. 142, and includes BID dosing results. Formula (XVIII) 200 mg QD dosing resulted in 94% - 99% BTK occupancy, 24 hour coverage, and less inter-patient variability. Ibrutinib 420 mg and 840 mg QD dosing resulted in 80% - 90% BTK occupancy, more inter-patient variability, and capped occupancy. Formula (XVIII) 100 mg BID dosing resulted in 97% - 99% BTK occupancy, complete BTK coverage, and less inter-patient variability. The PFS for patients with 11p deletions and 17q deletions are illustrated in FIG. 157, FIG. 158, and FIG. 159. Updated SPD results are illustrated in FIG. 160.

**[001072]** Treatment of CLL patients with Formula (XVIII) also resulted in increased apoptosis, as illustrated in FIG. 161. Apoptotic B-CLL was defined by flow cytometry as having cleaved $PARP^+$, Caspase $3^+$, $CD19^+$, and $CD5^+$ phenotypes. 82% of samples tested had a baseline change greater than 25%. Treatment of CLL patients also showed that Formula (XVIII) decreased plasma chemokines associated with MDSC homing and retention. A significant decrease in CXCL12 and CCL2 levels has been observed in patients treated with Formula (XVIII), as shown in FIG. 162 and FIG. 163, respectively.

**[001073]** Overall, Formula (XVIII) shows superior efficacy to first generation BTK inhibitors such as ibrutinib, or to monotherapy with PI3K-δ inhibitors such as idelalisib. Formula (XVIII) has better target occupancy and better pharmacokinetic and metabolic parameters than ibrutinib, leading to improved B cell apoptosis. Furthermore, unlike treatment with ibrutinib and PI3K-δ inhibitors, treatment with Formula (XVIII) does not affect NK cell function. Finally, treatment with Formula (XVIII) leads to a CLL tumor

microenvironmental effect by excluding MDSC cells from the marrow and lymph nodes and reducing their number.

Example 18 – Clinical Study of a BTK Inhibitor in Leukemia/Lymphoma in Combination with Obinutuzumab (GA-101)

**[001074]** The primary objectives of the study are (1) to determine the overall response rate (ORR) at 12 months with the combination of Formula (XVIII) and obinutuzumab in patients with relapsed or refractory CLL, (2) to determine the ORR at 12 months with the combination of Formula (XVIII) and obinutuzumab in patients with treatment-naive CLL, and (3) to establish the safety and feasibility of the combination of Formula (XVIII) and obinutuzumab.

**[001075]** The secondary objectives of this study are: (1) to determine the complete response (CR) rate and MRD-negative CR rate in previously untreated and relapsed and refractory CLL with this regimen; (2) to determine the progression-free survival (PFS), time to next treatment (TTNT), and overall survival (OS) with this regimen, (3) to perform baseline analysis of patients enrolled on this trial including fluorescence in situ hybridization (FISH), stimulated karyotype, Zap-70 methylation, and $IgV_H$ mutational status and describe relationships between these biomarkers and ORR or PFS for patients treated with this regimen; (4) to determine pharmacokinetics (PK) of orally administered Formula (XVIII); (5) to measure pharmacodynamic (PD) parameters including drug occupancy of BTK, change in miR and gene expression on day 8 and 29 of therapy of Formula (XVIII); (6) to determine the influence of Formula (XVIII) on NK cell and T cell function in vivo; (7) to assess for serial development of resistance by baseline and longitudinal assessment of mutations of BTK and PLCG2 at regular follow up intervals and by examining diagnosis to relapse samples by whole exome sequencing; (8) to determine the influence of Formula (XVIII) on emotional distress and quality of life in CLL patients; and (9) to determine trajectory of psychological and behavioral responses to Formula (XVIII) and covariation with response to therapy.

**[001076]** CLL is the most prevalent form of adult leukemia and has a variable clinical course, where many patients do not require treatment for years and have survival equal to age matched controls. Other patients, however, exhibit aggressive disease and have a

poor prognosis despite appropriate therapy. Byrd, *et al.*, Chronic lymphocytic leukemia. *Hematology Am. Soc. Hematol. Educ. Program.* **2004,** 163-183. While patients with early disease have not been shown to have a survival advantage with early treatment, most patients will eventually require therapy for their disease with the onset of symptoms or cytopenias, and despite the relatively long life expectancy for early stage disease, CLL remains an incurable disease. Patients diagnosed with or progressing to advanced disease have a mean survival of 18 months to 3 years. Unfortunately these patients with advanced disease are also more refractory to conventional therapy.

**[001077]** The treatment of CLL has progressed significantly over the previous decades. While alkylator therapy was used in the past, randomized trials have demonstrated a higher response rate and longer progression free survival (PFS) with fludarabine and subsequently with fludarabine-and cyclophosphamide-based combinations. O'Brien, *et al.*, Advances in the biology and treatment of B-cell chronic lymphocytic leukemia. *Blood* **1995,** *85,* 307-18; Rai, *et al.*, Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic leukemia. *N. Engl. J. Med.* **2000,** *343,* 1750-57; Johnson, *et al.*, Multicentre prospective randomised trial of fludarabine versus cyclophosphamide, doxorubicin, and prednisone (CAP) for treatment of advanced-stage chronic lymphocytic leukemia. The French Cooperative Group on CLL. *Lancet* **1996,** *347,* 1432-38; Leporrier, *et al.*, Randomized comparison of fludarabine, CAP, and ChOP in 938 previously untreated stage B and C chronic lymphocytic leukemia patients. *Blood* **2001,** 98, 2319-25; Catovsky, *et al.*, Assessment of fludarabine plus cyclophosphamide for patients with chronic lymphocytic leukemia (the LRF CLL4 Trial): A randomised controlled trial. *Lancet* **2007,** *370,* 230-239; Eichhorst, *et al.*, Fludarabine plus cyclophosphamide versus fludarabine alone in first-line therapy of younger patients with chronic lymphocytic leukemia. *Blood* **2006,** *107,* 885-91. At the same time, the chimeric anti-CD20 monoclonal antibody rituximab was introduced for the treatment of CLL. At high doses or with dose intensive treatment, single agent rituximab has shown efficacy; however complete responses and extended remissions are very rare. O'Brien, *et al.* Rituximab dose-escalation trial in chronic lymphocytic leukemia. *J. Clin. Oncol.* **2001,** *19,* 2165-70; Byrd, *et al.*, Rituximab using a thrice weekly dosing schedule in B-cell chronic lymphocytic leukemia and small lymphocytic lymphoma demonstrates clinical activity

and acceptable toxicity. *Clin. Oncol.* **2001,** *19,* 2153-64. The efficacy of rituximab has been improved by combining it with traditional cytotoxic agents such as fludarabine or fludarabine and cyclophosphamide, which have produced high CR rates and extended progression free survival (PFS) compared to historical controls. Indeed, a large randomized clinical trial reported by the German CLL study group has shown a benefit of the addition of antibody therapy with rituximab to fludarabine and cyclophosphamide in the prolongation of PFS and OS in patients with untreated CLL. Hallek, *et al.,* Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukemia: a randomised, open-label, phase 3 trial. *Lancet* **2010,** 376, 1164-74. This encouraging progress in therapy and our understanding of the disease has resulted in significantly improved response rates and PFS. However, significant improvements in overall survival (OS) and ultimately cure, remain elusive goals.

**[001078]** While fludarabine based chemoimmunotherapy is standard for younger patients, the therapy for older patients is less well defined. In the large Phase 2 and 3 trials outlined previously, median ages were typically in the early-60s, while the average age of patients diagnosed with CLL is 72, which calls into question whether these results are generalizable to the entire CLL population. In fact, the one randomized Phase 3 trial investigating primary CLL therapy in older patients demonstrated that in patients >65 years old, fludarabine is not superior to chlorambucil. Eichhorst, *et al.,* First-line therapy with fludarabine compared with chlorambucil does not result in a major benefit for elderly patients with advanced chronic lymphocytic leukemia. *Blood* **2009,** *114,* 3382-91. This finding was corroborated by a large retrospective study of front-line trials performed by the Alliance for Clinical Trials in Oncology, which demonstrated again that fludarabine is not superior to chlorambucil in older patients, but also showed that the addition of rituximab to chemotherapy was beneficial regardless of age. Woyach, *et al.,* Impact of age on outcomes after initial therapy with chemotherapy and different chemoimmunotherapy regimens in patients with chronic lymphocytic leukemia: Results of sequential cancer and leukemia group B studies. *J. Clin. Oncol.* **2013,** *31,* 440-7. Two studies have evaluated the combination of rituximab with chlorambucil, showing that this combination is safe and moderately effective. Hillmen, *et al.,* rituximab plus chlorambucil in patients with CD20-positive B-cell chronic lymphocytic leukemia

(CLL): Final response analysis of an open-label Phase II Study, ASH Annual Meeting Abstracts, *Blood* **2010,** *116,* 697; Foa, *et al.,* A Phase II study of chlorambucil plus rituximab followed by maintenance versus observation in elderly patients with previously untreated chronic lymphocytic leukemia: Results of the first interim analysis, ASH Annual Meeting Abstracts, *Blood* **2010,** *116,* 2462.

**[001079]** Recently, the type II glycoengineered CD20 monoclonal antibody obinutuzumab was introduced. In a Phase 1 trial of previously treated CLL as monotherapy, this antibody has a 62% response rate including 1 MRD-negative complete response, suggesting that alone this antibody may be more active in CLL than rituximab. Morschhauser, *et al.,* Phase I study of R05072759 (GA101) in relapsed/refractory chronic lymphocytic leukemia, ASH Annual Meeting Abstracts. *Blood*, **2009,** *114*, 884. The German CLL Study Group (GCLLSG) recently completed a Phase 3 trial of rituximab and chlorambucil or obinutuzumab and chlorambucil versus chlorambucil alone in patients with untreated CLL and significant comorbidities. In this population, obinutuzumab and chlorambucil (but not rituximab and chlorambucil) improved OS over chlorambucil alone (hazard ratio 0.41, p=0.002), and obinutuzumab and chlorambucil improved PFS over rituximab and chlorambucil (median PFS 26.7 months vs 14.9 months, p<0.001). Goede, *et al.*, Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions, *N. Engl. J. Med.* **2014,** *370,* 1101-10. On the basis of these favorable data, the combination of obinutuzumab and chlorambucil is FDA approved as frontline therapy for CLL patients.

**[001080]** Many older patients are also treated with the combination of bendamustine plus rituximab (BR). Although BR has not been compared directly with chlorambucil and rituximab, results of a recent Phase 2 trial show an ORR of 88% with a median event free survival of 33.9 months and 90.5% OS at 27 months. Fischer, *et al.,* Bendamustine in combination with rituximab for previously untreated patients with chronic lymphocytic leukemia: A multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. *J. Clin. Oncol.* **2012,** *30,* 3209-16. These results held for patients > 70 years old, and compare favorably with results published for chlorambucil and rituximab. While results with this regimen appear to be improved over historical controls, outcomes

are not as good as those observed in younger patients with chemoimmunotherapy. Therefore, the optimal therapy for older patients remains an unmet need in clinical trials.

**[001081]** Additionally, most patients eventually relapse with their disease and are frequently refractory to existing agents. Patients who relapse after combined chemoimmunotherapy have a poor outcome with subsequent standard therapies. While options for these patients include alemtuzumab, bendamustine, high dose corticosteroids, ofatumumab, and combination based approaches, none of these therapies produces durable remissions that exceed that observed with first line chemoimmunotherapy. Keating, *et al.*, Therapeutic role of alemtuzumab (Campath-1H) in patients who have failed fludarabine: results of a large international study. *Blood* **2002,** *99*, 3554-61; Bergmann, *et al.*, Efficacy of bendamustine in patients with relapsed or refractory chronic lymphocytic leukemia: results of a phase I/II study of the German CLL Study Group. *Haematologica* **2005,** *90,* 1357-64; Thornton PD, Matutes E, Bosanquet AG, et al. High dose methylprednisolone can induce remissions in CLL patients with p53 abnormalities. *Ann. Hematology* **2003,** *82,* 759-65; Coiffier, *et al.*, Safety and efficacy of ofatumumab, a fully human monoclonal anti-CD20 antibody, in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: A phase 1-2 study. *Blood* **2008,** *111,* 1094-1100; Tsimberidou, *et al.*, Phase I-II study of oxaliplatin, fludarabine, cytarabine, and rituximab combination therapy in patients with Richter's syndrome or fludarabine-refractory chronic lymphocytic leukemia. *J. Clin. Oncol.* **2008,** *26,* 196-203. Several of these therapies including alemtuzumab and high dose steroids are also associated with significant toxicities and sustained immunosuppression. Lozanski G, Heerema NA, Flinn 1W, et al. Alemtuzumab is an effective therapy for chronic lymphocytic leukemia with p53 mutations and deletions. *Blood* **2004,** *103,* 3278-81; Osuji, *et al.*, The efficacy of alemtuzumab for refractory chronic lymphocytic leukemia in relation to cytogenetic abnormalities of p53. *Haematologica* **2005,** 90, 1435-36; Thornton, *et al.*, High dose methyl prednisolone in refractory chronic lymphocytic leukemia. *Leuk. Lymphoma* **1999,** *34,* 167-70; Bowen, *et al.* Methylprednisolone-rituximab is an effective salvage therapy for patients with relapsed chronic lymphocytic leukemia including those with unfavorable cytogenetic features. *Leuk Lymphoma* **2007,** *48,* 2412-17; Castro, *et al.*, Rituximab in

combination with high-dose methylprednisolone for the treatment of fludarabine refractory high-risk chronic lymphocytic leukemia. *Leukemia* **2008,** *22,* 2048-53.

**[001082]** In an ongoing Phase Ib/2 study, the BTK inhibitor ibrutinib has shown activity in patients with relapsed or refractory CLL. In patients with relapsed or refractory CLL and measurable lymphadenopathy, the rate of lymph node shrinkage >50% is 89%. With a median follow-up of 4 months, ORR was 48% due to asymptomatic lymphocytosis, and with longer follow-up of 26 months in patients receiving the 420 mg dose, has improved to 71%, with an additional 20% of patients achieving a partial response with lymphocytosis (PR-L). Byrd, *et al.,* Activity and tolerability of the Bruton's tyrosine kinase (Btk) inhibitor PCI-32765 in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): Interim results of a phase Ib/II study. *J. Clin. Oncol.* ASCO Annual Meeting Abstracts, **2011,** *29,* Abstract 6508; Byrd, *et al.* Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. *N. Engl. J. Med.* **2013,** *369,* 32-42. This lymphocytosis is likely related to B cell release from lymph node, spleen and marrow microenvironment due to disruption of homing signals or chemoattractants that are relevant to usual lymphocyte circulation dynamics. Lymphocytosis with ibrutinib is seen within 1-2 weeks of starting therapy, reaches plateau within the first 2-3 cycles, and has resolved over time in virtually all patients. The duration of lymphocytosis does not appear to be related to the depth of eventual response nor to response duration. Woyach, *et al.*, Prolonged lymphocytosis during ibrutinib therapy is associated with distinct molecular characteristics and does not indicate a suboptimal response to therapy. *Blood* **2014,** *123,* 1810-7. Response to ibrutinib occurs independently of high-risk genomic features including $IgV_H$ mutational status and del(17p13.1). Responses to this drug have been durable as well, with an estimated 26 month PFS of 76% and OS of 83% for these relapsed and refractory patients. This study also included a cohort of 31 previously untreated patients. With 16.6 months of follow-up, ORR is 71%, with an additional 10% of patients having persistent lymphocytosis; estimated 22 month PFS is 96%. This agent is currently in Phase 3 trials in treatment-naïve disease and is currently FDA approved for the treatment of relapsed CLL. These data with ibrutinib support the potential benefits of selective BTK inhibition in CLL. However, while highly potent in inhibiting BTK, ibrutinib has also shown in

vitro activity against other kinases (*e.g.*, epidermal growth factor receptor), which may be the cause of ibrutinib-related diarrhea and rash. Honigberg, *et al.*, The Bruton tyrosine kinase inhibitor PCI-32765 blocks B-cell activation and is efficacious in models of autoimmune disease and B-cell malignancy. *Proc. Natl. Acad. Sci. USA* **2010,** *107,* 13075-13080. In addition, it is a substrate for both cytochrome P450 (CYP) enzymes 3A4/5, which increases the possibility of drug-drug interactions. Finally, the inhibition of ITK that is seen with ibrutinib has the potential to abrogate NK cell ADCC, which makes combination with monoclonal antibodies less effective. Kohrt, *et al.*, Ibrutinib antagonizes rituximab-dependent NK cell-mediated cytotoxicity. *Blood* **2014,** *123,* 1957-60. These liabilities support the development of alternative BTK inhibitors for use in the therapy of lymphoid cancers.

**[001083]** In this Phase 1B study, two cohorts (relapsed/refractory and treatment-naïve) will be evaluated with slightly staggered enrollment. First, 6 subjects with R/R CLL will be enrolled into Cohort 1. Once the safety has been evaluated, the R/R cohort will be expanded to 26 subjects and enrollment of 6 treatment-naïve subjects can begin in Cohort 2. Once safety is established for Cohort 2, then the cohort will be expanded to 19 subjects.

**[001084]** Formula (XVIII) will be administered starting cycle 1 day 1 and will be administered twice daily (100 mg BID) until disease progression. Obinutuzumab will be given in the standard dosing fashion starting on cycle 2 day 1. On cycle 2 day 1, patients will receive 100 mg IV. On cycle 2 day 2, patients will receive 900 mg. On cycle 2 days 8 and 15, patients will receive 1000 mg IV. On cycles 3-7, patients will receive 1000 mg on day 1 of each cycle. For patients treated at dose level -1, 100 mg will be given on Day 1 and 650 mg on Day 2 of Cycle 2. On cycle 2 day 8 and 15, patients will receive 750 mg IV and during cycles 3-7, patients will receive 750 mg on Day 1 of each cycle. It is acceptable for cycles to begin < a 24-hour (1 business day) window before and after the protocol-defined date for Day 1 of a new cycle.

**[001085]** The inclusion criteria for patient eligibility are as follows: (1) Patients with a diagnosis of intermediate or high risk CLL (or variant immunophenotype), SLL, or B-PLL by IWCLL 2008 criteria" who have: (a) COHORT 1: Previously received at least

one therapy for their disease; (b) COHORT 2: Previously untreated disease and > 65 years old OR under 65 years old and refuse or are ineligible for chemoimmunotherapy; (2) Patients on Cohort 1 may have received previous ibrutinib (or another BTK inhibitor) as long as discontinuation was for a reason other than "on-treatment" disease progression; (3) All patients must satisfy one of the following criteria for active disease requiring therapy: (a) Evidence of marrow failure as manifested by the development or worsening of anemia or thrombocytopenia (not attributable to autoimmune hemolytic anemia or thrombocytopenia); (b) Massive (> 6 cm below the costal margin), progressive or symptomatic splenomegaly; (c) Massive nodes (> 10 cm) or progressive or symptomatic lymphadenopathy; (d) Constitutional symptoms, which include any of the following: Unintentional weight loss of 10% or more within 6 months, Significant fatigue limiting activity, Fevers > 100.5 degrees F for 2 weeks or more without evidence of infection, Night sweats > 1 month without evidence of infection; (4) Measurable nodal disease by computed tomography (CT). Measurable nodal disease is defined as > 1 lymph node > 1.5 cm in the longest diameter in a site; (5) Patients with a history of Richter's syndrome are eligible if they now have evidence of CLL only, with < 10% large cells in the bone marrow; (6) Subjects must have adequate organ function, defined as creatinine < 2.5 times the upper limit of normal (ULN), ALT and AST < 3.0 x ULN, and bilirubin < 2.5 × ULN; (7) Platelets > 50 × $10^9$/L. In subjects with CLL involvement of the marrow, > 30 × $10^9$/L; (8) ANC > 750/$mm^3$ In subjects with CLL involvement of the marrow, ANC > 500/$mm^3$; (9) Subject must have an ECOG performance status < 2; (10) Subject must not have secondary cancers that result in a life expectancy of < 2 years or that would confound assessment of toxicity in this study; (11) Subjects must be > 18 years of age; (12) Subject must provide written informed consent. A signed copy of the consent form will be retained in the patient's chart; (13) Subject must be able to receive outpatient treatment and follow-up at the treating institution; (14) Subject must have completed all CLL therapies > 4 weeks prior to first study dose. Palliative steroids are allowed, but must be at a dose equivalent of < 20 mg prednisone daily for at least 1 week prior to treatment initiation; (15) Subjects capable of reproduction and male subjects who have partners capable of reproduction must agree to use an effective contraceptive method during the course of the study and for 2 months following the completion of their last

treatment. Females of childbearing potential must have a negative β-hCG pregnancy test result within 3 days of first study dose. Female patients who are surgically sterilized or who are > 45 years old and have not experienced menses for > 2 years may have ther3-hCG pregnancy test waived; (16) Subjects must be able to swallow whole capsules.

**[001086]** The exclusion criteria for patient eligibility are as follows: (1) For cohort 1, previous therapy for CLL. Treatment of autoimmune complications of CLL with steroids or rituximab is allowed, however, CD20 must have returned on 10% of the CLL cells if rituximab was recently administered. Palliative steroids are acceptable at doses < 20 mg prednisone equivalent daily; (2) Any life-threatening illness, medical condition, or organ dysfunction which, in the investigator's opinion, could compromise the patients' safety, interfere with the absorption or metabolism of Formula (XVIII), or put the study outcomes at undue risk; (3) Female subjects who are pregnant or breastfeeding; (4) Subjects with active cardiovascular disease not medically controlled or those who have had myocardial infarction in the past 6 months, or QTc > 480 ms; (5) Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel or gastric bypass, ulcerative colitis, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction; (6) Grade 2 toxicity (other than alopecia) continuing from prior anticancer therapy including radiation; (7) Major surgery within 4 weeks before first dose of study drug; (8) History of a bleeding diathesis (*e.g.*, hemophilia, von Willebrand disease); (9) Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenia purpura; (10) History of stroke or intracranial hemorrhage within 6 months before the first dose of study drug; (11) Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) within 28 days of first dose of study drug; (12) Requires treatment with long-acting proton pump inhibitors (*e.g.*, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole); (13) Subjects with active infections requiring IV antibiotic/antiviral therapy are not eligible for entry onto the study until resolution of the infection. Patients on prophylactic antibiotics or antivirals are acceptable; (14) Subjects with history of or ongoing drug-induced pneumonitis; (15) Subjects with human immunodeficiency virus (HIV) or active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV) or any uncontrolled active systemic infection; (16) Subjects who

are known to have Hepatitis B infection or who are hepatitis B core antibody or surface antigen positive. Patients receiving prophylactic WIG may have false positive hepatitis serologies. Patients who are on WIG who have positive hepatitis serologies must have a negative hepatitis B DNA to be eligible; (17) Subjects with substance abuse or other medical or psychiatric conditions that, in the opinion of the investigator, would confound study interpretation or affect the patient's ability to tolerate or complete the study; (18) Subjects cannot concurrently participate in another therapeutic clinical trial; (19) Subjects who have received a live virus vaccination within 1 month of starting study drug.

**[001087]** In this study, Formula (XVIII) is administered 100 mg BID, with the second dose 11-13 hours after the first. Obinutuzumab is administered by IV infusion as an absolute (flat) dose. Obinutuzumab is administered in a single day, with the exception of the first administration when patients receive their first dose of obinutuzumab over two consecutive days (split dose) in Cycle 2: 100 mg on Day 1 and 900 mg on Day 2. For patients treated at dose level -1 (750 mg obinutuzumab), - 100 mg will be given on Day 1 and 650 mg on Day 2. On days when both Formula (XVIII) and obinutuzumab are given, the order of study treatment administration will be Formula (XVIII) followed at least 1 hour later by obinutuzumab. The full dosing schedule is given in Table 15.

TABLE 15. Dosing of obinutuzumab during 6 treatment cycles each of 28 days duration.

| **Day of Treatment Cycle** | | **Dose of Obinutuzumab** | **Rate of Infusion (In the absence of infusion reactions/ hypersensitivity during previous infusions)** |
|---|---|---|---|
| **Cycle 2 (loading doses)** | Day 1 | 100 mg | Administer at 25 mg/hr over 4 hours. Do not increase the infusion rate. |
| | Day 2 | 900 mg | Administer at 50 mg/hr. The rate of the infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr. |
| | Day 8 | 1000 mg | Infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes |
| | Day 15 | 1000 mg | |

| | | | |
|---|---|---|---|
| **Cycles 3-7** | Day 1 | 1000 mg | to a maximum of 400 mg/hr. |

**[001088]** Anti-CD20 antibodies have a known safety profile, which include infusion related reactions (IRR). Anti-CD20 antibodies, and in particular obinutuzumab, can cause severe and life threatening infusion reactions. Sequelae of the infusion reactions include patient discontinuations from antibody treatment leading to suboptimal efficacy or increased medical resource utilization, such as hospitalization for hypotension or prolonged antibody infusion time. In the initial study of obinutuzumab in relapsed/refractory CLL patients (Cartron, *et al.*, *Blood* **2014**, *124*, 2196), all patients (n=13) in the Phase 1 portion experienced IRRs (15% Grade 3, no Grade 4, and 100% patients experienced all grade AE), with hypotension and pyrexia the most common symptoms. In the Phase 2 portion of the study, 95% of patients developed IRR, with 60% of cases developing symptoms of hypotension; of those, 25% were Grade 3 reactions. In the pivotal trial of obinutuzumab and chlorambucil in previously untreated patients, 69% developed infusion related reactions, of which 21% were grade 3-4.

**[001089]** The results of the Phase 1b study described in this example for Formula (XVIII) in combination with obinutuzumab for patients with relapsed/refractory or untreated CLL/SLL/PLL are as follows. 6 patients have been treated in the study to date with the combination of Formula (XVIII) and obinutuzumab. Patients are first treated with a month run-in of Formula (XVIII) alone, then on cycle 2, day 1, patients are given obinutuzumab. To date, 41 doses of obinutuzumab have been administered to 6 patients. Lymphocyte counts immediately prior to treatment with obinutuzumab have ranged from 8 to 213 $\times 10^9$/L. No cases of serious or Grade 3-4 IRRs have been reported. Only 2 patients have had obinutuzumab temporarily held for chills and arthralgias/sluured, respectively, and were able to complete the planned infusion. An additional 3 patients had adverse events within 24 hours of the infusion, all grade 1 (terms: flushing, palpitations in one patient, rash, and restlessness and headache). Consequently, there has been a substantial decrease in serious or Grade 3-4 IRRs with the one month lead-in of Formula (XVIII), which could potentially lead to higher efficacy for the combination as well as better tolerability, leading to a decrease in medical resource utilization.

Example 19 – Clinical Study of a Combination of Pembrolizumab and a BTK Inhibitor in B Cell Malignancies

**[001090]** The use of multidrug regimens has been shown to produce higher CR rates and more durable responses, resulting in improved survival in most oncology indications. However, these benefits are often outweighed with the increased toxicity associated with multidrug regimens. This high risk-benefit ratio limits the use of many effective multidrug regimens in elderly patients or patients with comorbid conditions.

**[001091]** The advent of highly selective, targeted active pharmaceutical ingredients such as BTK inhibitors has changed the risk-benefit paradigm traditionally associated with cytotoxic chemotherapy regimens. For example, ibrutinib, a first-generation oral, small-molecule BTK inhibitor, has been approved for the treatment for CLL and MCL. In addition, ibrutinib has shown clinical efficacy in other NHL histologies, including FL (Advani, *et al.*, *J. Clin. Oncol.* **2013,** *31,* 88-94), ABC-DLBCL (De Vos, *et al.*, *Haematologica* **2013,** 98(s1), S1180), and in WM (Treon, *et al.*, *Blood* **2013,** *122,* 251). Preliminary data suggests that patients with multiple myeloma (MM) with high BTK activity, as evidenced by phosphorylated Btk, may be particularly responsive to BTK inhibitor therapy (Liu, *et al.*, *Leuk Lymphoma* **2014,** *55,* 177-81). In preclinical studies, BTK inhibition significantly reduced MM cell growth and tumor-induced osteolysis in a murine model (Tai, *et al.*, *Blood* **2012,** *20,* 1877-1887). Despite these significant advances, the investigation of additional treatment regimens is essential to improve outcomes in B cell malignances. A low proportion of patients achieve CR when treated with single-active pharmaceutical ingredient BTK inhibitors compared with conventional chemotherapy or chemoimmunotherapy regimens. Moreover, the median duration of response can be brief (< 12 months) in aggressive histologies.

**[001092]** Chemical optimization, pharmacologic characterization, and toxicologic evaluation have led to identification of Formula (XVIII), an orally bioavailable, new chemical entity that covalently inhibits BTK and shows encouraging activity and acceptable safety in nonclinical studies. Within the class of BTK inhibitors, Formula (XVIII) is a more selective inhibitor of Btk than ibrutinib. Key nonclinical differentiators of Formula (XVIII) versus ibrutinib are:

Formula (XVIII) has been evaluated against ibrutinib in epidermal growth factor

receptor (EGFR) expressing cell lines, as described e.g. in Example 14. Ibrutinib is a potent covalent inhibitor of EGFR ($EC_{50}$ = 50 to 70 nM). Formula (XVIII) does not inhibit EGFR even at the highest concentration tested (10 μM).

Formula (XVIII) has been evaluated against ibrutinib in vitro antibody-dependent cell-mediated cytotoxicity (ADCC) assays, as described in Example 11. At physiologic concentrations, ibrutinib, but not Formula (XVIII), reduced natural killer (NK) cell-mediated lysis of Raji and autologous CLL tumor cells and significantly inhibited rituximab-induced NK cell cytokine secretion ($P < 0.05$).

Formula (XVIII) has been evaluated against ibrutinib in an *in vivo* thrombus formation model, as described in Example 9. At physiologic concentrations, ibrutinib, but not Formula (XVIII), significantly inhibited thrombus formation (P=0.001).

Formula (XVIII) has been evaluated against ibrutinib in standard drug metabolism and pharmacokinetics (DMPK) assays. Formula (XVIII) has greater solubility, less plasma protein binding, and better oral bioavailability than ibrutinib.

The nonclinical and toxicology results of Formula (XVIII) suggest it may have an improved therapeutic window relative to ibrutinib; it may be more readily combined with other active pharmaceutical ingredients for the treatment of cancer including monoclonal antibodies that activate effector cells.

**[001093]** Improved understanding of the molecular mechanisms governing the host response to tumors has led to the identification of checkpoint signaling pathways involved in limiting the anticancer immune response (Topalian, *et al., J. Clin. Oncol.* **2011,** *29,* 4828-4836). A critical checkpoint pathway responsible for mediating tumor-induced immune suppression is the PD-1 pathway (McDermott and Atkins, *Cancer Med.* **2013,** *2,* 662-673). To determine whether there is potential synergy between Btk inhibition and PD-1 blockade, a nonclinical study of Formula (XVIII) in combination with an anti-PD-L1 antibody in an orthotopic colon cancer murine model was conducted, as described in Example 5. Treatment with anti-PD-L1 as a single active pharmaceutical ingredient reduced tumor growth, but tumor regression was not observed (see Example 5). However, combined anti-PD-L1 and Formula (XVIII) treatment showed a further reduction in tumor growth (anti-PD-L1, 820 $mm^3$ versus anti-PD-L1/Formula (XVIII),

411 $mm^3$) and 6 of 9 animals displayed tumor regression. These results indicate the combination therapy of BTK inhibition and PD-1 blockade leads to greater benefit compared with PD-1 blockade alone.

**[001094]** A significant reduction in the number of MDSCs within the tumor in mice treated with the anti-PD-L1/Formula (XVIII) combination when compared with anti-PD-1L treatment alone (see Example 5). The decrease of MDSCs is directly related to BTK inhibition; this effect has been observed in monotherapy studies of Formula (XVIII) in murine pancreatic cancer models as described above. Together, these data implicate tumor-associated MDSCs in preventing the full benefit of immune checkpoint blockade and offer a translatable, therapeutic option by targeting the MDSC population with Formula (XVIII) to improve the efficacy of checkpoint blockade.

**[001095]** This proof-of-concept clinical study assesses the clinical potential of combined BTK inhibition and checkpoint blockade by evaluating the safety, PD, and efficacy of Formula (XVIII) and pembrolizumab in B-cell malignancies. This is a Phase 1b/2, open-label, nonrandomized study that will be conducted in 2 parts. Part 1 of the study will determine the safety and preliminary efficacy of Formula (XVIII) and pembrolizumab and Part 2 allows for possible expansion cohorts into a wider range of B-cell malignancies.

**[001096]** Part 1: Six subjects will be enrolled to receive Formula (XVIII) in combination with pembrolizumab. If the combination is safe with $\leq$ 1 dose-limiting toxicity (DLT) (6-week observation period) in the first 6 subjects, the cohort will be expanded to up to 24 subjects to obtain additional safety information and to assess the efficacy of the combination. Part 1 of the study will include adult subjects with the following disease types: Non-germinal center B-cell (non-GCB) diffuse large B-cell lymphoma (DLBCL); Follicular lymphoma (FL); and CLL/small lymphocytic lymphoma (SLL).

**[001097]** Part 2: Part 2 consists of expansion groups of up to 12 subjects per histology provided the safety and efficacy results from Part 1 of the study indicate that further evaluation of the combination is warranted. The possible expansion groups for Part 2 may include adult subjects with the following disease types: non-GCB DLBCL, germinal center B-cell (GCB) DLBCL, Richter's syndrome, mantle cell lymphoma

(MCL), indolent non-Hodgkin lymphoma (iNHL), FL, Waldenström macroglobulinemia (WM), CLL/SLL, multiple myeloma (MM), other B-cell malignancy (including but not limited to Hodgkin's lymphoma, Burkitt's lymphoma, marginal zone lymphomas, and hairy cell leukemia).

**[001098]** Treatment with Formula (XVIII) and pembrolizumab, in both Part 1 and Part 2, may be continued until disease progression or an unacceptable drug-related toxicity occurs as defined in the protocol. Combination treatment can end for subjects with confirmed CR (or stringent CR [sCR] for MM) if treatment has been administered for at least 24 weeks and 2 doses of pembrolizumab have been administered after confirmation of CR/sCR. At the end of 52 weeks of treatment, subjects who are tolerating the regimen and deriving clinical benefit may be eligible to roll over into a maintenance protocol under which they could receive Formula (XVIII) and/or pembrolizumab.

**[001099]** All subjects will have hematology, chemistry, and urinalysis safety panels performed at screening. Once dosing commences (Day 1), all subjects will be evaluated for safety, including serum chemistry and hematology, once weekly for the first 8 weeks and monthly thereafter. Radiologic tumor assessments will be done at screening and at 8- to 12-week intervals during the trial.

**[001100]** For Part 1, a DLT will be defined as the occurrence of any of the following study drug-related adverse events (note: adverse events clearly related to disease progression or the subject's current medical history and associated comorbidities will not be considered DLTs): (1) Any Grade ~ 3 non-hematologic toxicity (except Grade 3 nausea, vomiting, or diarrhea that respond to supportive therapy); (2) Any of the following hematologic toxicities: (a) Grade 4 neutropenia lasting > 7 days, (b) Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia with bleeding, or any requirement for platelets transfusion, (c) Grade ~ 3 febrile neutropenia (temperature ≥ 38.5°C), (d)Grade 4 anemia, unexplained by underlying disease; (3) Dosing delay due to toxicity for > 28 consecutive days.

**[001101]** The study objectives are as follows: (1) characterize the safety profile of Formula (XVIII) and pembrolizumab in subjects with relapsed or refractory B-cell malignancies; (2) evaluate the activity of Formula (XVIII) and pembrolizumab as

measured by overall response rate (ORR), duration of response, progression-free survival, overall survival, and time-to-next treatment; (3) determine the effects of Formula (XVIII) plus pembrolizumab on peripheral blood T cells and myeloid-derived suppressor cells (MDSCs); (4) determine if any characteristics of peripheral blood T cells and/or MDSCs correlate with immune-mediated toxicities, (5) determine if any characteristics of peripheral blood T cells and/or MDSCs correlate with response to Formula (XVIII) and pembrolizumab, and (6) determine if any baseline tumor characteristics correlate with response to Formula (XVIII) and pembrolizumab.

**[001102]** The safety parameters for the study include type, frequency, severity, timing of onset, duration, and relationship to study drug of any treatment-emergent adverse events (AEs) or abnormalities of laboratory tests; serious adverse events (SAEs); and DLTs or AEs leading to discontinuation of study treatment.

**[001103]** The pharmacodynamic and biomarker parameters for the study are as follows. The occupancy of BTK by Formula (XVIII) will be measured in peripheral blood mononuclear cells (PBMCs) and bone marrow, if available, with the aid of a biotin-tagged Formula (XVIII) analogue probe. The effect of Formula (XVIII) and pembrolizumab on B cells, T cells, and MDSCs will also be evaluated. Tumor tissue, when available, will be evaluated for PD-L1 expression.

**[001104]** The efficacy parameters for the study include ORR, duration of response, progression-free survival, overall survival, and time-to-next treatment.

**[001105]** The sample size for part 1 is up to 24 subjects, and for part 2 is between 12 and 108 subjects.

**[001106]** The inclusion criteria for part 1 are:

(1) Diagnosis of non-GCB DLBCL or iNHL as documented by medical records and with histology based on criteria established by the World Health Organization (WHO) (If a subject has DLBCL, it is characterized as *de novo* non-GCB DLBCL (Choi, *et al., Clin. Cancer Res.* **2009,** *15,* 5494-5502; Hans, *et al., Blood* **2004,** *103,* 275-282); If the subject has iNHL, the histology shows 1 of the following subtypes: FL Grade 1, 2, or 3a, or CLL/SLL);

(2) Prior treatment for lymphoid malignancy (applies to Part 1 and Part 2): If the

subject has DLBCL, there is no curative option with conventional therapy and the prior treatment included ≥ 1 prior combination chemoimmunotherapy regimen (eg, anthracycline based therapy with rituximab); if the subject has MCL or iNHL, the prior treatment comprised any of the following: ~ 1 regimen containing an anti-CD20 antibody administered for ≥ 2 doses and/or ≥ 1 regimen containing ~ 1 cytotoxic active pharmaceutical ingredient (eg, bendamustine, chlorambucil, cyclophosphamide, cytarabine, doxorubicin) administered for ~ 2 cycles, and/or ≥ 1 regimen containing $^{90}$Y-ibritumomab tiuxetan (ZEVALIN) or $^{131}$I-tositumomab (BEXXAR);

(3) Presence of radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (defined as the presence of a ≥ 2.0 cm lesion, as measured in the longest dimension by computed tomography [CT] scan). Note: not applicable to subjects with WM and MM.

(4) Absolute neutrophil count (ANC) ≥ 1.5 x 109/L or platelet count ≥ 100 x $10^9$/L unless due to disease involvement in the bone marrow (Part 1 only).

**[001107]** The inclusion criteria for part 2, which are in addition to the Part 1 criteria, are:

(1) DLBCL (GCB): Confirmed diagnosis of DLBCL with disease characterized as GCB subtype by immunohistochemistry (Choi, *et al., Clin. Cancer Res.* **2009,** *15,* 5494-5502; Hans, *et al., Blood* **2004,** *103,* 275-282) and meeting the rest of the criteria as defined above.

(2) If the subject has MCL, it is characterized by documentation of monoclonal B-cell that have a chromosome translocation t(11;14)(q13;q32) and/or overexpression of cyclin D1;

(3) Richter's syndrome: Confirmed diagnosis of and biopsy-proven DLBCL due to Richter transformation and meeting the rest of the criteria as defined above;

(4) WM: Confirmed diagnosis of WM, which has relapsed after, or been refractory to ≥ 1 prior therapy for WM, and is progressing at the time of study entry and meeting the rest of the criteria as defined above. Must be able to provide archival or newly obtained bone marrow aspirate/biopsy material for biomarker analysis.

(5) MM: Confirmed diagnosis of MM, which has relapsed after, or been refractory to ≥ 1 prior therapy for MM, and is progressing at the time of study entry and

meeting the rest of the criteria as defined above. Must be able to provide archival or newly obtained bone marrow aspirate/biopsy material for biomarker analysis.

(6) Other B-cell malignancy (including but not limited to: Hodgkin's lymphoma, Burkitt's lymphoma, marginal zone lymphomas, mediastinal large B-cell lymphoma, and hairy cell leukemia): Confirmed diagnosis of previously treated B-cell malignancy and meeting the rest of the criteria as defined above.

**[001108]** Formula (XVIII) is provided as hard gelatin capsules for oral administration. Pembrolizumab is provided as a lyophilized powder in single-use vial for reconstitution and is administered as an intravenous infusion over 30 minutes. The regimen used in the study is: Formula (XVIII) 100 mg twice a day (BID) continuous oral dosing; KEYTRUDA (pembrolizumab) 2 mg/kg by intravenous (IV) infusion every 3 weeks.

**[001109]** Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions and confidence intervals [CIs] for discrete variables) will be used to summarize data as appropriate. Depending on Part 1 and the number of expansion cohorts opened in Part 2, 6 to 132 evaluable subjects will be enrolled. In Part 1 (DLT review), enrollment of 6 subjects for DLT review is consistent with sample sizes used in oncology studies for determination of maximum tolerated dose (MTD). The trial employs the standard National Cancer Institute definition of MTD (dose associated with DLT in $< 33.3\%$ of subjects). Provided $\leq 1$ DLT occurs during the DLT review, then expansion will occur in Part 1 to include up to 24 subjects in a select group of histologies. The safety and preliminary efficacy results from Part 1 will be used to determine opening Part 2 of the protocol. In Part 2 (expansion groups), enrollment of 12 subjects per group offers the opportunity to determine if there is sufficient antitumor activity to warrant further development in the selected tumor types. An ORR of $\geq 20\%$ is considered the minimum value of potential interest in each of the selected indications. If 0/12 subjects in a group experience an objective response, the probability is $> 0.90$ that an ORR of $\geq 20\%$ will be excluded for that cancer (1-sided exact binomial 90% CI upper bound=17.5%).

Example 20 – Clinical Study of a BTK Inhibitor Alone and in Combination with Pembrolizumab in Subjects with Advanced or Metastatic Pancreatic Cancer

**[001110]** In 2014, approximately 46,420 people in the United States will be diagnosed

with pancreatic cancer (Siegel, *et al.*, *CA Cancer J. Clin.* **2014,** *64*, 9-29). Because of the aggressive nature of this cancer, the annual mortality rate almost matches the incidence rate, and it is expected that ~39,590 will die from this disease in the same year. For the 20% of patients with disease involving only the pancreas, surgical resection is the primary therapy. In the ~80% of patients with regional disease extension or metastases at presentation, chemotherapy is the primary treatment (Tempero, *et al.*, *J. Natl. Compr. Canc. Netw.* **2014,** *12*, 1083-1093). Among the therapeutic options, polychemotherapy with infusional 5-fluorouracil (5-FU), leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) or gemcitabine plus albumin-bound paclitaxel (nab-paclitaxel) are commonly employed (Tempero, *et al.*, *J. Natl. Compr. Canc. Netw.* **2014,** *12*, 1083-1093). However, because of the inherent chemoresistance of pancreatic cancer, median PFS with these intensive regimens is $\leq$ 6 months (Conroy, *et al.*, *N. Engl. J. Med.* **2011,** *364*, 1817-25, Von Hoff, *et al.*, *N. Engl. J. Med.* **2013,** *369*, 1691-1703). Approximately 45% of patients who receive such first-line regimens are alive and sufficiently fit to receive second-line therapy, but no therapies have been approved by the United States Food and Drug Administration (FDA) for such patients. Despite off-label use of existing chemotherapeutic active pharmaceutical ingredients, survival at 2 years is < 10%. Thus, while antitumor benefit has been observed with such regimens, toxicity is substantial and therapeutic options are limited. Novel, less toxic approaches are desperately needed for this lethal cancer, particularly in patients who experience failure of existing first-line therapies.

**[001111]** The importance of pancreatic cancer stroma in the biology of pancreatic cancer has been increasingly recognized (Feig, *et al.*, *Clin. Cancer Res.* **2012,** *18*, 4266-76, Rucki, *et al.*, *World J. Gastroenterol.* **2014,** *20*, 2237-46, Wilson, *et al.*, *Front Physiol.* **2014,** *5*, 52). Pancreatic ductal adenocarcinoma exists in a complex desmoplastic microenvironment that provides stromal support for tumor growth and conceals the tumor from immune surveillance. Tumor-associated stroma comprises a mix of fibroblasts (pancreatic stellate cells) and an abundance of mast cells, immunosuppressive Tregs, MDSCs, and TAMs that promote tumor growth and restrain immunologically mediated tumor cell killing (Shibuya, *et al.*, *PLoS One* **2014,** *9*, e96565). Pancreatic cancers secrete chemokines that recruit immune cells to the tumor site. These immune cells are

then activated either by direct contact or by cancer cell–derived triggers to selectively release "procancer" mediators (Feig, *et al.*, *Clin. Cancer Res.* **2012,** *18,* 4266-76, Ma, *et al.*, *Cancer Immunol. Immunother.* **2014,** *63,* 247-57). These mediators induce angiogenesis, promote tumor proliferation, inhibit antitumor responses, and alter the surrounding stroma to permit metastases. Treatment of tumor-bearing mice with active pharmaceutical ingredients that block immunocyte migration and function has been shown to decrease the growth of pancreatic cancer (Ma, *et al.*, *Cancer Immunol. Immunother.* **2014,** *63,* 247-57; Shibuya, *et al.*, *PLoS One* **2014,** *9,* e96565).

**[001112]** Several negative regulatory checkpoint molecules function to check overstimulation of immune responses and contribute to the maintenance of immune tolerance to self-antigens (McDermott and Atkins, *Cancer Med.* **2013,** *2,* 662-673). These molecules include cytotoxic T-lymphocyte antigen-4 (CTLA-4), as well as the programmed death (PD)-1 receptor and its ligands (PD-L1 and PD-L2). CTLA-4 acts as a signal dampener, largely within the lymph nodes, to regulate the magnitude of early activation of naive and memory T cells. By contrast, PD-1 is induced on T cells after activation in response to inflammatory signals and limits T-cell function at sites of infection or tumor in peripheral tissues. As the T-cell response progresses, these negative regulatory molecules are induced, limiting the magnitude and duration of the response to prevent healthy tissue damage. Tumors are capable of exploiting the homeostatic mechanisms regulated by these checkpoint molecules, thus limiting immune destruction.

**[001113]** Such checkpoint pathways appear to be operative in pancreatic cancer. Immunohistochemistry analyses have indicated a significantly worse prognosis for patients with PD-L1-positive pancreatic cancer than for those with PD-L1-negative tumors (Nomi, *et al.*, *Clin. Cancer Res.* **2007,** *13,* 2151-57; Loos, *et al.*, Cancer Lett. **2008,** *268,* 98-109). These data have been corroborated in murine pancreatic cancer models in which genetic engineered cells expressing high or low levels of PD-L1 showed hyperproliferative or hypoproliferative phenotypes, respectively (Song, *et al.*, *Oncol. Rep.* **2014,** *31,* 1191-98). In human cancers, a positive correlation between PD-L1 expression and Treg infiltration (Loos, *et al.*, *Cancer Lett.* **2008,** *268,* 98-109), and an inverse correlation between PD-L1 expression and cytotoxic T lymphocyte infiltration (Nomi, *et al.*, *Clin. Cancer Res.* **2007,** *13,* 2151-57) has been reported. Among clinical

subjects, PD-L1 tumor expression has been associated with response to therapeutic anti-PD-1 blockade (Taube, *et al., Clin. Cancer Res.* **2014,** *20,* 5064-74). Evaluation of intratumoral T cells in pancreatic cancer has shown that the majority expressed PD-1 (Shibuya, *et al., PLoS One* **2014,** *9,* e96565), further supporting the concept that pancreatic cancer evades antitumor immunity via PD-L1/PD-1 signaling in the stroma.

**[001114]** BTK is expressed among cells of hematopoietic origin, including B cells, myeloid cells, mast cells and platelets, where it regulates multiple cellular processes including proliferation, differentiation, apoptosis, and cell migration (Khan, *Immunol. Res.* **2001,** *23,* 147-156; Mohamed, *et al., Immunol. Rev.* **2009,** *228,* 58-73; Bradshaw, *Cell Signal.* **2010,** *22,* 1175-84). In addition, BTK-dependent activation of mast cells, myeloid cells and other immunocytes in peritumoral inflammatory stroma has been shown to sustain the complex microenvironment needed for lymphoid and solid tumor maintenance (Soucek, *et al., Neoplasia* **2011,** *13,* 1093-1100, Ponader, *et al., Blood* **2012,** *119,* 1182-1189, de Rooij, *et al., Blood* **2012,** *119,* 2590-4).

**[001115]** In model systems, *ex vivo* analyses demonstrated BTK inhibition results in macrophages that polarize into M1 macrophages, instead of showing enhanced induction of immunosuppressive M2 macrophages (Ni Gabhann, *et al., PLoS One* **2014,** *9,* e85834). These data suggest inhibition of BTK may impair the capacity of tumor-associated macrophages critical for promotion of tumor invasion and metastasis (Mouchemore, *et al., FEBS J.* **2013,** *280,* 5228-5236). Several lines of evidence demonstrate BTK inhibition interferes with cross-talk between malignant cells and their microenvironment, suggesting disruption of intrinsic and extrinsic survival signals may be a critical mechanism for the clinical activity of BTK inhibitors (Ponader, *et al., Blood* **2012,** *119,* 1182-89, Herman, *et al., Leukemia* **2013,** *27,* 2311-21). Furthermore, epithelial derived tumors contain large numbers of TAMs, which are the dominant innate immune cell in mammary cancers of humans (Pollard, *Nat. Rev. Immunol.* **2009,** *9,* 259–270).

**[001116]** BTK is also a signaling hub in immature myeloid cells known as MDSCs (Schmidt, *et al., Int. Arch. Allergy Immunol.* **2004,** *134,* 65-78). Recent evidence suggests MDSC play an important part in suppression of host immune responses through

several mechanisms such as production of arginase 1, release of reactive oxygen species, nitric oxide and secretion of immune-suppressive cytokines. This leads to an immunosuppressive environment necessary for the growth of malignant cells (Wesolowski, *et al.*, *J. Immunother. Cancer* **2013,** *1,* 10).

**[001117]** Immune evasion is one of the multiple characteristics of cancer. Monoclonal antibodies that block negative regulators of T cells, such as PD-1, amplify immune responses. Antibodies against PD-1 are showing impressive results in advanced hematologic and solid malignancies (Hamid, *et al.*, *N. Engl. J. Med.* **2013,** *369,* 134-44; Westin, *et al.*, *Lancet Oncol.* **2014,** *15,* 69-77; Berger, *et al.*, *Clin. Cancer Res.* **2008,** *14,* 3044-51; Topalian, *et al.*, *J. Clin. Oncol.* **2014,** *32,* 1020-30). Studies examining circulating MDSCs in anti-CTL4 and anti-PD-1/PD-L1-treated patients have shown that alterations in the myeloid cell compartment correlate with clinical outcome. Specifically, solid tumor progressors had proportionally higher circulating MDSC levels and a high myeloid gene signature (Powles, *et al.*, *J. Clin. Oncol.* **2014,** *32,* 5s (suppl; abstr 5011); Heery, *et al.*, *J. Clin. Oncol.* 2014, 32, 5s (suppl; abstr 3064); Weide, *et al.*, *Clin. Cancer Res.* **2014,** *20,* 1601-09). Recent preclinical results show elevated MDSC levels are responsible for this lack of response (Highfill, *et al.*, *Sci. Transl. Med.* **2014,** *6,* 237ra67; Kim, *et al.*, *Proc. Nat'l. Acad. Sci. USA,* **2014,** *111,* 11774-79).

**[001118]** Given the potential for BTK inhibition to affect TAMs and MDSCs, single-active pharmaceutical ingredient Formula (XVIII) was evaluated in mice with advanced pancreatic cancer arising as the result of genetic modifications of oncogenes KRAS and p53, and the pancreatic differentiation promoter PDX-1 (KPC mice), as described in Example 10. Similar single-active pharmaceutical ingredient activity was also observed with Formula (XVIII) (15 mg/kg BID) in the ID8 syngeneic orthotopic ovarian model described in Example 6, where a substantial decrease of tumor growth was observed compared with vehicle. This antitumor effect correlated with a significant decrease in immunosuppressor cells and an increase in cytolytic T cells similar to the KPC pancreatic model. The activity of Formula (XVIII) was confirmed in an orthotopic mouse model evaluating both single-active pharmaceutical ingredient and combination efficacy (see Examples 8 and 9).

**[001119]** The study design is as follows. The clinical trial is a Phase 2, multicenter, open-label, randomized study evaluating Formula (XVIII) monotherapy and the combination of Formula (XVIII) and pembrolizumab in subjects who have advanced or metastatic pancreatic cancer. Subjects meeting the eligibility criteria for the study will be randomized 1:1 to one of the following arms: Arm 1: Formula (XVIII) 100 mg administered orally (PO) twice per day (BID) Arm 2: Formula (XVIII) 100 mg PO BID plus pembrolizumab 200 mg administered as an intravenous (IV) infusion every 3 weeks (Q3W). Although Formula (XVIII) has not demonstrated any dose limiting toxicities (DLTs) to date, the safety of Formula (XVIII) in combination with pembrolizumab in this patient population will be assessed and standard DLT criteria will be applied to Arm 2 of the study. Therefore an interim safety analysis will occur once 12 subjects (6 subjects per arm) have been successfully randomized and have been treated a minimum of 6 weeks. Enrollment will be paused while the safety interim analysis occurs. If $\leq 1$ DLT is observed in Arm 2, then randomization will continue to evaluate the objective response rates of Formula (XVIII) monotherapy and the combination of pembrolizumab and Formula (XVIII) (i.e., up to 38 subjects per arm). If $\geq 2$ DLTs are observed in Arm 2, then enrollment will continue until an additional 6 subjects are randomized to Arm 2, but with a reduced dose level for Formula (XVIII) (Level -1). If the DLT review is cleared in those additional 6 subjects in Arm 2 then continued enrollment will occur at Level -1 for the combination arm. If $\geq 2$ DLTs are observed in Arm 2 at Level -1, then an additional 6 subjects will be randomized at Level -2 and assessed for DLTs. If the DLT review is cleared, continued enrollment will occur at Level -2 for the combination arm. If the DLT review is not cleared, enrollment will be halted in Arm 2. In addition, analyses for futility and toxicity will also be done. Treatment can continue for up to 52 weeks for subjects who are tolerating therapy and not progressing. Subjects who have confirmed progressive disease on the combination of pembrolizumab and Formula (XVIII) will come off study while those in the Formula (XVIII) monotherapy arm with confirmed progressive disease will continue on Formula (XVIII) (dose may be reduced depending on DLT review of combination arm) with the addition of pembrolizumab until a second disease progression. Treatment can end for subjects with confirmed complete response (CR) if treatment has been administered for at least 24 weeks and, for subjects receiving

pembrolizumab, 2 doses of pembrolizumab have been administered after confirmation of CR. At the end of 52 weeks of treatment, subjects who are tolerating the regimen and deriving clinical benefit may be eligible to roll over into a maintenance protocol under which they could receive Formula (XVIII) and/or pembrolizumab.

**[001120]** A DLT will be defined as the occurrence of any of the following study drug-related adverse events (AEs) (note: AEs clearly related to disease progression or the subject's current medical history and associated comorbidities will not be considered DLTs): (1) Grade 4 vomiting or diarrhea; (2) Grade 3 nausea, vomiting, or diarrhea lasting for > 72 hours; (3) Other Grade $\geq$ 3 toxicities; (4) Dosing delay due to toxicity for > 21 consecutive days.

**[001121]** The objectives of the study are as follows: (1) to characterize the safety profile of Formula (XVIII) and pembrolizumab in subjects with advanced or metastatic pancreatic cancer; (2) to evaluate the efficacy of Formula (XVIII) monotherapy and Formula (XVIII) and pembrolizumab combination treatment in subjects with advanced or metastatic pancreatic cancer using standard response criteria; (3) to determine the effects of Formula (XVIII) alone and Formula (XVIII) plus pembrolizumab on peripheral blood T cells and MDSCs; (4) to determine if any characteristics of peripheral blood T cells and/or MDSCs correlate with immune-mediated toxicities; (5) to determine if any characteristics of peripheral blood T cells and/or MDSCs correlate with response to Formula (XVIII) alone or Formula (XVIII) and pembrolizumab; (6) to determine if any baseline tumor characteristics correlate with response to Formula (XVIII) alone or Formula (XVIII) and pembrolizumab; (7) to evaluate the efficacy of adding pembrolizumab to Formula (XVIII) in subjects who progress on Formula (XVIII) monotherapy.

**[001122]** Safety endpoints and pharmacodynamic and biomarker parameters are as in Example 18.

**[001123]** Efficacy endpoints are as follows: (1) disease control rate (DCR) defined as stable disease (SD), partial response (PR) or CR based on modified RECIST 1.1 criteria; (2) ORR, defined as PR or CR based on modified RECIST 1.1 criteria; (3) Duration of response (DOR); (4) Progression-free survival (PFS); (5) Overall survival (OS); (6)

Change in serum cancer antigen 19-9 (CA19-9). Exploratory endpoints for efficacy based on immune-related response criteria (irRC) are: (1) Immune-related DCR (irDCR), defined as immune-related SD (irSD), immune-related PR (irPR), and immune-related CR (irCR); (2) irORR, defined as irPR and irCR; (3) irDOR; (4) irPFS.

**[001124]** Sample size is as follows: Interim safety analysis (DLT review): 12 subjects (6 subjects receiving Formula (XVIII) monotherapy and 6 subjects receiving Formula (XVIII) and pembrolizumab combination). Provided the DLT period is cleared in the combination arm and neither arm is stopped early due to futility or toxicity, the study will proceed to full enrollment of 38 subjects per arm for a total enrollment of 76 subjects.

**[001125]** Formula (XVIII) is provided as hard gelatin capsules for oral administration. KEYTRUDA (pembrolizumab) is provided as a lyophilized powder in single-use vial for reconstitution. It is administered as an IV infusion over 30 minutes. The dosing regimen for Arm 1 is 100 mg BID of Formula (XVIII). The dosing regimen for Arm 2 is s starting dose of 100 mg BID Formula (XVIII) and 200 mg of pembrolizumab every three weeks, a Level -1 dose of 100 mg QD Formula (XVIII) and 200 mg of pembrolizumab every three weeks, and a Level -2 dose of 100 mg BID Formula (XVIII) and 200 mg of pembrolizumab every three weeks.

**[001126]** The statistical methods used in the study use the following analysis methods. Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions and confidence intervals [CIs] for discrete variables) will be used to summarize data as appropriate. The statistical basis for the sample size is as follows. For the safety interim analysis (DLT review), enrollment of 6 subjects in the combination arm for DLT review is consistent with sample sizes used in oncology studies for determination of maximum tolerated dose (MTD). The trial employs the standard National Cancer Institute definition of MTD (dose associated with DLT in $\leq$ 17% of subjects). Provided $\leq$ 1 DLT occurs during the DLT review in the combination arm, then up to 32 subjects will be added per arm. The sample size for this study was estimated based on the primary endpoint of DCR (SD, PR, CR). In a Phase 2 trial of oxaliplatin plus capecitabine as second line therapy for patients with advanced pancreatic cancer, a DCR of 28% was observed (Xiong, *et al.*, *Cancer* **2008,** *113,* 2046–2052). To reject the

null hypothesis of 28% DCR in favor of an alternative hypothesis that the DCR is ≤ 5%, approximately 36 subjects per arm will preserve at least 80% power to detect the difference at a 0.05 level of significance by 2-sided chi-square test. The study will enroll up to 38 subjects per arm to account for up to 2 drop outs per arm. Should the necessary condition of minimum cell counts for a valid chi-square test fail to exist, an exact test will be employed to perform the comparison analysis of the primary endpoint.

Example 21 – Clinical Study of a Combination of a BTK Inhibitor and Pembrolizumab in Subjects with Platinum-Refractory Metastatic Bladder Cancer

**[001127]** In 2014, approximately 141,610 people in the United States will be diagnosed with urothelial carcinoma of the bladder, renal pelvis, or ureter (Siegel, *et al.*, *CA Cancer J. Clin.* **2014,** *64*, 9-29). Although many newly diagnosed patients have localized disease, urothelial carcinoma is often fatal for those diagnosed with metastatic disease. Approximately 30,350 people are anticipated to die from this disease in 2014. In most patients with localized disease, treatment includes localized excision with transurethral resection of bladder tumor (TURBT) and intravesicular Bacillus Calmette Guerin (BCG) infusions (Martyn-Hemphill, *et al.*, *Int. J. Surg.* **2013,** *11*, 749-52). In the ~30% of patients who develop metastatic disease, chemotherapy with a platinum-based regimen is the primary treatment (Gartrell and Sonpavde, *Expert Opin. Emerg. Drugs*, **2013,** *18*, 477-94). Current standard of care first-line therapy includes combination chemotherapy with cisplatin or carboplatin with gemcitabine, or the combination of methotrexate, vinblastine, adriamycin, and cisplatin (MVAC). However, because of the inherent chemoresistance of bladder cancer, median progression-free survival (PFS) with these chemotherapy regimens is approximately 7.4 months (Von der Maase, *et al.*, *J. Clin. Oncol.* **2000,** *17*, 3068-3077). The addition of paclitaxel to gemcitabine/cisplatin has improved PFS to 8.3 months (Bellmunt, *et al.*, *J. Clin. Oncol.* **2012,** *30*, 1107-1113). Currently, second-line therapies are limited, and no therapies have been approved by the United States Food and Drug Administration (FDA) for patients who survive to undergo second-line treatment. Survival at 2 years is therefore < 20% (Bellmunt, *et al.*, *J. Clin. Oncol.* **2012,** *30*, 1107-1113). Thus, while antitumor benefit has been observed with such regimens, toxicity is substantial and therapeutic options are limited. Novel, less toxic approaches are needed for metastatic, platinum-refractory urothelial carcinoma.

**[001128]** The importance of the stroma in urothelial carcinoma has been increasingly recognized (Van der Horst, *et al.*, *Mol. Cancer Res.* **2012,** *10,* 995-1009), particularly in its role in tumor progression and formation of metastases. Several stromal-changing growth factors, such as FGF2, VEGF, PDGF, EGFR ligands, and TGF-13 are important in mediating tumor progression, supporting tumor associated fibroblasts in urinary bladder tumor specimens (Enkelmann, *et al.*, *J. Cancer Res. Clin. Oncol.* **2011,** *137,* 751-759). Tumor-associated fibroblasts have also shown increased populations in invasive bladder tumors and not in superficial bladder tumors, thus associating with muscle invasion and formation of metastases (Alexa, *et al.*, *Rom. J. Morphol. Embryol.* **2009,** *50,* 639-643). Furthermore, tumor-associated macrophages have been shown to mediate (Onita, *et al.*, *Clin. Cancer Res.* **2002,** *8,* 471-480). The TGF-13 mediator is also known to shift macrophages from an M1 antitumor phenotype to an M2 protumor phenotype, leading to remodeling of the microenvironment, angiogenesis, and epithelial plasticity (Fuxe, *et al.*, *Semin. Cancer Biol.* **2012,** *22,* 455-461). In summary, urothelial carcinoma exists in a complex desmoplastic microenvironment providing stromal support for tumor growth, resembling wound healing, thus increasing motility, invasion, and angiogenesis.

**[001129]** Such checkpoint pathways appear to be operative in urothelial carcinoma. Immunohistochemistry analyses have shown PD-L1 positivity is associated with increased staging, high-grade tumors, and tissue-infiltrating mononuclear cells in urothelial carcinoma (Inman, *et al.*, *Cancer* **2007,** *109,* 1499-1505). In a series of 318 patients with urothelial carcinoma, PD-L1 and PD-1 expression were associated with advanced disease, and PD-L1 expression independently predicted for mortality (Boorjian, *et al.*, *Clin. Cancer Res.* **2008,** *14,* 4800-08). PD-L1 expression may protect cancer cells from immune-mediated destruction. In a clinical study of subjects with urothelial carcinoma evaluating the efficacy of an anti-PD-L1 antibody, high expression of PD-L1 in tumor-infiltrating immune cells correlated with a higher overall response rate (ORR, 40% to 50%) compared with an ORR of 13% and 8% for low PD-L1 or no PD-L1 expression (Powles, *et al.*, *J. Clin. Oncol.* **2014,** *32,* 5s(suppl; abstr 5011)). In a clinical study of the anti-PD-1 monoclonal antibody, pembrolizumab, in subjects with recurrent or metastatic urothelial carcinoma, a 24% ORR, including 10% complete response (CR) rate, was observed across the 33 subjects treated. Analysis of the relationship between

PD-L1 expression and pembrolizumab efficacy was pending (Plimack, *et al.*, "A phase IB study of pembrolizumab in patients with advanced urothelial tract cancer," 2014 ESMO Annual Meeting).

**[001130]** The preclinical rationale for use of a combination of a BTK inhibitor and a PD-1 or PD-L1 inhibitor in solid tumor cancers is discussed in Example 19 and in the other examples provided herein.

**[001131]** This proof-of-concept study will assess the clinical potential of a targeted dual inhibition approach by evaluating the safety, pharmacodynamics (PD), and efficacy of Formula (XVIII) and pembrolizumab in subjects with metastatic urothelial carcinoma who have progressed after treatment with cisplatin-based chemotherapy. This clinical trial is a Phase 2, multicenter, open-label, randomized study evaluating pembrolizumab monotherapy and the combination of Formula (XVIII) and pembrolizumab in subjects who have metastatic bladder cancer with disease progression on or after platinum-based chemotherapy. Subjects meeting the eligibility criteria for the study will be randomized 1:1 to one of the following arms: Arm 1: Pembrolizumab 200 mg administered as an intravenous (IV) infusion every 3 weeks (Q3W); Arm 2: Formula (XVIII) 100 mg administered orally (PO) twice per day (BID) plus pembrolizumab 200 mg IV Q3W.

**[001132]** Although Formula (XVIII) has not demonstrated any dose-limiting toxicities (DLTs) to date, the safety of Formula (XVIII) in combination with pembrolizumab in this patient population needs to be assessed. Thus, standard DLT criteria will be applied to Arm 2 of the study. Therefore an interim safety analysis will occur once 12 subjects (6 subjects per arm) have been successfully randomized and have been treated a minimum of 6 weeks. Enrollment will be paused while the safety interim analysis occurs. I f ~ 1 DLT is observed in Arm 2 (*i.e.*, DLT review is cleared), then randomization will continue to evaluate the objective response rates of Formula (XVIII) monotherapy and the combination of pembrolizumab and Formula (XVIII) (i.e., up to 37 subjects per arm). If ~ 2 DLTs are observed in Arm 2, then enrollment (1:1) will continue until an additional 6 subjects are randomized to Arm 2, but with a reduced dose level for Formula (XVIII) (Level -1). If the DLT review is cleared in those additional 6 subjects in Arm 2 then continued enrollment will occur at Level -1 for the combination arm. If ~ 2 DLTs are

observed in Arm 2 at Level -1, then an additional 6 subjects will be randomized at Level -2 and assessed for DLTs. If the DLT review is cleared, continued enrollment will occur at Level -2 for the combination arm. If the DLT review is not cleared, enrollment will be halted in Arm 2.

**[001133]** Treatment can continue for up to 52 weeks for subjects who are tolerating therapy and not progressing. Subjects who have confirmed progressive disease on the combination of pembrolizumab and Formula (XVIII) will come off study while those with confirmed progressive disease in the pembrolizumab monotherapy arm will continue on pembrolizumab with the addition of Formula (XVIII) until a second disease progression. Treatment can end for subjects with confirmed complete response (CR) if treatment has been administered for at least 24 weeks and 2 doses of pembrolizumab have been administered after confirmation of CR. At the end of 52 weeks of treatment, subjects who are tolerating the regimen and deriving clinical benefit may be eligible to roll over into a maintenance protocol under which they could receive Formula (XVIII) and/or pembrolizumab.

**[001134]** For assessment of the first 12 subjects randomized, DLT will be defined as the occurrence of any of the following study drug-related adverse events (note: adverse events clearly related to disease progression or the subject's current medical history and associated comorbidities will not be considered DLTs): (1) Any Grade ~ 3 toxicity (except Grade 3 nausea, vomiting, or diarrhea that respond to supportive therapy); (2) Dosing delay due to toxicity for > 21 consecutive days.

**[001135]** The study objectives are as follows: (1) to characterize the safety profile of Formula (XVIII) and pembrolizumab in subjects with metastatic, platinum-refractory bladder cancer; (2) to determine the overall response rate (ORR) of pembrolizumab monotherapy and the combination of Formula (XVIII) and pembrolizumab in subjects with metastatic, platinum-refractory bladder cancer; (3) to determine progression-free survival (PFS) in subjects treated with pembrolizumab monotherapy and the combination of Formula (XVIII) and pembrolizumab; (4) to evaluate the overall survival (OS) in subjects treated with pembrolizumab monotherapy and the combination of Formula (XVIII) and pembrolizumab; (5) to determine the effects of Formula (XVIII) plus

pembrolizumab on peripheral blood T cells and myeloid-derived suppressor cells (MDSCs); (6) determine if any characteristics of peripheral blood T cells and/or MDSCs correlate with immune-mediated toxicities; (7) determine if any characteristics of peripheral blood T cells and/or MDSCs correlate with response to Formula (XVIII) and pembrolizumab; (8) determine if any baseline tumor characteristics correlate with response to Formula (XVIII) and pembrolizumab; and (9) to evaluate the efficacy of adding Formula (XVIII) to pembrolizumab in subjects who progress on pembrolizumab monotherapy.

**[001136]** Safety endpoints and pharmacodynamic and biomarker parameters are as in Example 18. Efficacy endpoints are as in Example 19.

**[001137]** The sample size is as follows: Interim safety analysis (DLT review): 12 subjects (6 subjects receiving pembrolizumab monotherapy and 6 subjects receiving Formula (XVIII) and pembrolizumab combination). Provided the DLT period is cleared in the combination arm, the study will proceed to full enrollment of 37 subjects per arm for a total enrollment of 74 subjects.

**[001138]** The dosing regimen and routes of administration for Formula (XVIII) and pembrolizumab are as in Example 19.

**[001139]** The statistical methods are as follows. Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions and confidence intervals [CIs] for discrete variables) will be used to summarize data as appropriate. The statistical basis for the sample size is as follows. For the safety interim analysis (DLT review), enrollment of 6 subjects in the combination arm for DLT review is consistent with sample sizes used in oncology studies for determination of maximum tolerated dose (MTD). The trial employs the standard National Cancer Institute definition of MTD (dose associated with DLT in ~ 17% of subjects). Provided ~ 1 DLT occurs during the DLT review in the combination arm, then up to 31 subjects will be added per arm. A sample size for a 2-arm pick-the-winner, non-comparative trial was determined by a Z-test for normal approximation of binomial distribution, based on one-sided a = 0.05, 80% power, with projected response rates of 40% in pembrolizumab/Formula (XVIII) arm and 18% in pembrolizumab arm. Accounting for 10% drop-out rate (3 in

each arm), final sample size is 37 in each arm.

Example 22 – Clinical Study of a Combination of a BTK Inhibitor, a PI3K-δ Inhibitor, and Pembrolizumab in Subjects with Advanced Head and Neck Squamous Cell Carcinoma

**[001140]** Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide; approximately 600,000 new cases are diagnosed per year worldwide (International Agency for Research on Cancer. World Health Organisation. Globocan 2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012). While early stage disease may be treated with a single modality such as surgery or RT, most patients (60%) present with Stage III/IV poor prognosis disease (Seiwert, *et al., Nat. Clin. Pract. Oncol.* **2007,** *4,* 156-171). These patients are generally treated with a combination of RT, surgery, and cytotoxic or targeted chemotherapy. Despite this aggressive multimodal treatment, most patients will relapse. The survival rates for all patients with HNSCC are approximately 40% to 60% at 5 years (Grégoire, *et al., Ann. Oncol.* **2010,** *21,* 184-186). While the addition of cetuximab, an immunoglobulin G1 (IgG1) monoclonal antibody targeting the epidermal growth factor receptor (EGFR), improves OS when combined with RT or chemotherapy (median OS is 10.1 months for the combination of cisplatin or carboplatin with 5-fluorouracil and cetuximab), few patients will benefit from anti-EGFR monoclonal antibodies, and the objective response rate in monotherapy is between 6% and 13% (Bonner, *et al., Lancet Oncol.* **2010,** *11,* 21-28; Machiels, *et al., Lancet Oncol.* **2011,** *12* ,333-343; Vermorken, *et al., N. Engl. J. Med.* **2008,** *359,* 1116-1127; Vermorken, *et al., Cancer* **2008,** *112,* 2710-2709). Based on recent developments in HNSCC molecular biology, new compounds are currently being investigated including immune checkpoint inhibitors (Schmitz, *et al., Cancer Treat. Rev.* **2014,** *40,* 390-404).

**[001141]** Over half of solid tumors (including HNSCC, lung cancer, melanoma, renal cell carcinoma, pancreatic cancer, ovarian cancer, and others) express PD-L1 in the tumor microenvironment which results in immune tolerance and impaired immune response against the tumor (Zou and Chen, *Nat. Rev. Immunol.* **2008,** *8,* 467-77). Additionally, PD-L1 expression in the tumor microenvironment has been shown to be a poor prognostic factor in several cancers (Pardoll, *Nat. Rev. Cancer* **2012,** *12,* 252-264). In a

clinical study of the anti-PD-1 monoclonal antibody, pembrolizumab, in subjects with advanced unresectable HNSCC (N=60), a 20% ORR was observed with response lasting up to 41 weeks (Chow, *et al.*, ESMO 2014 Abstract LBA31). Pembrolizumab was well tolerated with few serious drug-related AEs (Seiwert, *et al., Nat. Clin. Pract. Oncol.* **2007,** *4,* 156-171).

**[001142]** The clinical study is a Phase 2, multicenter, open-label, randomized study evaluating pembrolizumab monotherapy and the combination of Formula (XVIII) and pembrolizumab in subjects who have recurrent, metastatic or unresectable HNSCC. Subjects meeting the eligibility criteria for the study will be randomized 1:1 to one of the following arms: Arm 1: Pembrolizumab 200 mg administered as an intravenous (IV) infusion every 3 weeks (Q3W); Arm 2: Formula (XVIII) 100 mg administered orally (PO) twice per day (BID) plus pembrolizumab 200 mg IV Q3W. Although Formula (XVIII) has not demonstrated any dose-limiting toxicity (DLT) to date, the safety of Formula (XVIII) in combination with pembrolizumab in this patient population needs to be assessed. Thus, standard DLT criteria will be applied to Arm 2 of the study. An interim safety analysis will occur once 12 subjects (6 subjects per arm) have been successfully randomized and have been treated a minimum of 6 weeks. Enrollment will be paused while the safety interim analysis occurs. If $\leq 1$ DLT is observed in Arm 2 (i.e., DLT review is cleared), then randomization will continue to evaluate the objective response rates of pembrolizumab monotherapy and the combination of pembrolizumab and Formula (XVIII) (i.e., up to 37 subjects per arm). If $\geq 2$ DLTs are observed in Arm 2, then enrollment (1:1) will continue until an additional 6 subjects are randomized to Arm 2, but with a reduced dose level for Formula (XVIII) (Level -1). If the DLT review is cleared in those additional 6 subjects in Arm 2 then continued enrollment will occur at Level -1 for the combination arm. If $\geq 2$ DLTs are observed in Arm 2 at Level -1, then an additional 6 subjects will be randomized at Level -2 and assessed for DLTs. If the DLT review is cleared, continued enrollment will occur at Level -2 for the combination arm. If the DLT review is not cleared, enrollment will be halted in Arm 2. In addition, analyses for futility and toxicity will also be done as outlined in 5.5. Treatment can continue for up to 52 weeks for subjects who are tolerating therapy and have not developed disease progression. Subjects who have confirmed progressive disease on the combination of

pembrolizumab and Formula (XVIII) will come off study while those with confirmed progressive disease in the pembrolizumab monotherapy arm will continue on pembrolizumab with the addition of Formula (XVIII) until a second disease progression is observed. Treatment will end for subjects with confirmed complete response (CR) once treatment has been administered for at least 24 weeks and 2 doses of pembrolizumab have been administered after confirmation of CR.

**[001143]** DLT will be defined as the occurrence of any of the following study drug-related adverse events (AEs): (1) any Grade $\geq 3$ toxicity (note: AEs clearly related to disease progression or the subject's current medical history and associated comorbidities will not be considered DLTs); (2) dosing delay due to toxicity for > 28 consecutive days.

**[001144]** The objectives of the study are as follows: (1) to characterize the safety and tolerability of Formula (XVIII) in combination with pembrolizumab in subjects with recurrent, metastatic or unresectable HNSCC; (2) to determine the overall response rate (ORR) of pembrolizumab monotherapy and the combination of Formula (XVIII) and pembrolizumab in subjects with recurrent, metastatic or unresectable HNSCC; (3) to determine progression-free survival (PFS) in subjects treated with pembrolizumab monotherapy and the combination of Formula (XVIII) and pembrolizumab; (4) to evaluate the overall survival (OS) in subjects treated with pembrolizumab monotherapy and the combination of Formula (XVIII) and pembrolizumab; (5) to determine the effects of Formula (XVIII) plus pembrolizumab on peripheral blood T cells and myeloid-derived suppressor cells (MDSCs); (6) to determine if any characteristics of peripheral blood T cells and/or MDSCs correlate with immune-mediated toxicities; (7) to determine if any characteristics of peripheral blood T cells and/or MDSCs correlate with response to Formula (XVIII) and pembrolizumab; (8) to determine if any baseline tumor characteristics correlate with response to Formula (XVIII) and pembrolizumab; and (9) to evaluate the efficacy of adding Formula (XVIII) to pembrolizumab in subjects who progress on pembrolizumab monotherapy.

**[001145]** Safety endpoints and pharmacodynamic and biomarker parameters are as in Example 18.

**[001146]** Efficacy endpoints are as follows: (1) ORR, defined as partial response (PR)

and CR, based on modified RECIST 1.1 criteria; (2) duration of response (DOR); (3) PFS; (4) OS. Exploratory endpoints for efficacy based on immune-related response criteria (irRC) are: (1) Immune-related ORR (irORR), defined as immune-related partial response (irPR) and immune-related complete response (irCR); (2) Immune-related duration of response (irDOR); (3) Immune-related progression-free survival (irPFS).

**[001147]** Interim safety analysis (DLT review): 12 subjects (6 subjects receiving pembrolizumab monotherapy and 6 subjects receiving Formula (XVIII) and pembrolizumab combination). Provided the DLT period is cleared in the combination arm and neither arm is stopped early due to futility or toxicity, the study will proceed to full enrollment of 37 subjects per arm for a total enrollment of 74 subjects.

**[001148]** The dosing regimen and routes of administration for Formula (XVIII) and pembrolizumab are as in Example 19.

**[001149]** The statistical methods are as follows. Descriptive statistics (including means, standard deviation [SD], and medians for continuous variables and proportions and confidence intervals [CIs] for discrete variables) will be used to summarize data as appropriate. For the safety interim analysis (DLT review), enrollment of 6 subjects in the combination arm for DLT review is consistent with sample sizes used in oncology studies for determination of maximum tolerated dose (MTD). The trial employs the standard National Cancer Institute definition of MTD (dose associated with DLT in $\leq$ 17% of subjects). Provided $\leq$ 1 DLT occurs during the DLT review in the combination arm and the study is not stopped early due to futility or toxicity, then up to 31 subjects will be added per arm. A sample size for a 2-arm pick-the-winner, non-comparative trial was determined by a Z-test for normal approximation of binomial distribution, based on one-sided $\alpha = 0.05$, 80% power, with projected response rates of 40% in the pembrolizumab and Formula (XVIII) arm and 18% in the pembrolizumab arm. Accounting for 10% drop-out rate (3 in each arm), the final sample size is 37 in each arm.

Example 23 – BTK Inhibitory Effects on MDSCs in the Solid Tumor Microenvironment

**[001150]** A molecular probe assay was used to calculate the percent irreversible occupancy of total BTK. MDSCs were purified from tumor bearing PDA mice (as described previously) dosed at 15 mg/kg BID of Formula (XVIII). Complete BTK

occupancy is observed for both the granulocytic and monocytic MDSC compartment on Day 8 at 4 hours post dose (N=5). The results are shown in FIG. 164.

Example 24 – BTK Inhibitory Effects on Solid Tumor Microenvironment in a Non-small Cell Lung Cancer (NSCLC) Model

**[001151]** A genetic tumor model of NSCLC (KrasLA2) was studied as a model for lung cancer using the treatment schema shown in FIG. 165. The model is designed to have sporadic expression in single cells of G12D mutant Kras off its own promoter triggered by spontaneous intrachromosomal recombination. Johnson, *et al. Nature* **2001,** *410,* 1111-16. While the mutant Kras protein is expressed in a few cells in all tissues, tumor development is seen only in the lung at high penetrance. Mice treated with Formula (XVIII) showed a significant decrease in tumor volumes versus vehicle (FIG. 166) and fewer overall tumors with dosing of 15 mg/kg. The effects on TAMs (FIG. 167), MDSCs (FIG. 168), Tregs (FIG. 169), and CD8+ cells (FIG. 170) were consistent with suppression of the solid tumor microenvironment as demonstrated previously.

Example 25 – Additional Preclinical Characteristics of BTK Inhibitors

**[001152]** The *in vitro* potency in whole blood of Formula (XVIII), ibrutinib and CC-292 in inhibiting signals through the B cell receptor was also assessed. Blood from four healthy donors was incubated for 2 hours with the compounds shown over a concentration range, and then stimulated with anti-human IgD [10 µg/mL] for 18 hours. The mean fluorescent intensity (MFI) of CD69 (and CD86, data not shown) on gated CD19+ B cells was measured by flow cytometry. MFI values were normalized so that 100% represents CD69 level in stimulated cells without inhibitor, while 0% represents the unstimulated/no drug condition. The results are shown in FIG. 171. The $EC_{50}$ values obtained were 8.2 nM (95% confidence interval: 6.5 – 10.3), 6.1 nM (95% confidence interval: 5.2 – 7.2), and 121 nM (95% confidence interval: 94 - 155) for Formula (XVIII), ibrutinib, and CC-292, respectively.

**[001153]** The EGF receptor phosphorylation *in vitro* was also determined for Formula (XVIII) and ibrutinib. Epidermoid carcinoma A431 cells were incubated for 2h with a dose titration of Formula (XVIII) or ibrutinib, before stimulation with EGF (100 ng/mL) for 5 min to induce EGFR phosphorylation (p-EGFR). Cells were fixed with 1.6% paraformaldehyde and permeabilized with 90% MeOH. Phosphoflow cytometry was

performed with p-EGFR (Y1069). MFI values were normalized so that 100% represents the p-EGFR level in stimulated cells without inhibitor, while 0% represents the unstimulated/no drug condition. The results are shown in FIG. 172. EGF-induced p-EGFR inhibition was determined to be 7% at 10 μM for Formula (XVIII), while ibrutinib has an $EC_{50}$ of 66 nM. The much more potent inhibition of EGF-induced p-EGFR by ibrutinib may be associated with increased side effects including diarrhea and rash.

Example 26 – Effects of BTK Inhibition on Antibody-Dependent NK Cell Mediated Cytotoxicity Using Obinutuzumab

**[001154]** It has been shown above that ibrutinib undesirably antagonizes rituximab ADCC effects mediated by NK cells, and that Formula (XVIII) does not antagonize rituximab ADCC effects and instead allows for a synergistic combination. As noted previously, this may be due to ibrutinib's secondary irreversible binding to ITK, which is required for FcR-stimulated NK cell function including calcium mobilization, granule release, and overall ADCC. H. E. Kohrt, *et al.*, *Blood* **2014,** *123,* 1957-60. The potential for ibrutinib antagonization of obinutuzumab (GA-101) ADCC as mediated by NK cells was also explored and compared to the effects of Formula (XVIII).

**[001155]** The NK cell degranulation/ADCC assay was performed using a whole blood assay with CLL targets added to normal donor whole blood, in the presence or absence of different doses of Formula (XVIII) and ibrutinib, followed by opsonization with the anti-CD20 antibody obinutuzumab. Ibrutinib was used as a control, and two blinded samples of BTK inhibitors, Formula (XVIII) and a second sample of ibrutinib, were provided to the investigators. Degranulation in whole blood was performed as follows. CLL targets (MEC-1 cells) were expanded in RPMI 1640 medium (Life Technologies, Inc.) with 10% fetal bovine serum (FBS). Exponentially growing cells were used. On the day of the experiment, 8 mL of blood was drawn from a normal volunteer into a test tube containing desirudin to obtain a final concentration of 50 μg/mL. A white blood cell (WBC) count of whole blood was performed. MEC-1 cells were re-suspended at the concentration of WBC in whole blood (*e.g.*, if $6 \times 10^6$ WBC/mL was measured, MEC-1 cells were re-suspended at $6 \times 10^6$ cells/mL, to allow for a final WBC:MEC-1 cell ratio of 1:1). The ibrutinib control and two blinded BTK inhibitors were diluted in X-VIVO 15 serum-free hematopoietic cell medium (Lonza Group, Ltd.) to concentrations of 200 μM, 20 μM and

2 μM. 170 μL aliquots of unmanipulated whole blood were incubated with 10 μL BTK inhibitors or X-VIVO 15 medium for one hour into a plate. Cetuximab and obinutuzumab (GA-101) were diluted in X-VIVO 15 medium to a concentration of 20 μg/mL. Equal volumes of MEC-1 cells and antibodies were incubated for 5 minutes. After incubation, 20 μL of MEC-1 cells and antibodies was added to whole blood and the BTK inhibitors/X-VIVO 15 medium (for a final volume of 200 μL). The samples were placed in a 5% $CO_2$ incubator for 4 hours at 37 °C. The experimental conditions thus achieved a WBC:MEC-1 cell ratio of 1:1, with final concentrations of the BTK inhibitors in the assay of 10 μM, 1 μM and 0.1 μM and final concentrations of the antibodies of 1 μg/mL.

**[001156]** After 4 hours, the samples were mixed gently and 50 μL aliquots were removed from each well and placed in fluorescence-activated cell sorting (FACS) test tubes. A 20 μL aliquot of anti-CD56-APC antibody and anti-CD107a-PE antibody was added. The samples were incubated for 20 minutes at room temperature in the dark. An aliquot of 2 mL of FACS lysing solution (BD Biosceinces) was added. The samples were again incubated for 5 minutes, and then centrifuged at 2000 rpm for 5 minutes. Supernatant was discarded and the cell pellet was resuspended in 500 μL of PBS. The samples were analyzed on the flow cytometer for $CD107a^+$ NK cells ($CD56^+$).

**[001157]** The NK cell degranulation results are summarized in FIG. 173 for n = 3 experiments, which shows the effects on whole blood after pretreatment for 1 hour with the BTK inhibitors at the concentrations shown and subsequent stimulation with MEC-1 opsonised with obinutuzumab or cetuximab at 1 μg/mL for 4 hours. A strong reduction in the percentage of $CD56^+/CD107a^+$ NK cells is observed using ibrutinib (both as a control and blinded BTK inhibitor), which indicates that ibrutinib undesirably antagonizes NK cells. In contrast, Formula (XVIII) shows little antagonism towards NK cells, and had a minimal effect on obinutuzumab-stimulated NK cell degranulation while ibrutinib reduced obinutuzumab-stimulated NK degranulation by greater than 40%. These results support the synergistic combination of obinutuzumab and Formula (XVIII) in treatment of human B cell malignancies.

Example 27 – Effects of BTK Inhibition on Generalized NK Cell Mediated Cytotoxicity

**[001158]** An assay was performed to assess the effects of BTK inhibition using Formula (XVIII) on generalized NK killing (non-ADCC killing). The targets (K562 cells) do not express MHC class I, so they do not inactivate NK cells. Target cells were grown to mid-log phase, and $5\times10^5$ cells were labeled in 100 µL of assay medium (IMDM with 10% FCS and penicillin/streptomycin) with 100 µCi of $^{51}Cr$ for 1 hour at 37 °C. Cells were washed twice and resuspended in assay medium. A total of 5000 target cells/well was used in the assay. Effector cells were resuspended in assay medium, distributed on a V-bottom 96-well plate, and mixed with labeled target cells at 40:1 E:T ratios. Maximum release was determined by incubating target cells in 1% Triton X-100. For spontaneous release, targets were incubated without effectors in assay medium alone. After a 1 minute centrifugation at 1000 rpm, plates were incubated for 4 and 16 hours at 37 °C. Supernatant was harvested and $^{51}Cr$ release was measured in a gamma counter. Percentage of specific release was calculated as (experimental release-spontaneous release)/(maximum release-spontaneous release) × 100. The results are shown in FIG. 174.

Example 28 – Effects of BTK Inhibition on T Cells

**[001159]** An assay was performed to assess the effects of BTK inhibition using Formula (XVIII) on T cells. Enriched $CD4^+$ T cells are plated on 24-well culture dishes that have been precoated 2 hr with 250 µL anti-TCRβ (0.5 µg/mL) plus anti-CD28 (5 µg/mL) at 37 °C in PBS. The cells are then supplemented with media containing BTK inhibitors along with the skewing cytokines as indicated in the following. The Th17 and Treg cultures are grown for 4 days before analysis. The cells are maintained for an additional 3 days with skewing cytokines (Th17; 20 ng/mL IL-6, 0.5 ng/mL TGF-β, 5 µg/mL IL-4, 5 µg/mL IFN-γ and Treg; 0.5 ng/mL TGF-β, 5 µg/mL IL-4, 5 µg/mL IFN-γ) and are supplemented with IL2 as a growth factor.

**[001160]** The results are shown in FIG. 175 and FIG. 176, and further illustrate the surprising properties of Formula (XVIII) in comparison to ibrutinib. Because of the lack of activity of Formula (XVIII) on Itk and Txk, no adverse effects on Th17 and Treg development was observed. Since ibrutinib inhibits both Itk and Txk, a profound inhibition of Th17 cells and an increase in Treg development is observed, which is

comparable to the murine Itk/Txk double knock-out cells which were used as a control.

**[001161]** The effects of ibrutinib in comparison to Formula (XVIII) on $CD8^+$ T cell viability were also assessed. Total T cells were plated on anti-TCR and anti-CD28 coated wells in the presence of both BTK inhibitors. Neutral culture conditions were used that will not polarize T cells to a helper lineage. The cells are grown for 4 days and are then stained with anti-CD4, anti-CD8 and LIVE/DEAD reagent to determine if the drugs have selective effects on either the $CD4^+$ or $CD8^+$ cells. Statistical significance was calculated using the Mann Whitney T-test. The results, shown in FIG. 177, indicate that higher concentrations of ibrutinib have a strong, negative effect on $CD8^+$ T cell viability that is not observed with Formula (II) at any concentration.

**[001162]** Without being bound by any theory, $CD8^+$ T cells have two primary effector functions: (1) produce large amounts of IFN-γ (which activates macrophages), and (2) cytolytic activity. A cytotoxic T cell (CTL) assay was performed to compare the BTK inhibitors of Formula (XVIII) and Formula (XX-A) (ibrutinib). Effectors were prepared by generating CTL by culturing MHC mismatched splenocytes for 4 days with (500 nM) and without Formula (XVIII) or Formula (XX-A) (ibrutinib). The targets were B lymphoblasts from lipopolysaccharide (LPS) treated cultures. The assay was performed by incubating different ratios of effectors:targets for 4 hours. In FIG. 178, the results show that Formula (XX-A) (ibrutinib) affects $CD8^+$ T cell function as measured by % cytotoxicity. Formula (XVIII), in contrast, has no effect on $CD8^+$ T cell function as measured by % cytotoxicity relative to vehicle. The effect on $CD8^+$ T cell function can also be observed by measurement of IFN-γ levels, as shown in FIG. 179, where Formula (XX-A) (ibrutinib) again results in a significant loss of function relative to Formula (XVIII) and vehicle.

Example 29 – Blood-Brain Barrier Penetration of BTK Inhibitors in Rats

**[001163]** P-glycoprotein substrates can have relatively low brain exposure, due to activity of efflux pumps including P-glycoprotein at the blood-brain barrier (BBB). In a biodistribution study using radiolabeled Formula (XVIII), low relative concentrations (3% to 4% of plasma concentrations) were observed in the brain. Preliminary brain PK experiments were performed to evaluate the potential for Formula (XVIII) to cross the

blood brain barrier, with results illustrated in FIG. 180. Four Sprague-Dawley rats per group were treated by oral gavage with 5 or 30 mg/kg/day Formula (XVIII) and tissues were collected at 30 minutes after dosing – the approximate time of $C_{max}$ – on Days 1, 3 and 5. Two vehicle treated rats were sacrificed on each sampling day for comparison. Cerebral spinal fluid (CSF) was collected; and the brains were flushed with heparinized saline prior to collection and snap frozen for analysis of Formula (XVIII). Bioanalytical methods specific to CSF and brain tissue were used to measure Formula (XVIII) concentrations in these matrices. Results (FIG. 180) showed low but detectable levels of Formula (XVIII) in the brain and CSF samples. Penetration of Formula (XVIII) into the brain was surprising because of the efflux ratio observed with in vitro studies in Caco-2 cells. However, the ratio of Formula (XVIII) in the flushed brains, compared with matched plasma concentrations, showed that brain extracts had ~3-4% of the observed plasma concentrations, consistent with the results from the biodistribution study. The ratios observed in clean CSF samples from rats treated with 5 and 30 mg/kg/day were between 1-2% of the plasma levels. The results indicate that Formula (XVIII) can penetrate the BBB, and because of the covalent binding of Formula (XVIII) and low BTK resynthesis rates, high levels of BTK occupancy in tumor cells in the brain (such as infiltrating lymphocyties and microglia) as well as in cells of the solid tumor microenvironment in order to treat cancers such as gliomas and primary central nervous system lymphoma (Schideman, *et al., J. Neurosci. Res.* **2006,** *83(8),* 1471-84).

Example 30 – Synergistic Combination of a BTK Inhibitor and an α-PD-1 Inhibitor in the ID8 Ovarian Cancer Model

**[001164]** The ID8 ovarian cancer model of Examples 6 and 7 was also used to investigate potential synergistic effects between the BTK inhibitor of Formula (XVIII) and an α-PD-1 inhibitor. Doses of 15 mg/kg BID of Formula (XVIII) and 150 μg of α-PD-1 antibody (anti-mouse PD-1 antibody Clone J43, BE0033-2) or anti-mouse PD-1 antibody Clone RMP1-14 (BioXcell, BE0146)). The experiments were performed as described in Example 7.

**[001165]** The results of tumor volume assessment for mice treated with vehicle, Formula (XVIII) alone, the α-PD-1 inhibitor alone, and a combination of Formula (XVIII) and the α-PD-1 inhibitor are shown in FIG. 181. The results show that Formula (XVIII) alone or

in combination with an anti-PD-1 antibody impairs ID8 ovarian cancer growth in a syngeneic murine model. The results also show that the combination of Formula (XVIII) and the α-PD-1 inhibitor exhibits a synergistic effect on the reduction of tumor volumes.

Example 31 – Synergistic Combination of a BTK Inhibitor and a PI3K-δ Inhibitor

**[001166]** A study was also performed using the approach described above in Example 2 with the BTK inhibitor of Formula (XXVIII-R) (ONO-4059) and the PI3K-δ inhibitor of Formula (XVI) (idelalisib). Proliferation was again determined with MTS (CellTiter 96 AQueous, Promega). Incubations were performed for 96 hours. The detailed results of the additional cell line studies for the BTK inhibitor of Formula (XXVIII-R) and the PI3K-δ inhibitor of Formula (XVI) are given in FIG. 182 to FIG. 187. The results of these combination studies are summarized in Table 16.

TABLE 16. Summary of results of the combination of a BTK inhibitor with a PI3K-δ inhibitor (S = synergistic, A = additive, X = no effect).

| Cell Line | Indication | ED25 | ED50 | ED75 | ED90 |
|---|---|---|---|---|---|
| TMD-8 | DLBCL-ABC | A | S | S | S |
| Mino | MCL | S | S | S | S |
| RI-1 | NHL | A/X | S | S | S |
| DOHH-2 | FL | A | A | A | S |
| SU-DHL-6 | DLBCL-GCB | X | X | A | S |

**[001167]** Synergistic effects of the combination of the BTK inhibitor of Formula (XXVIII-R) with the PI3K-δ inhibitor of Formula (XVI) are observed in cell lines that are representative of a number of clinically-significant B cell malignancies.

Attorney Docket No. 055112-5014-01-WO

CLAIMS

We claim:

1. A method of treating a cancer, comprising the steps of co-administering, to a mammal in need thereof, a therapeutically effective amount of (1) a programmed death 1 (PD-1) inhibitor or a programmed death ligand 1 (PD-L1) inhibitor, or an antigen-binding fragment, variant, conjugate, or biosimilar thereof, and (2) a Bruton's tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

2. The method of Claim 1, further comprising the step of administering a therapeutically effective amount of a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

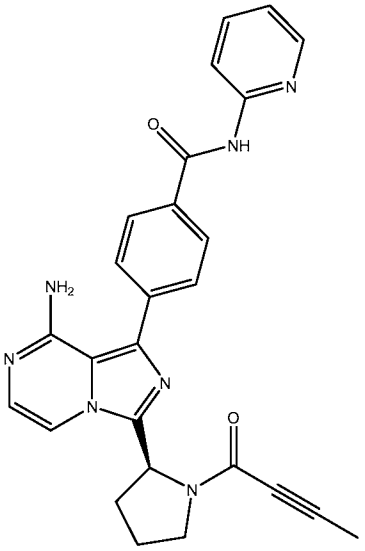
3. The method of Claim 2, wherein the PI3K inhibitor is a PI3K-δ inhibitor.

4. The method of any of Claims 1-3, wherein the PD-1 inhibitor or PD-L1 inhibitor is administered before administration of the BTK inhibitor.

5. The method of any of Claims 1-3, wherein the PD-1 inhibitor or PD-L1 inhibitor is administered concurrently with the administration of the BTK inhibitor.

6. The method of any of Claims 1-3, wherein the PD-1 inhibitor or PD-L1 inhibitor is administered after administration of the BTK inhibitor.

7. The method of any of Claims 1-6, wherein the BTK inhibitor is selected from the group consisting of: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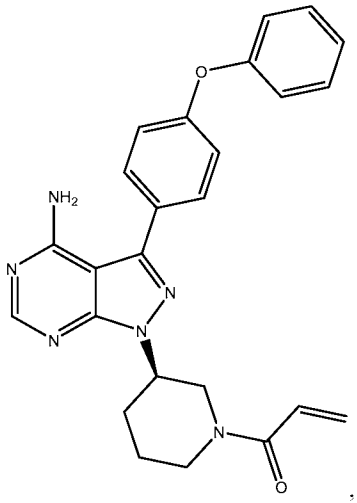
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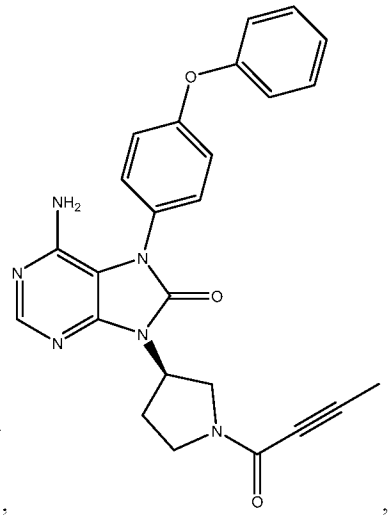
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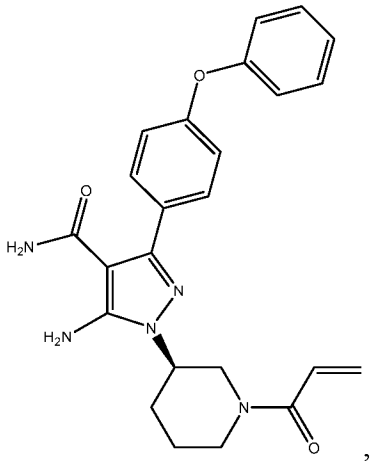
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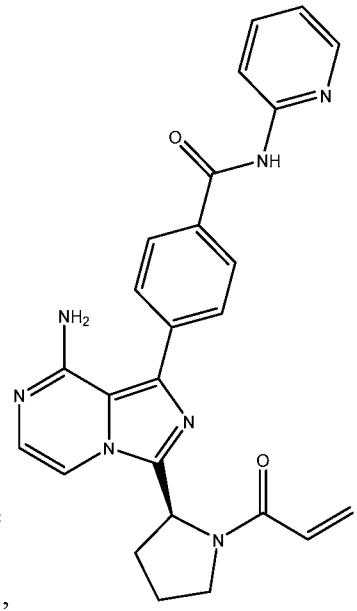
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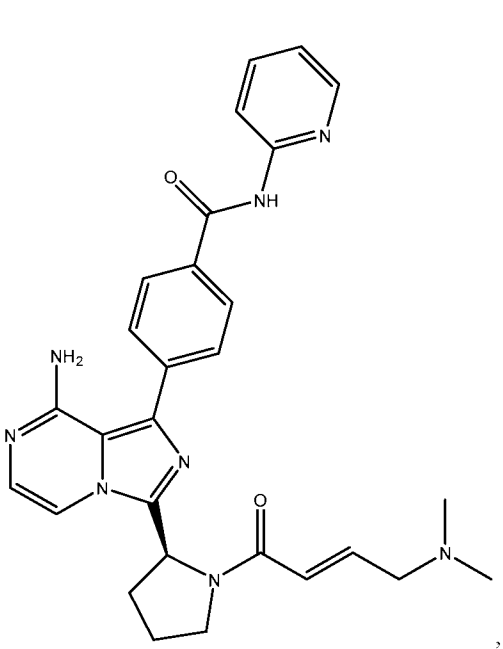
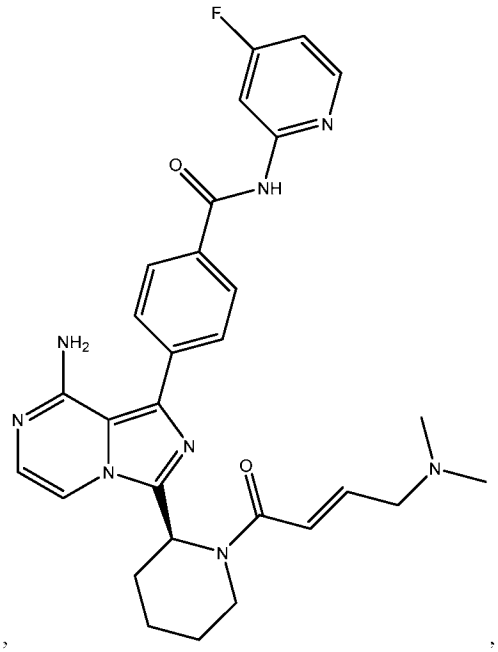
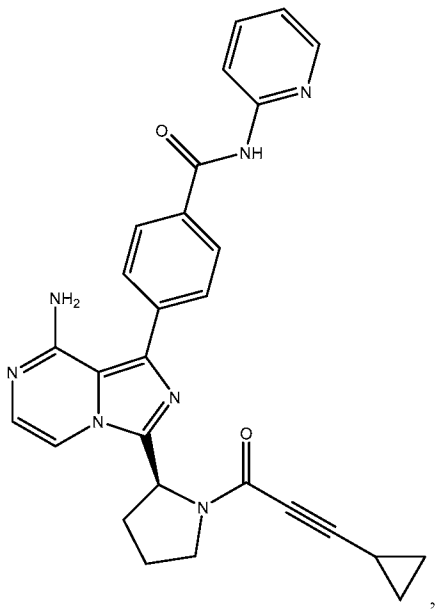
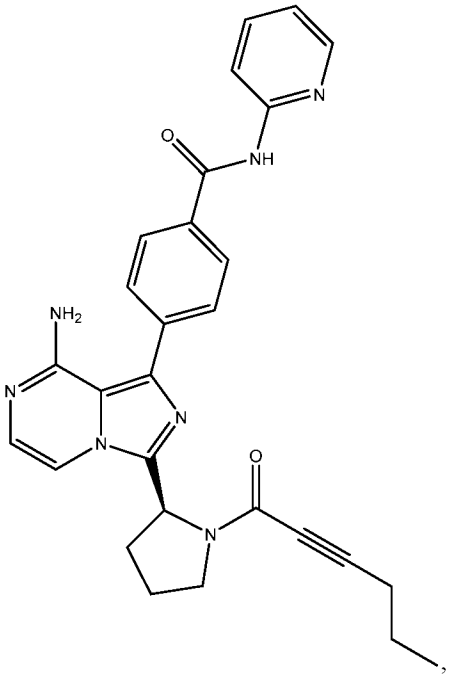








or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof.

8. The method of Claim 7, further comprising the step of administering a therapeutically effective dose of an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, $^{131}$I-tositumomab, ibritumomab, $^{90}$Y-ibritumomab, $^{111}$In-ibritumomab, ibritumomab tiuxetan,

and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof.

9. The method of any of Claims 1-8, wherein the PD-1 inhibitor is an antibody comprising the heavy and light chain regions having the sequences set forth in SEQ ID NOs:1 and 2, respectively, or antigen-binding fragments, variants, conjugates, or biosimilars thereof.

10. The method of any of Claims 1-8, wherein the PD-1 inhibitor is an antibody comprising the heavy and light chain regions having the sequences set forth in SEQ ID NOs:12 and 14, respectively, or antigen-binding fragments, variants, conjugates, or biosimilars thereof.

11. The method of any of Claims 1-8, wherein the PD-L1 inhibitor is an antibody comprising the heavy and light chain variable regions having the sequences set forth in SEQ ID NOs:21 and 22, respectively, or antigen-binding fragments, variants, conjugates, or biosimilars thereof.

12. The method of any of Claims 1-8, wherein the PD-L1 inhibitor is an antibody comprising the heavy and light chain variable regions having the sequences set forth in SEQ ID NOs:53 and 54, respectively, and antigen-binding fragments, variants, conjugates, or biosimilars thereof.

13. The method of any of Claims 1-8, wherein the PD-L1 inhibitor is an antibody comprising the heavy and light chain variable regions having the sequences set forth in SEQ ID NOs:61 and 62, respectively, or antigen-binding fragments, variants, conjugates, or biosimilars thereof.

14. The method of any of Claims 1-8, wherein the PD-1 inhibitor is an anti-PD-1 monoclonal antibody, and wherein the anti-PD-1 monoclonal antibody is selected from the group consisting of nivolumab, pembrolizumab, pidilizumab, or antigen-binding fragments, variants, conjugates, or biosimilars thereof.

15. The method of any of Claims 1-8, wherein the PD-L1 inhibitor is an anti-PD-L1 monoclonal antibody, and wherein the anti-PD-L1 monoclonal antibody is selected from the group consisting of durvalumab, atezolizumab, avelumab, or antigen-binding

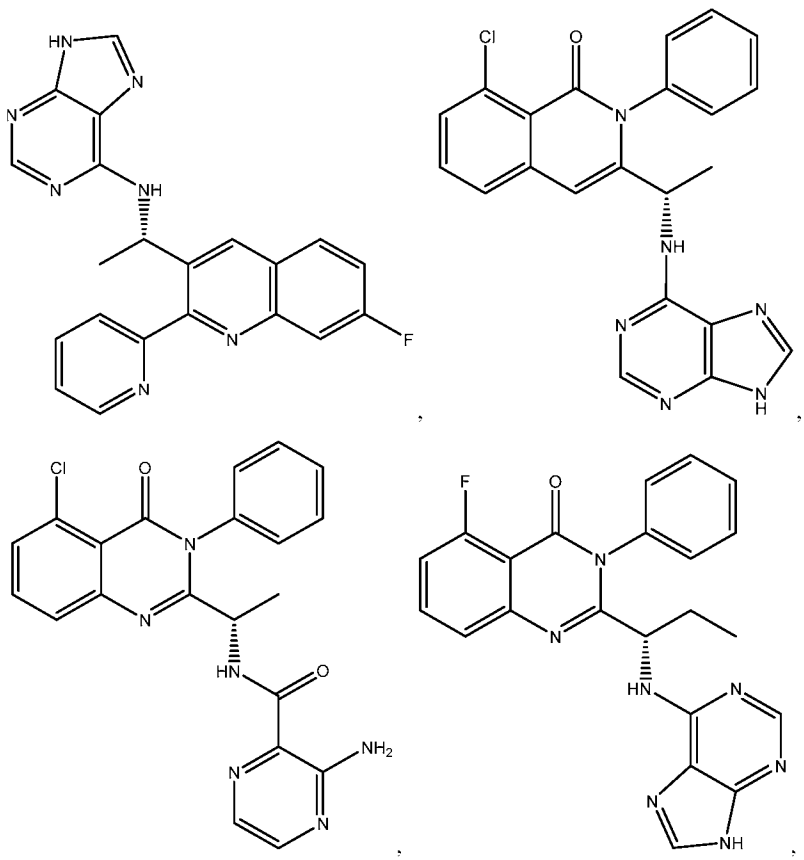
fragments, variants, conjugates, or biosimilars thereof.

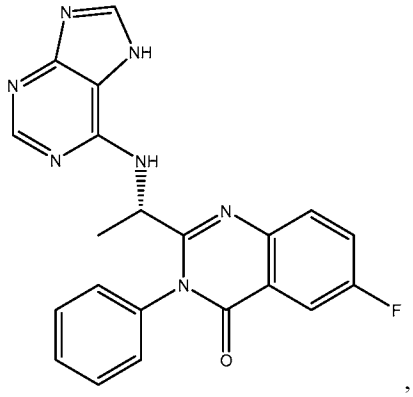
16. The method of any of Claims 2-15, wherein the PI3K inhibitor is administered before administration of the BTK inhibitor.

17. The method of any of Claims 2-15, wherein the PI3K inhibitor is administered concurrently with the administration of the BTK inhibitor.

18. The method of any of Claims 2-15, wherein the PI3K inhibitor is administered after administration of the BTK inhibitor.

19. The method of any of Claims 2-15, wherein the PI3K inhibitor is selected from the group consisting of:

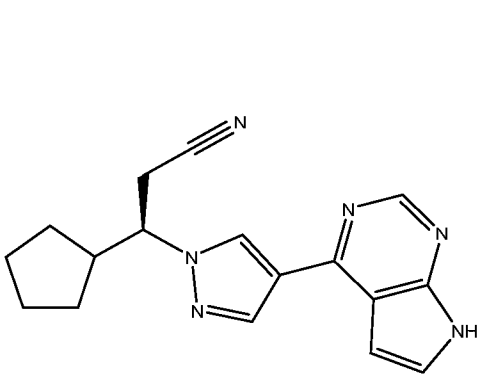


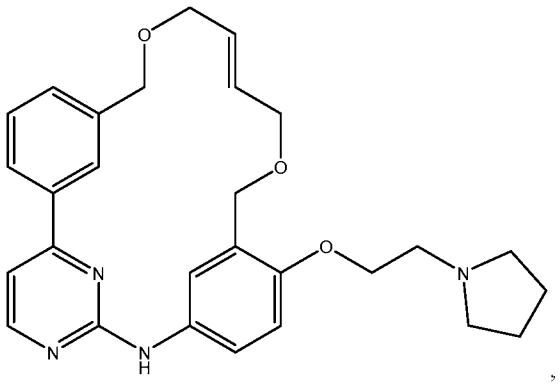


and pharmaceutically acceptable salts, solvates, hydrates, cocrystals, or prodrugs thereof.

20. The method of any of Claims 1-19, wherein the method further comprises the step of co-administering, to a mammal in need thereof, a composition comprising a therapeutically effective amount of a JAK-2 inhibitor.

21. The method of Claim 20, wherein the JAK-2 inhibitor is selected from the group consisting of





and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof.

22. The method of any of Claims 1-21, wherein the cancer is a B cell hematological malignancy selected from the group consisting of chronic lymphocytic leukemia (CLL), small lymphocytic leukemia (SLL), non-Hodgkin's lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Hodgkin's lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Burkitt's lymphoma, Waldenström's macroglobulinemia (WM), Burkitt's lymphoma, multiple myeloma (MM), myelodysplastic syndrome, or myelofibrosis.

23. The method of any of Claims 1-21, wherein the cancer is a solid tumor cancer, and wherein the solid tumor cancer is selected from the group consisting of bladder cancer, non-small cell lung cancer, cervical cancer, anal cancer, pancreatic cancer, squamous cell carcinoma including head and neck cancer, renal cell carcinoma, melanoma, ovarian cancer, small cell lung cancer, glioblastoma, glioma, gastrointestinal stromal tumor, breast cancer, lung cancer, colorectal cancer, thyroid cancer, bone sarcoma, stomach cancer, oral cavity cancer, oropharyngeal cancer, gastric cancer, kidney cancer, liver cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, colon cancer, primary central nervous system lymphoma, and brain cancer.

24. The method of Claim 23, further comprising the step of administering a therapeutically effective dose of a chemotherapeutic active pharmaceutical ingredient selected from the group consisting of gemcitabine, albumin-bound paclitaxel, thalidomide, pomalidomide, lenalidomide, bortezomib, and combinations thereof.

25. A method of treating a solid tumor cancer in a human comprising the steps of co-administering, to a mammal in need thereof, (1) a programmed death 1 (PD-1) inhibitor or a programmed death ligand 1 (PD-L1) inhibitor, or an antigen-binding fragment, variant, or conjugate thereof, and (2) a Bruton's tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein the dose is effective to inhibit signaling between the cells of the solid tumor cancer and at least one tumor microenvironment selected from the group consisting of macrophages, monocytes, mast cells, helper T cells, cytotoxic T cells, regulatory T cells, natural killer cells, myeloid-derived suppressor cells, regulatory B cells, neutrophils, dendritic cells, and fibroblasts.

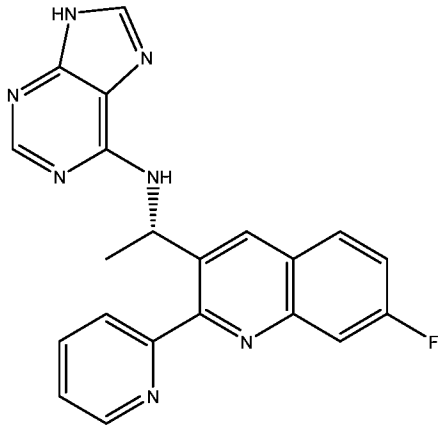
26. The method of Claim 25, further comprising the step of administering a therapeutically effective amount of a phosphoinositide 3-kinase (PI3K) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

27. The method of any of Claims 25 or 26, wherein the solid tumor cancer is selected from the group consisting of bladder cancer, non-small cell lung cancer, cervical cancer, anal cancer, pancreatic cancer, squamous cell carcinoma including head and neck cancer,

renal cell carcinoma, melanoma, ovarian cancer, small cell lung cancer, glioblastoma, glioma, gastrointestinal stromal tumor, breast cancer, lung cancer, colorectal cancer, thyroid cancer, bone sarcoma, stomach cancer, oral cavity cancer, oropharyngeal cancer, gastric cancer, kidney cancer, liver cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, colon cancer, primary central nervous system lymphoma, and brain cancer.

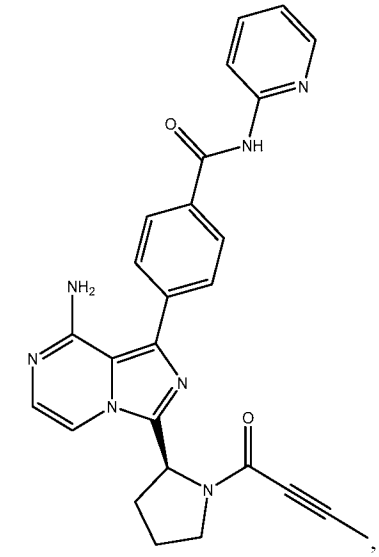
28. The method of any of Claims 25-27, wherein the dose is effective to increase immune system recognition and rejection of the solid tumor by the human.

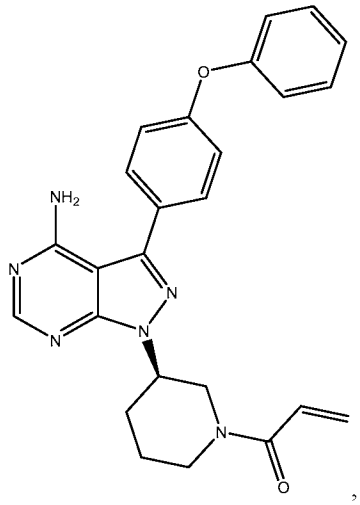
29. The method of Claim 28, wherein the PI3K-δ inhibitor is:

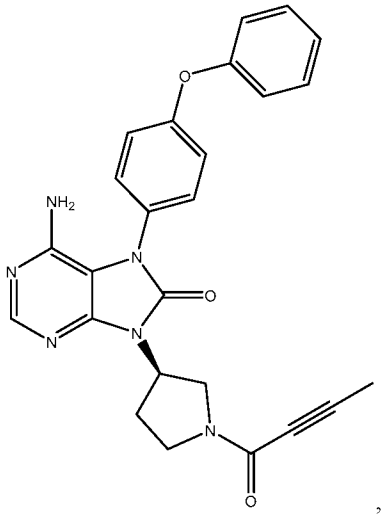


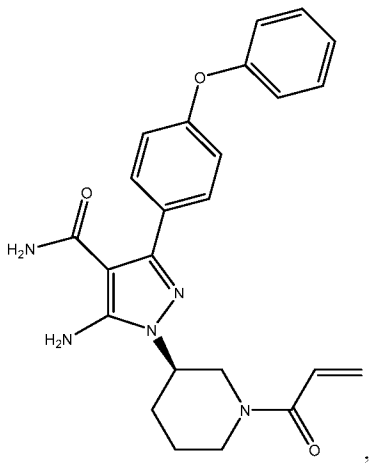

or a pharmaceutically acceptable salt, hydrate, solvate, cocrystal, or prodrug thereof.

30. The method of any of Claims 25-29, wherein the BTK inhibitor is selected from the group consisting of:







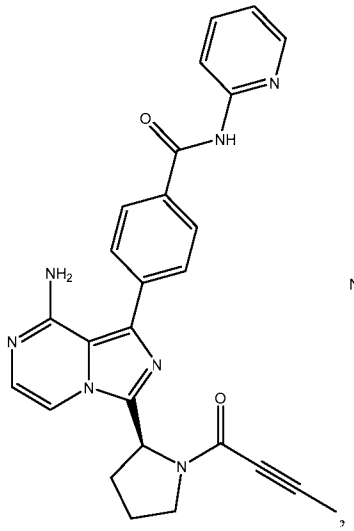
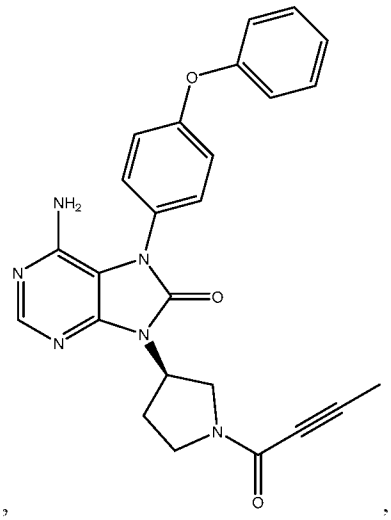
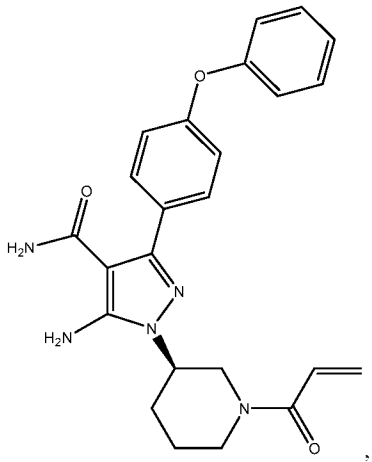


and a pharmaceutically acceptable salt, hydrate, solvate, cocrystal, or prodrug thereof.

31. The method of any of Claims 25-30, wherein the PD-1 inhibitor is an anti-PD-1 monoclonal antibody, and wherein the anti-PD-1 monoclonal antibody is selected from the group consisting of nivolumab, pembrolizumab, or antigen-binding fragments, variants, conjugates, or biosimilars thereof.

32. The method of any of Claims 25-30, wherein the PD-L1 inhibitor is an anti-PD-L1 monoclonal antibody, and wherein the anti-PD-L1 monoclonal antibody is selected from the group consisting of durvalumab, atezolizumab, avelumab, or antigen-binding fragments, variants, conjugates, or biosimilars thereof.

33. A method of treating a cancer in a human sensitive to bleeding events comprising the step of administering a therapeutically effective dose of a BTK inhibitor and a programmed death 1 (PD-1) inhibitor and/or a programmed death ligand 1 (PD-L1) inhibitor or an antigen-binding fragment, variant, conjugate, or biosimilar thereof, wherein the BTK inhibitor is selected from the group consisting of:

and a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof.

34. The method of Claim 33, wherein the bleeding event is selected from the group consisting of subdural hematoma, gastrointestinal bleeding, hematuria, post-procedural hemorrhage, bruising, and petechiae.

35. The method of any of Claims 33 or 34, wherein the PD-1 inhibitor is an anti-PD-1 monoclonal antibody, and wherein the anti-PD-1 monoclonal antibody is selected from the group consisting of nivolumab, pembrolizumab, or antigen-binding fragments, variants, conjugates, or biosimilars thereof.

36. The method of any of Claims 33 or 34, wherein the PD-L1 inhibitor is an anti-PD-L1 monoclonal antibody, and wherein the anti-PD-L1 monoclonal antibody is selected from the group consisting of durvalumab, atezolizumab, avelumab, or antigen-binding fragments, variants, conjugates, or biosimilars thereof.

37. The method of any of Claims 33-36, further comprising the step of administering a therapeutically effective dose of an anticoagulant or antiplatelet active pharmaceutical

ingredient.

38. The method of Claim 37, wherein the anticoagulant or antiplatelet active pharmaceutical ingredient is selected from the group consisting of acenocoumarol, anagrelide, anagrelide hydrochloride, abciximab, aloxiprin, antithrombin, apixaban, argatroban, aspirin, aspirin with extended-release dipyridamole, beraprost, betrixaban, bivalirudin, carbasalate calcium, cilostazol, clopidogrel, clopidogrel bisulfate, cloricromen, dabigatran etexilate, darexaban, dalteparin, dalteparin sodium, defibrotide, dicumarol, diphenadione, dipyridamole, ditazole, desirudin, edoxaban, enoxaparin, enoxaparin sodium, eptifibatide, fondaparinux, fondaparinux sodium, heparin, heparin sodium, heparin calcium, idraparinux, idraparinux sodium, iloprost, indobufen, lepirudin, low molecular weight heparin, melagatran, nadroparin, otamixaban, parnaparin, phenindione, phenprocoumon, prasugrel, picotamide, prostacyclin, ramatroban, reviparin, rivaroxaban, sulodexide, terutroban, terutroban sodium, ticagrelor, ticlopidine, ticlopidine hydrochloride, tinzaparin, tinzaparin sodium, tirofiban, tirofiban hydrochloride, treprostinil, treprostinil sodium, triflusal, vorapaxar, warfarin, warfarin sodium, ximelagatran, salts thereof, solvates thereof, hydrates thereof, and combinations thereof.

39. The method of any of Claims 33-38, wherein the cancer is selected from the group consisting of bladder cancer, squamous cell carcinoma including head and neck cancer, pancreatic ductal adenocarcinoma (PDA), pancreatic cancer, colon carcinoma, mammary carcinoma, breast cancer, fibrosarcoma, mesothelioma, renal cell carcinoma, lung carcinoma, thyoma, prostate cancer, colorectal cancer, ovarian cancer, acute myeloid leukemia, thymus cancer, brain cancer, squamous cell cancer, skin cancer, eye cancer, retinoblastoma, melanoma, intraocular melanoma, oral cavity and oropharyngeal cancers, gastric cancer, stomach cancer, cervical cancer, head, neck, renal cancer, kidney cancer, liver cancer, ovarian cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, acquired immune deficiency syndrome (AIDS)-related cancers (e.g., lymphoma and Kaposi's sarcoma), viral-induced cancer, glioblastoma, glioma, esophogeal tumors, hematological neoplasms, non-small-cell lung cancer, chronic myelocytic leukemia, diffuse large B-cell lymphoma, esophagus tumor, follicle center lymphoma, head and neck tumor, hepatitis C virus infection, hepatocellular carcinoma, Hodgkin's disease, metastatic colon cancer,

multiple myeloma, non-Hodgkin's lymphoma, indolent non-Hodgkin's lymphoma, ovary tumor, pancreas tumor, renal cell carcinoma, small-cell lung cancer, stage IV melanoma, chronic lymphocytic leukemia, B-cell acute lymphoblastic leukemia (ALL), mature B-cell ALL, follicular lymphoma, mantle cell lymphoma, primary central nervous system lymphoma, and Burkitt's lymphoma.

40. A programmed death 1 (PD-1) inhibitor and a BTK inhibitor in combination, for use in treating a cancer.

41. A programmed death ligand 1 (PD-L1) inhibitor and a BTK inhibitor in combination, for use in treating a cancer.

42. A programmed death 1 (PD-1) inhibitor, a BTK inhibitor, and a PI3K-δ inhibitor in combination, for use in treating a cancer.

43. A programmed death ligand 1 (PD-L1) inhibitor, a BTK inhibitor, and a PI3K-δ inhibitor in combination, for use in treating a cancer.

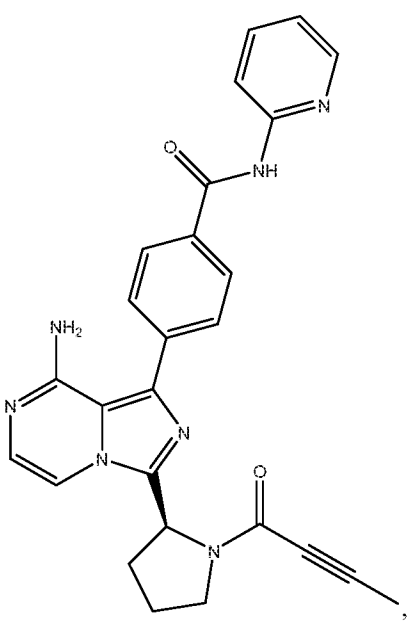
44. The combination of any of Claims 40 or 42, wherein the PD-1 inhibitor is selected from the group consisting of nivolumab, pembrolizumab, pidilizumab, or antigen-binding fragments, variants, conjugates, or biosimilars thereof.

45. The combination of any of Claims 41 or 43, wherein the PD-L1 inhibitor is selected from the group consisting of durvalumab, atezolizumab, avelumab, or antigen-binding fragments, variants, conjugates, or biosimilars thereof.

46. The combination of any of Claims 40-43, wherein the cancer is selected from the group consisting of bladder cancer, squamous cell carcinoma including head and neck cancer, pancreatic ductal adenocarcinoma (PDA), pancreatic cancer, colon carcinoma, mammary carcinoma, breast cancer, fibrosarcoma, mesothelioma, renal cell carcinoma, lung carcinoma, thyoma, prostate cancer, colorectal cancer, ovarian cancer, acute myeloid leukemia, thymus cancer, brain cancer, squamous cell cancer, skin cancer, eye cancer, retinoblastoma, melanoma, intraocular melanoma, oral cavity and oropharyngeal cancers, gastric cancer, stomach cancer, cervical cancer, head, neck, renal cancer, kidney cancer, liver cancer, ovarian cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, acquired immune

deficiency syndrome (AIDS)-related cancers (e.g., lymphoma and Kaposi's sarcoma), viral-induced cancer, glioblastoma, glioma, esophogeal tumors, hematological neoplasms, non-small-cell lung cancer, chronic myelocytic leukemia, diffuse large B-cell lymphoma, esophagus tumor, follicle center lymphoma, head and neck tumor, hepatitis C virus infection, hepatocellular carcinoma, Hodgkin's disease, metastatic colon cancer, multiple myeloma, non-Hodgkin's lymphoma, indolent non-Hodgkin's lymphoma, ovary tumor, pancreas tumor, renal cell carcinoma, small-cell lung cancer, stage IV melanoma, chronic lymphocytic leukemia, B-cell acute lymphoblastic leukemia (ALL), mature B-cell ALL, follicular lymphoma, mantle cell lymphoma, primary central nervous system lymphoma, and Burkitt's lymphoma.

47. The combination of any of Claims 40-46, wherein the BTK inhibitor is selected from the group consisting of:



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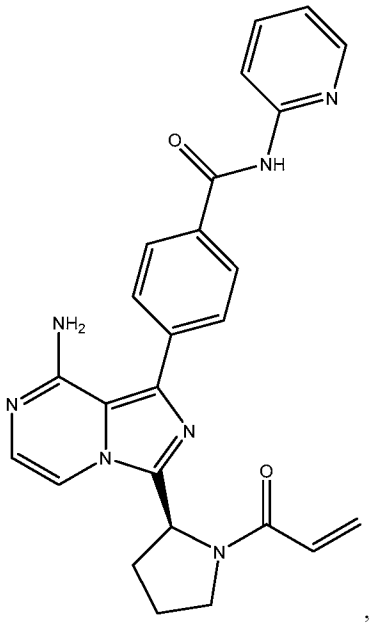

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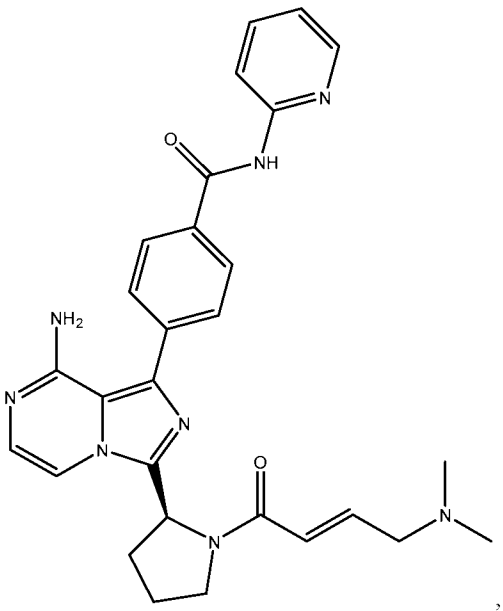

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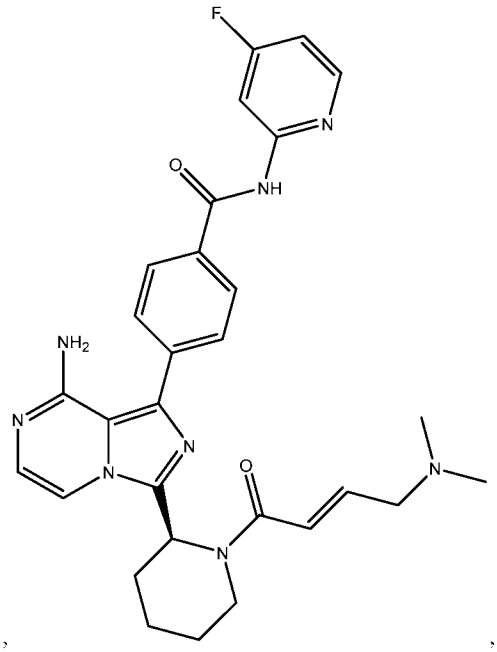

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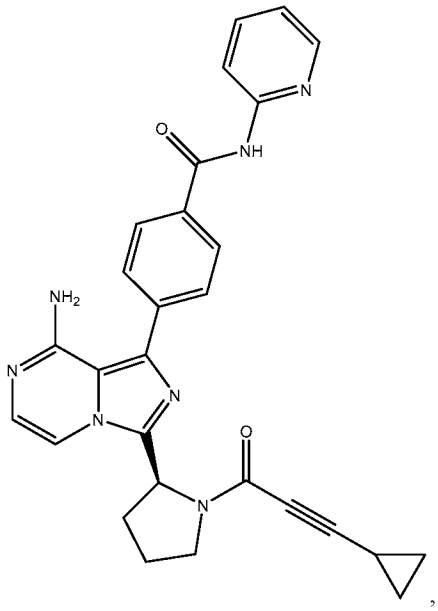

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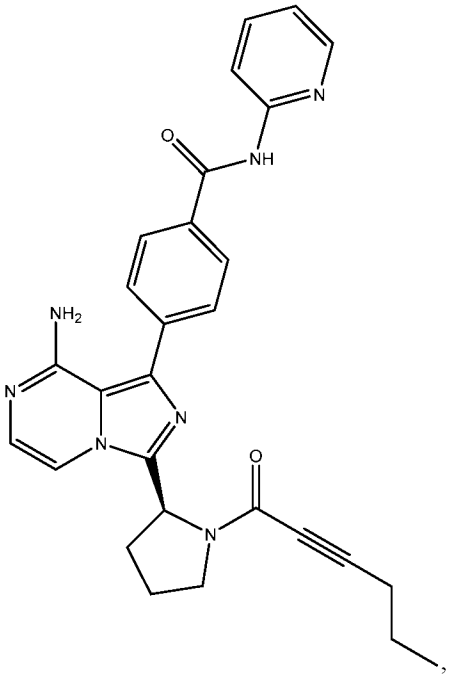

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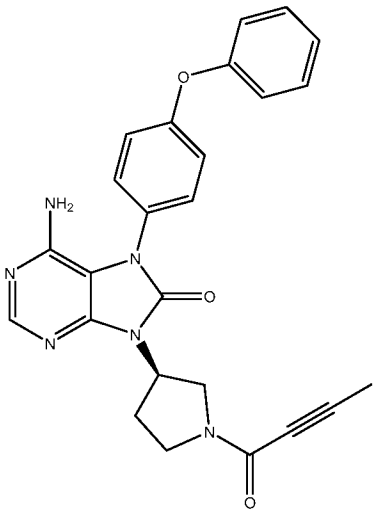
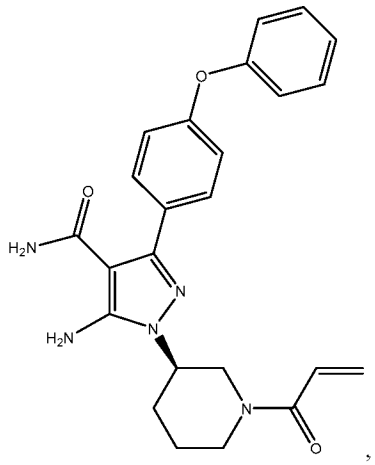
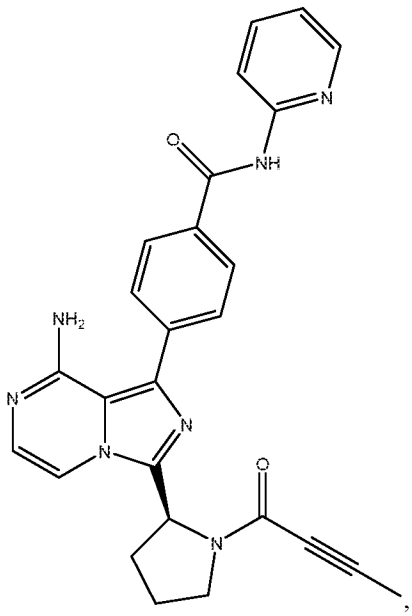
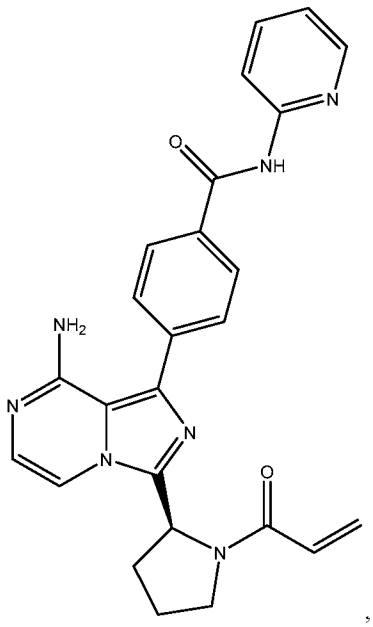


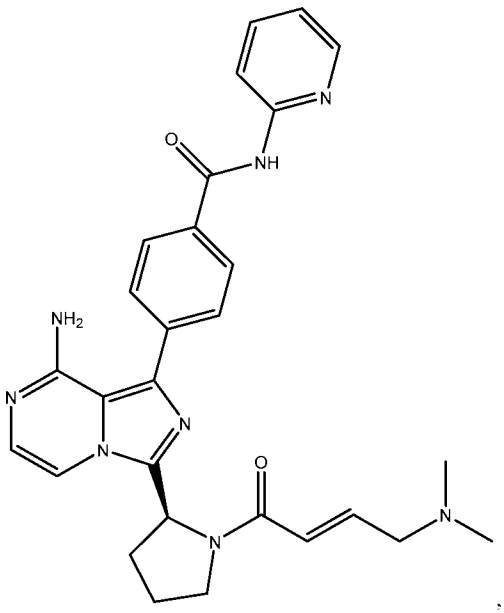


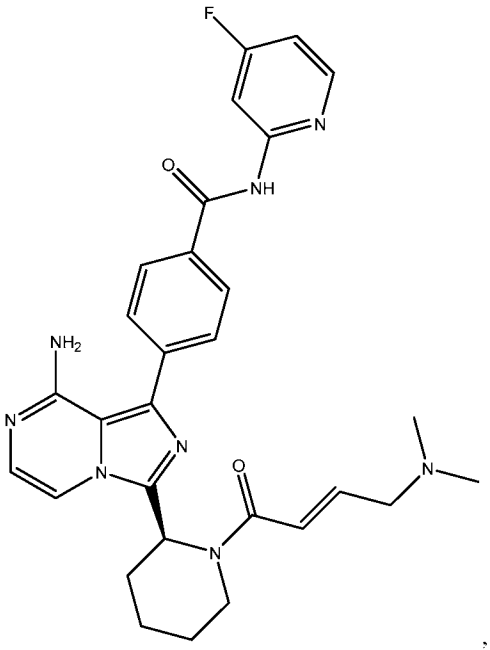
and a pharmaceutically-acceptable salt, cocrystal, solvate, or hydrate thereof.

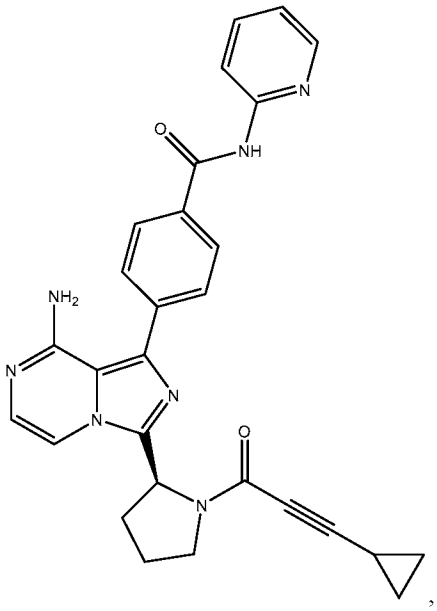
48. A composition comprising a programmed death 1 (PD-1) inhibitor and a Bruton's tyrosine kinase (BTK) inhibitor, wherein the PD-1 inhibitor is selected from the group consisting of nivolumab, pembrolizumab, pidilizumab, or antigen-binding fragments, variants, conjugates, or biosimilars thereof; and wherein the BTK inhibitor is selected from the group consisting of:

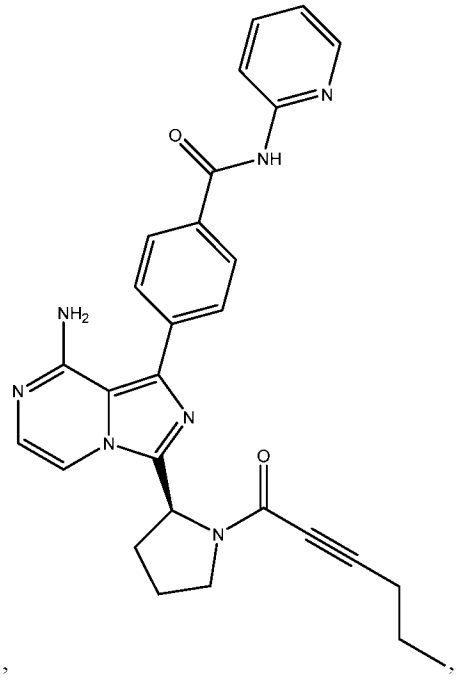


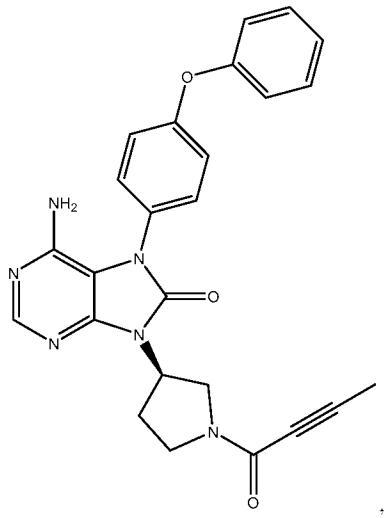


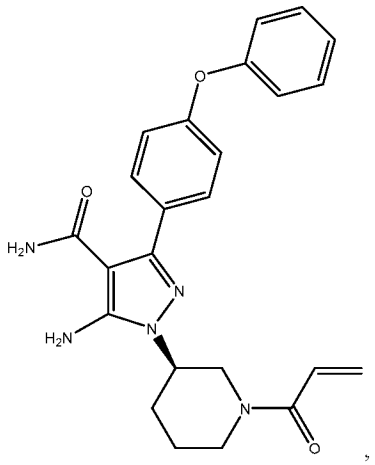










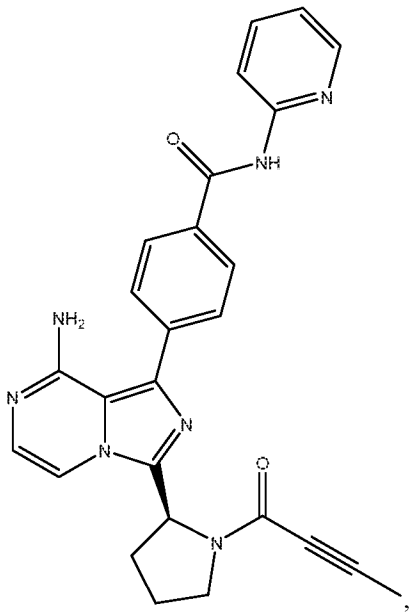


and a pharmaceutically-acceptable salt, cocrystal, solvate, or hydrate thereof.

49. The composition of Claim 48, comprising an amount of the BTK inhibitor selected from the group consisting of 5 mg, 10 mg, 12.5 mg, 15 mg, 20 mg, 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 375 mg, 400 mg, 425 mg, 450 mg, 475 mg, or 500 mg.

50. The composition of any of Claims 48 to 49, comprising an amount of the PD-1 inhibitor selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, 1800 mg, 1900 mg, and 2000 mg.

51. A composition comprising a programmed death ligand 1 (PD-L1) inhibitor and a Bruton's tyrosine kinase (BTK) inhibitor, wherein the PD-L1 inhibitor is selected from the group consisting of durvalumab, atezolizumab, avelumab, or antigen-binding fragments, variants, conjugates, or biosimilars thereof; and wherein the BTK inhibitor is selected from the group consisting of:



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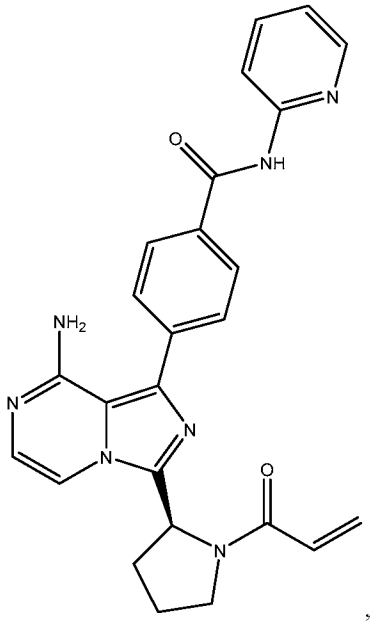

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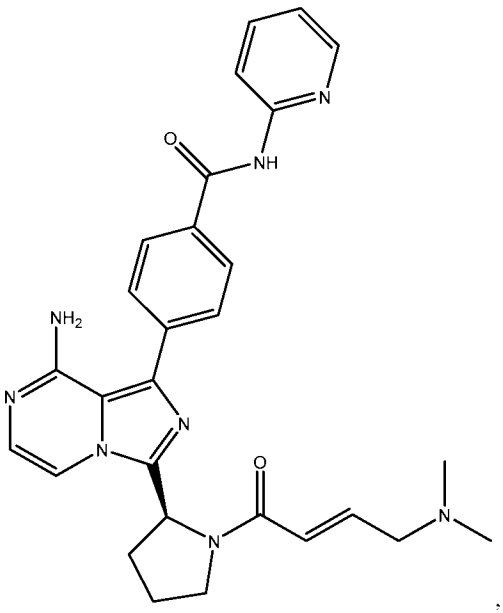

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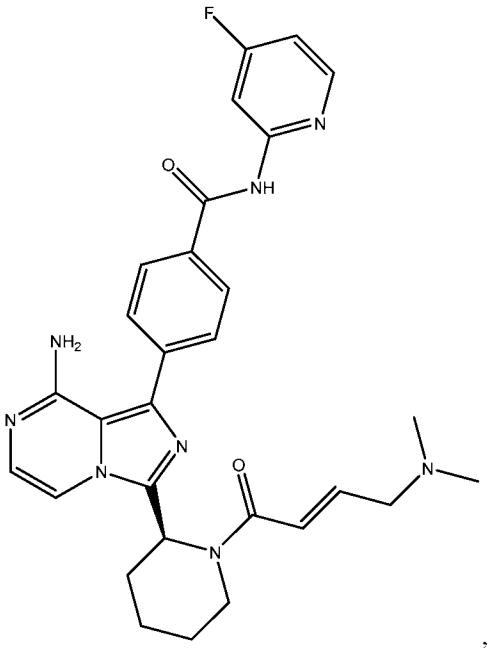
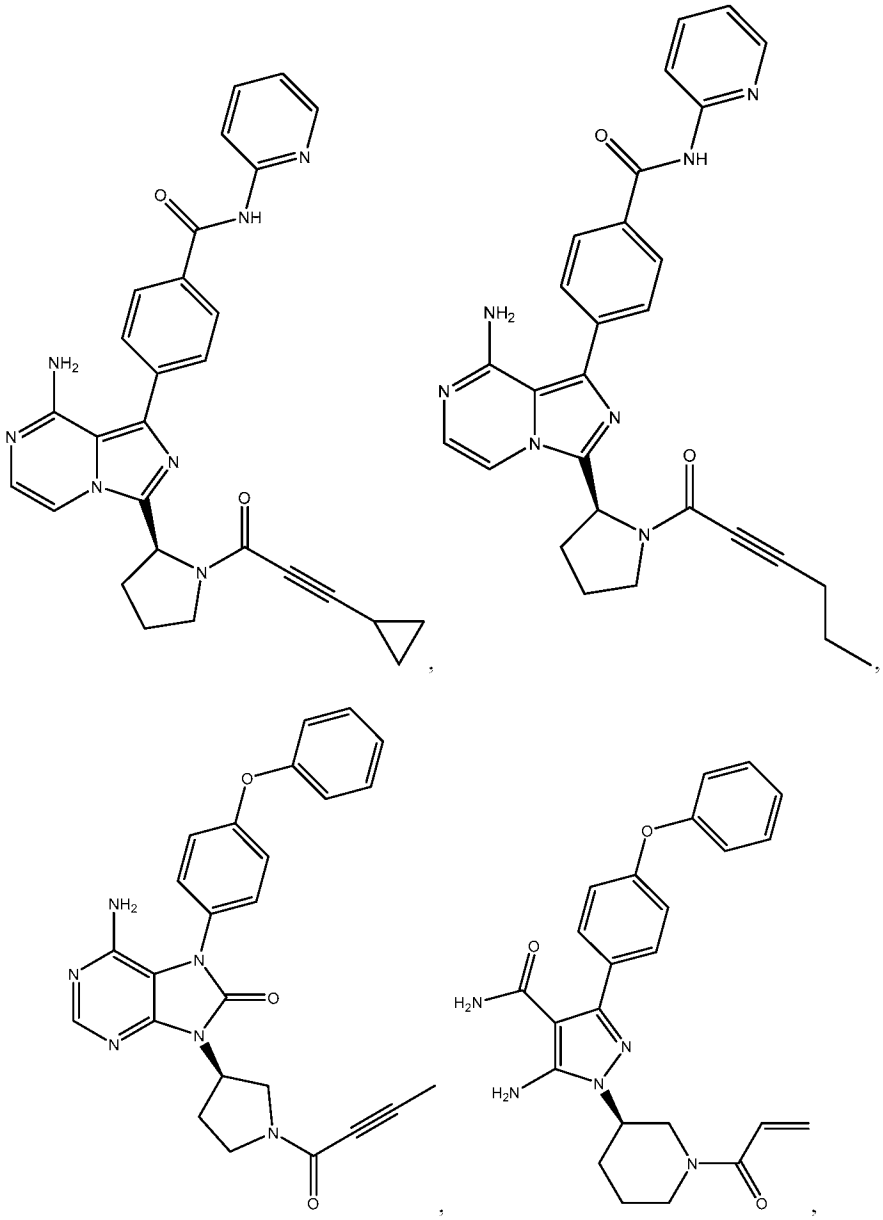


,



and a pharmaceutically-acceptable salt, cocrystal, solvate, or hydrate thereof.

52. The composition of Claim 51, comprising an amount of the BTK inhibitor selected from the group consisting of 5 mg, 10 mg, 12.5 mg, 15 mg, 20 mg, 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 375 mg, 400 mg, 425 mg, 450 mg, 475 mg, or 500 mg.

53. The composition of any of Claims 51 to 52, comprising an amount of the PD-L1 inhibitor selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 200 mg,

300 mg, 400 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, 1800 mg, 1900 mg, and 2000 mg.

54. A kit comprising a pharmaceutical composition comprising a programmed death 1 (PD-1) inhibitor and a pharmaceutical composition comprising a BTK inhibitor, for co-administration of the PD-1 inhibitor and the BTK inhibitor, either simultaneously or separately.

55. A kit comprising a pharmaceutical composition comprising a programmed death ligand 1 (PD-L1) inhibitor and a pharmaceutical composition comprising a BTK inhibitor, for co-administration of the PD-L1 inhibitor and the BTK inhibitor, either simultaneously or separately.

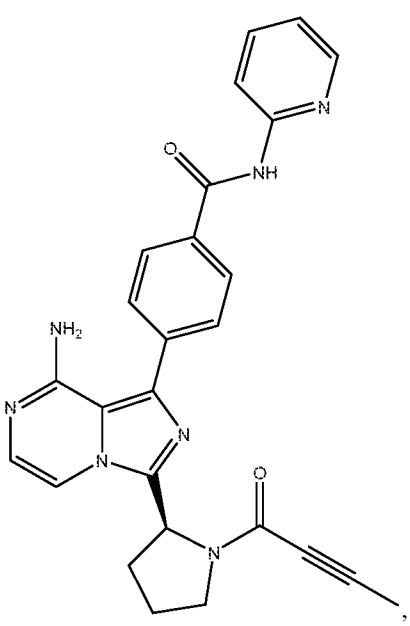
56. The kit of any of Claims 54 or 55, further comprising a JAK-2 inhibitor.

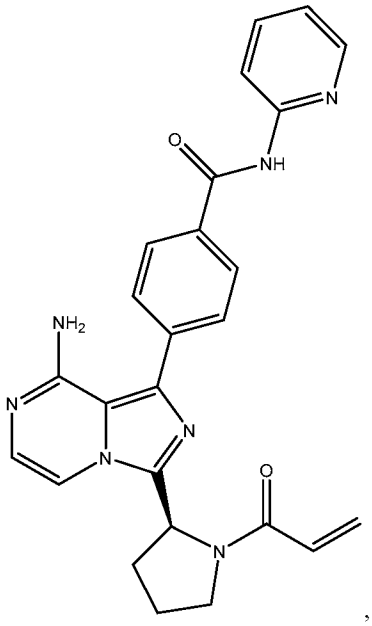
57. The kit of any of Claims 54 to 56, for use in treating a cancer.

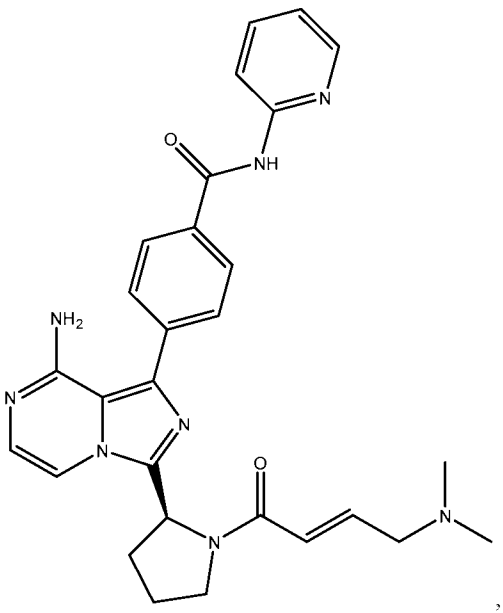
58. The kit of Claim 57, wherein the cancer is selected from the group consisting of bladder cancer, squamous cell carcinoma including head and neck cancer, pancreatic ductal adenocarcinoma (PDA), pancreatic cancer, colon carcinoma, mammary carcinoma, breast cancer, fibrosarcoma, mesothelioma, renal cell carcinoma, lung carcinoma, thyoma, prostate cancer, colorectal cancer, ovarian cancer, acute myeloid leukemia, thymus cancer, brain cancer, squamous cell cancer, skin cancer, eye cancer, retinoblastoma, melanoma, intraocular melanoma, oral cavity and oropharyngeal cancers, gastric cancer, stomach cancer, cervical cancer, head, neck, renal cancer, kidney cancer, liver cancer, ovarian cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, acquired immune deficiency syndrome (AIDS)-related cancers (*e.g.*, lymphoma and Kaposi's sarcoma), viral-induced cancer, glioblastoma, glioma, esophogeal tumors, hematological neoplasms, non-small-cell lung cancer, chronic myelocytic leukemia, diffuse large B-cell lymphoma, esophagus tumor, follicle center lymphoma, head and neck tumor, hepatitis C virus infection, hepatocellular carcinoma, Hodgkin's disease, metastatic colon cancer, multiple myeloma, non-Hodgkin's lymphoma, indolent non-Hodgkin's lymphoma, ovary tumor, pancreas tumor, renal cell carcinoma, small-cell lung cancer, stage IV melanoma, chronic lymphocytic leukemia, B-cell acute lymphoblastic leukemia (ALL), mature B-cell ALL,

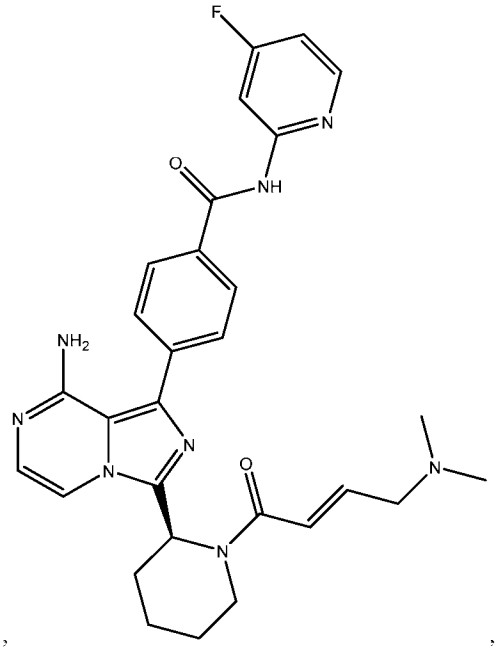
follicular lymphoma, mantle cell lymphoma, primary central nervous system lymphoma, and Burkitt's lymphoma.

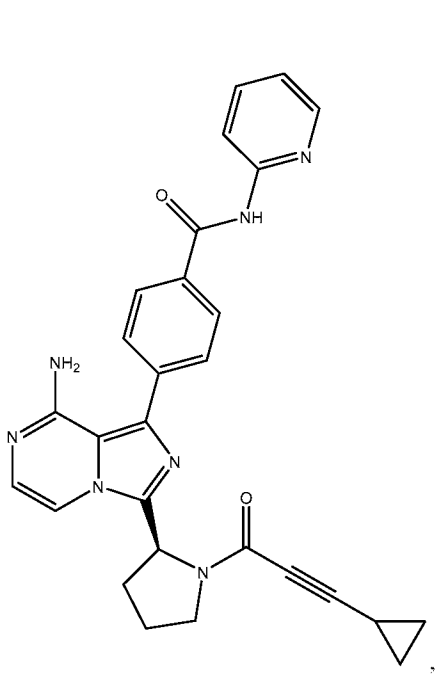
59. The kit of Claim 58, wherein the BTK inhibitor is selected from the group consisting of:

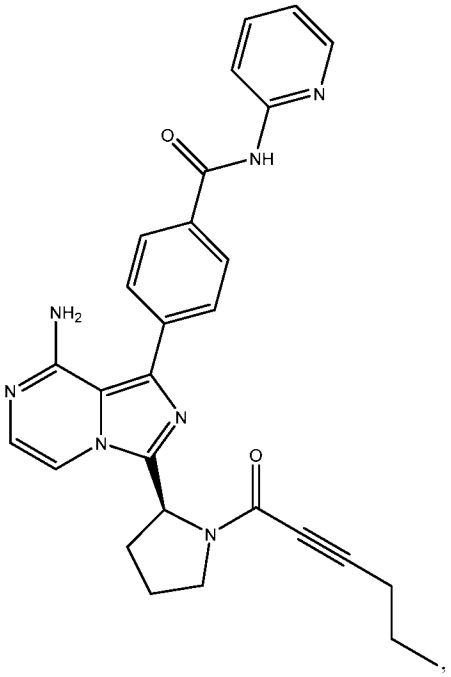


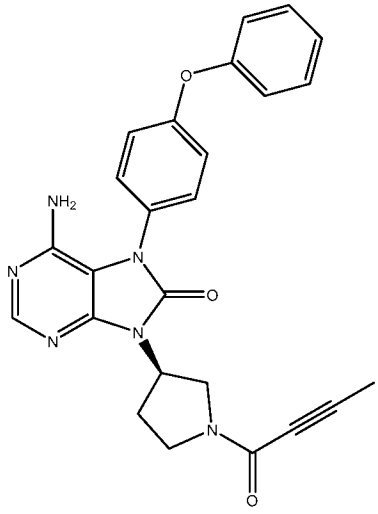


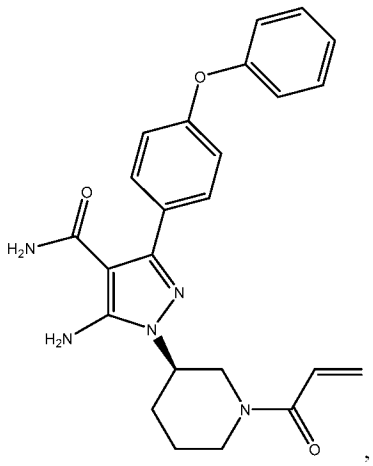












and a pharmaceutically-acceptable salt, cocrystal, solvate, or hydrate thereof.

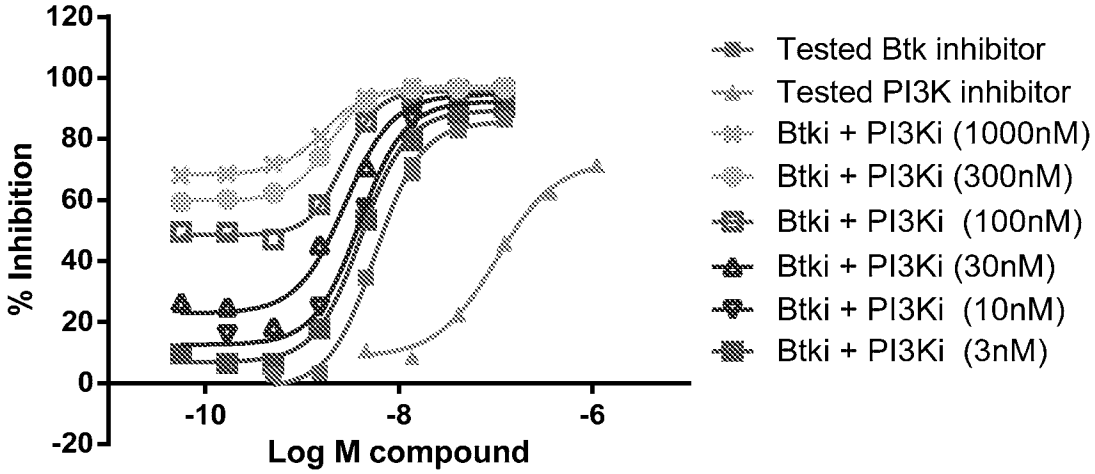

120
100
80
60
40
20
0
-20
% Inhibition
-10
-8
-6
Log M compound
Tested Btk inhibitor
Tested PI3K inhibitor
Btki + PI3Ki (1000nM)
Btki + PI3Ki (300nM)
Btki + PI3Ki (100nM)
Btki + PI3Ki (30nM)
Btki + PI3Ki (10nM)
Btki + PI3Ki (3nM)

FIG. 1

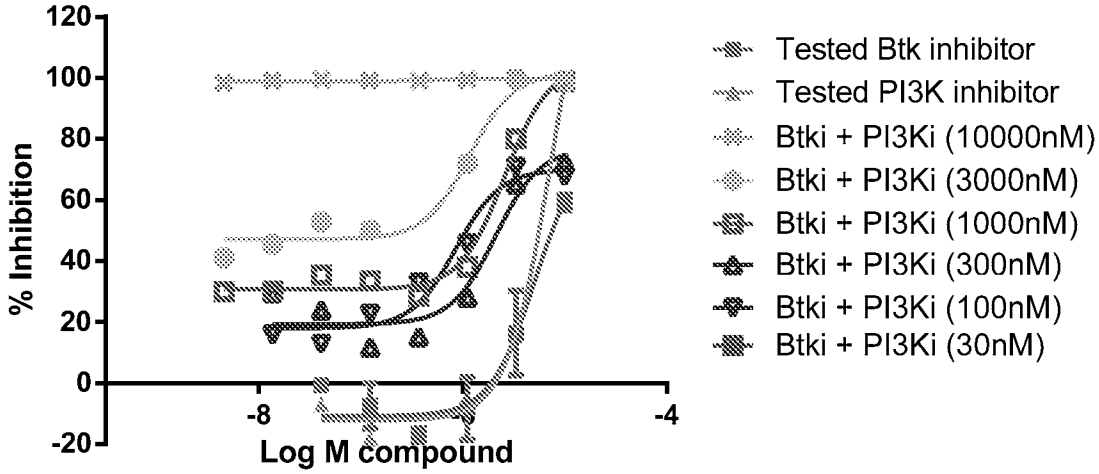

120
100
80
60
40
20
0
-20
% Inhibition
-8
-4
Log M compound
Tested Btk inhibitor
Tested PI3K inhibitor
Btki + PI3Ki (10000nM)
Btki + PI3Ki (3000nM)
Btki + PI3Ki (1000nM)
Btki + PI3Ki (300nM)
Btki + PI3Ki (100nM)
Btki + PI3Ki (30nM)

FIG. 2

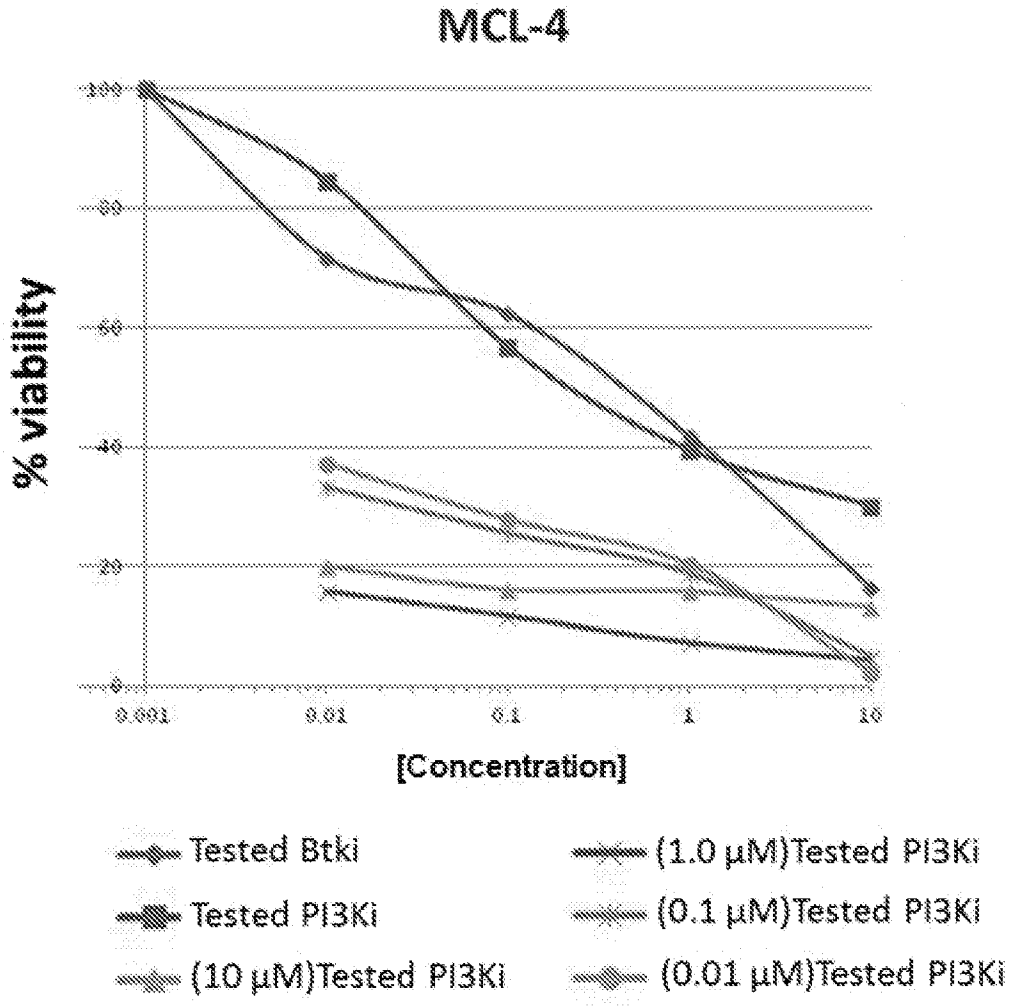

MCL-4
% viability
[Concentration]
Tested Btki
Tested PI3Ki
(10 µM)Tested PI3Ki
(1.0 µM)Tested PI3Ki
(0.1 µM)Tested PI3Ki
(0.01 µM)Tested PI3Ki

FIG. 3

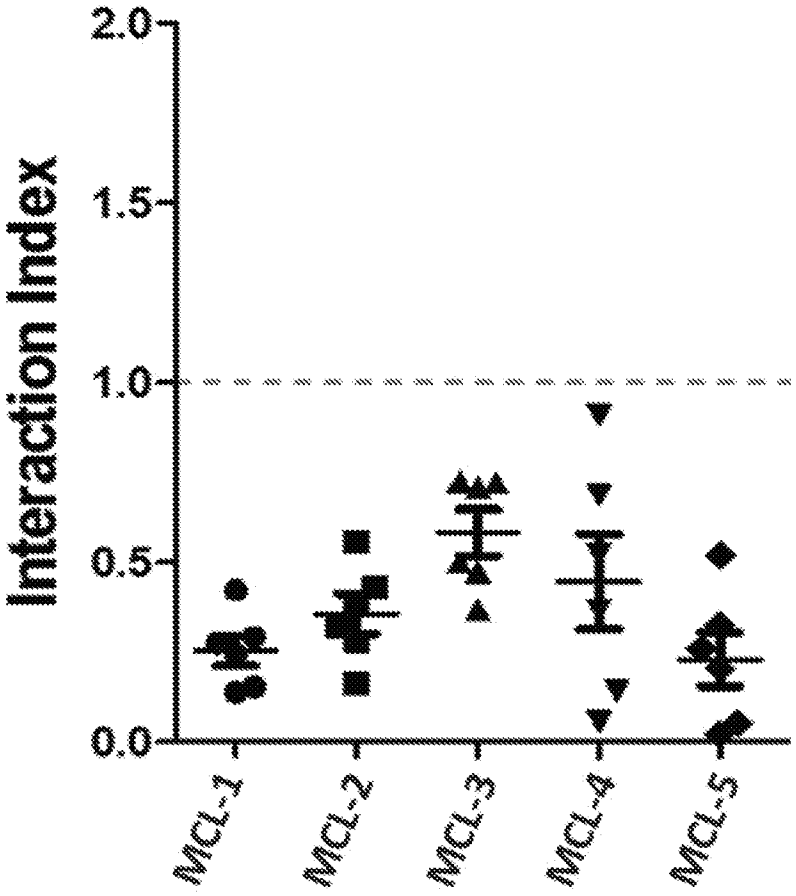



FIG. 4

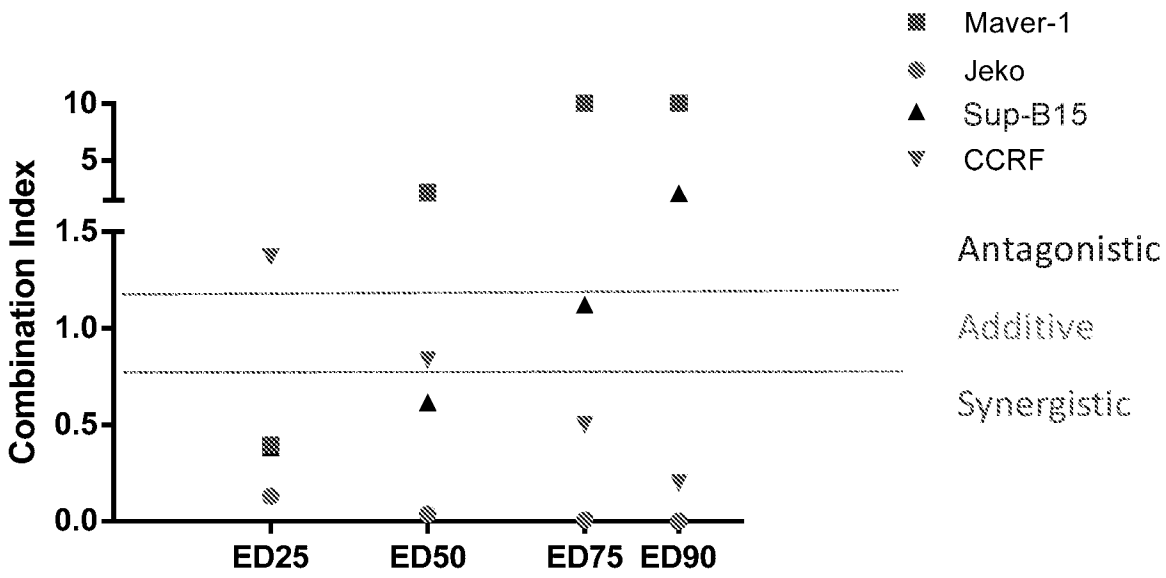

Maver-1
Jeko
Sup-B15
CCRF
Combination Index
10
5
1.5
1.0
0.5
0.0
Antagonistic
Additive
Synergistic
ED25
ED50
ED75
ED90

FIG. 5

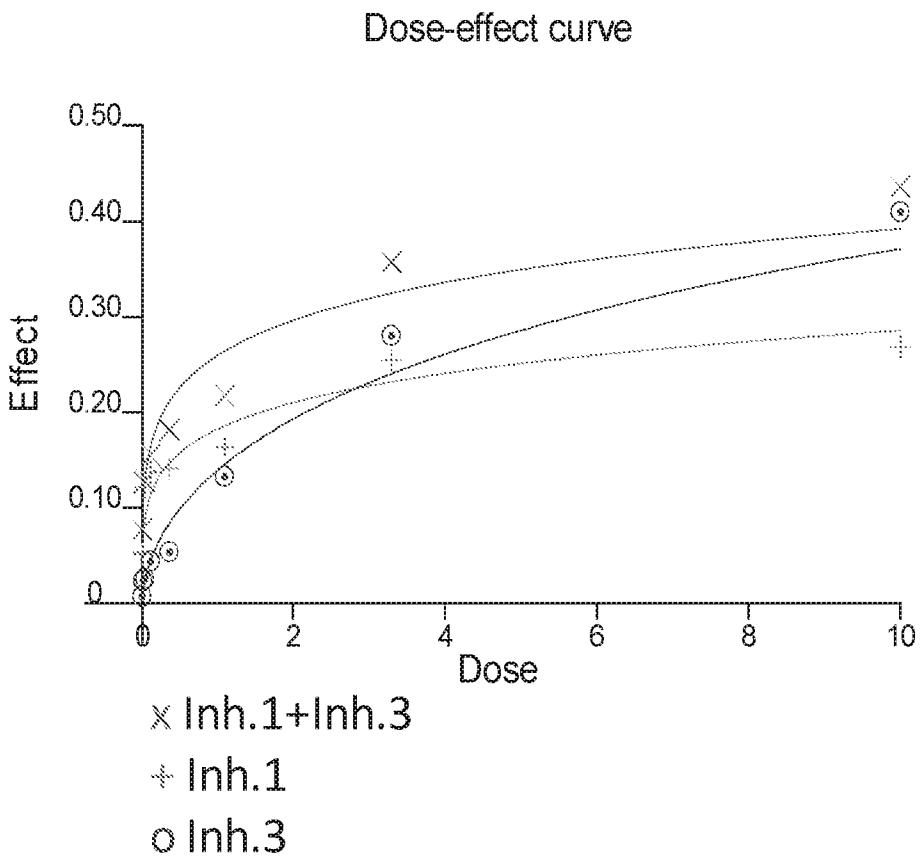

Dose-effect curve
Effect
0.50
0.40
0.30
0.20
0.10
0
0
2
4
6
8
10
Dose
Inh.1+Inh.3
Inh.1
Inh.3

FIG. 6

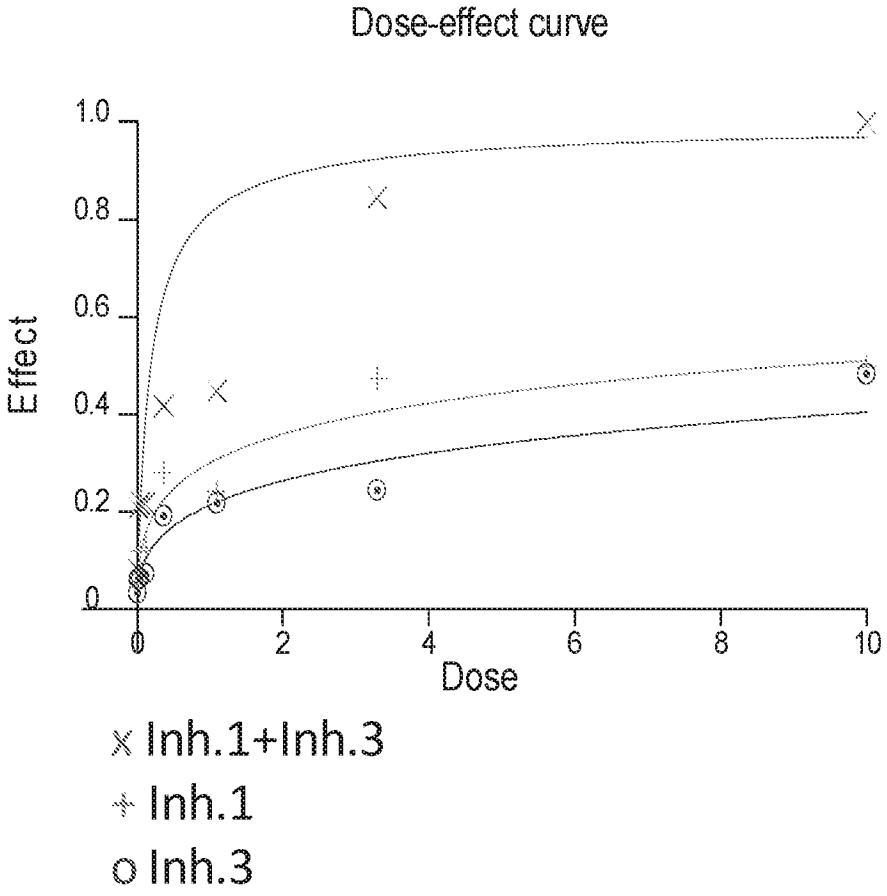

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.1+Inh.3
Inh.1
Inh.3

FIG. 7

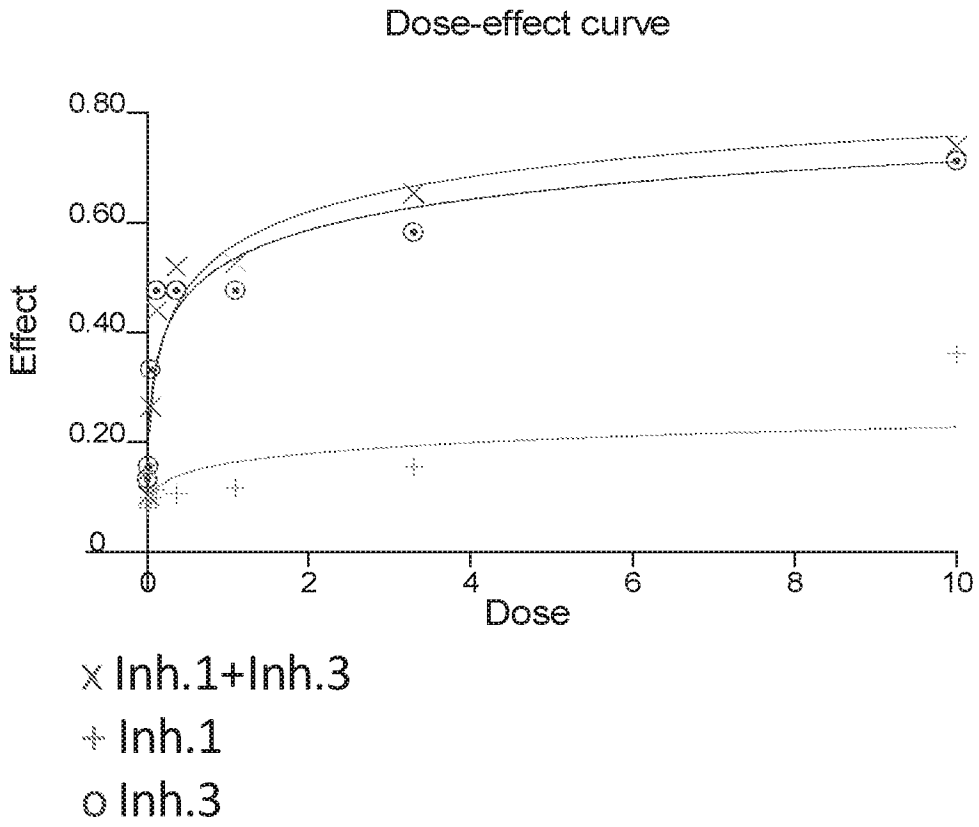

Dose-effect curve
Effect
0.80
0.60
0.40
0.20
0
0
2
4
6
8
10
Dose
Inh.1+Inh.3
Inh.1
Inh.3

FIG. 8

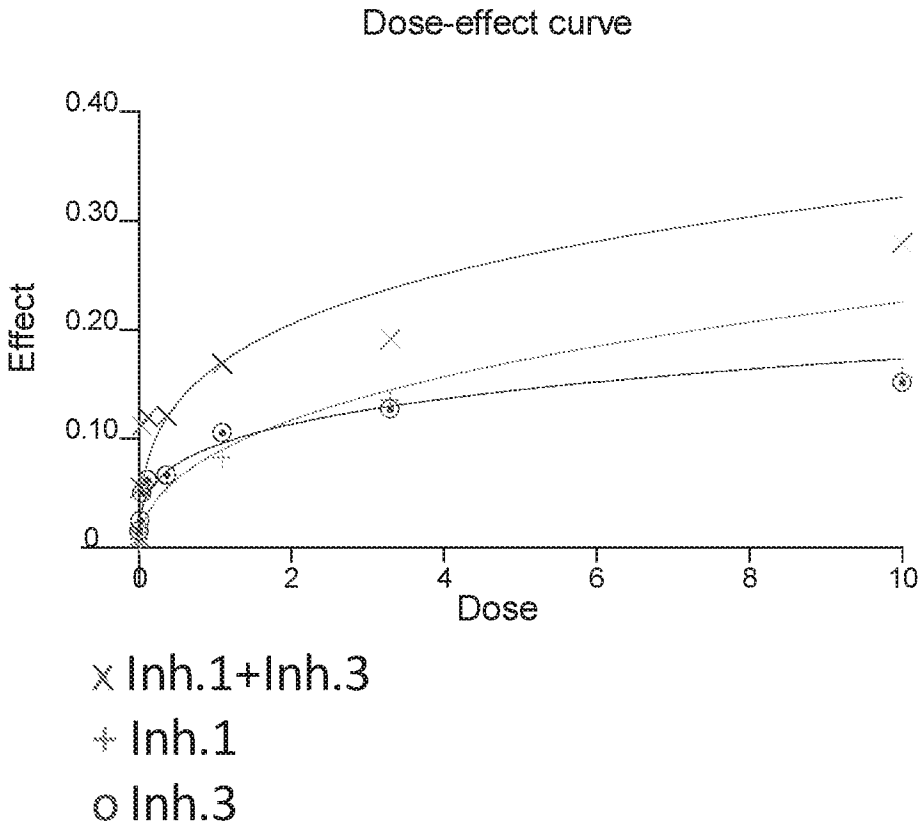

Dose-effect curve
0.40
0.30
0.20
0.10
0
Effect
0
2
4
6
8
10
Dose
Inh.1+Inh.3
Inh.1
Inh.3

FIG. 9

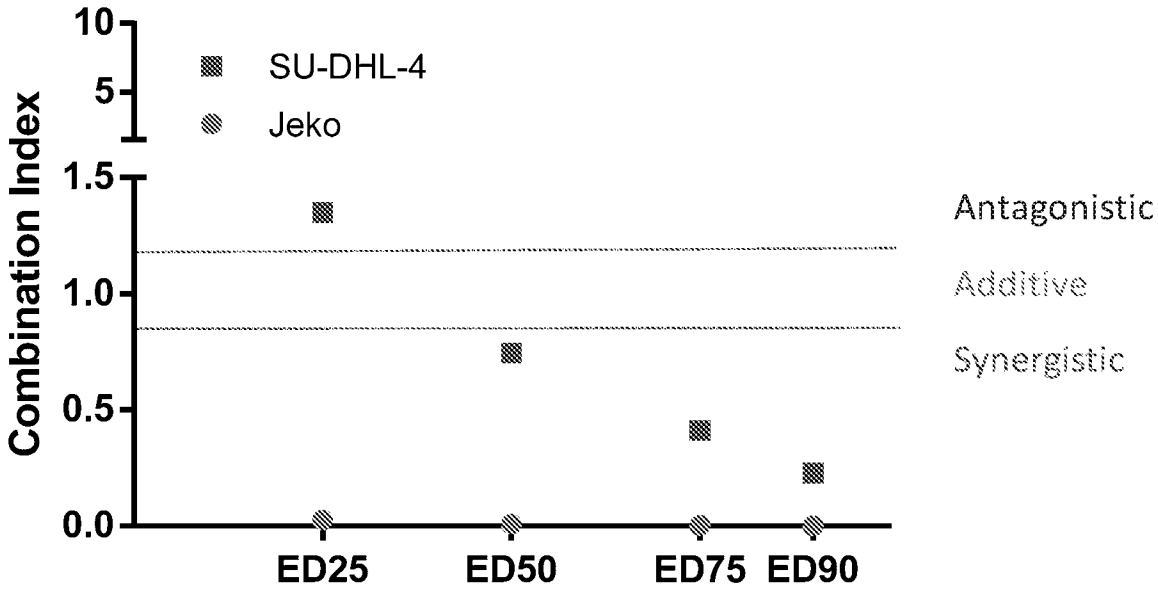

10
5
1.5
1.0
0.5
0.0
Combination Index
SU-DHL-4
Jeko
Antagonistic
Additive
Synergistic
ED25
ED50
ED75
ED90

FIG. 10

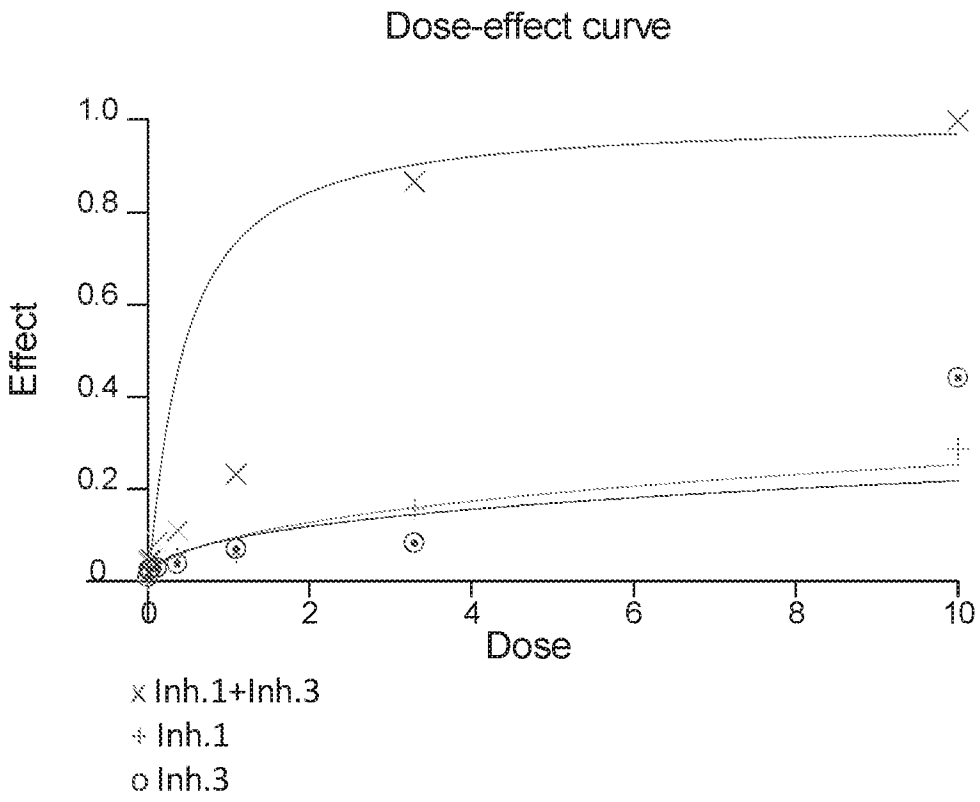

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.1+Inh.3
Inh.1
Inh.3

FIG. 11

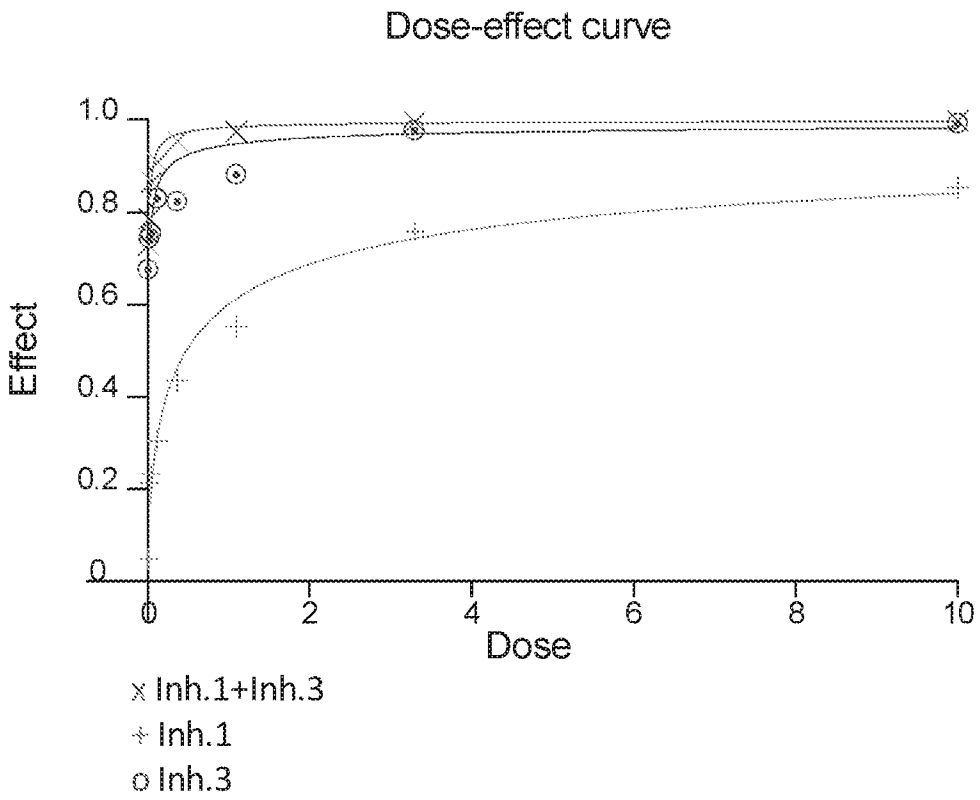

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.1+Inh.3
Inh.1
Inh.3

FIG. 12

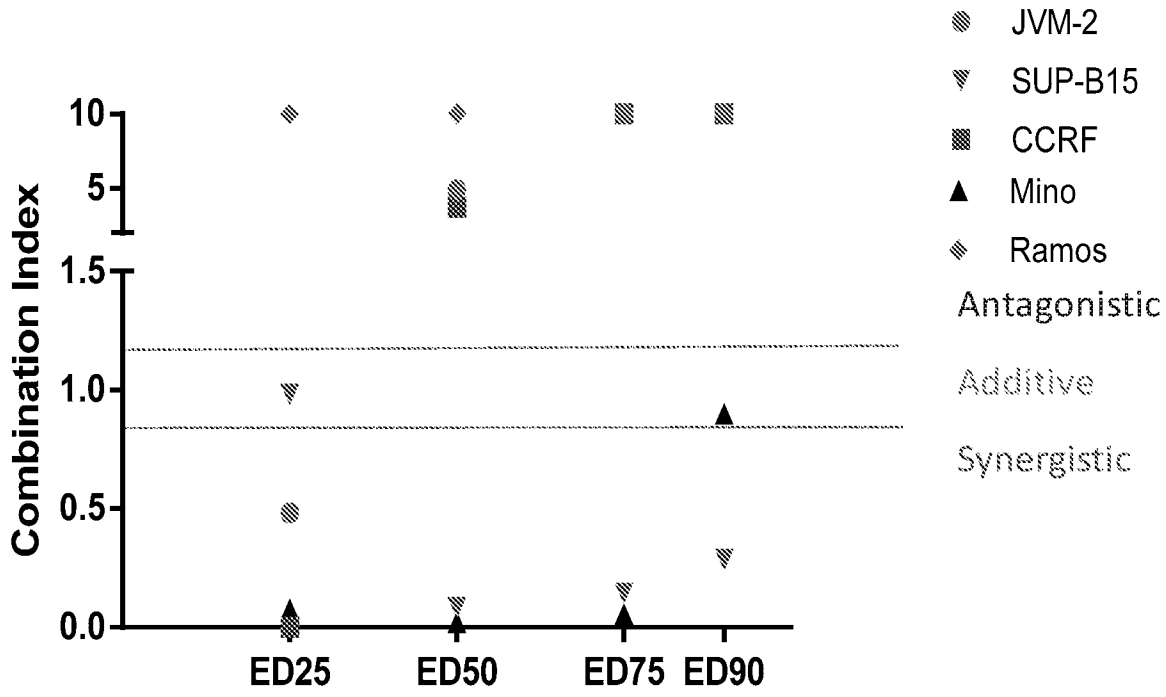

JVM-2
SUP-B15
CCRF
Mino
Ramos
Antagonistic
Additive
Synergistic
Combination Index
10
5
1.5
1.0
0.5
0.0
ED25
ED50
ED75
ED90

FIG. 13

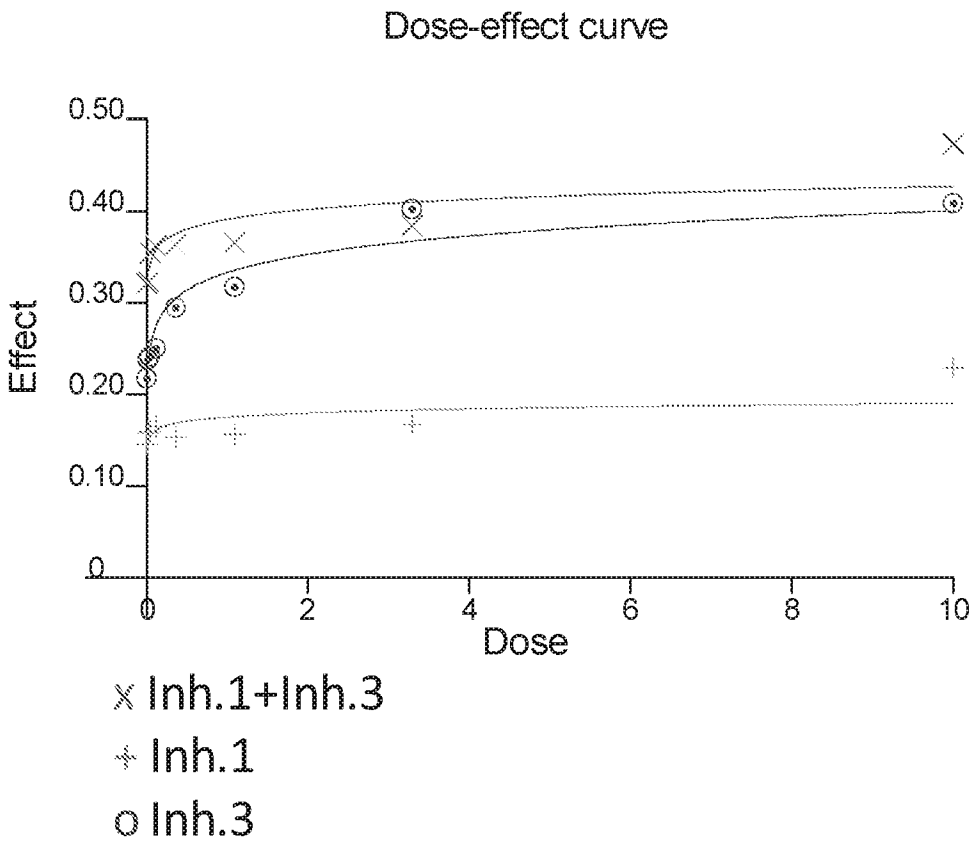

Dose-effect curve
Effect
0.50
0.40
0.30
0.20
0.10
0
0
2
4
6
8
10
Dose
Inh.1+Inh.3
Inh.1
Inh.3

FIG. 14

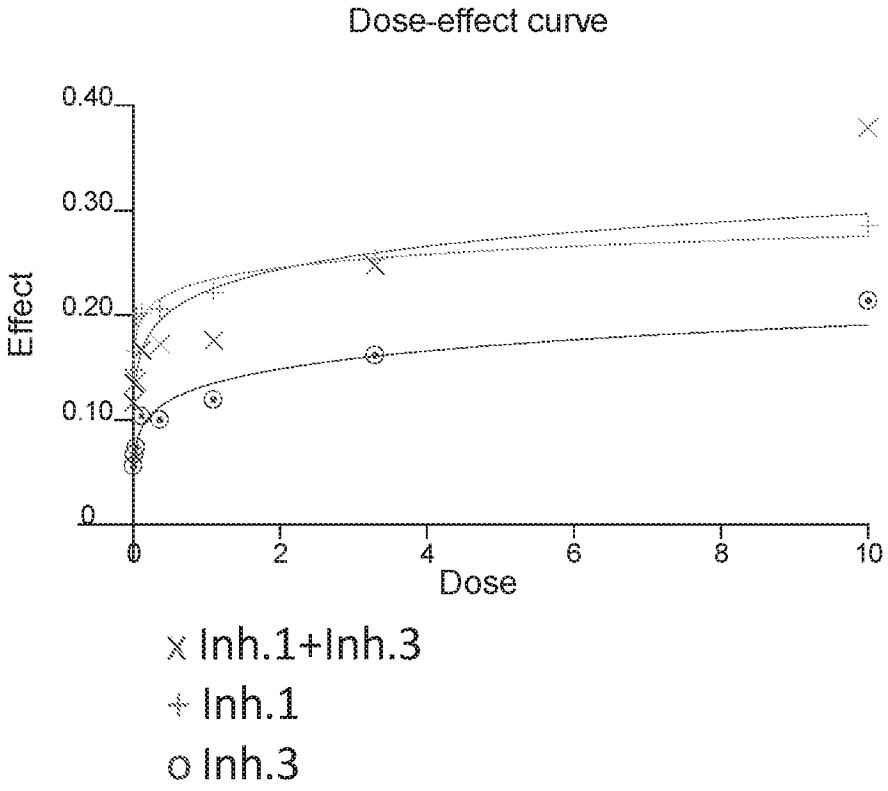

Dose-effect curve
0.40
0.30
0.20
0.10
0
Effect
0
2
4
6
8
10
Dose
Inh.1+Inh.3
Inh.1
Inh.3

FIG. 15

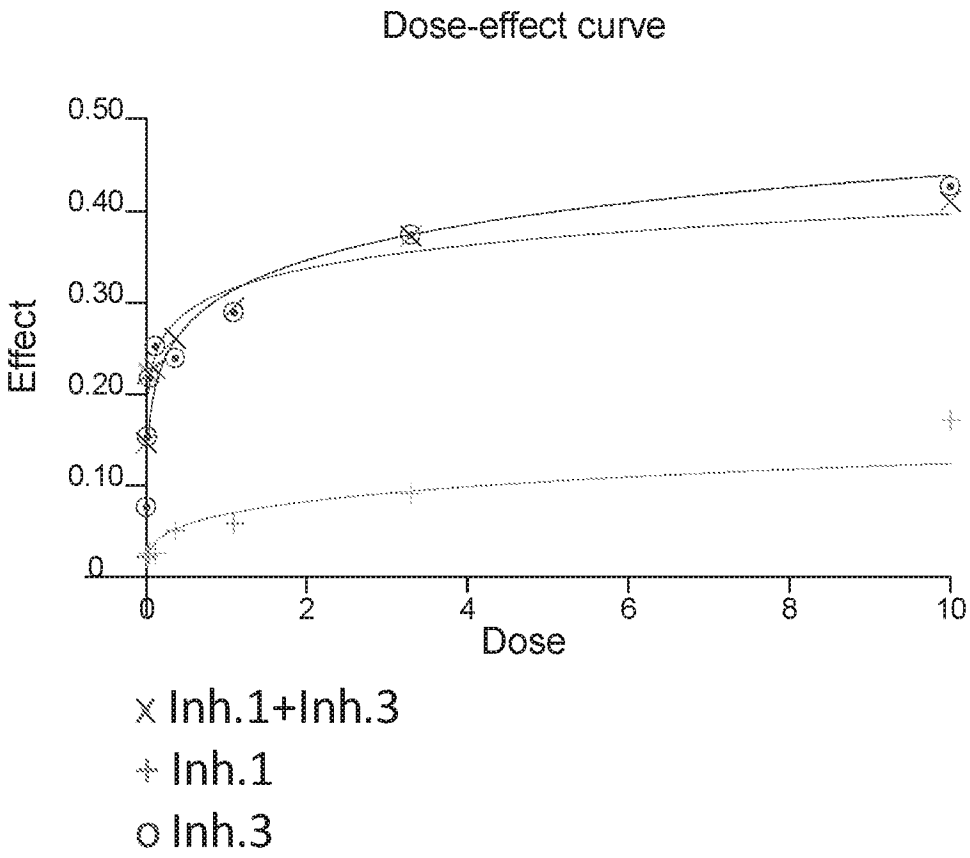

Dose-effect curve
Effect
0.50
0.40
0.30
0.20
0.10
0
0
2
4
6
8
10
Dose
Inh.1+Inh.3
Inh.1
Inh.3

FIG. 16

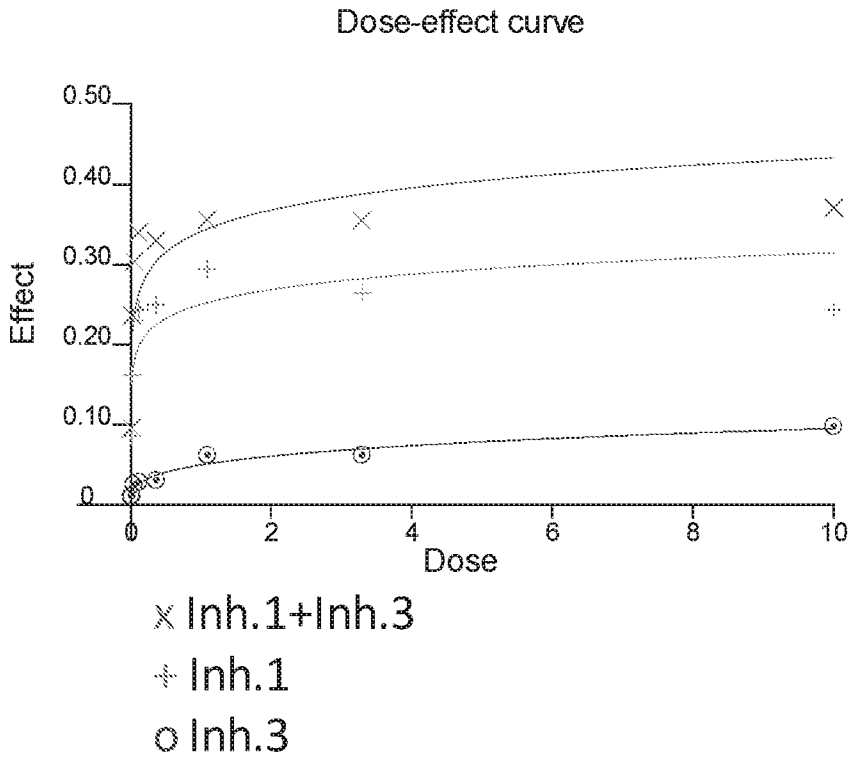

Dose-effect curve
Effect
0.50
0.40
0.30
0.20
0.10
0
0
2
4
6
8
10
Dose
Inh.1+Inh.3
Inh.1
Inh.3

FIG. 17

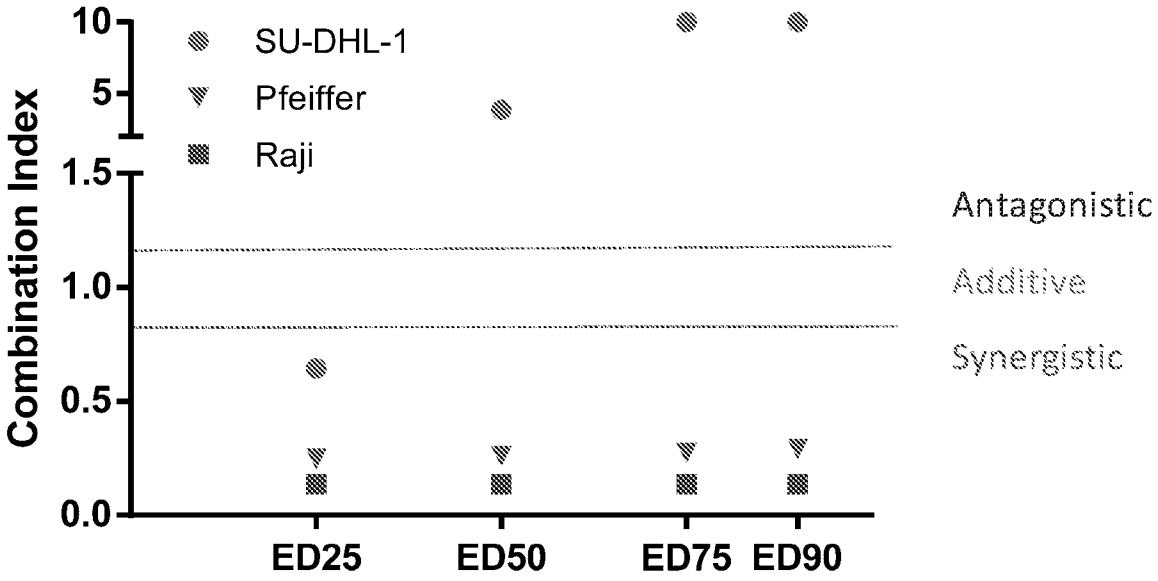

Combination Index
10
5
1.5
1.0
0.5
0.0
SU-DHL-1
Pfeiffer
Raji
Antagonistic
Additive
Synergistic
ED25
ED50
ED75
ED90

FIG. 18

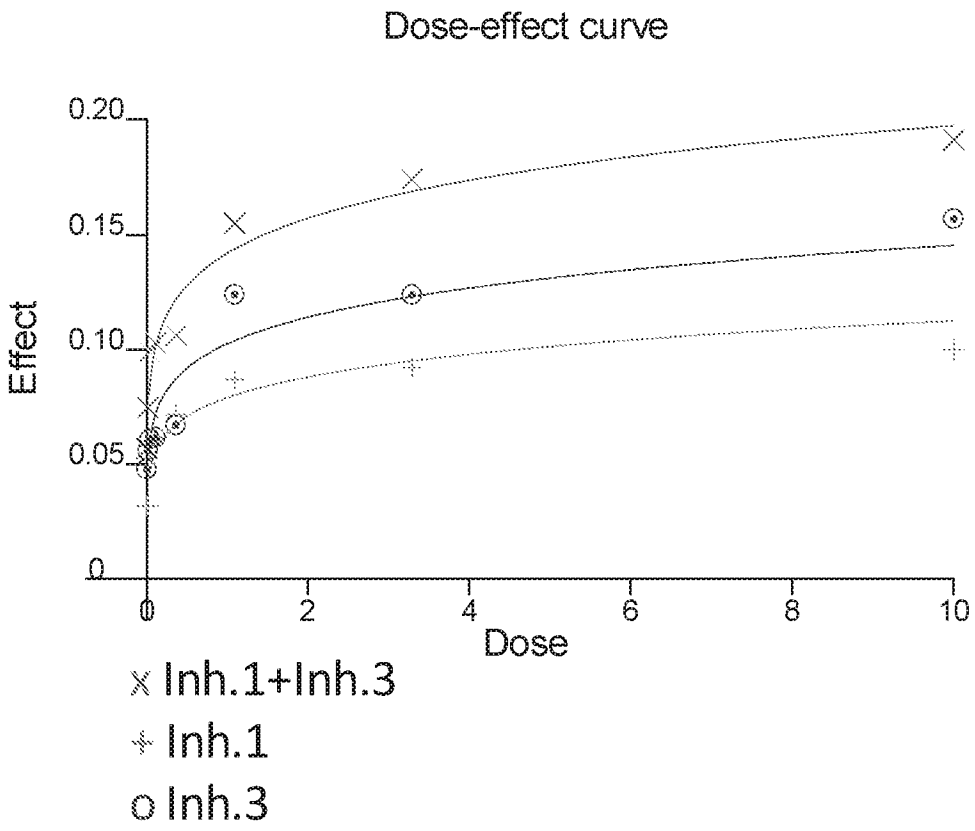

Dose-effect curve
Effect
0.20
0.15
0.10
0.05
0
0
2
4
6
8
10
Dose
Inh.1+Inh.3
Inh.1
Inh.3

FIG. 19

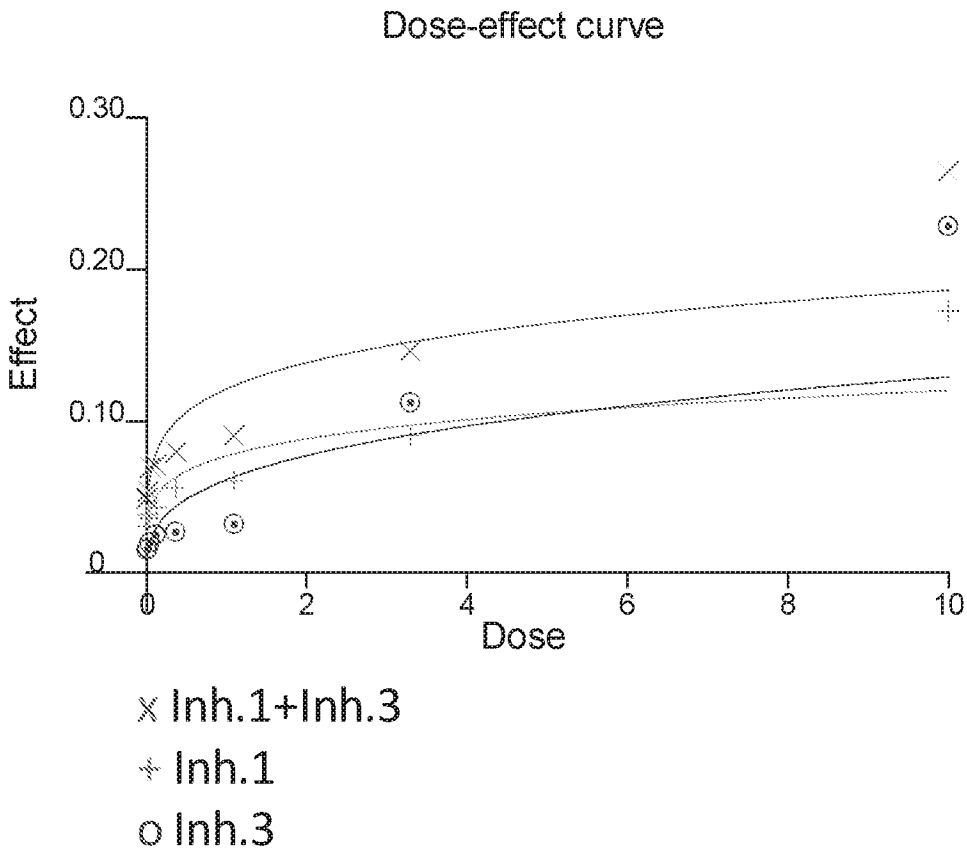

Dose-effect curve
0.30
0.20
0.10
0
Effect
0
2
4
6
8
10
Dose
Inh.1+Inh.3
Inh.1
Inh.3

FIG. 20

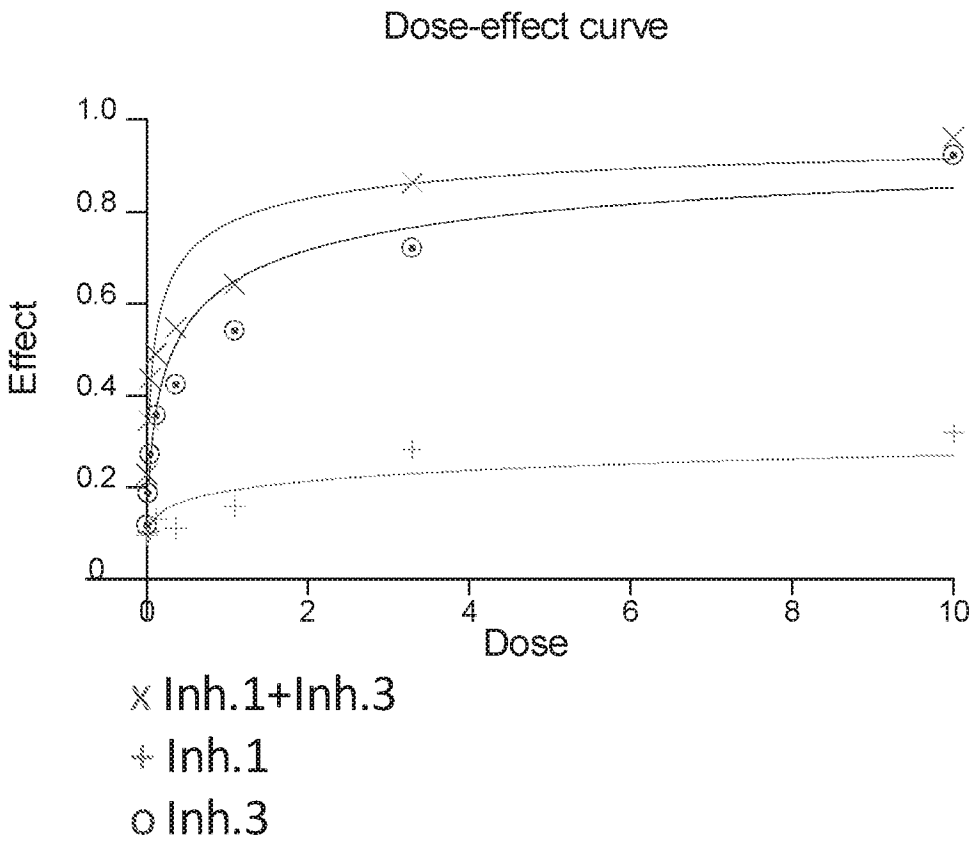

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.1+Inh.3
Inh.1
Inh.3

FIG. 21

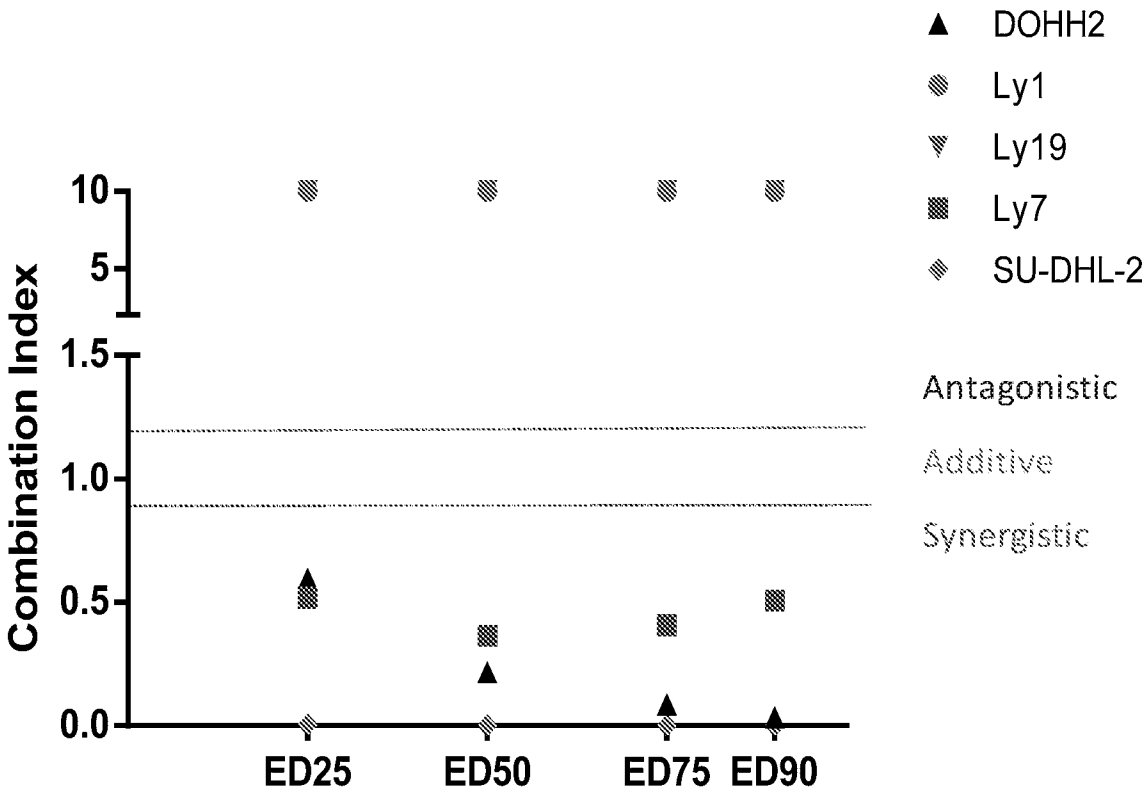

DOHH2
Ly1
Ly19
Ly7
SU-DHL-2
Antagonistic
Additive
Synergistic
Combination Index
10
5
1.5
1.0
0.5
0.0
ED25
ED50
ED75
ED90

FIG. 22

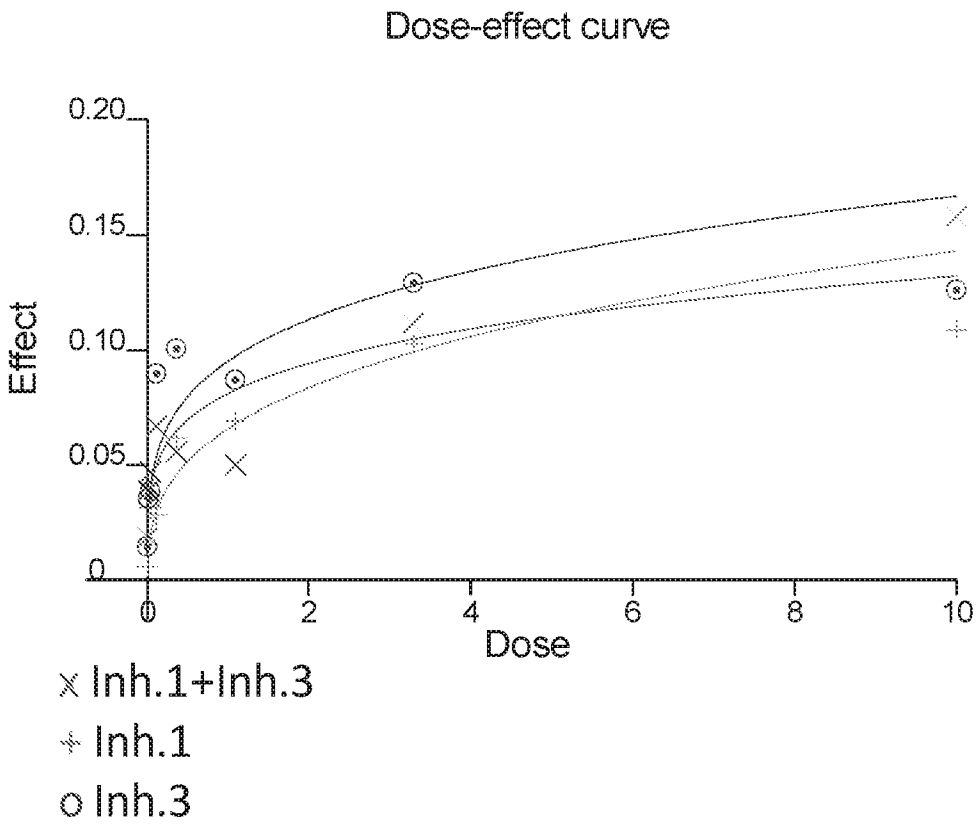

Dose-effect curve
Effect
0.20
0.15
0.10
0.05
0
0
2
4
6
8
10
Dose
Inh.1+Inh.3
Inh.1
Inh.3

FIG. 23

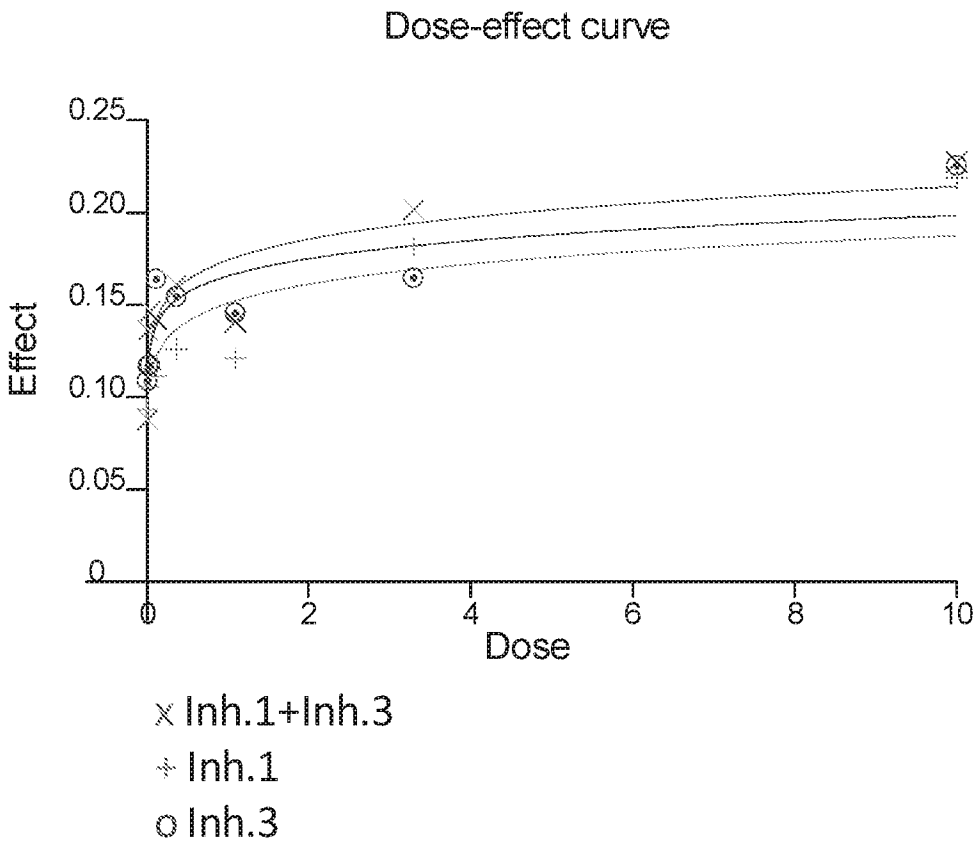

Dose-effect curve
Effect
0.25
0.20
0.15
0.10
0.05
0
0
2
4
6
8
10
Dose
Inh.1+Inh.3
Inh.1
Inh.3

FIG. 24

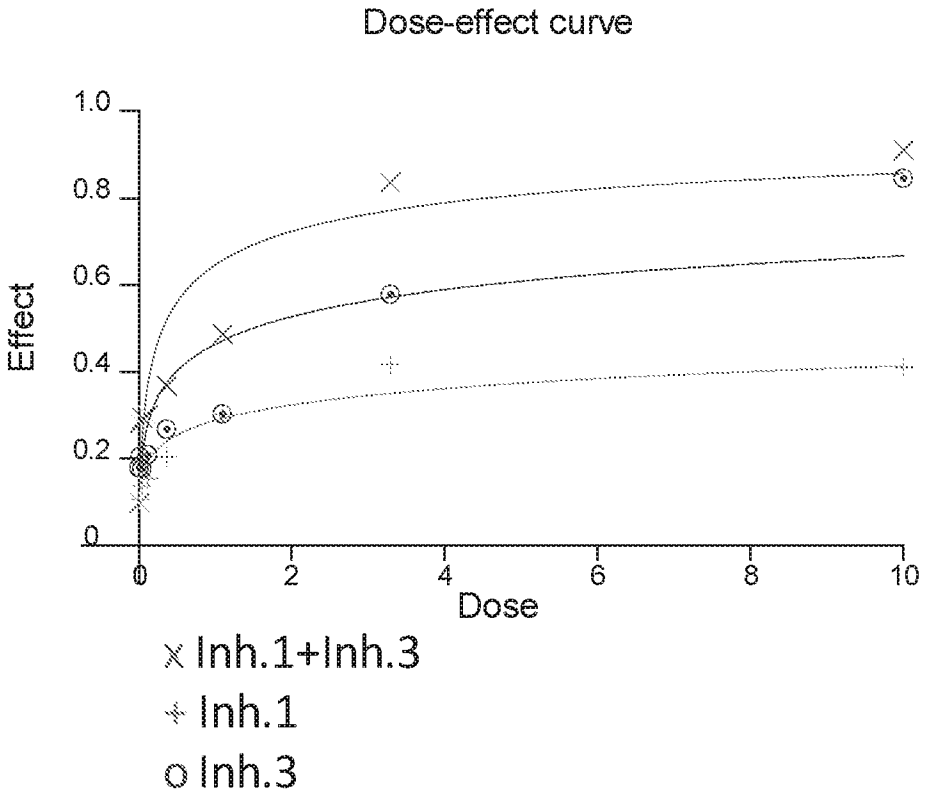

Dose-effect curve
1.0
0.8
0.6
0.4
0.2
0
Effect
0
2
4
6
8
10
Dose
Inh.1+Inh.3
Inh.1
Inh.3

FIG. 25

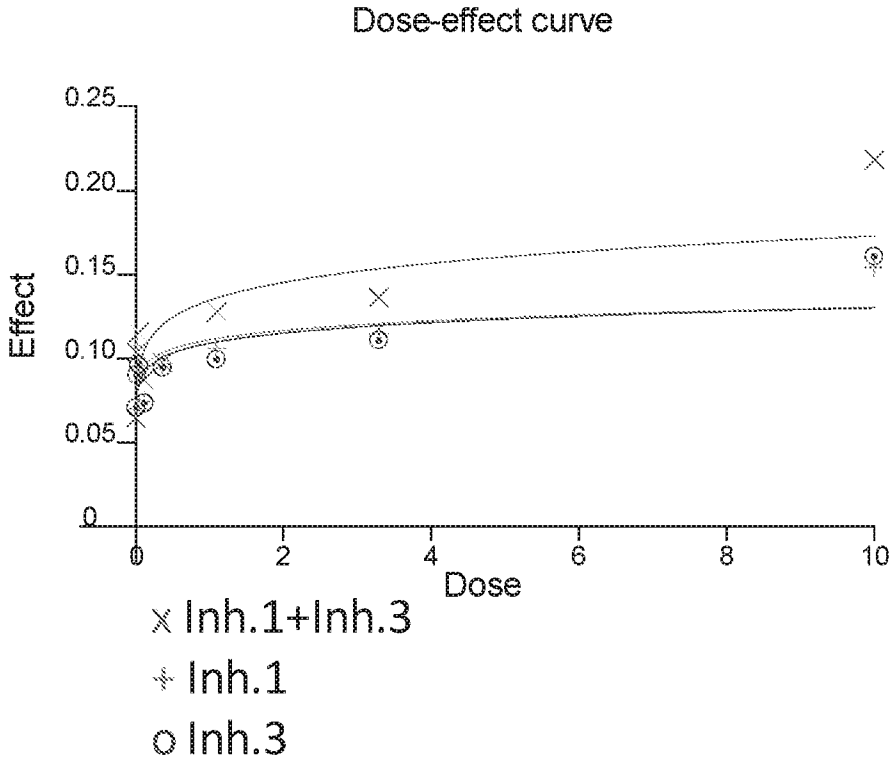

Dose-effect curve
Effect
0.25
0.20
0.15
0.10
0.05
0
0
2
4
6
8
10
Dose
Inh.1+Inh.3
Inh.1
Inh.3

FIG. 26

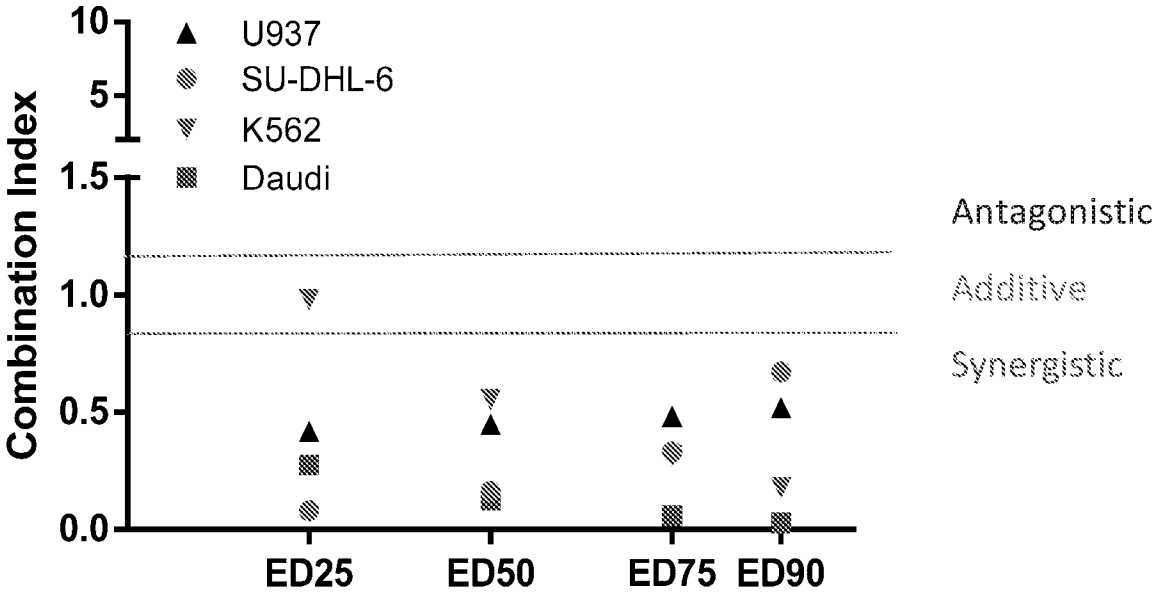

10
5
1.5
1.0
0.5
0.0
Combination Index
U937
SU-DHL-6
K562
Daudi
Antagonistic
Additive
Synergistic
ED25
ED50
ED75
ED90

FIG. 27

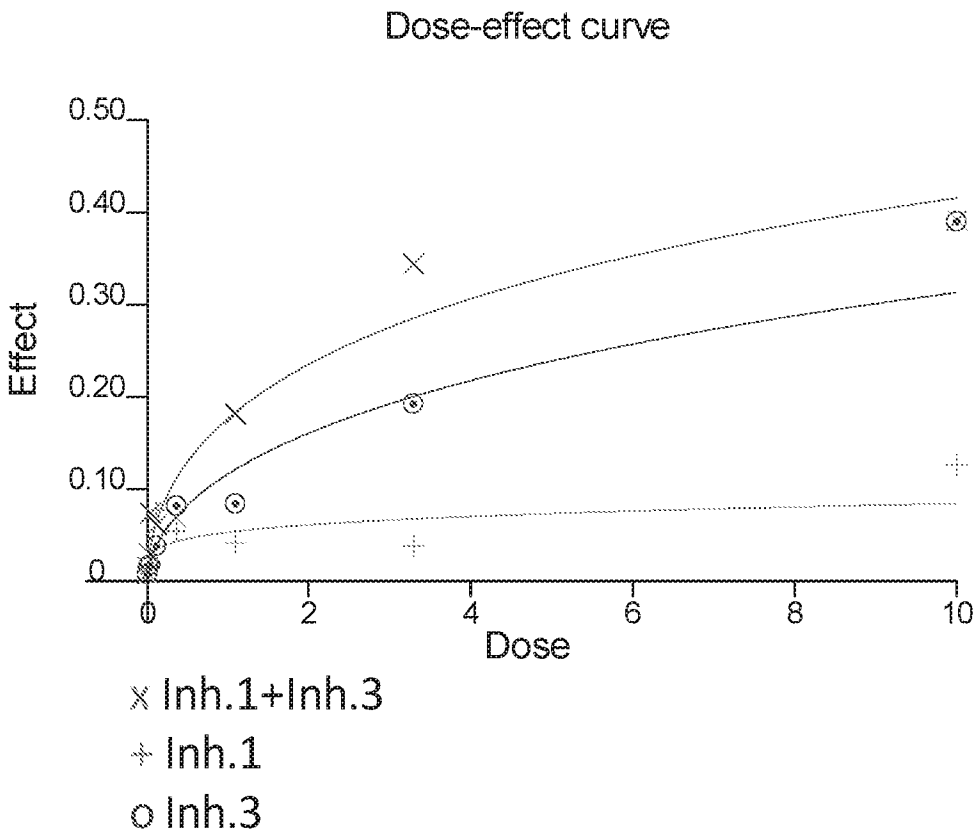

Dose-effect curve
Effect
0.50
0.40
0.30
0.20
0.10
0
0
2
4
6
8
10
Dose
Inh.1+Inh.3
Inh.1
Inh.3

FIG. 28

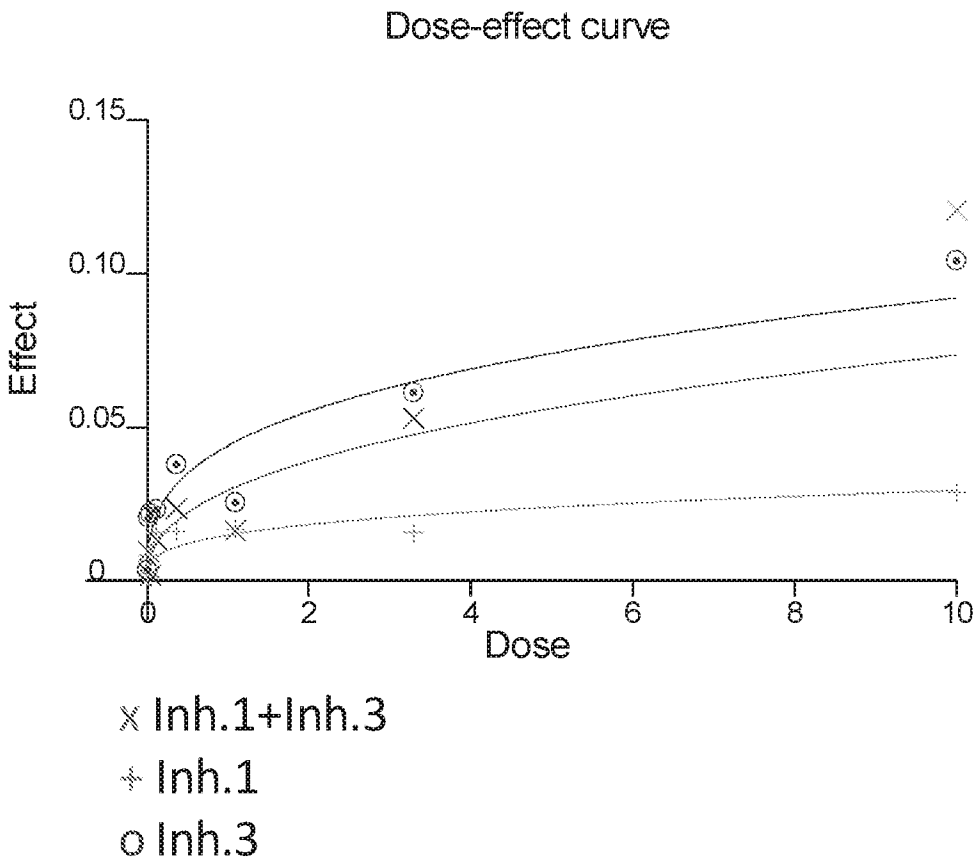

Dose-effect curve
0.15
0.10
0.05
0
Effect
0
2
4
6
8
10
Dose
Inh.1+Inh.3
Inh.1
Inh.3

FIG. 29

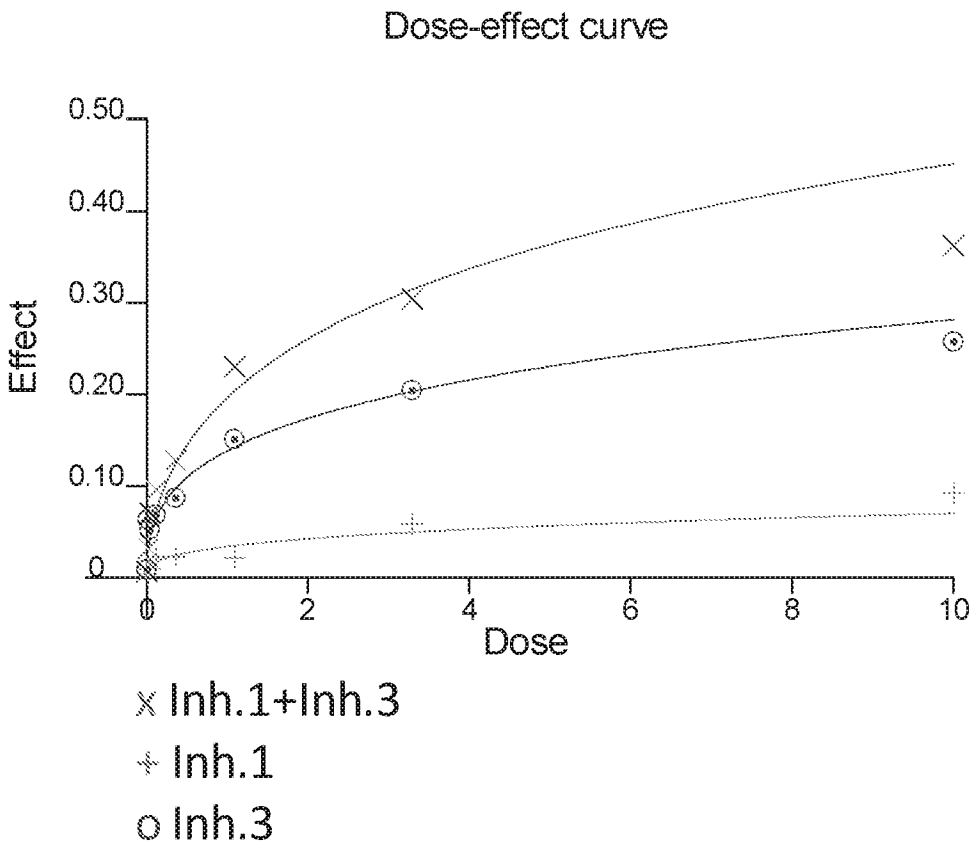

Dose-effect curve
Effect
0.50
0.40
0.30
0.20
0.10
0
0
2
4
6
8
10
Dose
Inh.1+Inh.3
Inh.1
Inh.3

FIG. 30

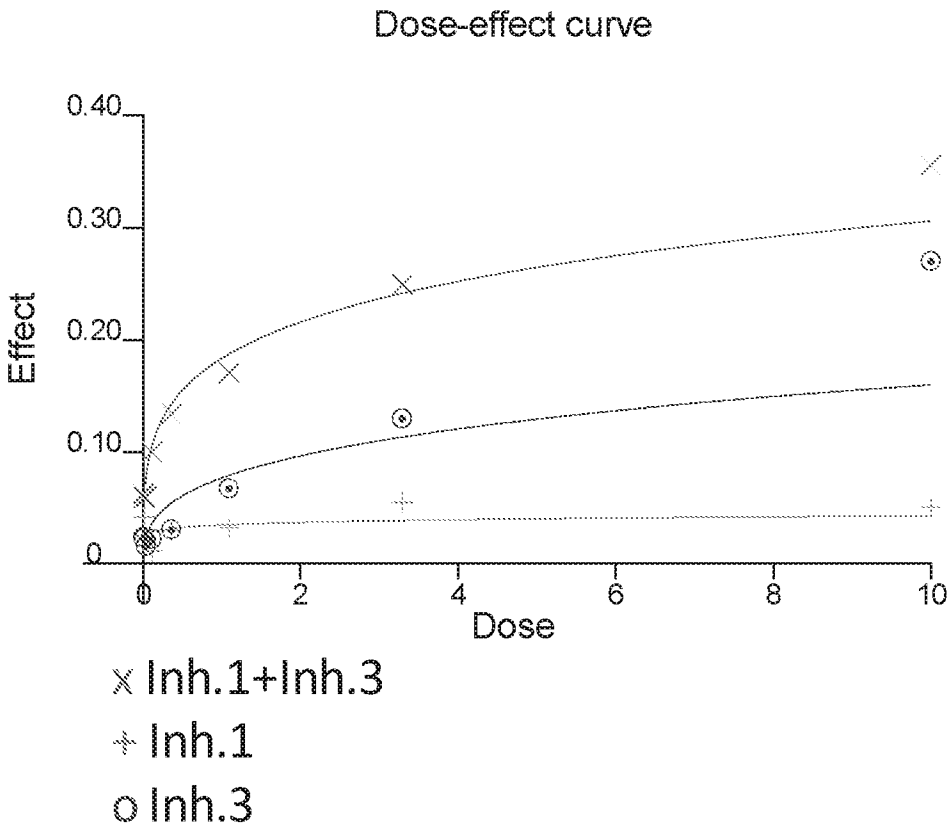



FIG. 31

Rec-1:Follicular lymphoma

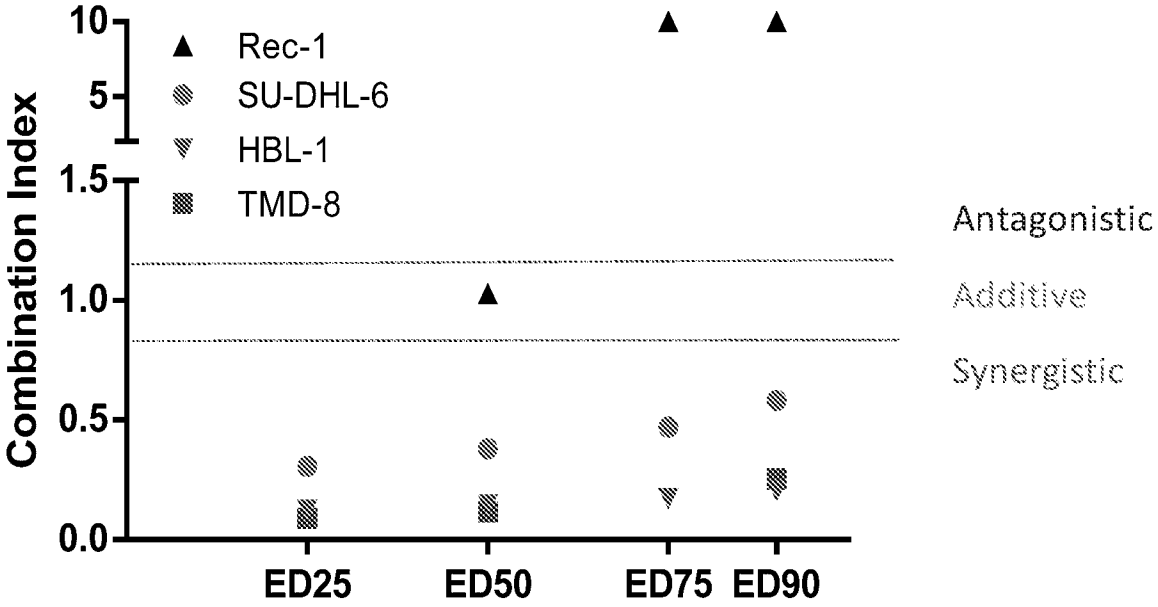

Combination Index
10
5
1.5
1.0
0.5
0.0
Rec-1
SU-DHL-6
HBL-1
TMD-8
Antagonistic
Additive
Synergistic
ED25
ED50
ED75
ED90

FIG. 32

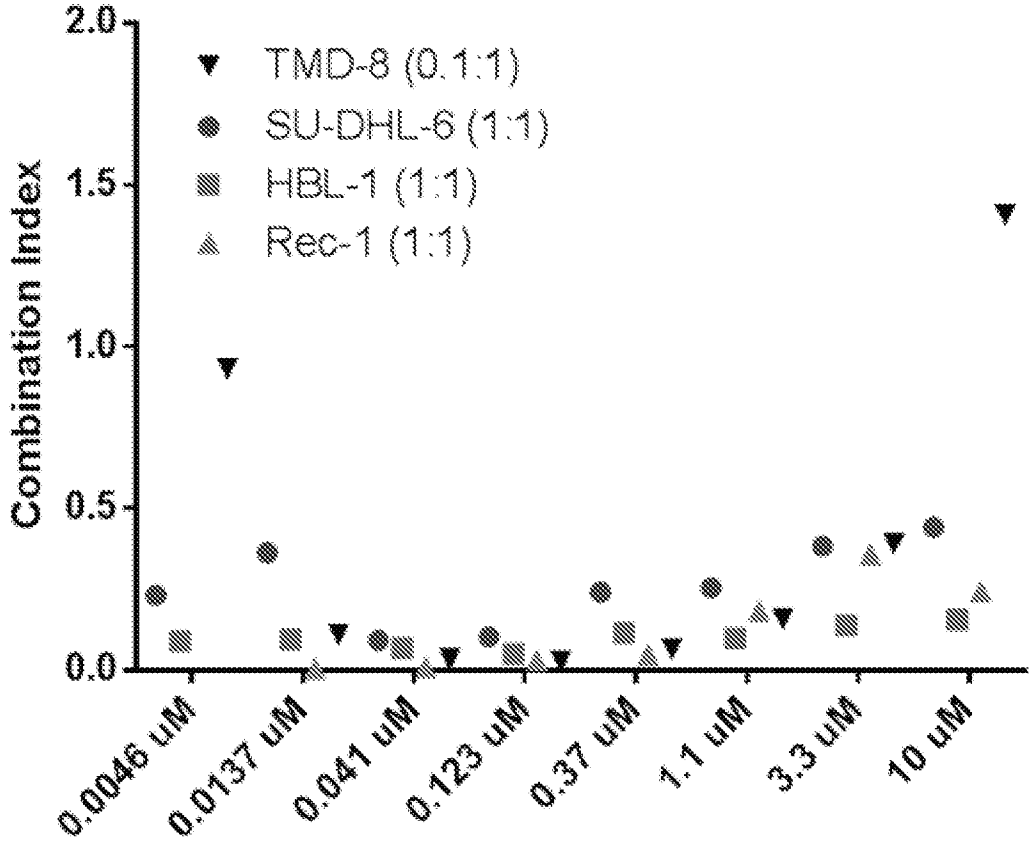

Combination Index
2.0
1.5
1.0
0.5
0.0
TMD-8 (0.1:1)
SU-DHL-6 (1:1)
HBL-1 (1:1)
Rec-1 (1:1)
0.0046 uM
0.0137 uM
0.041 uM
0.123 uM
0.37 uM
1.1 uM
3.3 uM
10 uM

FIG. 33

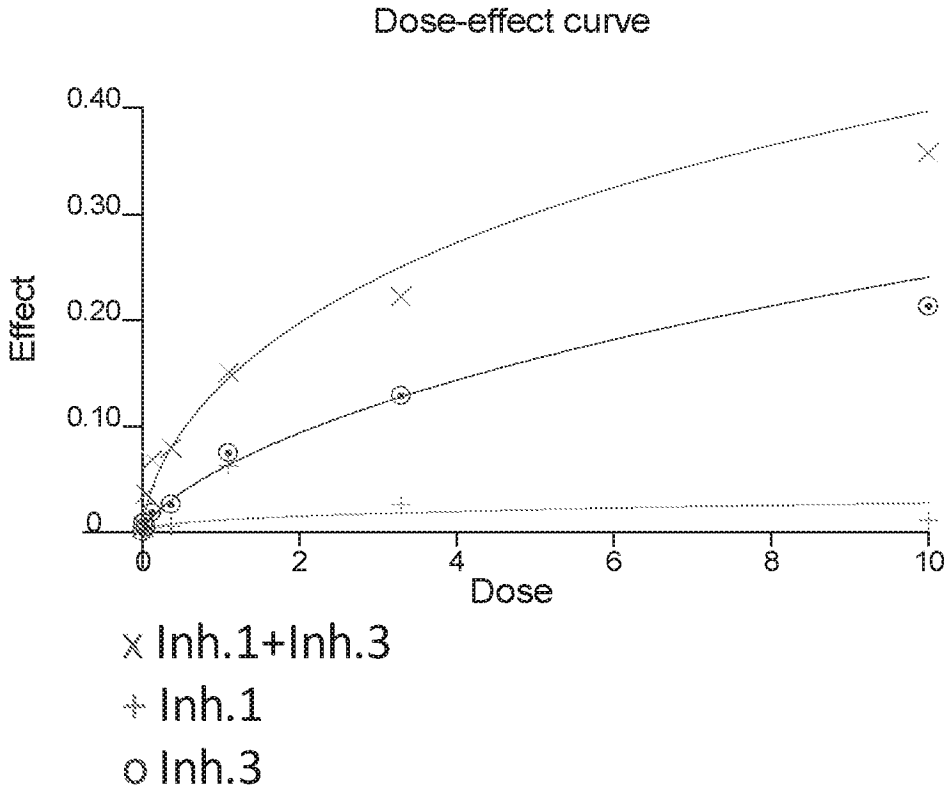

Dose-effect curve
Effect
0.40
0.30
0.20
0.10
0
0
2
4
6
8
10
Dose
Inh.1+Inh.3
Inh.1
Inh.3

FIG. 34

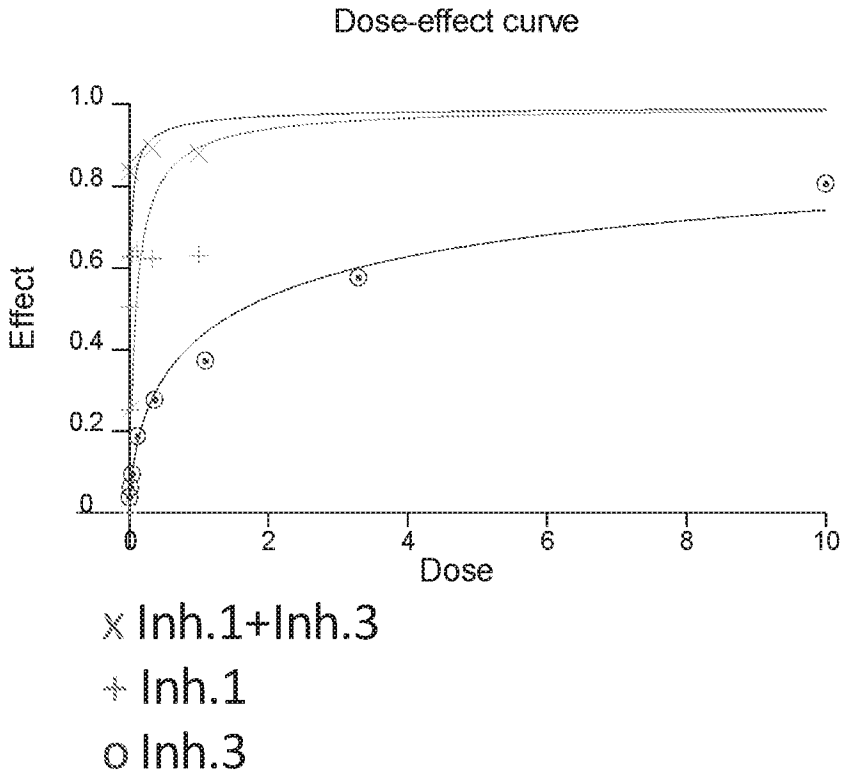

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.1+Inh.3
Inh.1
Inh.3

FIG. 35

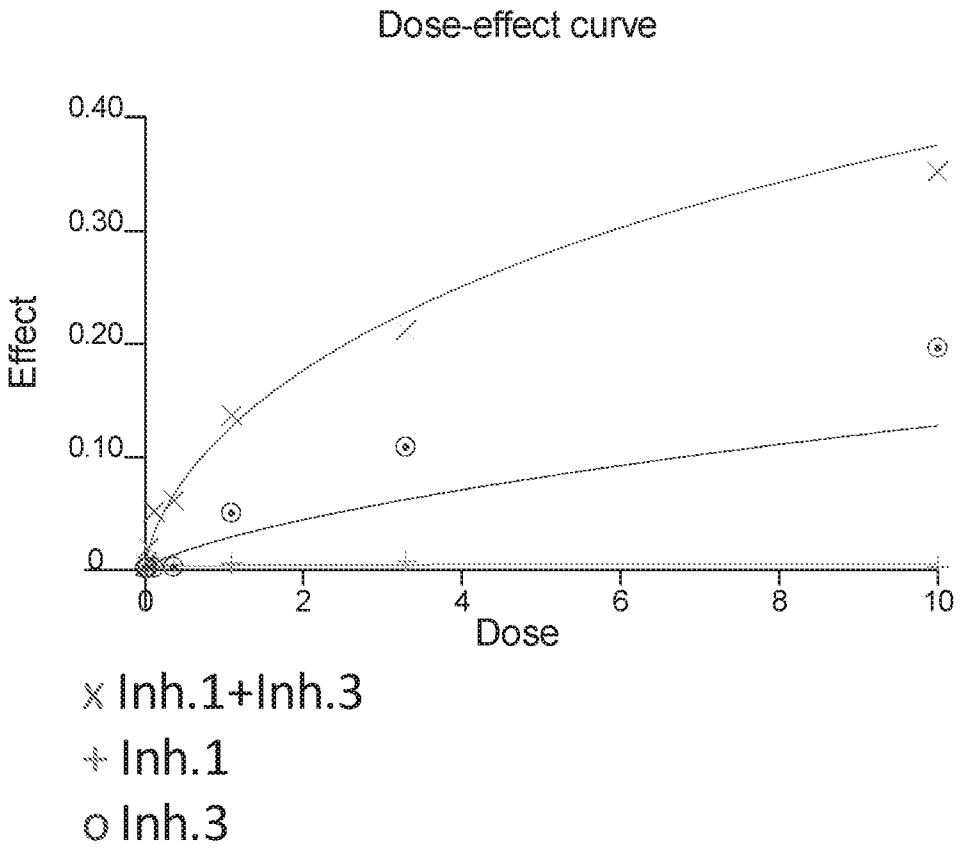

Dose-effect curve
0.40
0.30
0.20
0.10
0
Effect
0
2
4
6
8
10
Dose
Inh.1+Inh.3
Inh.1
Inh.3

FIG. 36

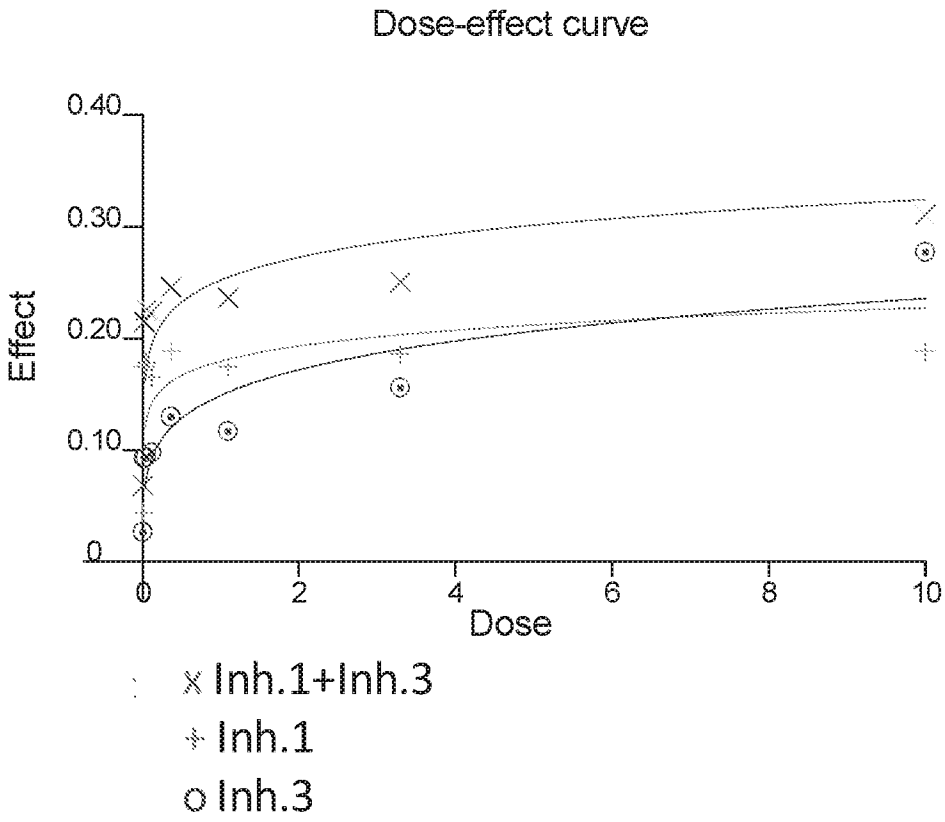

Dose-effect curve
Effect
0.40
0.30
0.20
0.10
0
0
2
4
6
8
10
Dose
Inh.1+Inh.3
Inh.1
Inh.3

FIG. 37

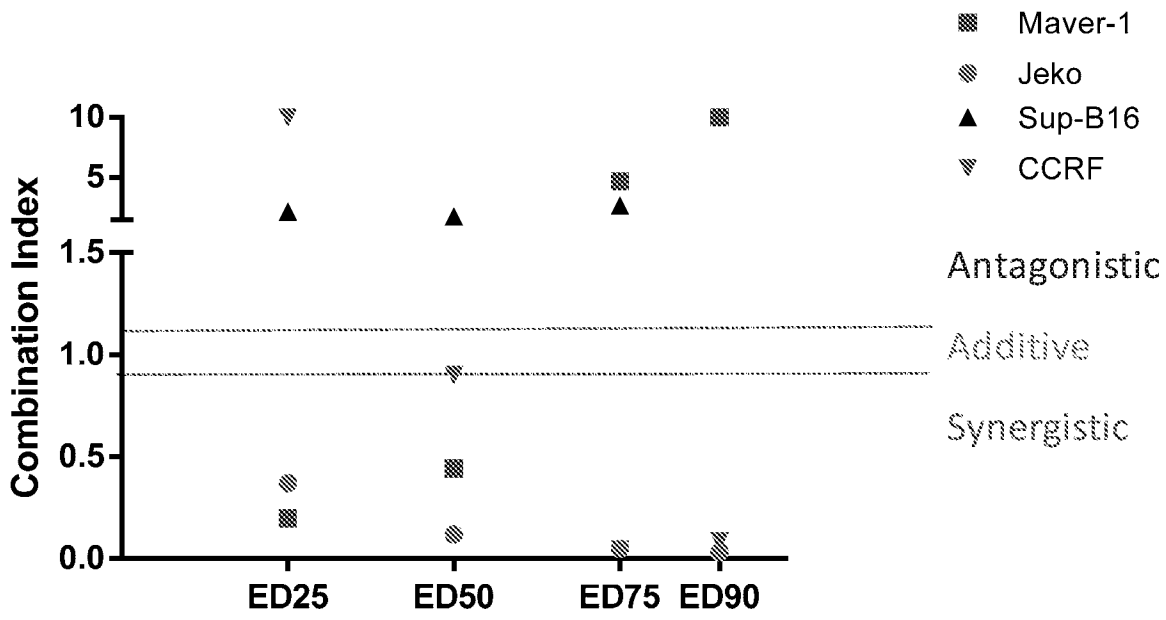

Maver-1
Jeko
Sup-B16
CCRF
Combination Index
10
5
1.5
1.0
0.5
0.0
Antagonistic
Additive
Synergistic
ED25
ED50
ED75
ED90

FIG. 38

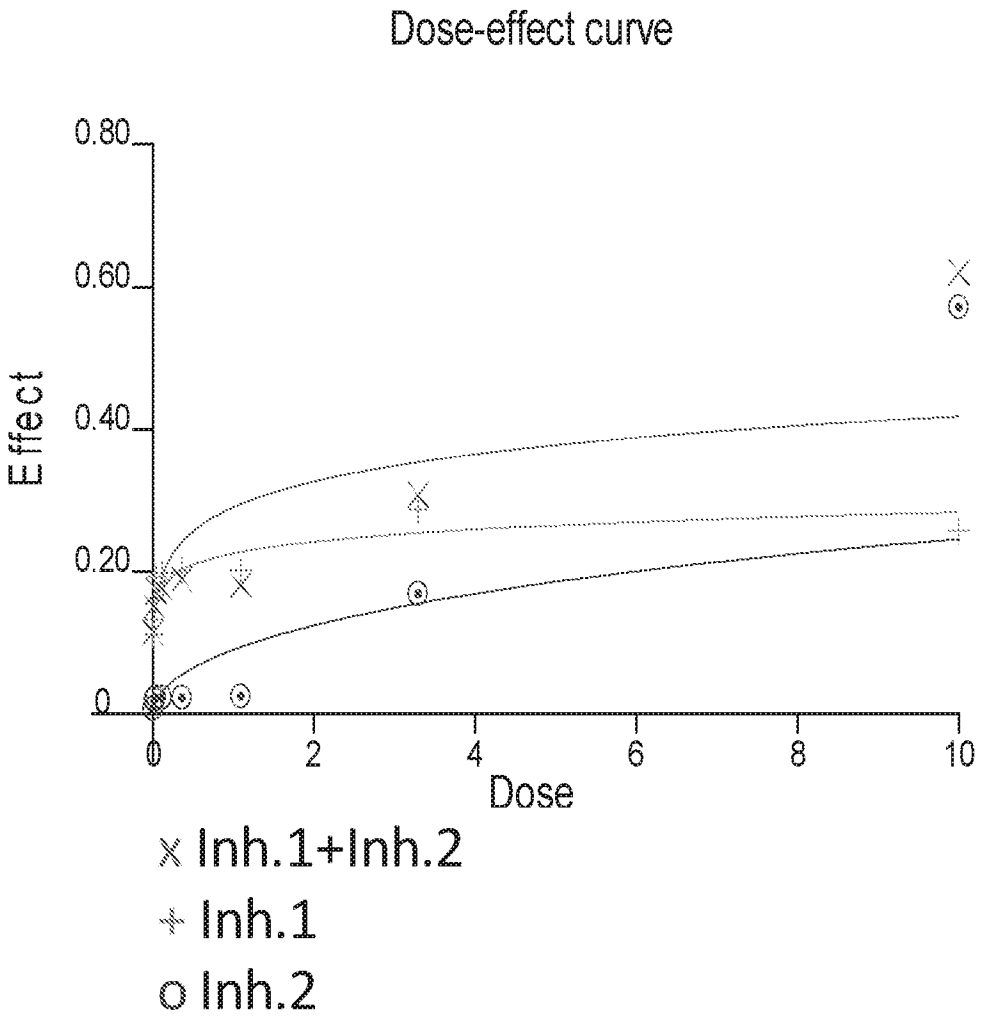

Dose-effect curve
Effect
0.80
0.60
0.40
0.20
0
0
2
4
6
8
10
Dose
Inh.1+Inh.2
Inh.1
Inh.2

FIG. 39

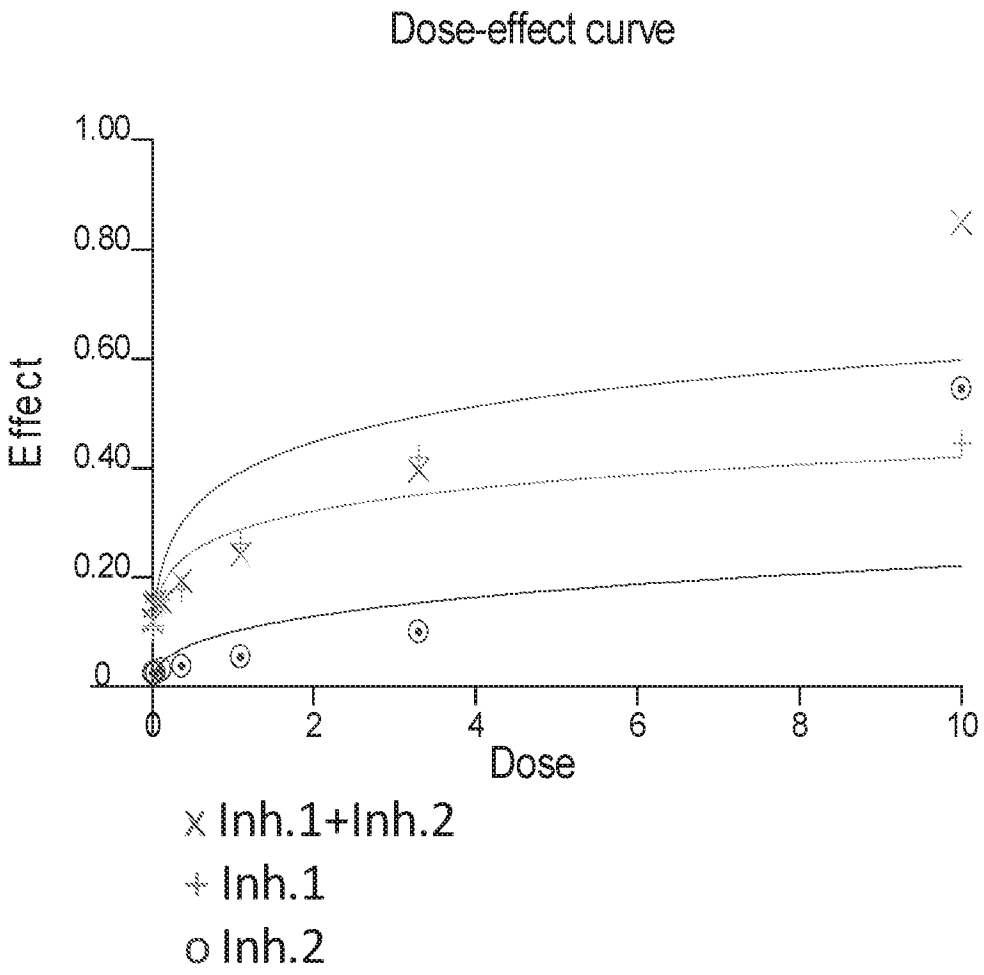

Dose-effect curve
1.00
0.80
0.60
0.40
0.20
0
Effect
0
2
4
6
8
10
Dose
Inh.1+Inh.2
Inh.1
Inh.2

FIG. 40

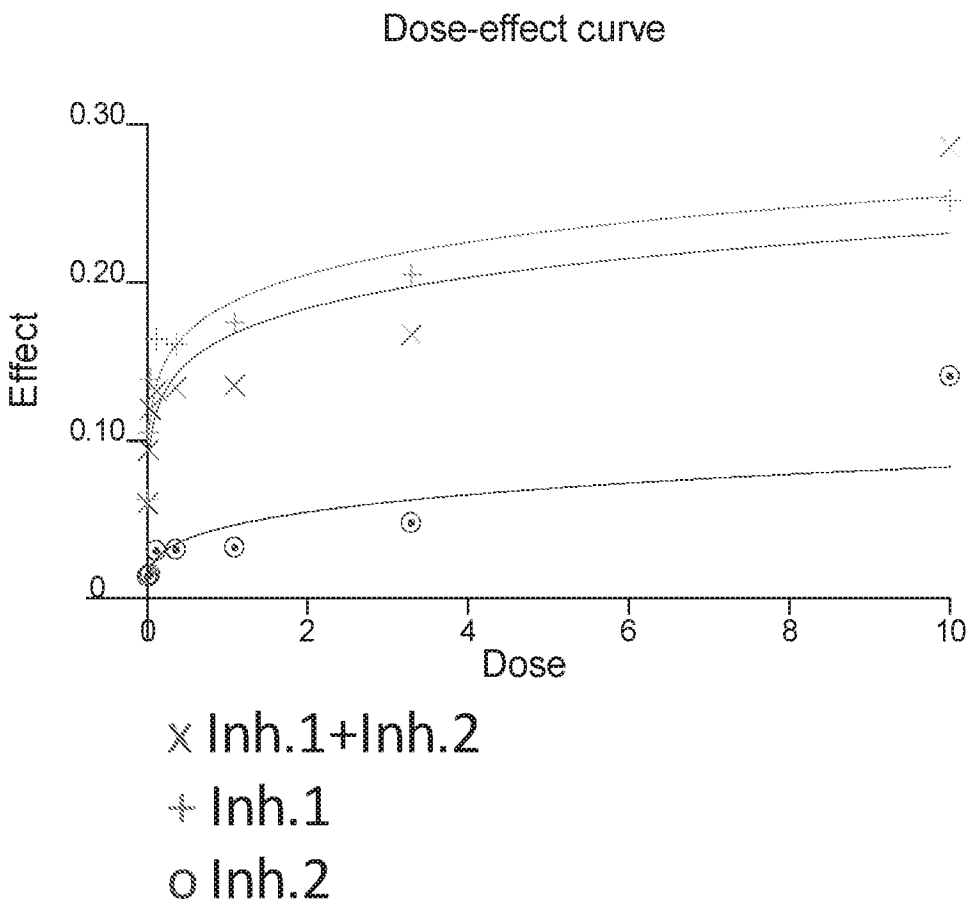

Dose-effect curve
0.30
0.20
0.10
0
Effect
0
2
4
6
8
10
Dose
Inh.1+Inh.2
Inh.1
Inh.2

FIG. 41

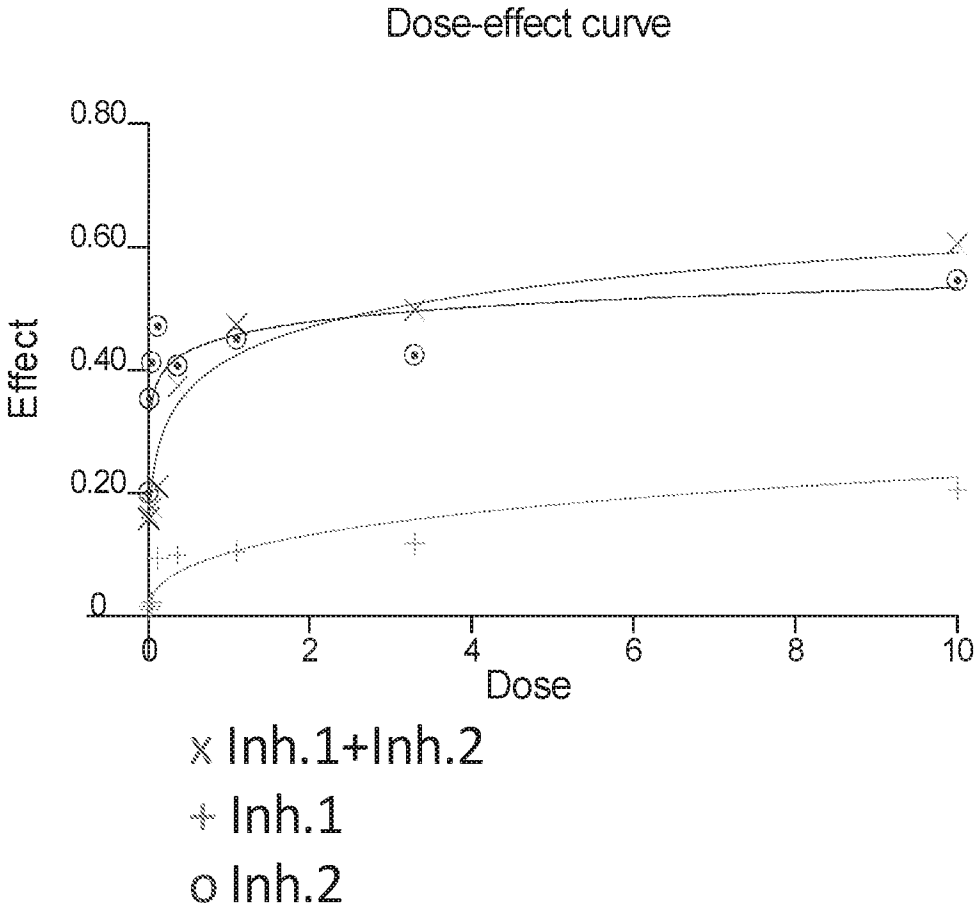

Dose-effect curve
Effect
0.80
0.60
0.40
0.20
0
0
2
4
6
8
10
Dose
x Inh.1+Inh.2
+ Inh.1
o Inh.2

FIG. 42

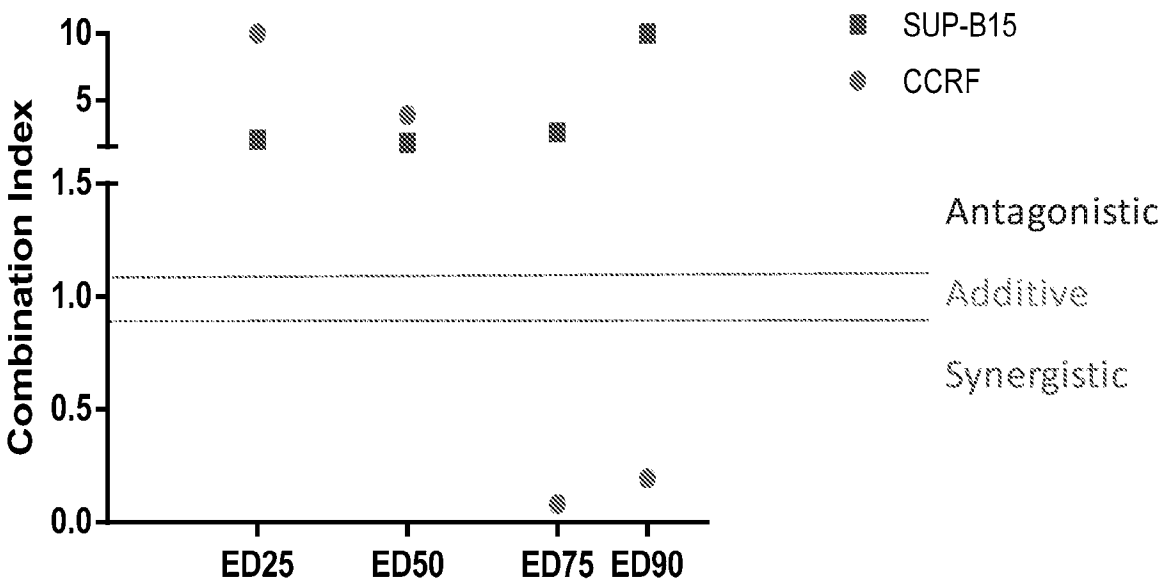

Combination Index
10
5
1.5
1.0
0.5
0.0
ED25
ED50
ED75
ED90
SUP-B15
CCRF
Antagonistic
Additive
Synergistic

FIG. 43

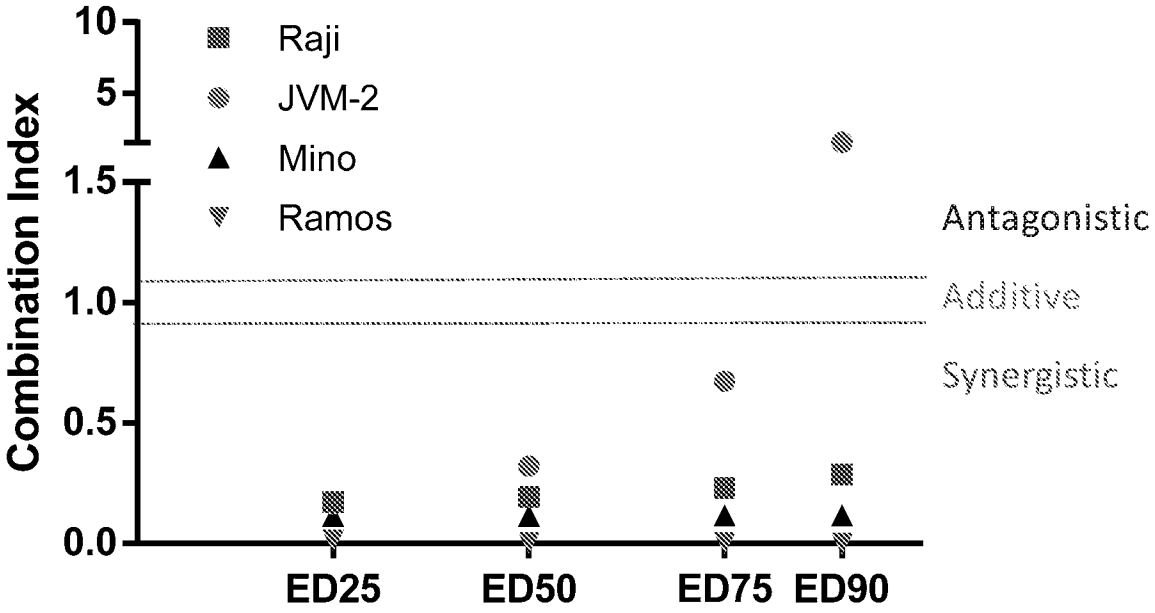

Combination Index
10
5
1.5
1.0
0.5
0.0
Raji
JVM-2
Mino
Ramos
Antagonistic
Additive
Synergistic
ED25
ED50
ED75
ED90

FIG. 44

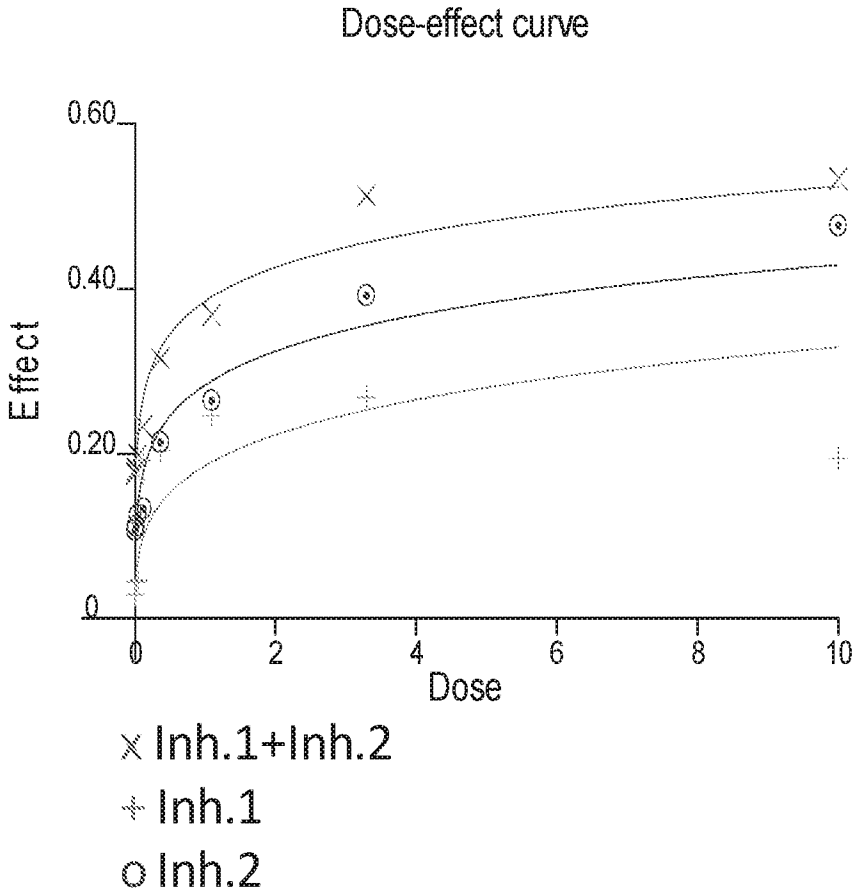

Dose-effect curve
0.60
0.40
0.20
0
Effect
0
2
4
6
8
10
Dose
Inh.1+Inh.2
Inh.1
Inh.2

FIG. 45

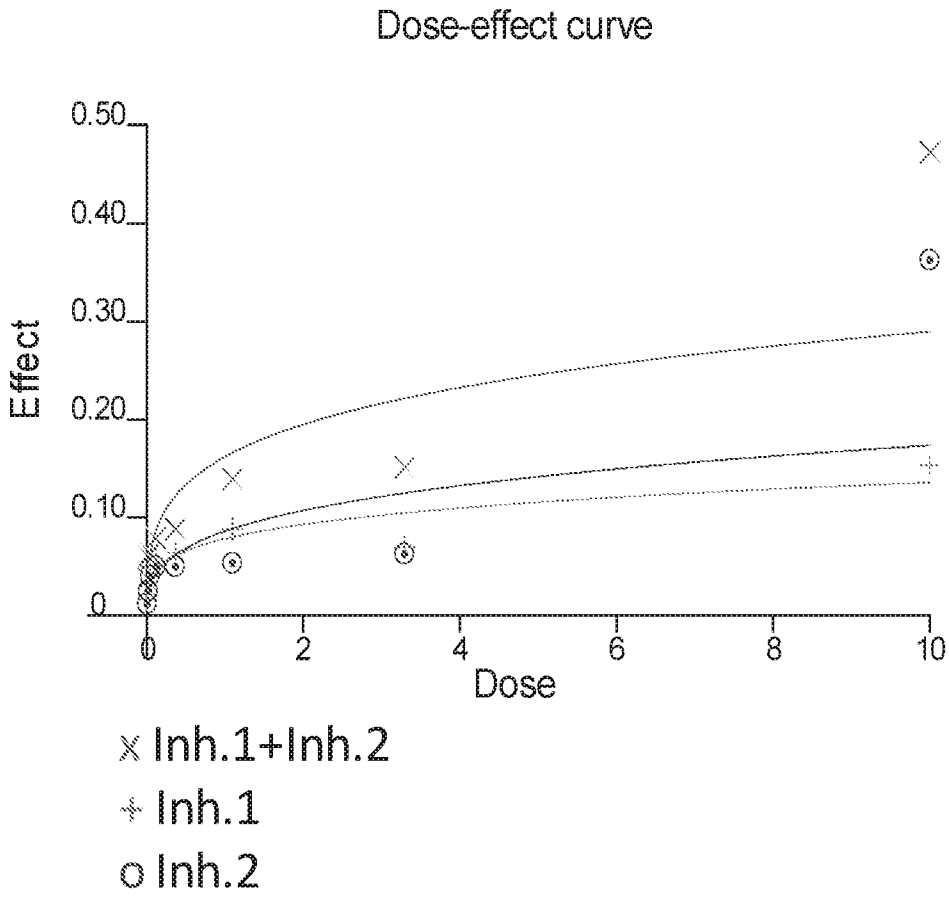

Dose-effect curve
Effect
0.50
0.40
0.30
0.20
0.10
0
0
2
4
6
8
10
Dose
Inh.1+Inh.2
Inh.1
Inh.2

FIG. 46

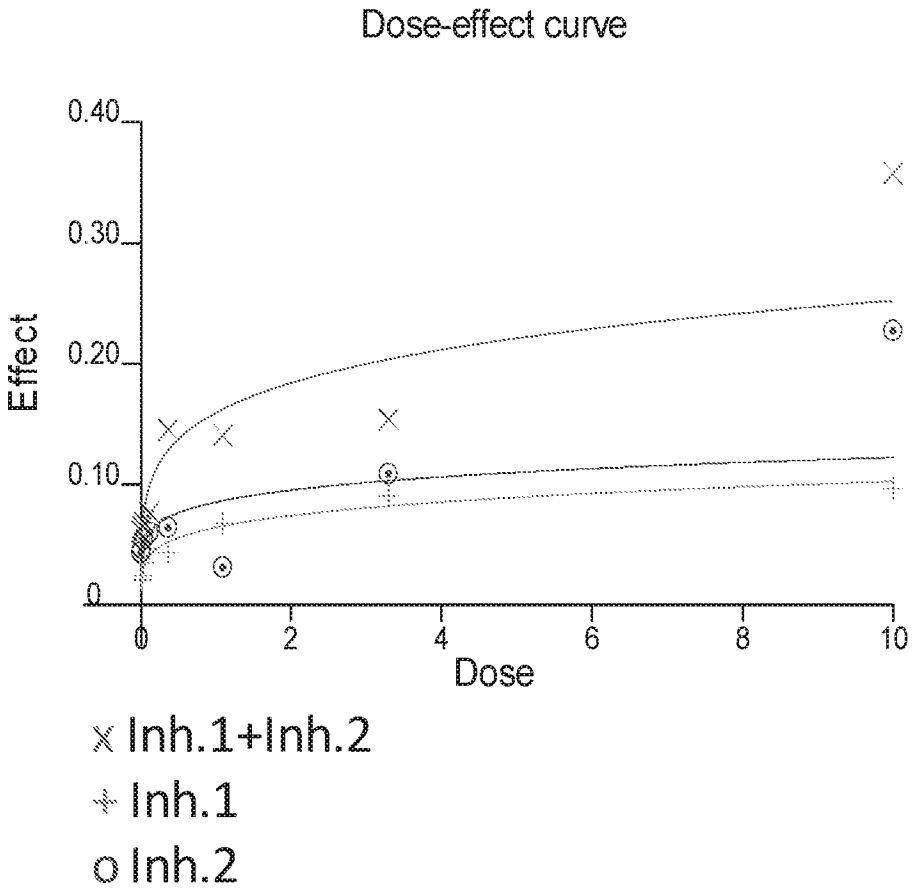

Dose-effect curve
0.40
0.30
0.20
0.10
0
Effect
0
2
4
6
8
10
Dose
Inh.1+Inh.2
Inh.1
Inh.2

FIG. 47

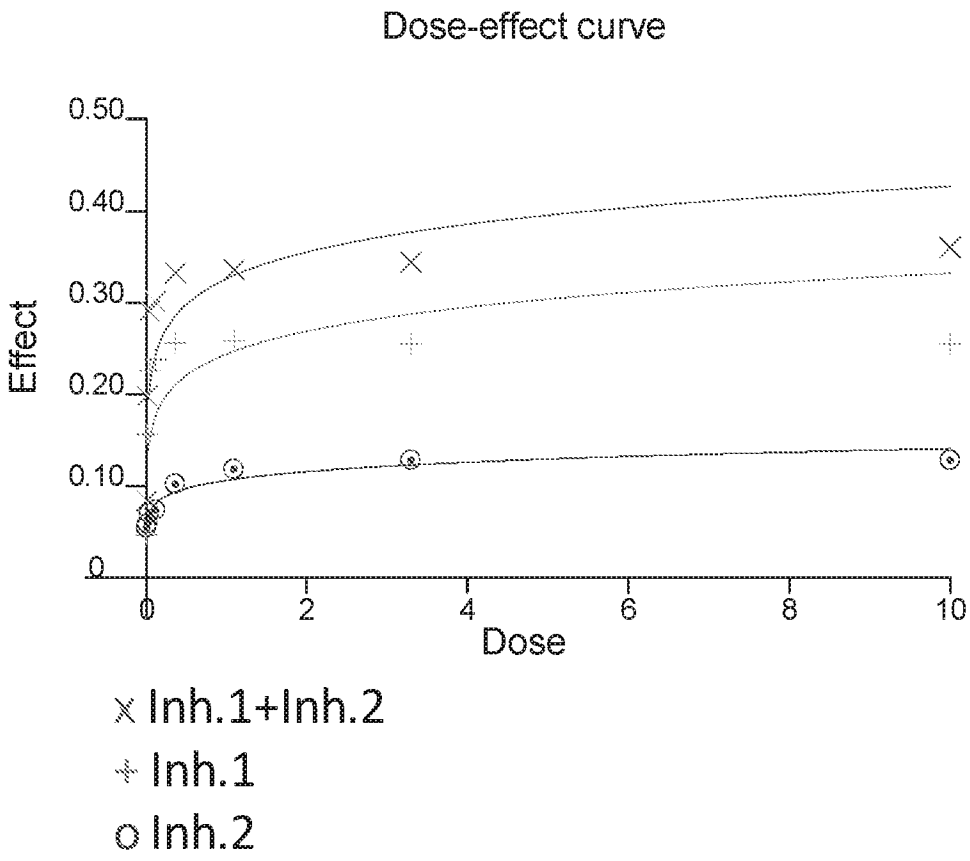

Dose-effect curve
Effect
0.50
0.40
0.30
0.20
0.10
0
0
2
4
6
8
10
Dose
Inh.1+Inh.2
Inh.1
Inh.2

FIG. 48

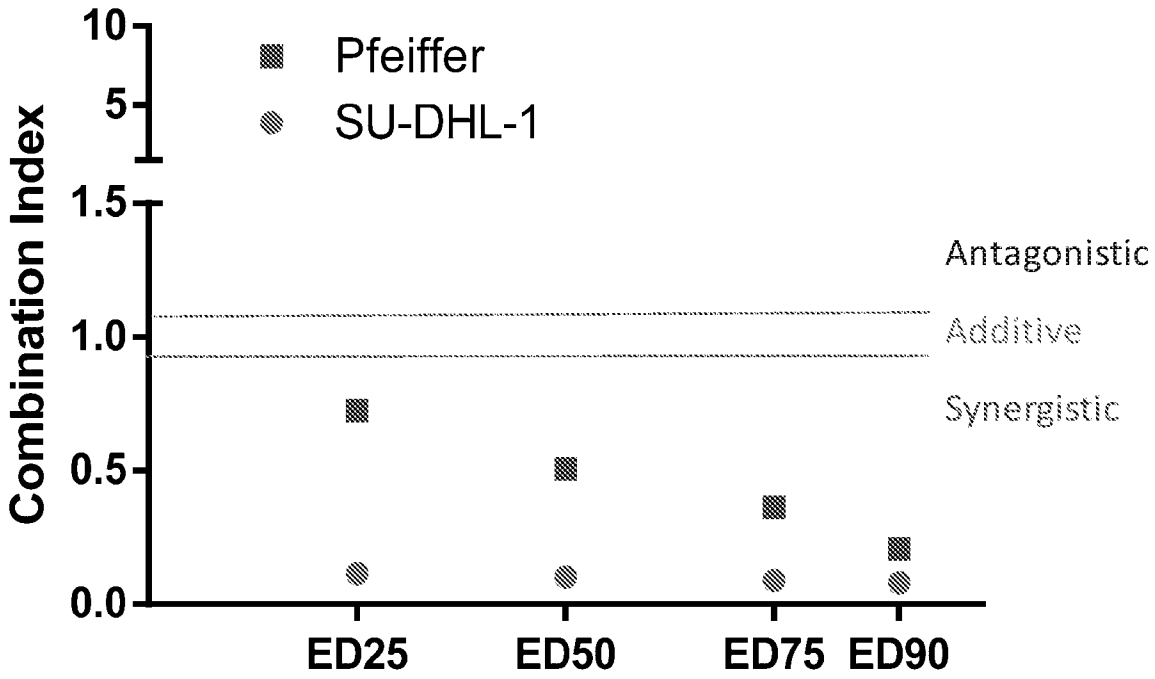

Combination Index
10
5
1.5
1.0
0.5
0.0
Pfeiffer
SU-DHL-1
Antagonistic
Additive
Synergistic
ED25
ED50
ED75
ED90

FIG. 49

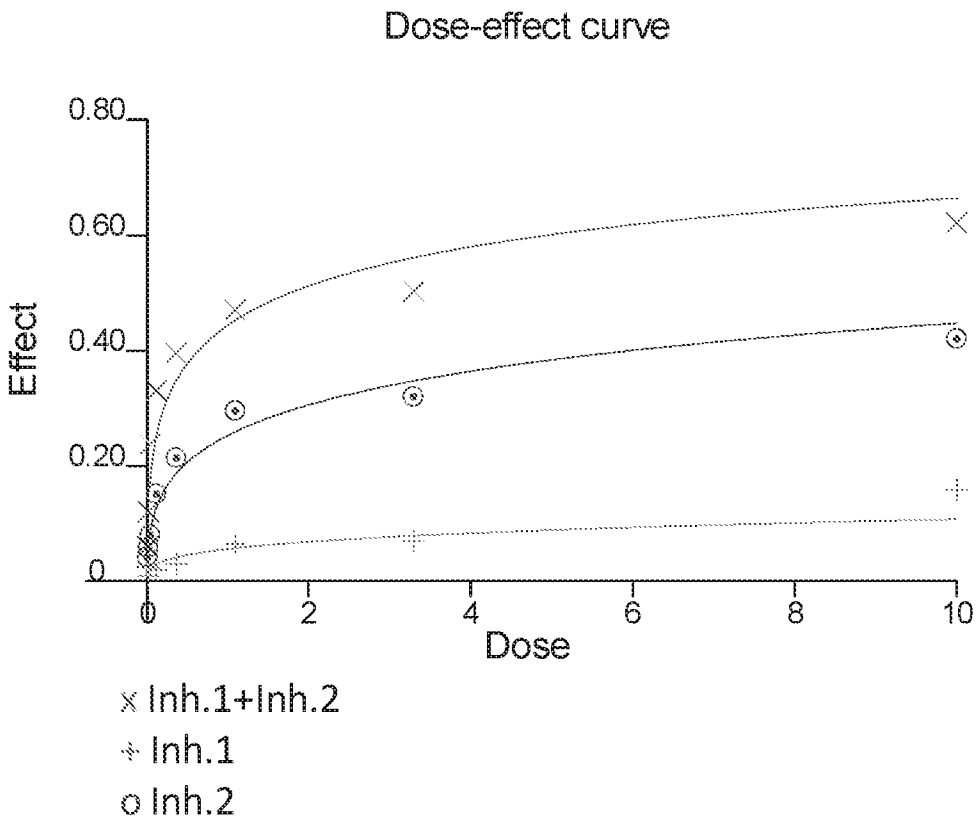

Dose-effect curve
Effect
0.80
0.60
0.40
0.20
0
0
2
4
6
8
10
Dose
Inh.1+Inh.2
Inh.1
Inh.2

FIG. 50

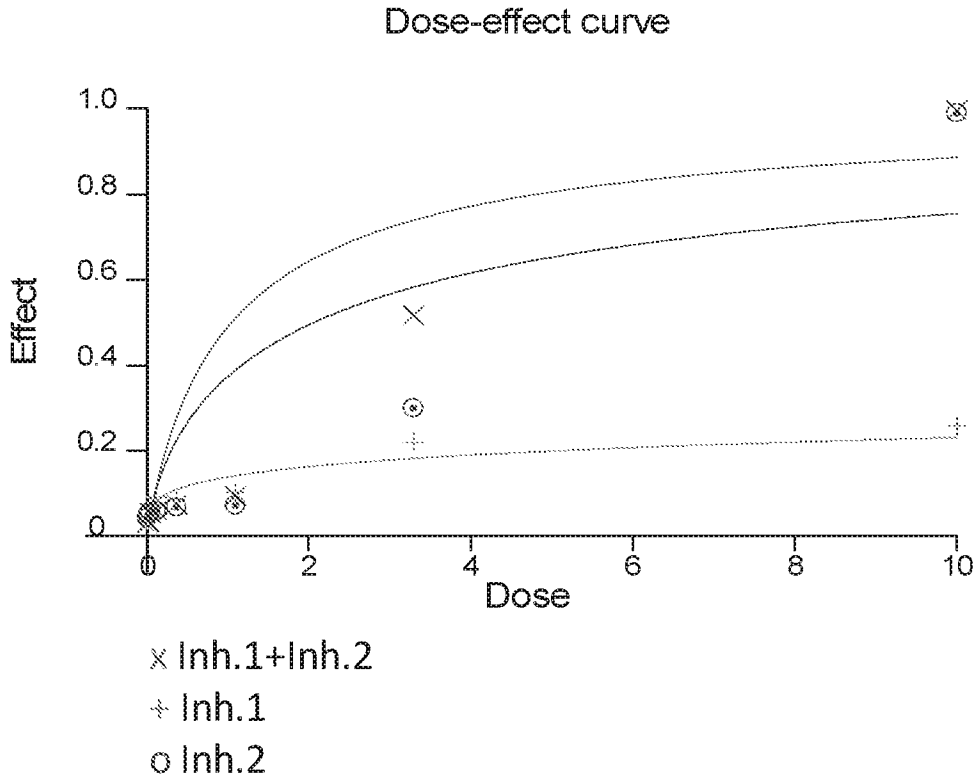

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.1+Inh.2
Inh.1
Inh.2

FIG. 51

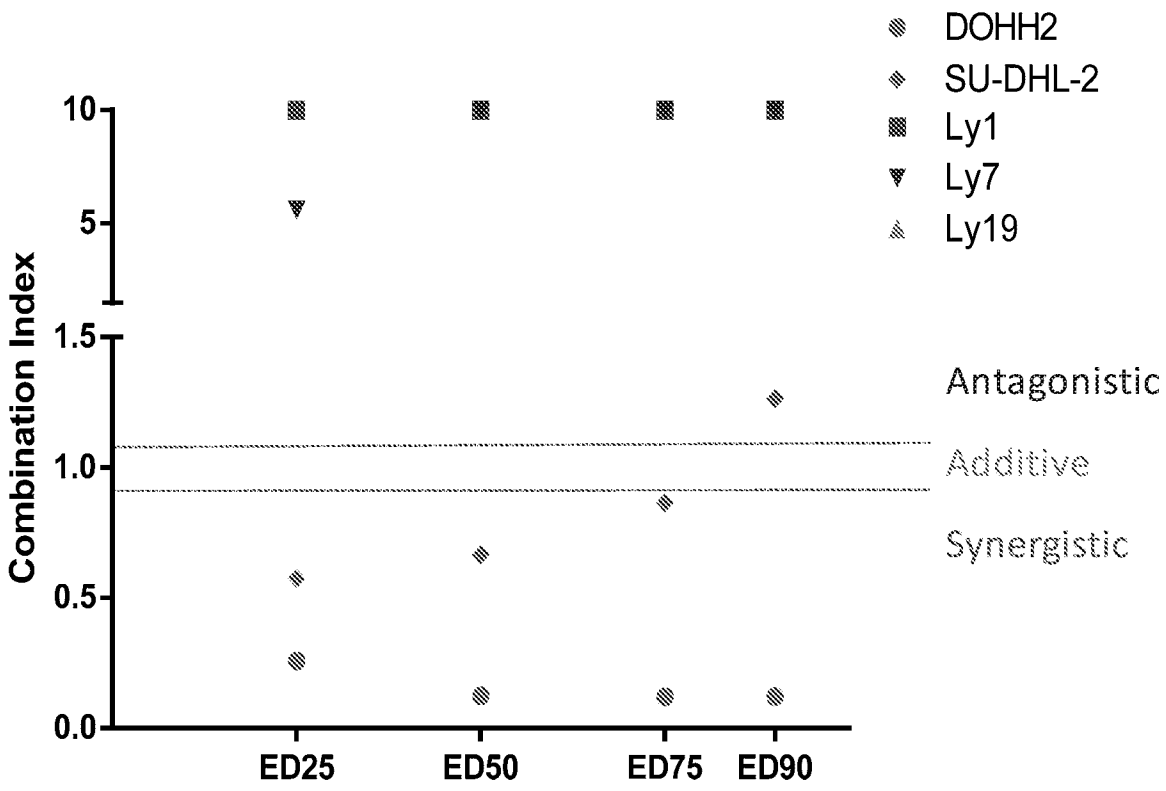

DOHH2
SU-DHL-2
Ly1
Ly7
Ly19
Combination Index
10
5
1.5
1.0
0.5
0.0
Antagonistic
Additive
Synergistic
ED25
ED50
ED75
ED90

FIG. 52

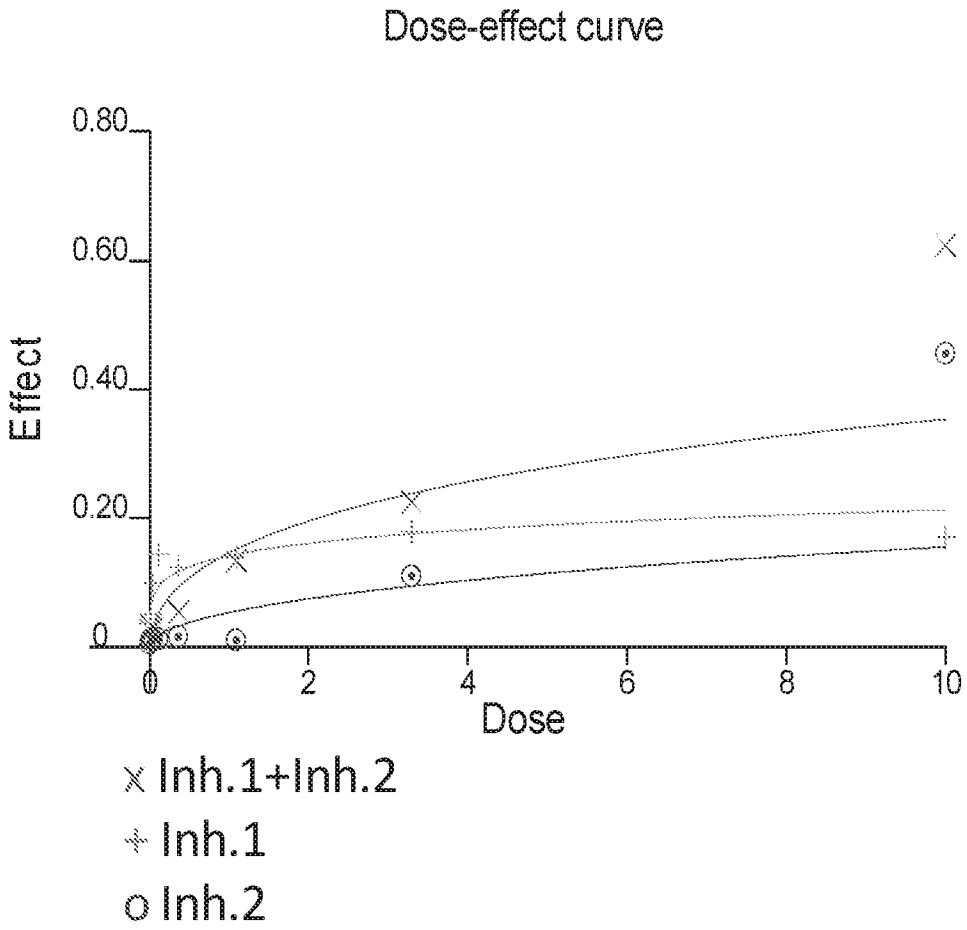

Dose-effect curve
Effect
0.80
0.60
0.40
0.20
0
0
2
4
6
8
10
Dose
Inh.1+Inh.2
Inh.1
Inh.2

FIG. 53

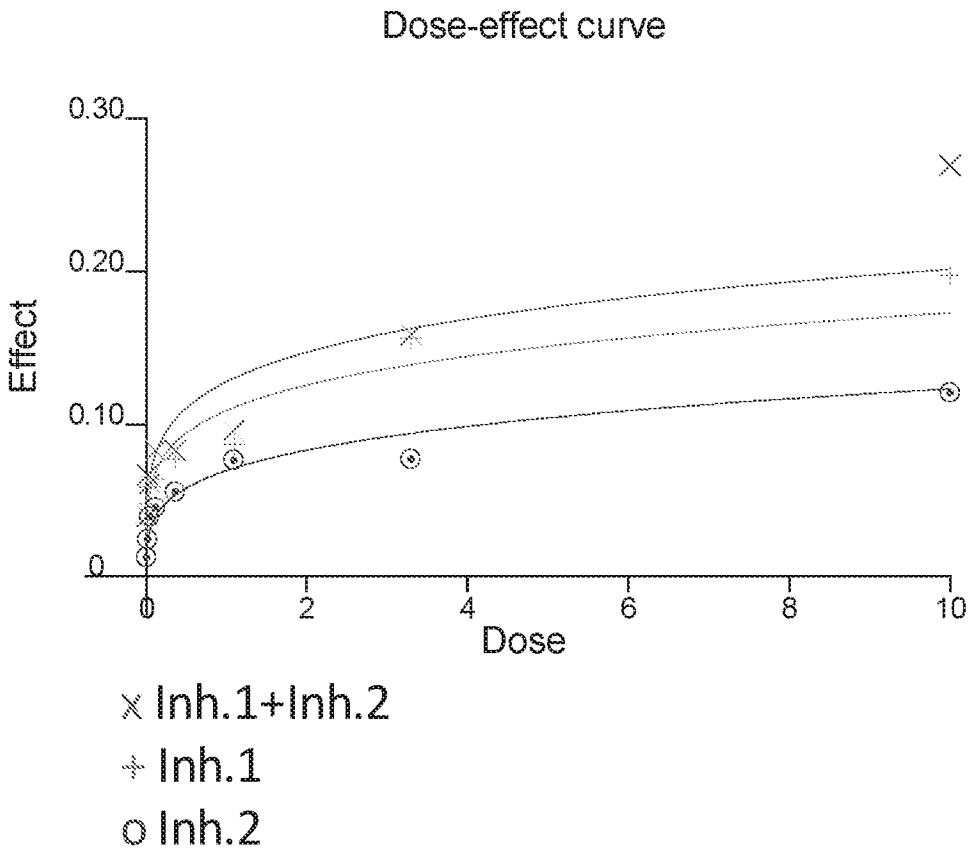

Dose-effect curve
0.30
0.20
0.10
0
Effect
0
2
4
6
8
10
Dose
Inh.1+Inh.2
Inh.1
Inh.2

FIG. 54

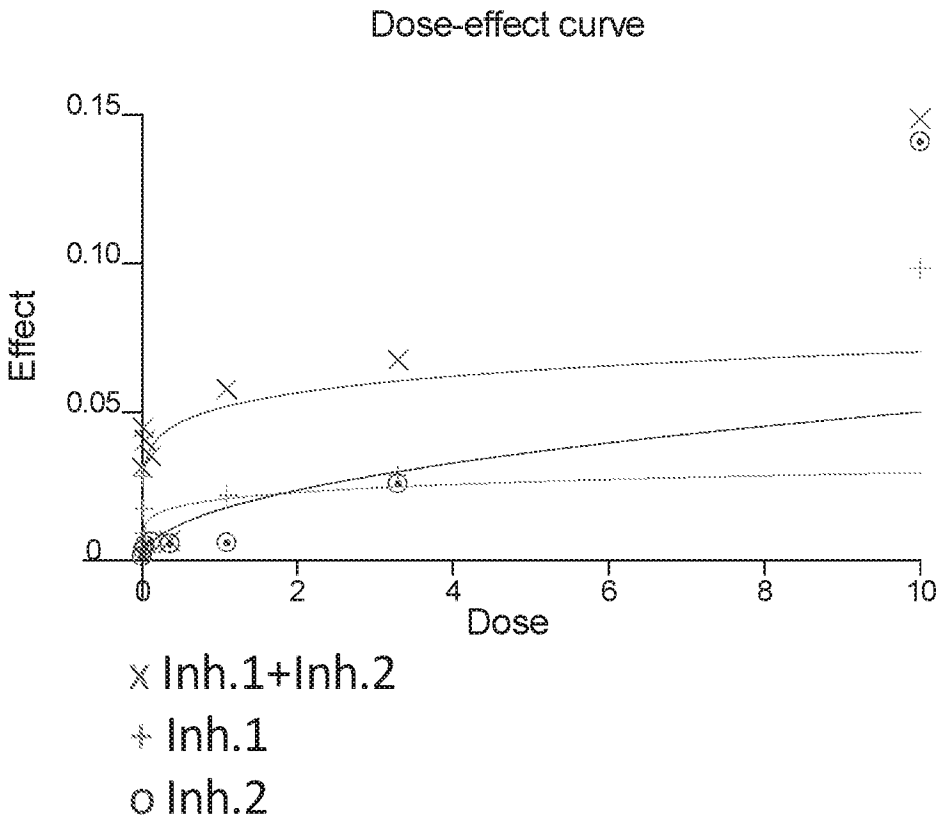

Dose-effect curve
0.15
0.10
0.05
0
Effect
0
2
4
6
8
10
Dose
Inh.1+Inh.2
Inh.1
Inh.2

FIG. 55

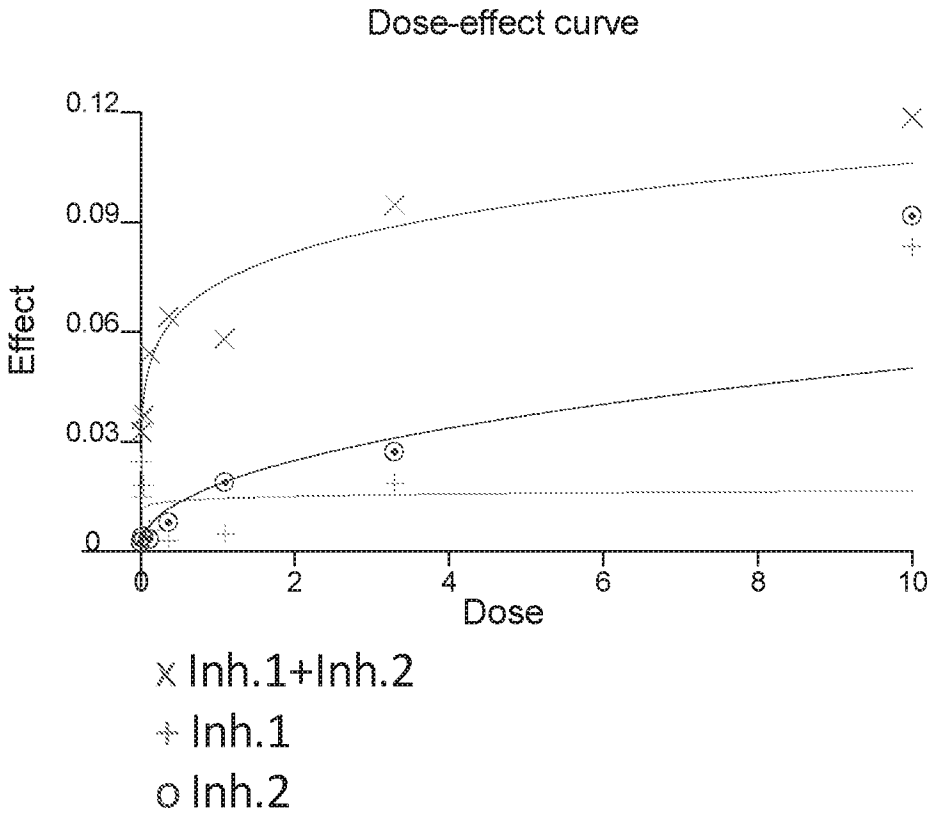

Dose-effect curve
0.12
0.09
0.06
0.03
0
Effect
0
2
4
6
8
10
Dose
Inh.1+Inh.2
Inh.1
Inh.2

FIG. 56

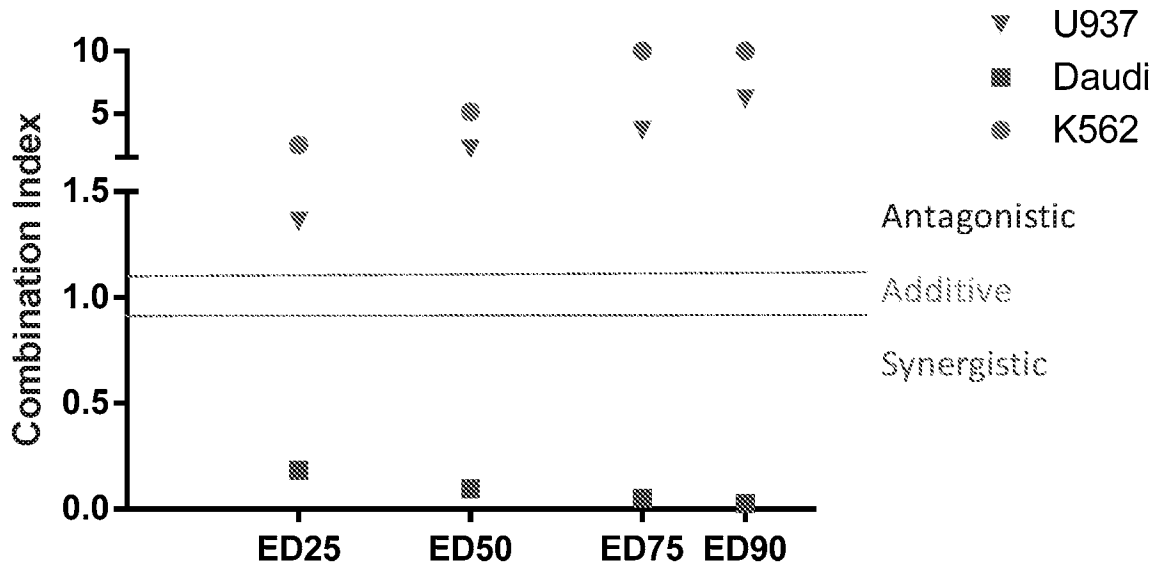

Combination Index
10
5
1.5
1.0
0.5
0.0
ED25
ED50
ED75
ED90
U937
Daudi
K562
Antagonistic
Additive
Synergistic

FIG. 57

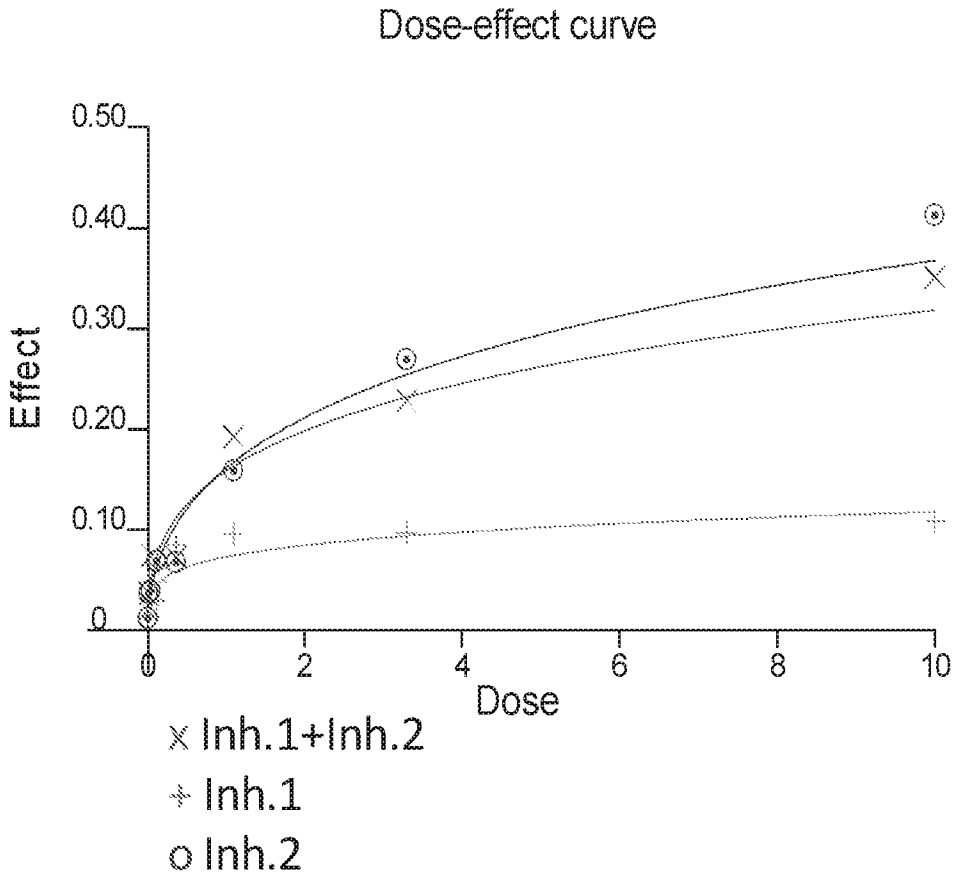

Dose-effect curve
Effect
0.50
0.40
0.30
0.20
0.10
0
0
2
4
6
8
10
Dose
Inh.1+Inh.2
Inh.1
Inh.2

FIG. 58

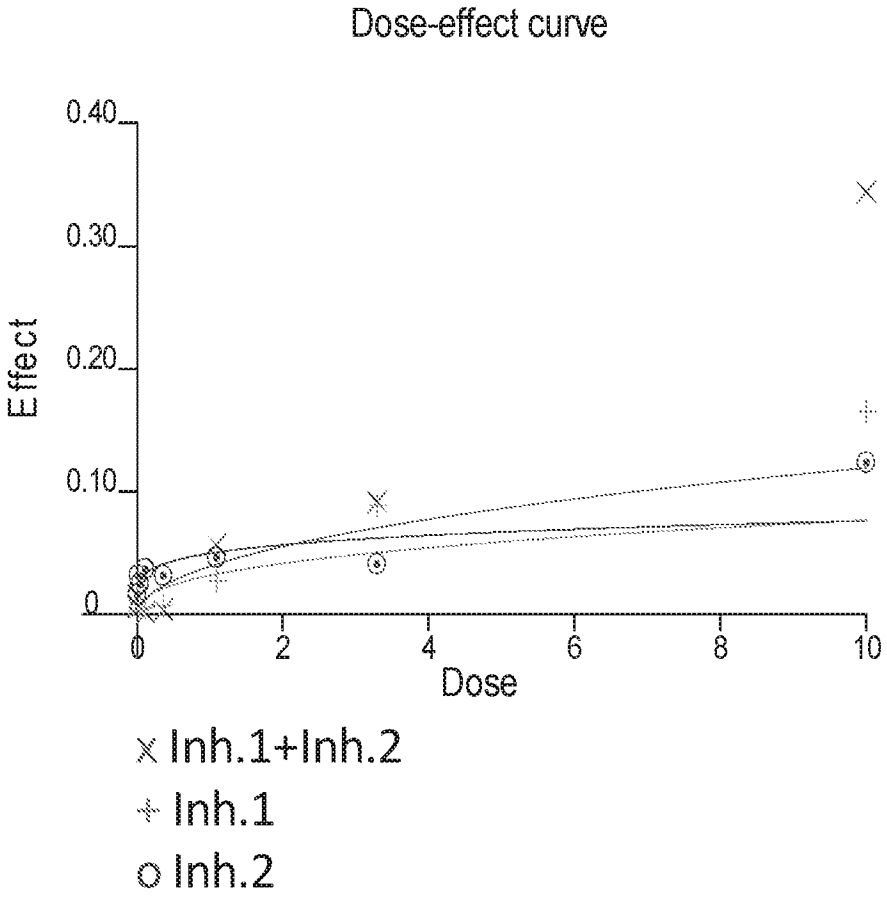

Dose-effect curve
0.40
0.30
0.20
0.10
0
Effect
0
2
4
6
8
10
Dose
Inh.1+Inh.2
Inh.1
Inh.2

FIG. 59

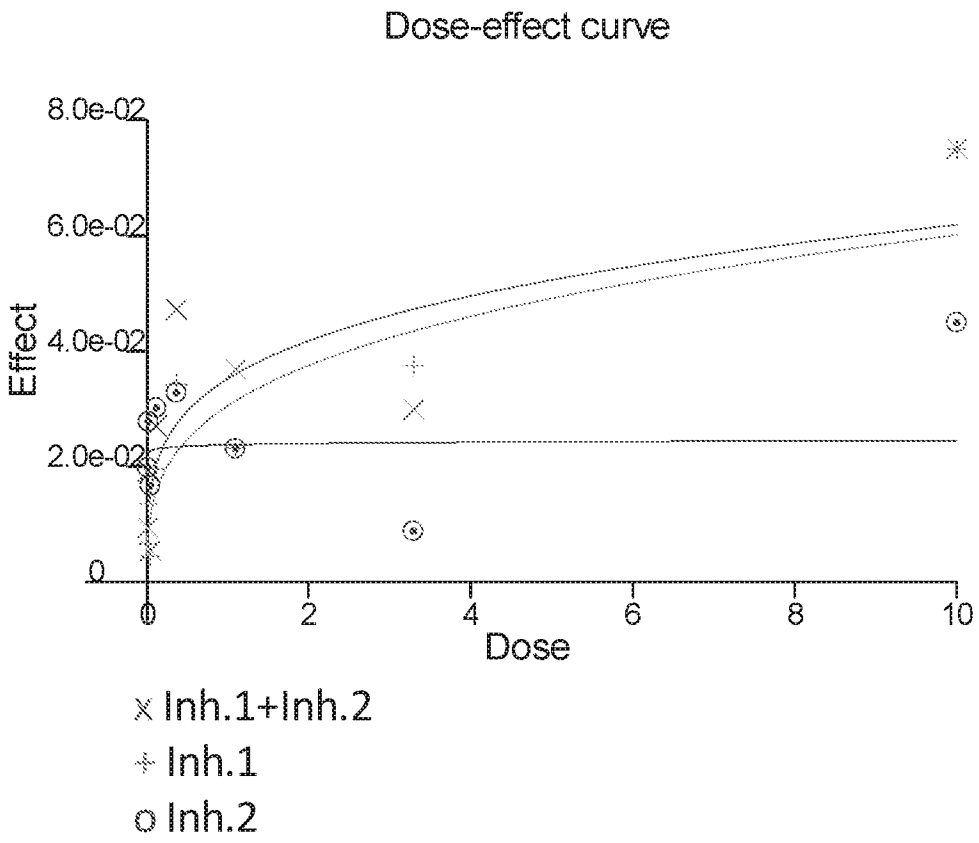

Dose-effect curve
8.0e-02
6.0e-02
4.0e-02
2.0e-02
0
Effect
0
2
4
6
8
10
Dose
Inh.1+Inh.2
Inh.1
Inh.2

FIG. 60

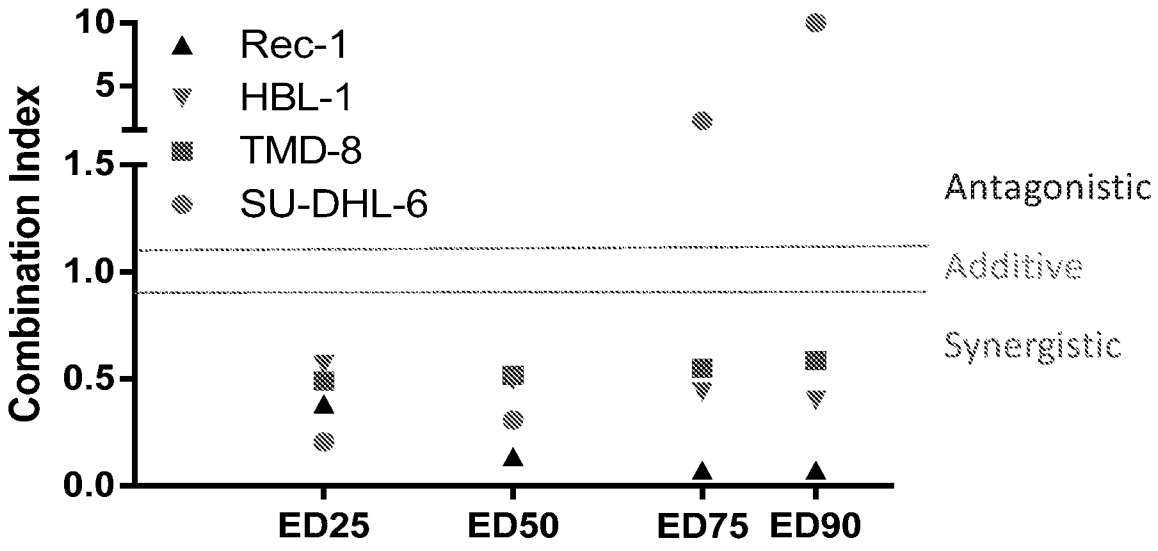

Combination Index
10
5
1.5
1.0
0.5
0.0
Rec-1
HBL-1
TMD-8
SU-DHL-6
Antagonistic
Additive
Synergistic
ED25
ED50
ED75
ED90

FIG. 61

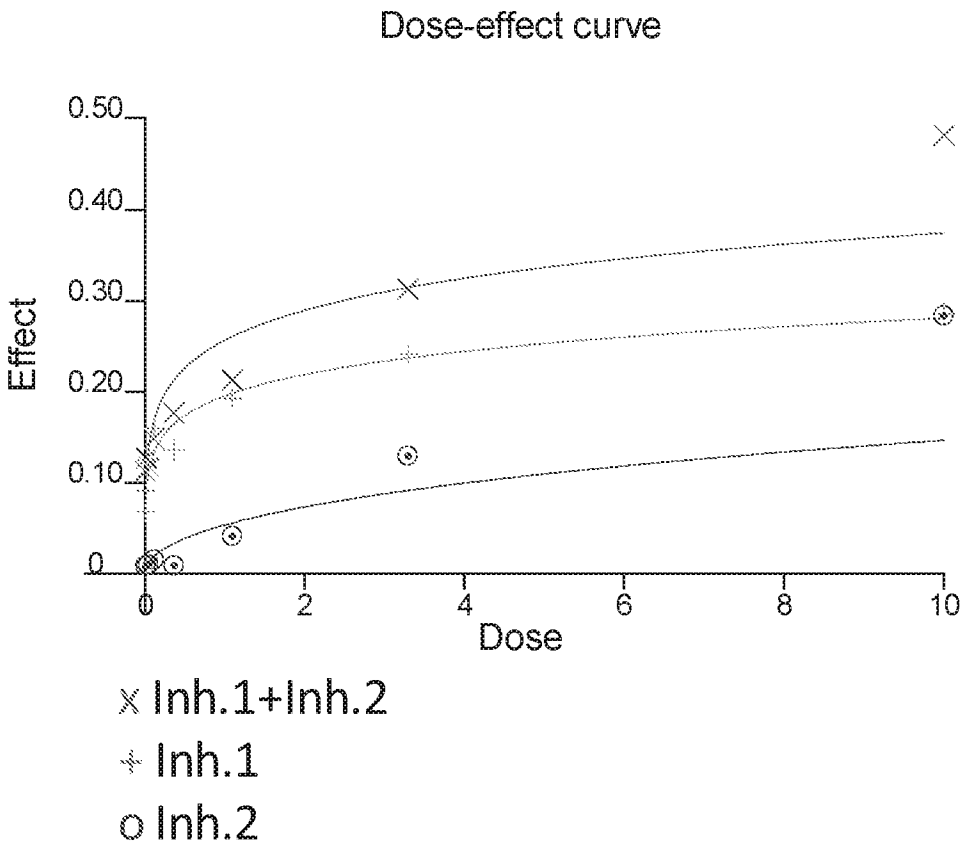

Dose-effect curve
Effect
0.50
0.40
0.30
0.20
0.10
0
0
2
4
6
8
10
Dose
Inh.1+Inh.2
Inh.1
Inh.2

FIG. 62

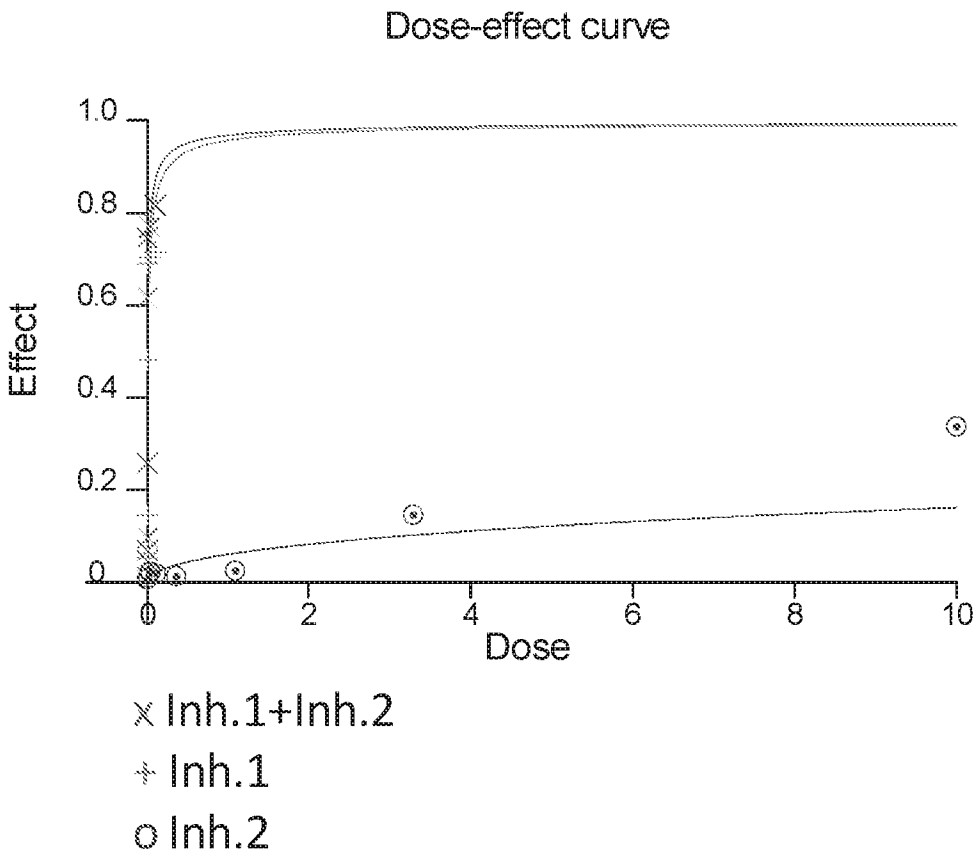

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.1+Inh.2
Inh.1
Inh.2

FIG. 63

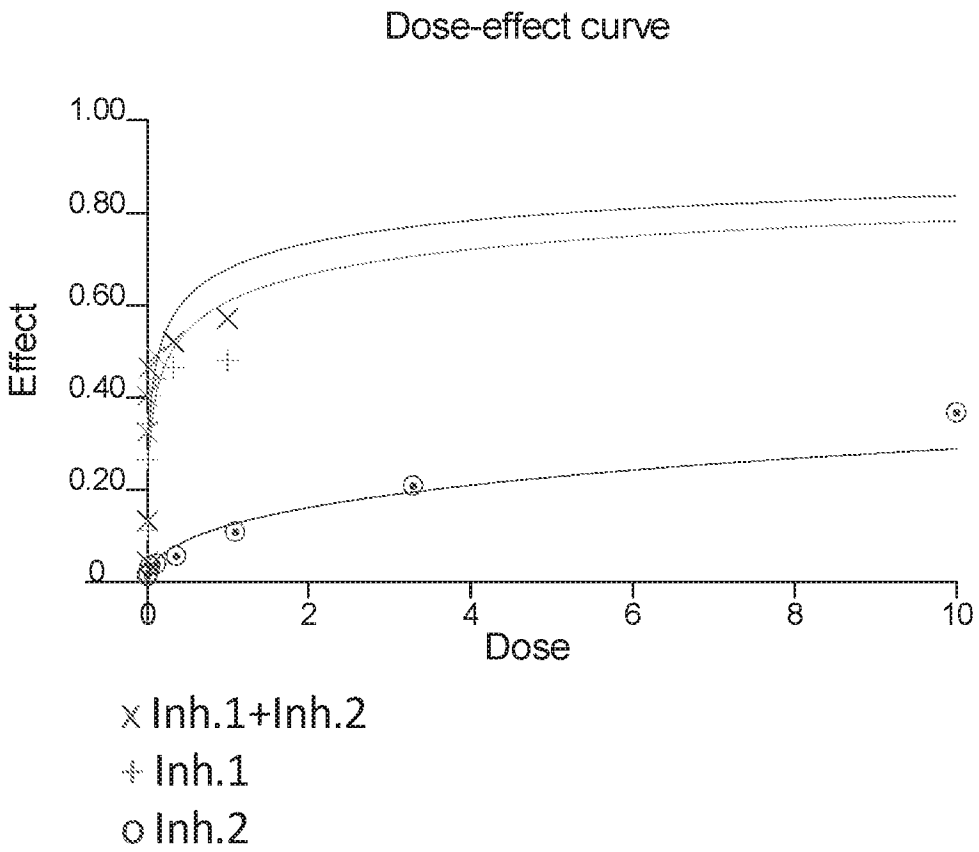

Dose-effect curve
1.00
0.80
0.60
0.40
0.20
0
Effect
0
2
4
6
8
10
Dose
Inh.1+Inh.2
Inh.1
Inh.2

FIG. 64

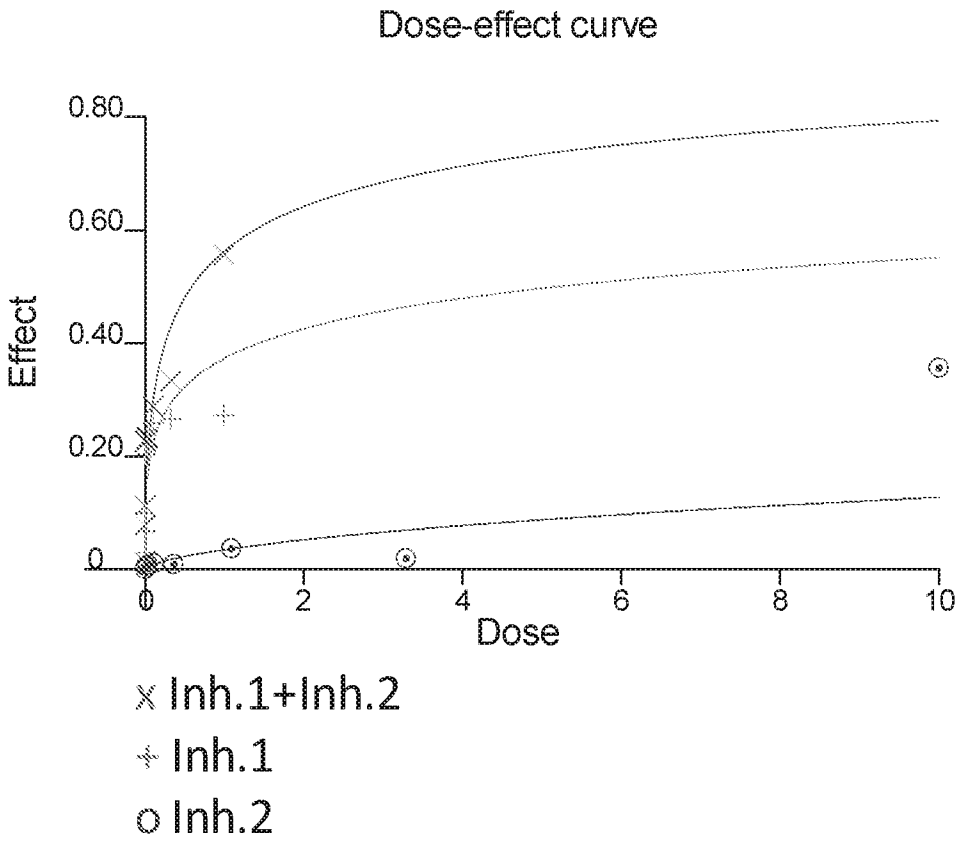

Dose-effect curve
Effect
0.80
0.60
0.40
0.20
0
0
2
4
6
8
10
Dose
Inh.1+Inh.2
Inh.1
Inh.2

FIG. 65

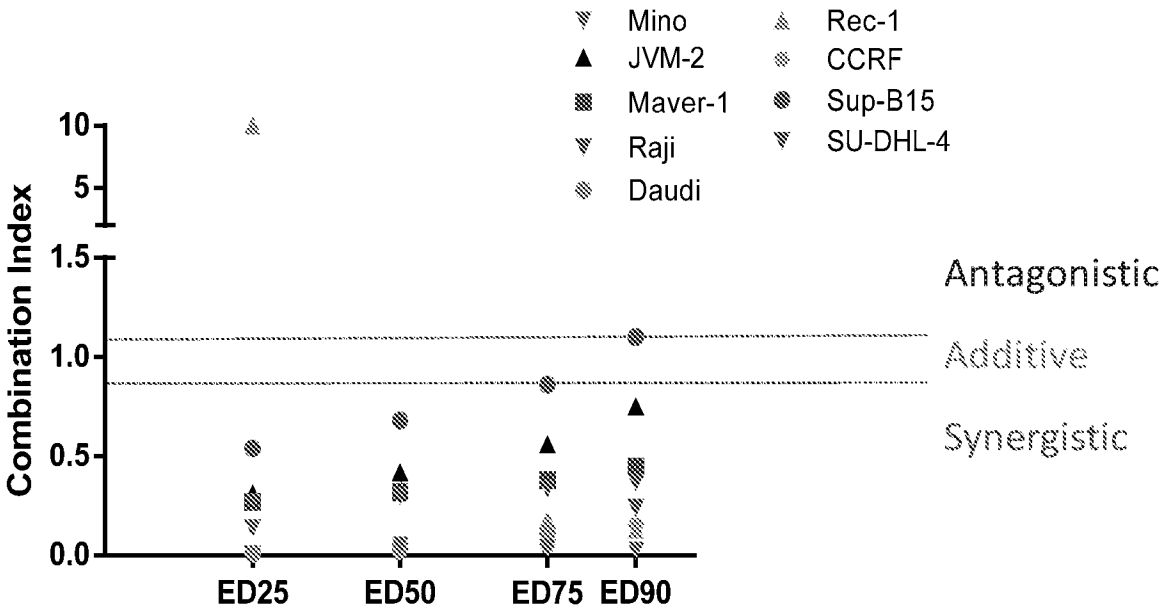

Mino
JVM-2
Maver-1
Raji
Daudi
Rec-1
CCRF
Sup-B15
SU-DHL-4
Combination Index
10
5
1.5
1.0
0.5
0.0
Antagonistic
Additive
Synergistic
ED25
ED50
ED75
ED90

FIG. 66

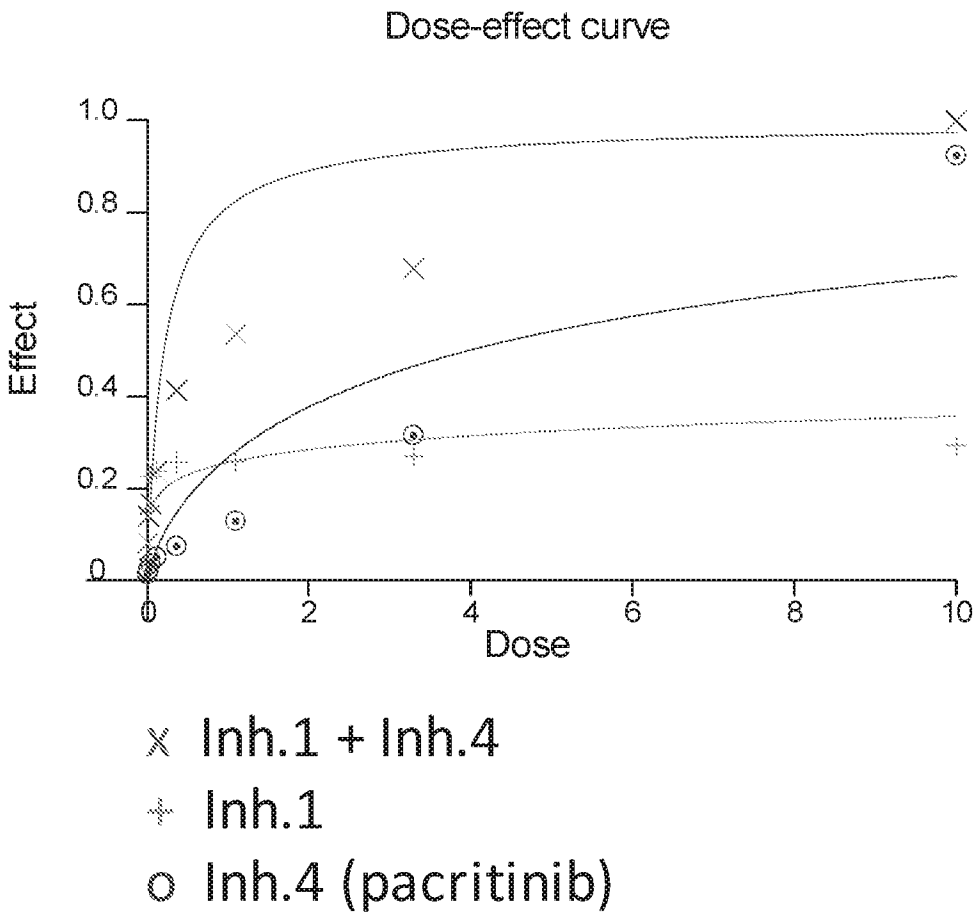

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.1 + Inh.4
Inh.1
Inh.4 (pacritinib)

FIG. 67

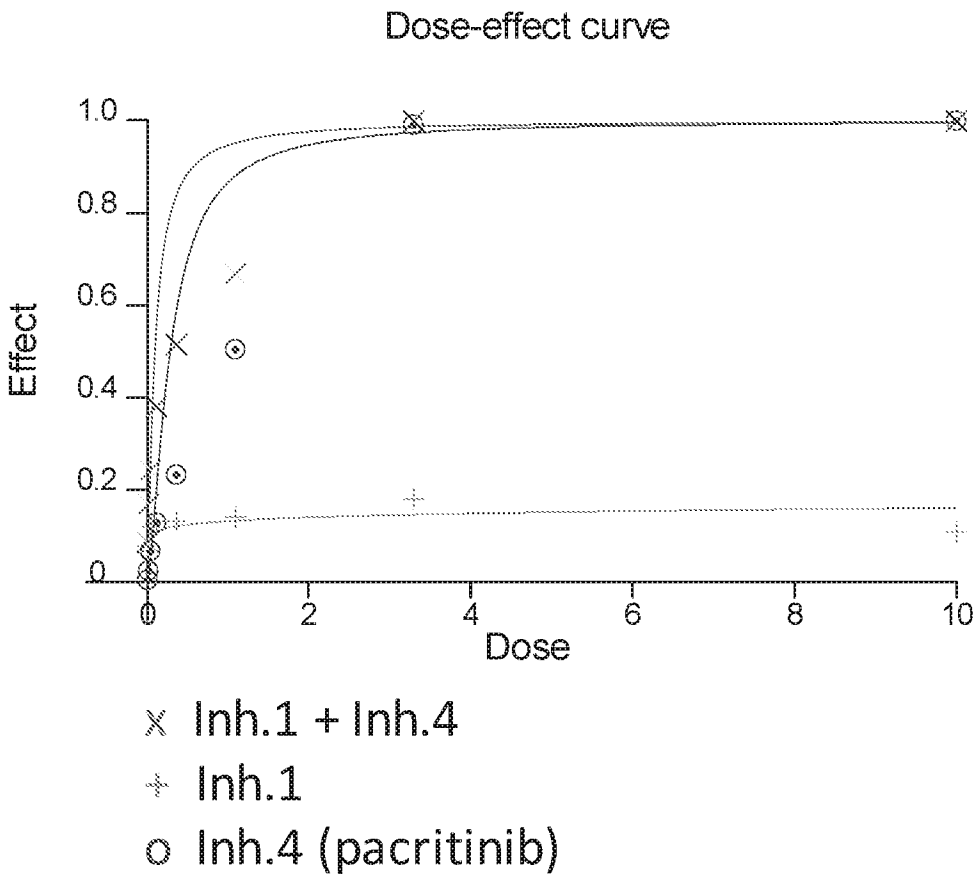

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.1 + Inh.4
Inh.1
Inh.4 (pacritinib)

FIG. 68

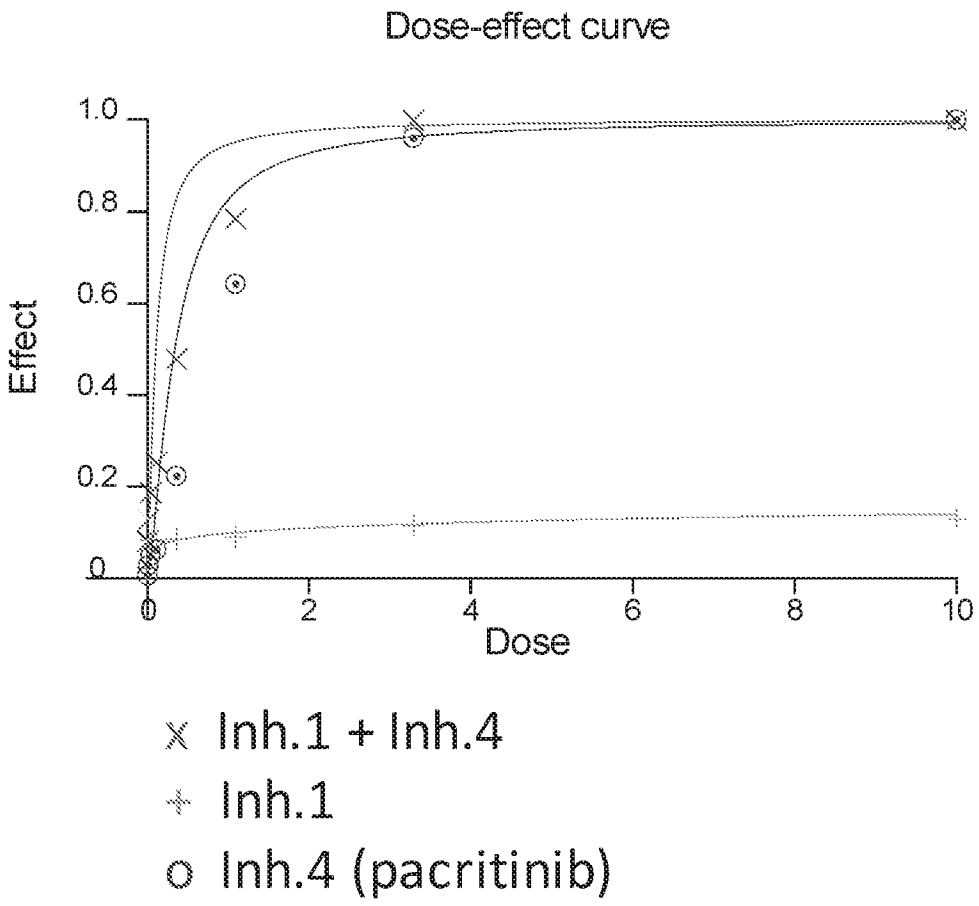

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.1 + Inh.4
Inh.1
Inh.4 (pacritinib)

FIG. 69

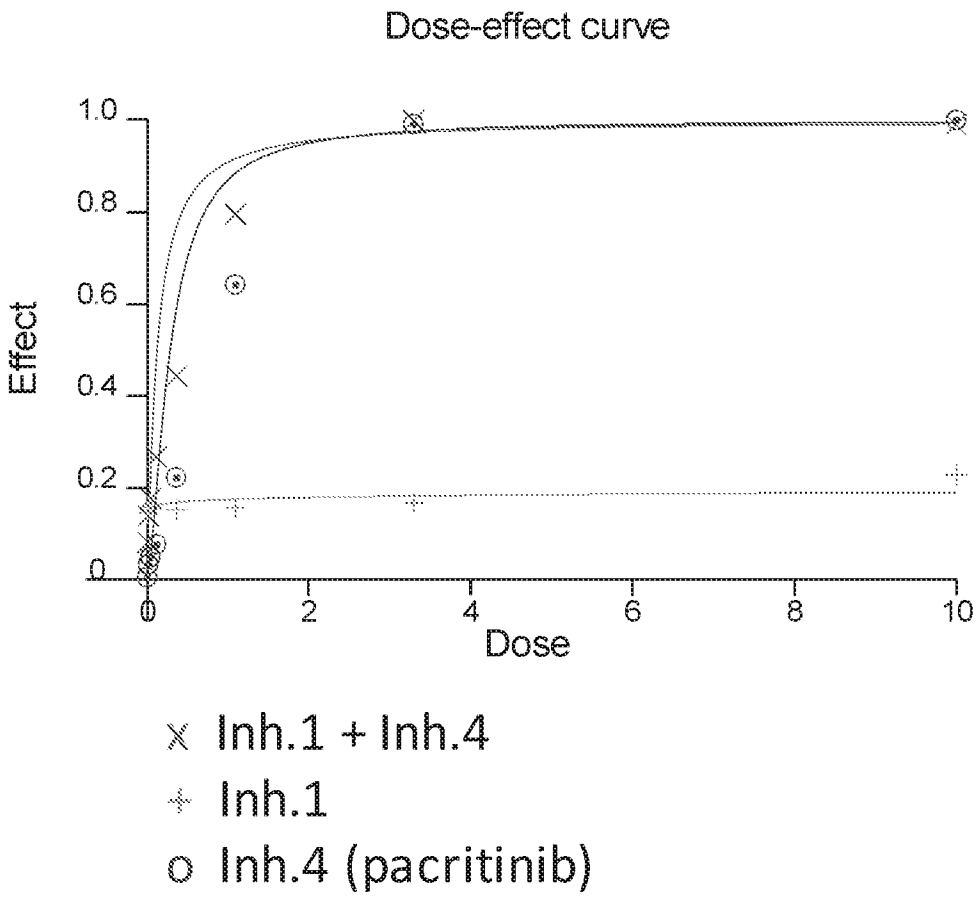

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.1 + Inh.4
Inh.1
Inh.4 (pacritinib)

FIG. 70

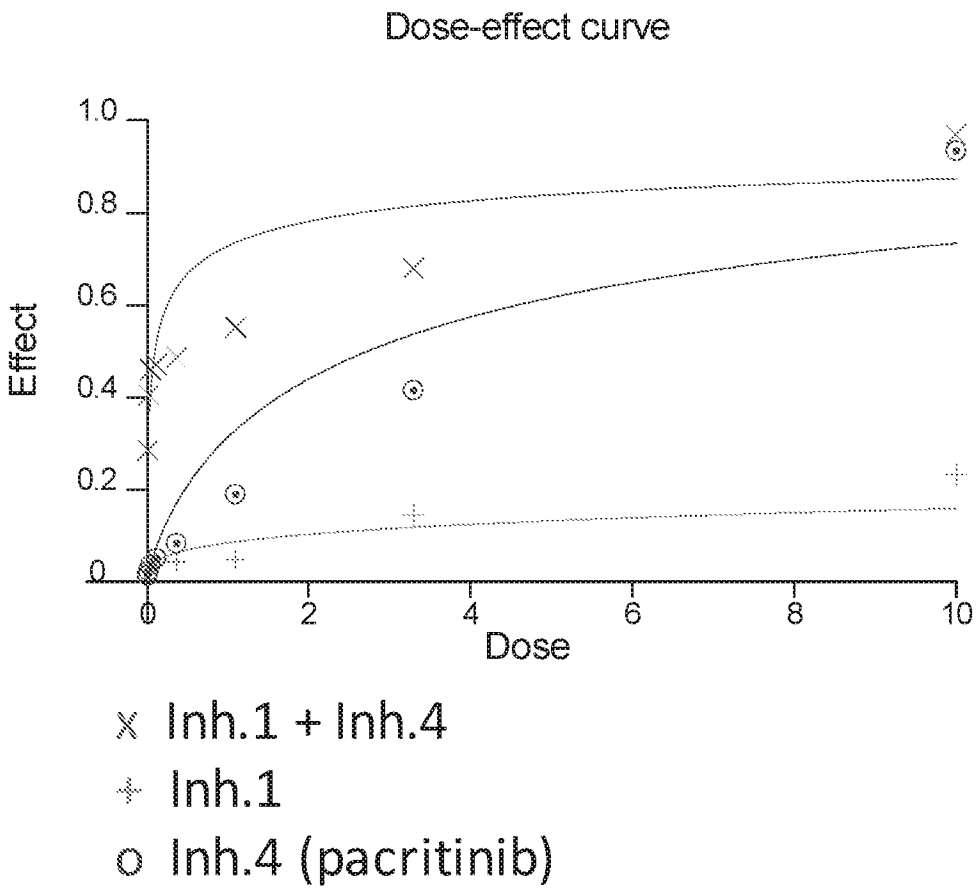

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.1 + Inh.4
Inh.1
Inh.4 (pacritinib)

FIG. 71

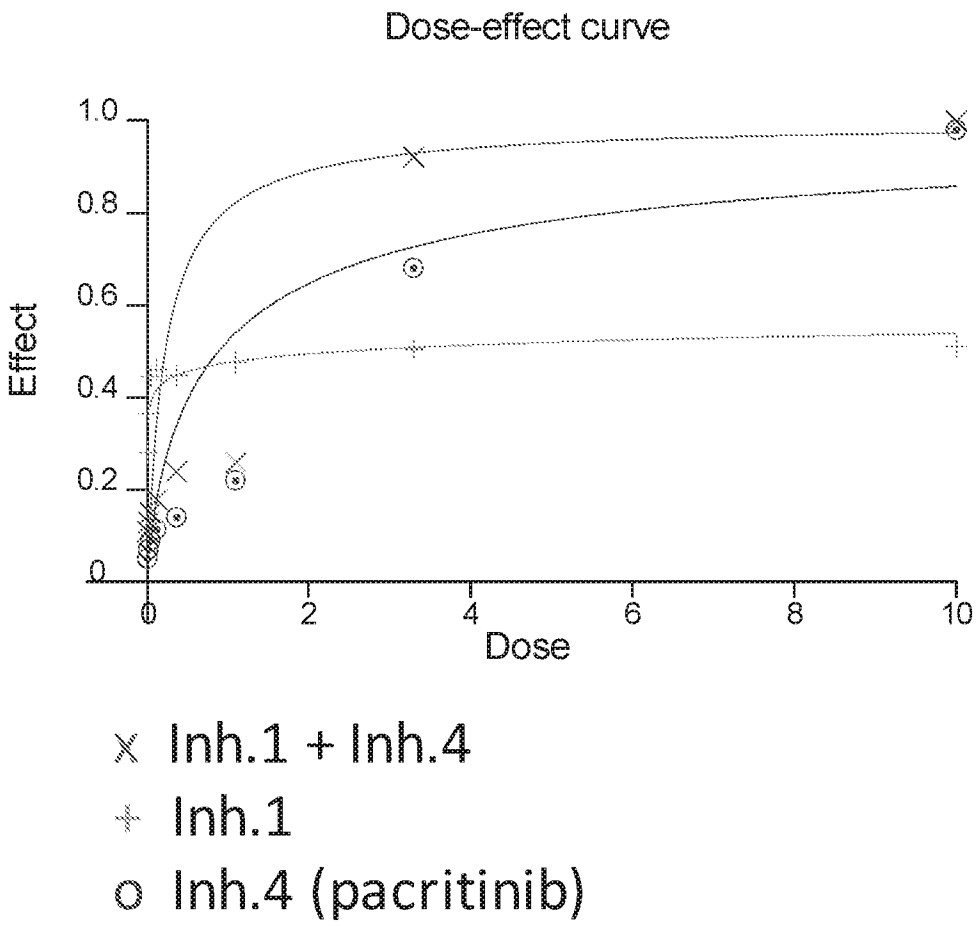

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.1 + Inh.4
Inh.1
Inh.4 (pacritinib)

FIG. 72

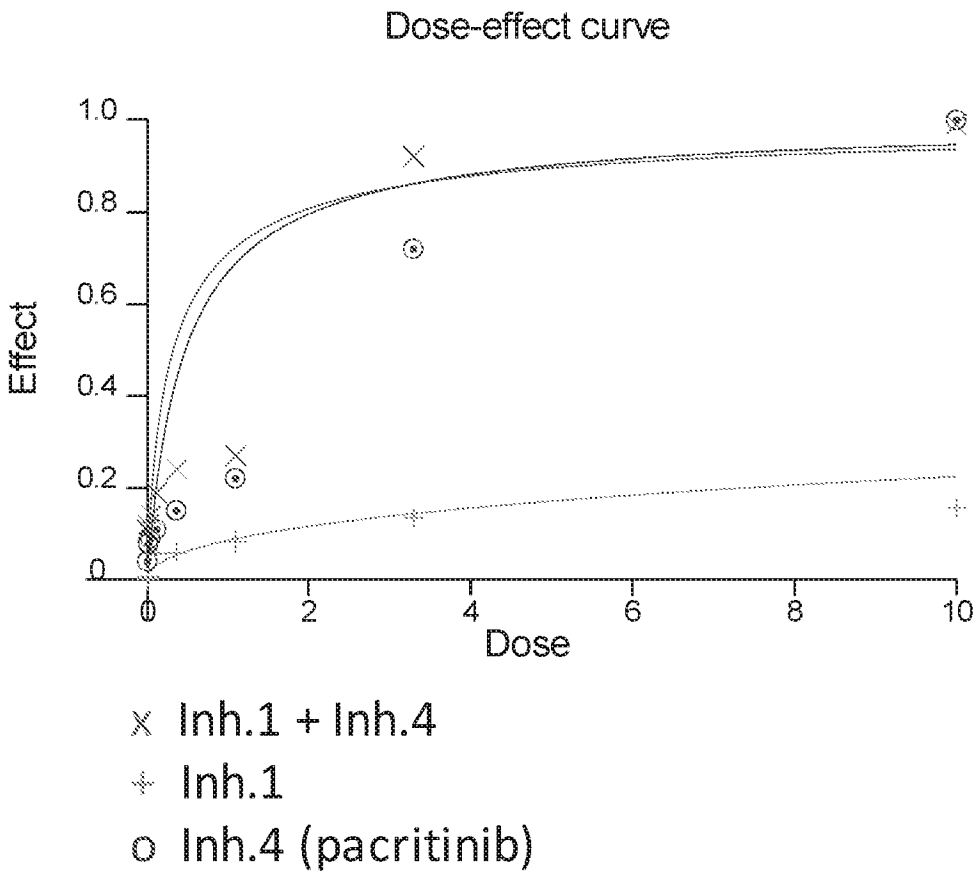

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.1 + Inh.4
Inh.1
Inh.4 (pacritinib)

FIG. 73

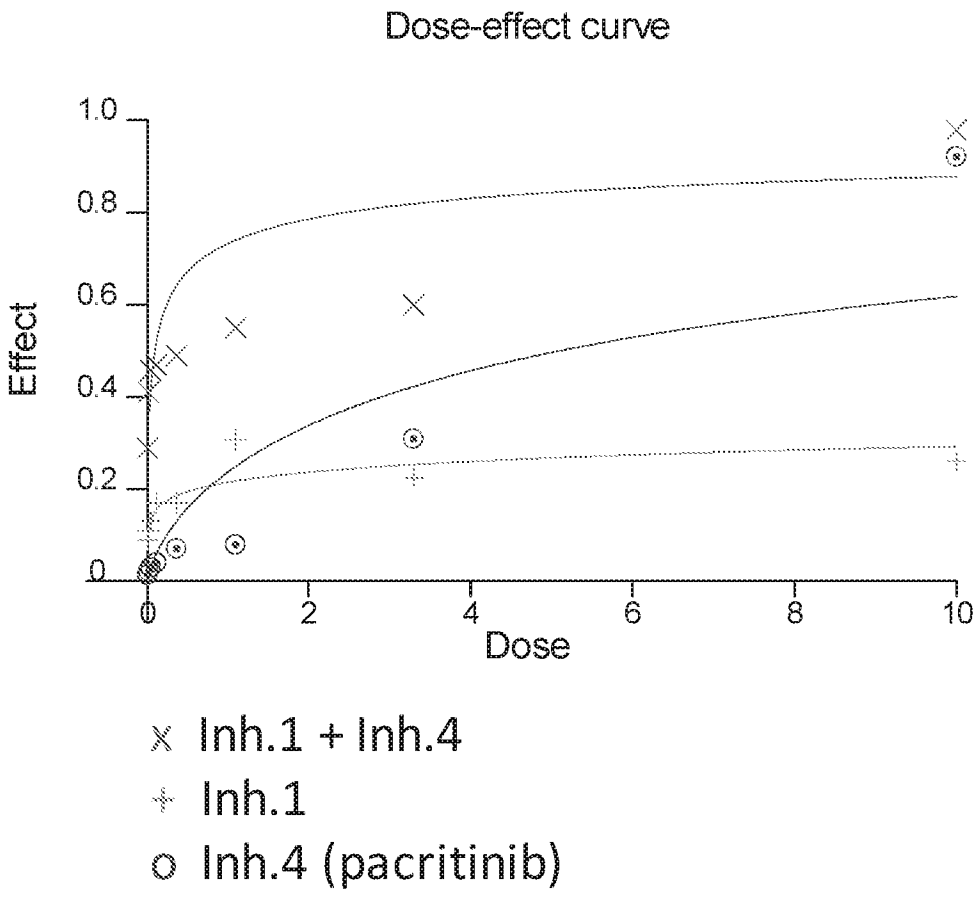

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.1 + Inh.4
Inh.1
Inh.4 (pacritinib)

FIG. 74

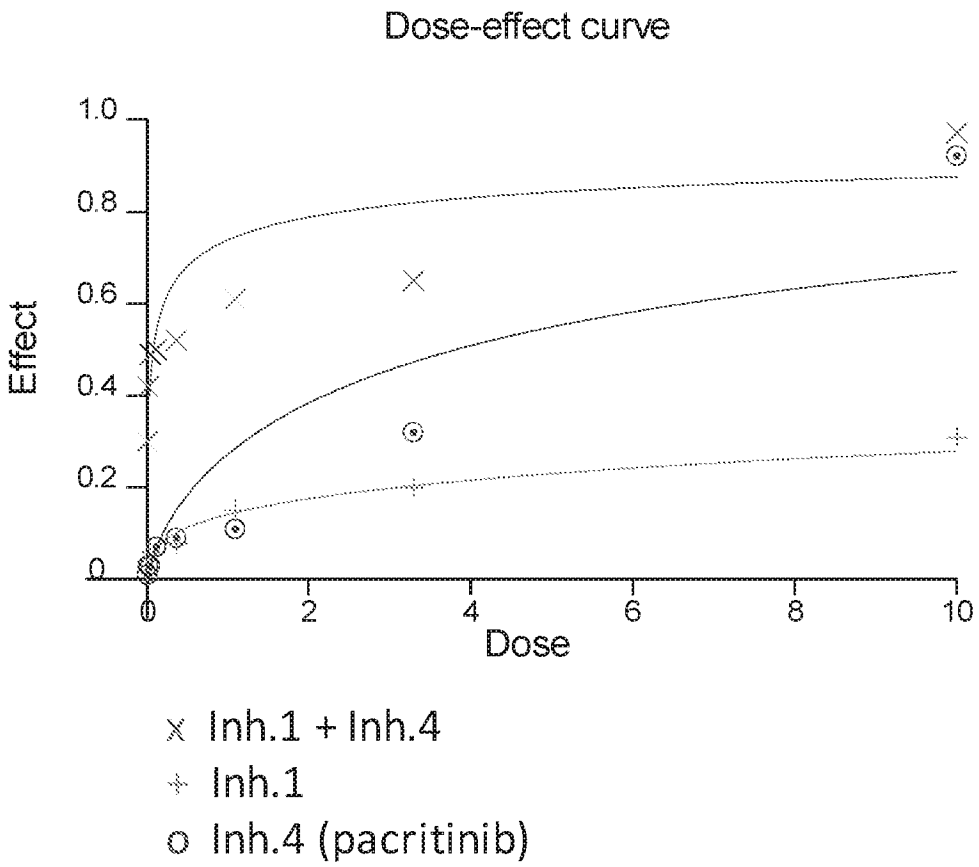

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.1 + Inh.4
Inh.1
Inh.4 (pacritinib)

FIG. 75

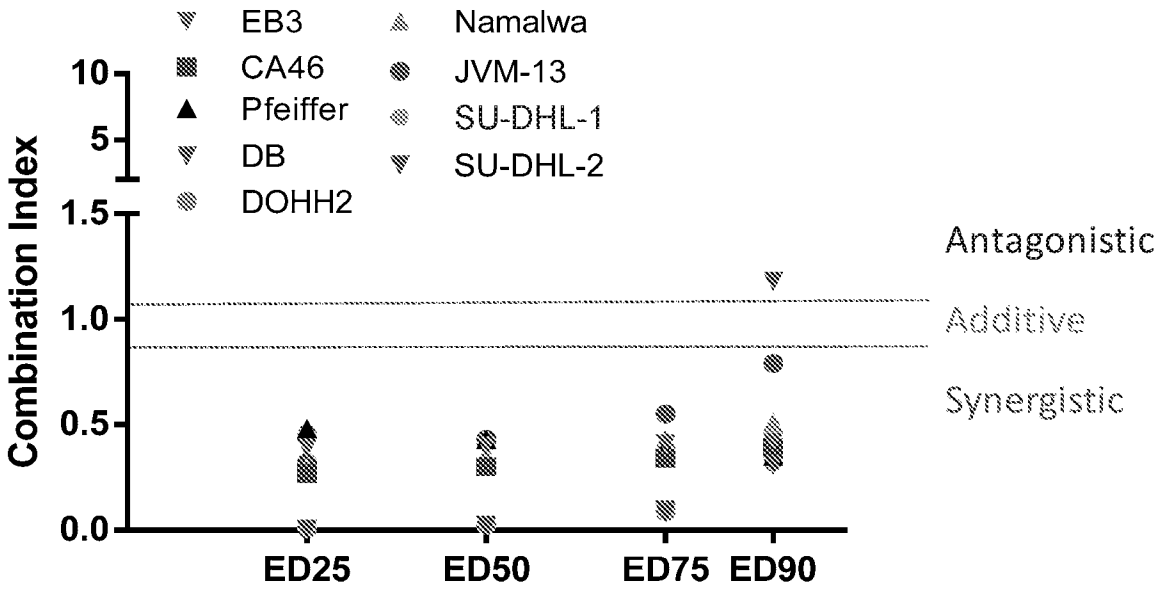

EB3
CA46
Pfeiffer
DB
DOHH2
Namalwa
JVM-13
SU-DHL-1
SU-DHL-2
Combination Index
10
5
1.5
1.0
0.5
0.0
Antagonistic
Additive
Synergistic
ED25
ED50
ED75
ED90

FIG. 76

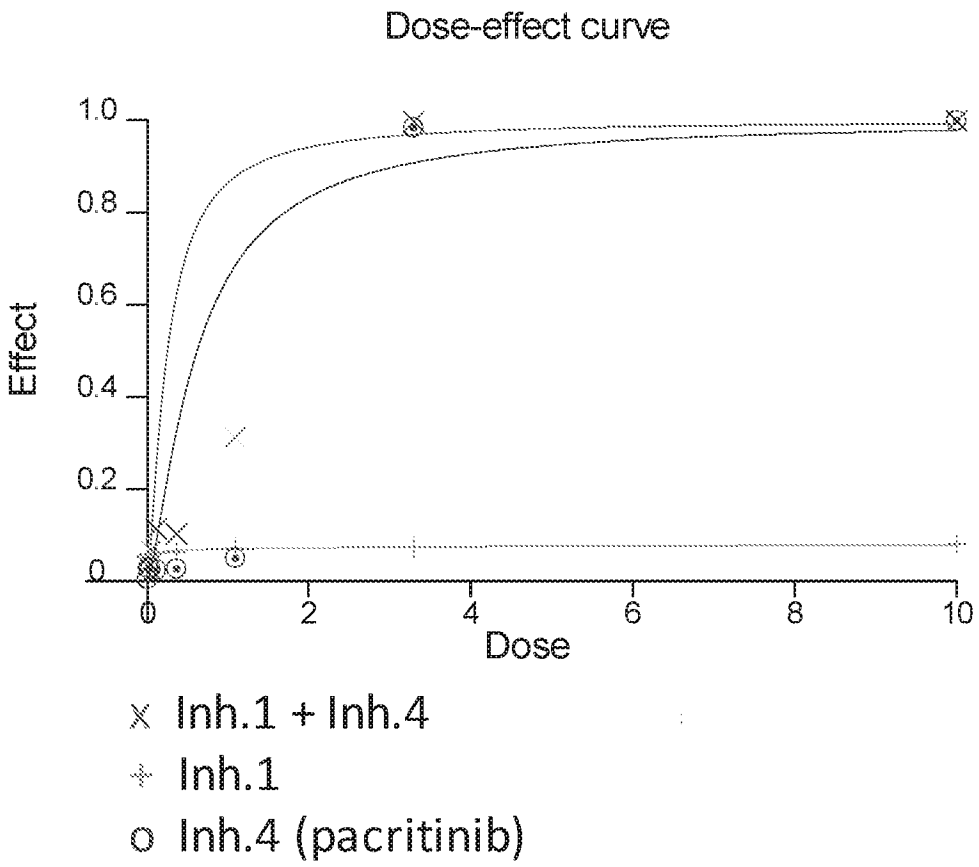

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.1 + Inh.4
Inh.1
Inh.4 (pacritinib)

FIG. 77

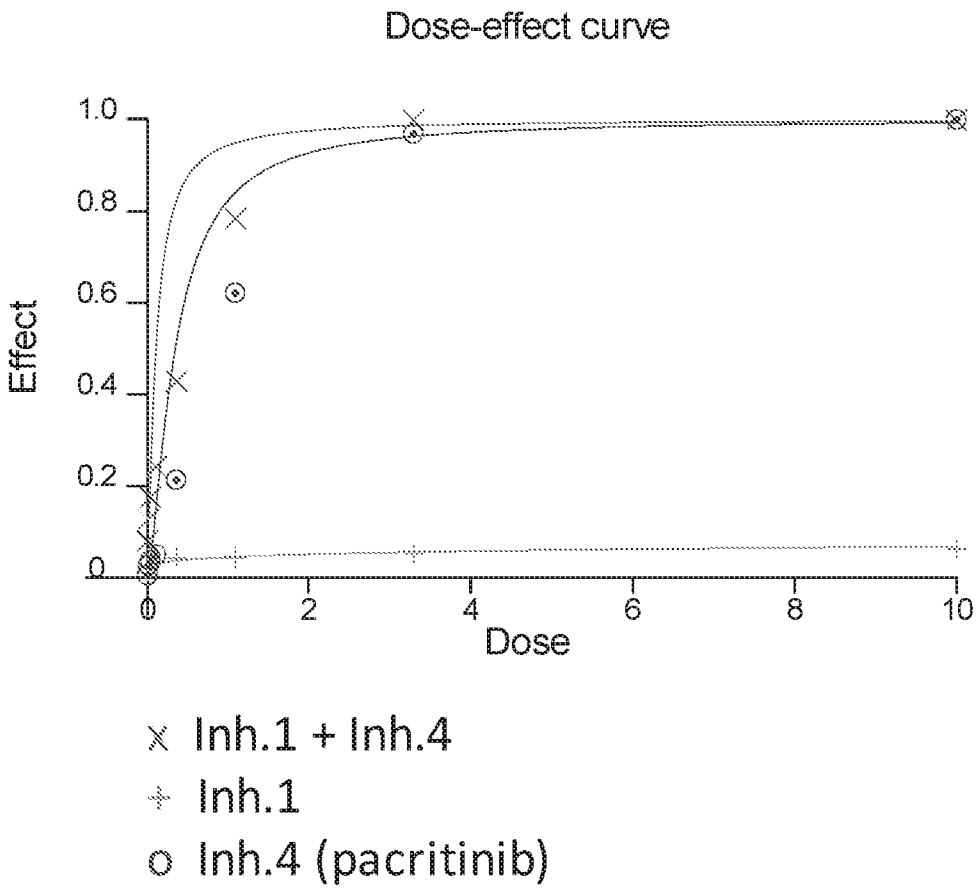

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.1 + Inh.4
Inh.1
Inh.4 (pacritinib)

FIG. 78

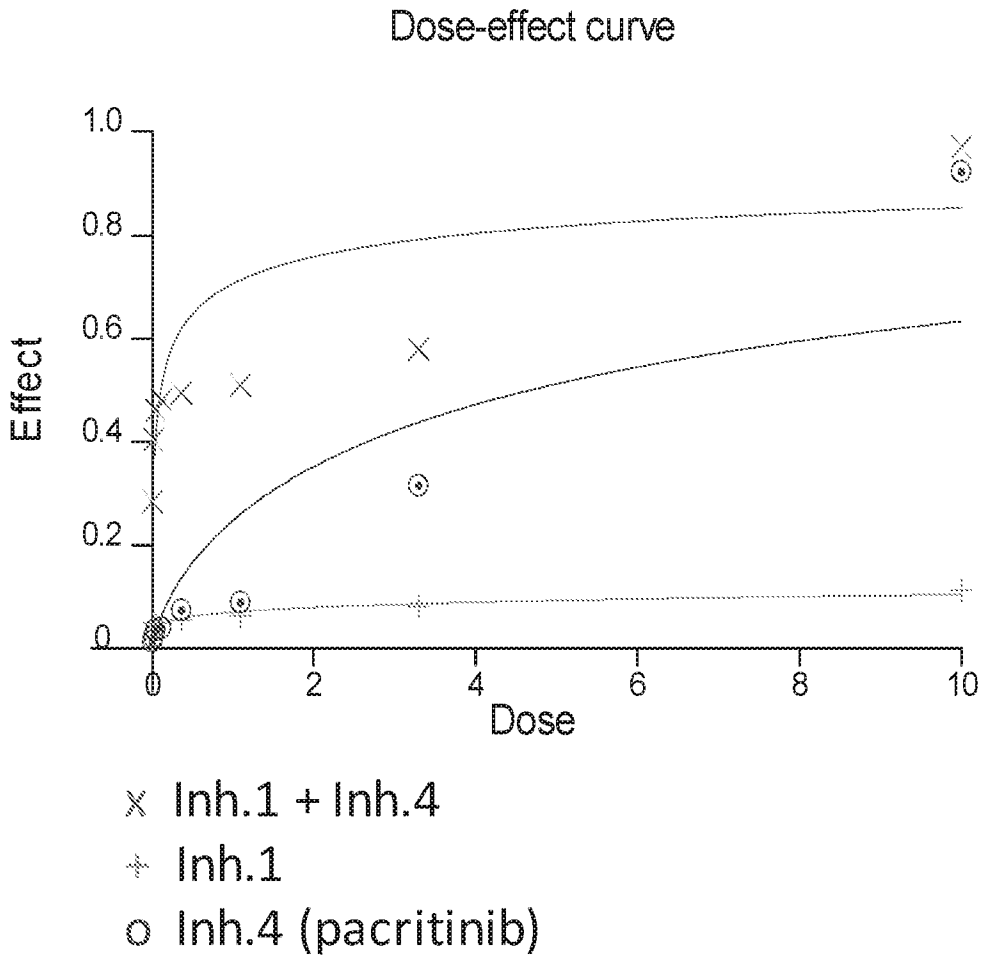

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.1 + Inh.4
Inh.1
Inh.4 (pacritinib)

FIG. 79

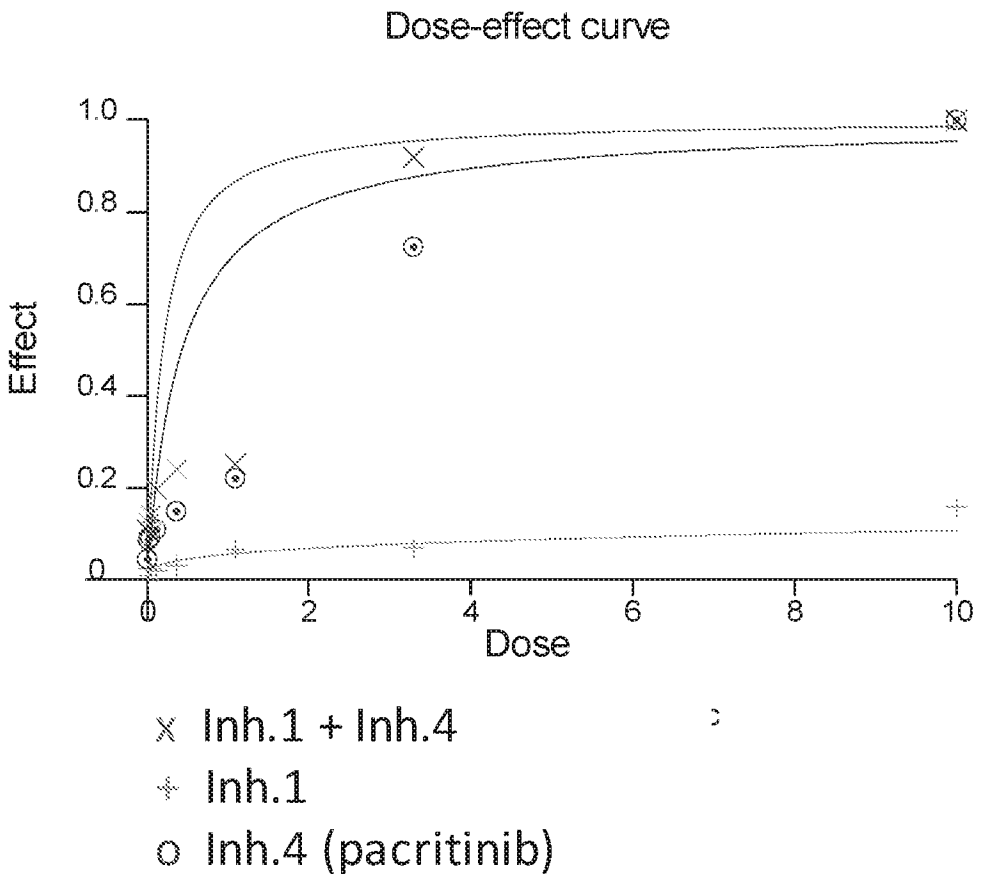

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.1 + Inh.4
Inh.1
Inh.4 (pacritinib)

FIG. 80

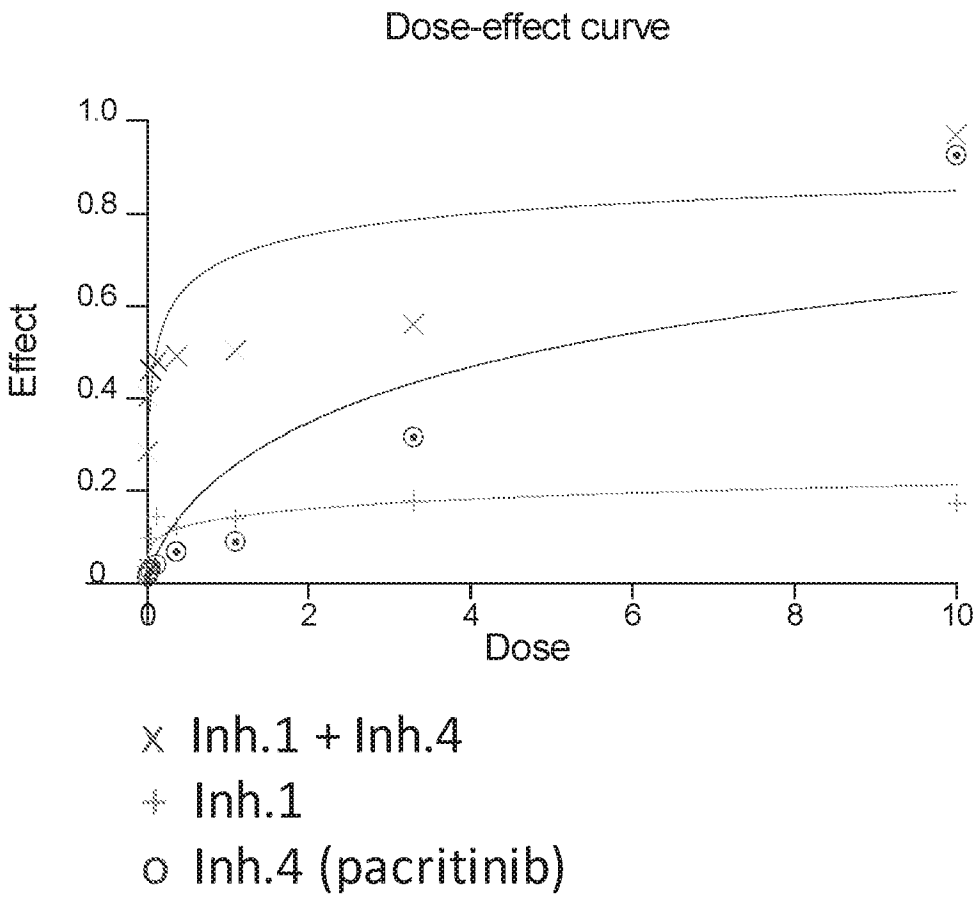

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.1 + Inh.4
Inh.1
Inh.4 (pacritinib)

FIG. 81

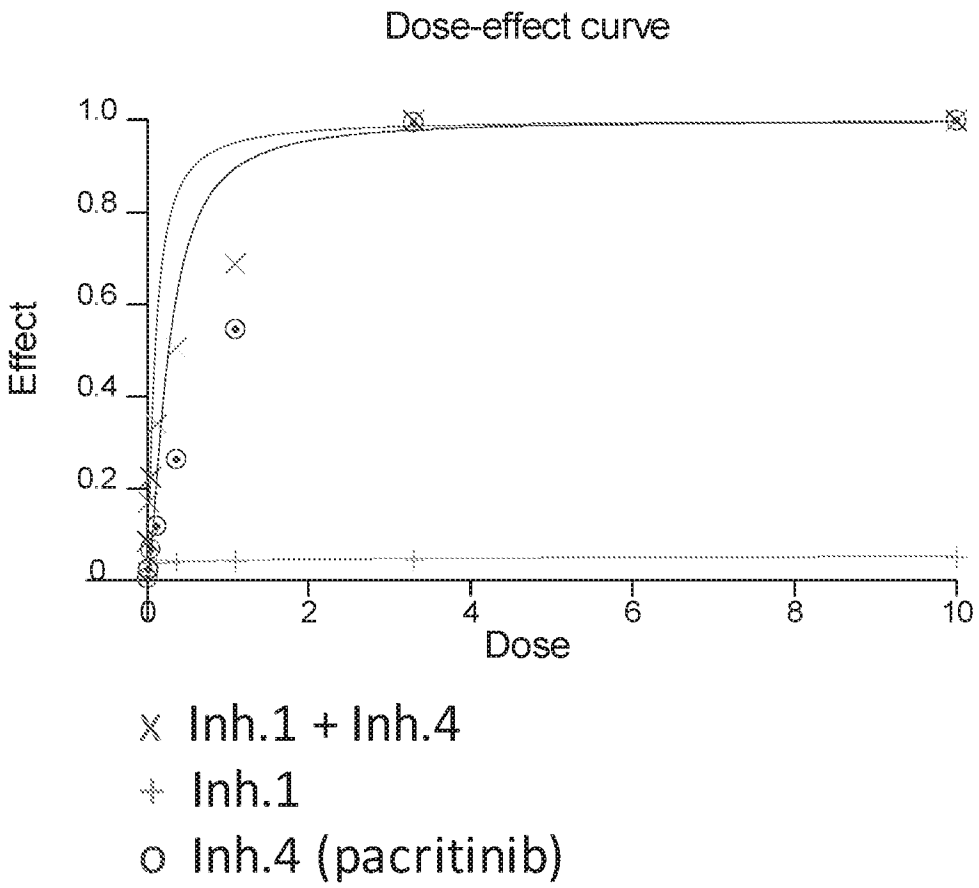

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.1 + Inh.4
Inh.1
Inh.4 (pacritinib)

FIG. 82

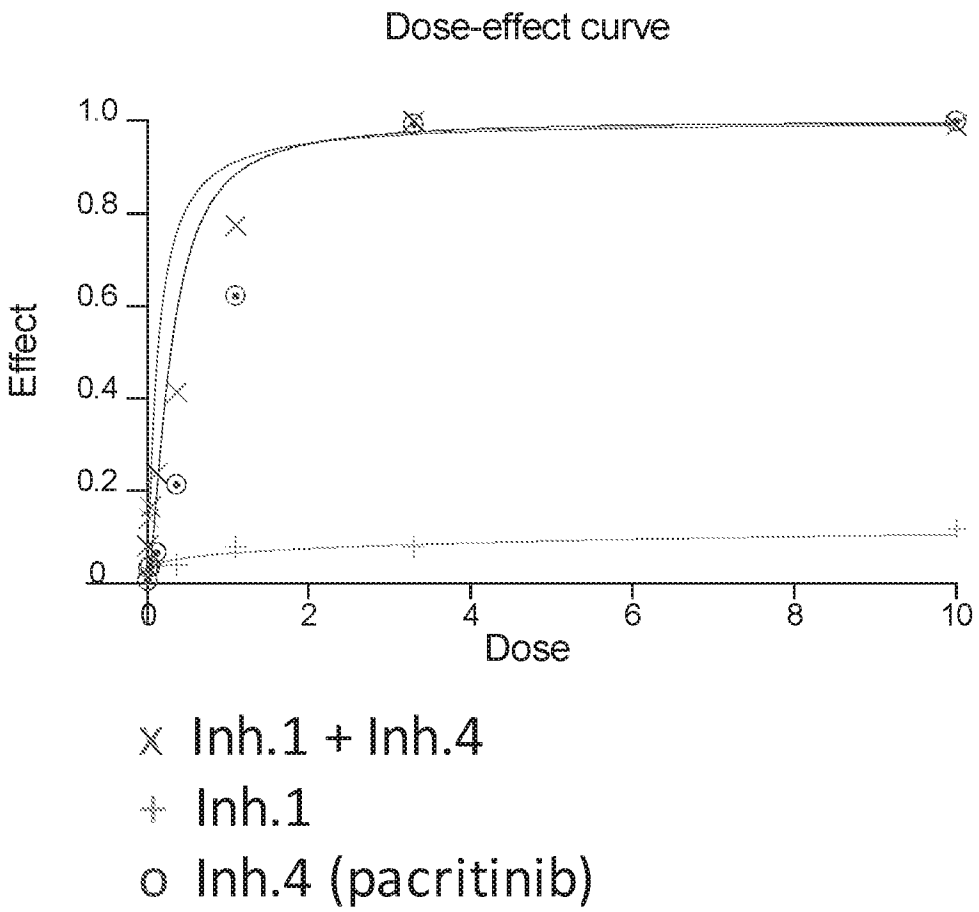

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.1 + Inh.4
Inh.1
Inh.4 (pacritinib)

FIG. 83

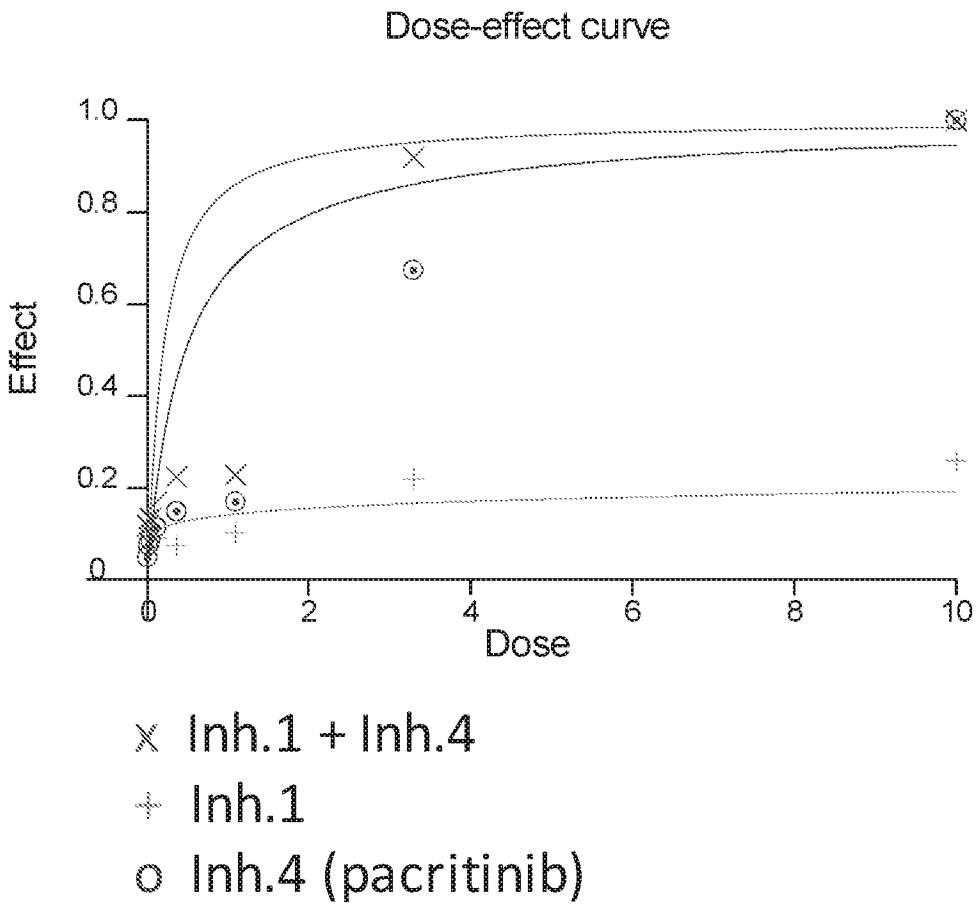

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.1 + Inh.4
Inh.1
Inh.4 (pacritinib)

FIG. 84

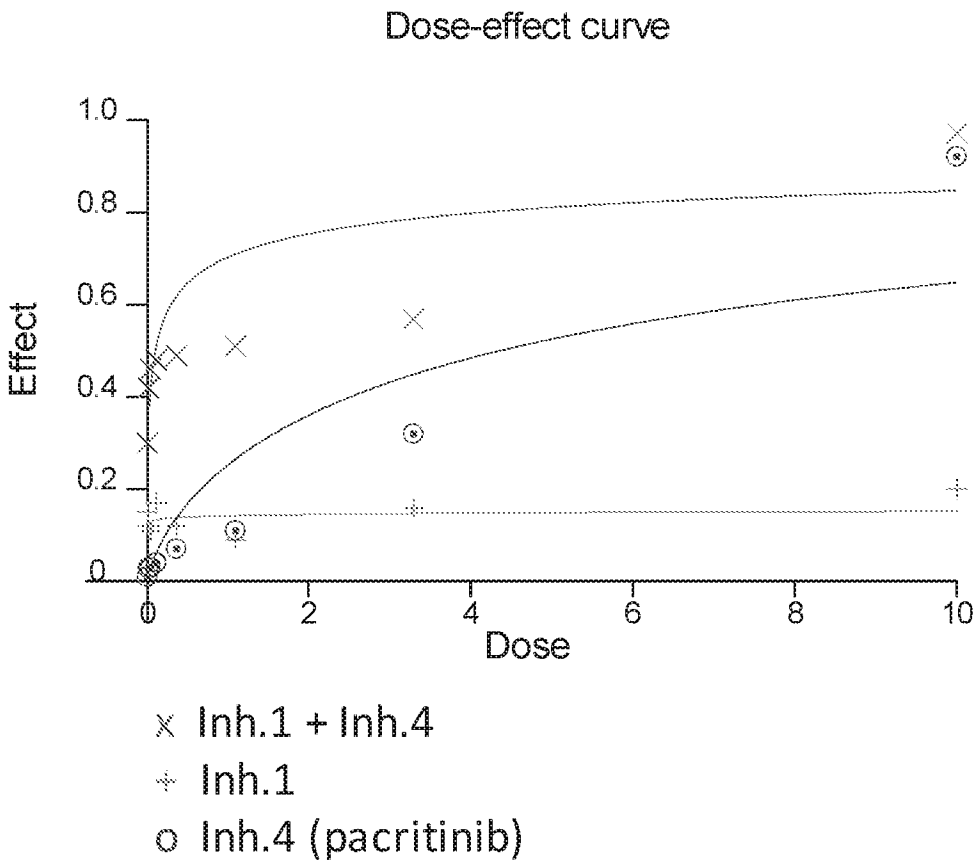

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.1 + Inh.4
Inh.1
Inh.4 (pacritinib)

FIG. 85

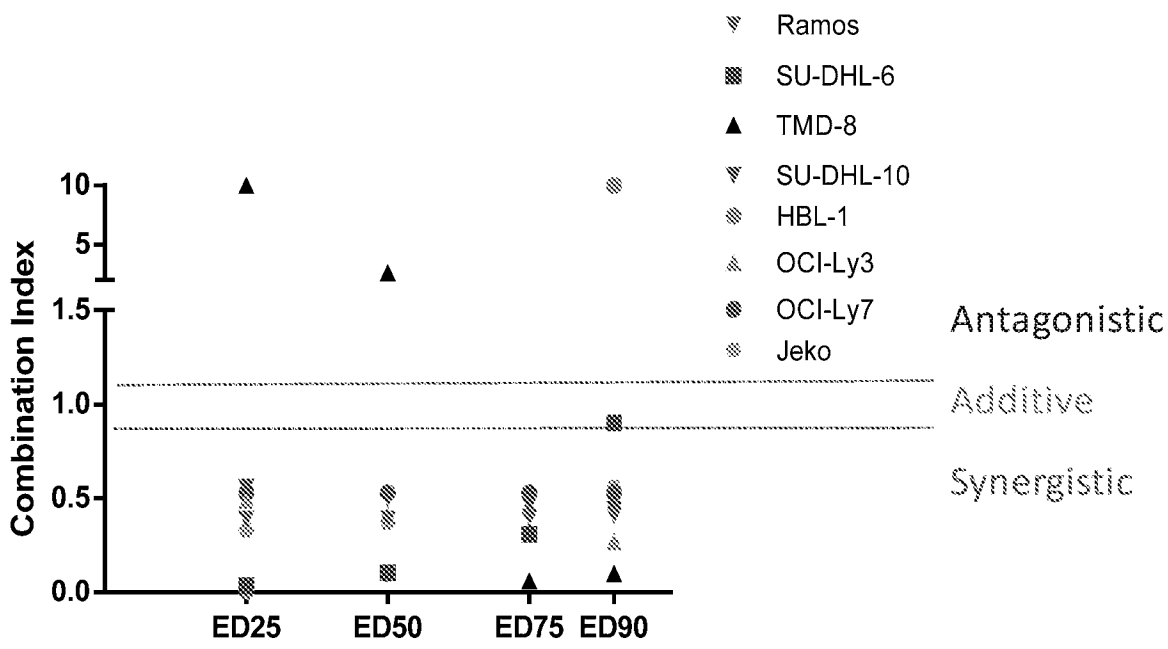

Ramos
SU-DHL-6
TMD-8
SU-DHL-10
HBL-1
OCI-Ly3
OCI-Ly7
Jeko
Antagonistic
Additive
Synergistic
Combination Index
10
5
1.5
1.0
0.5
0.0
ED25
ED50
ED75
ED90

FIG. 86

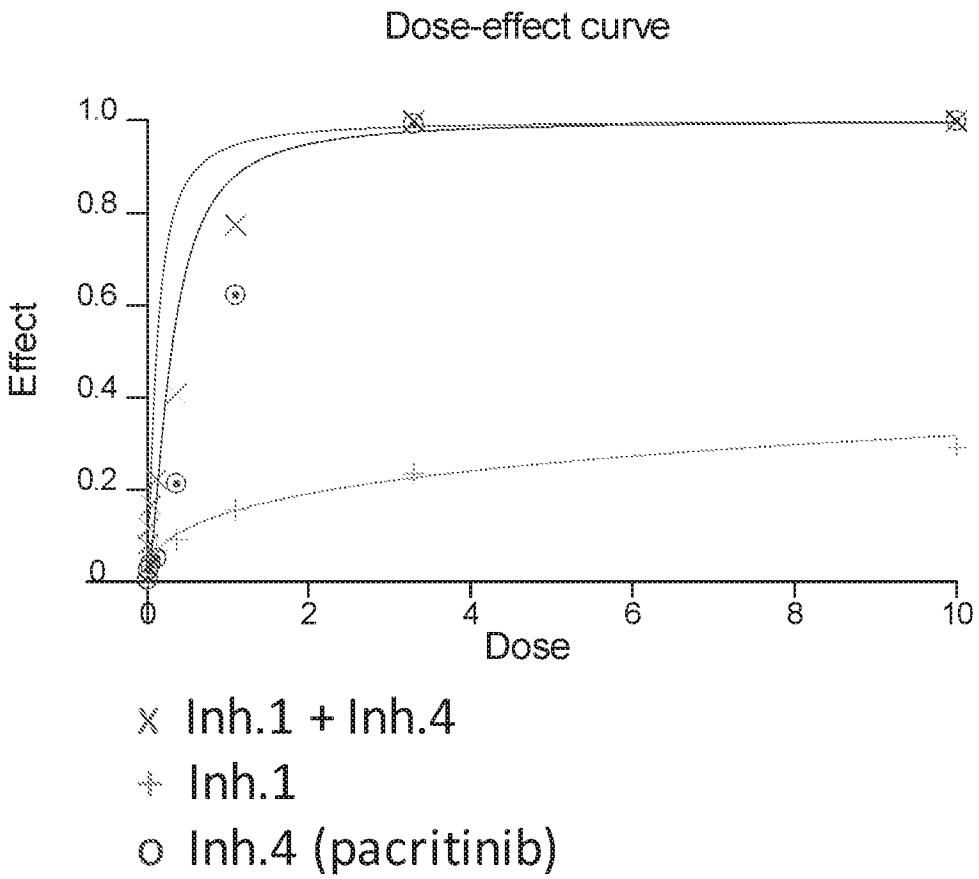

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.1 + Inh.4
Inh.1
Inh.4 (pacritinib)

FIG. 87

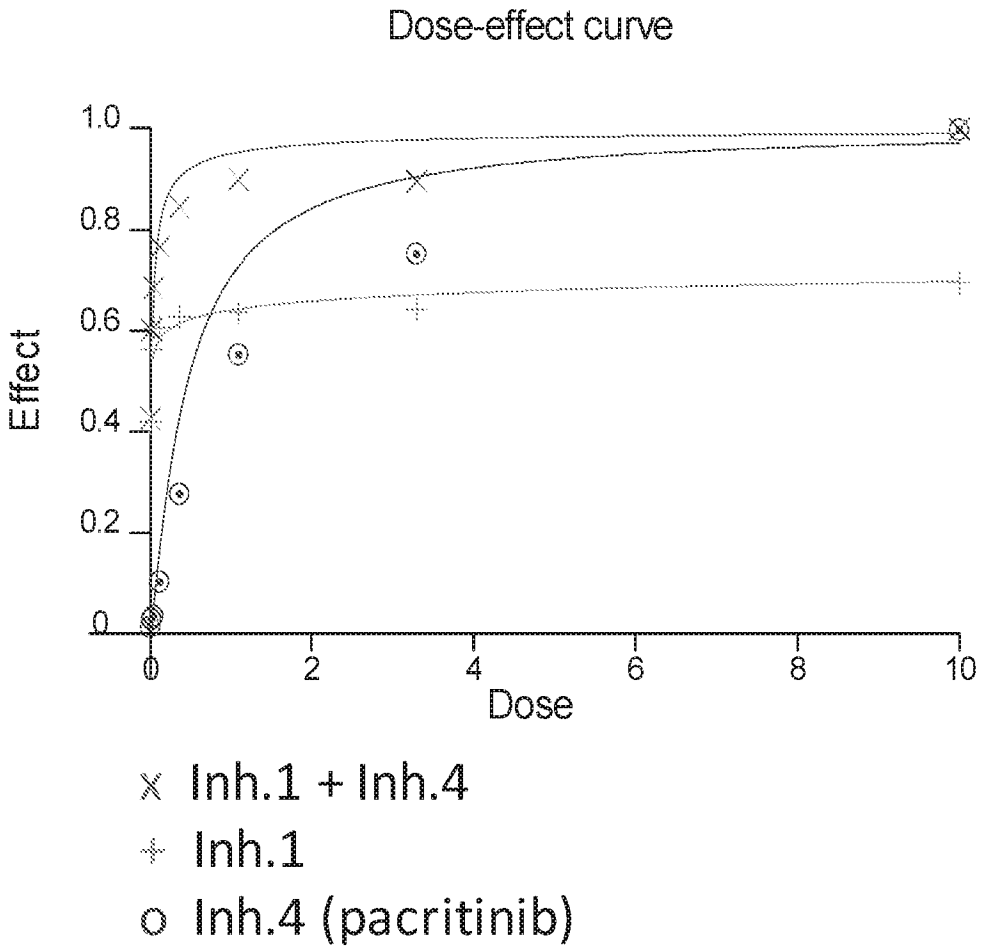

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.1 + Inh.4
Inh.1
Inh.4 (pacritinib)

FIG. 88

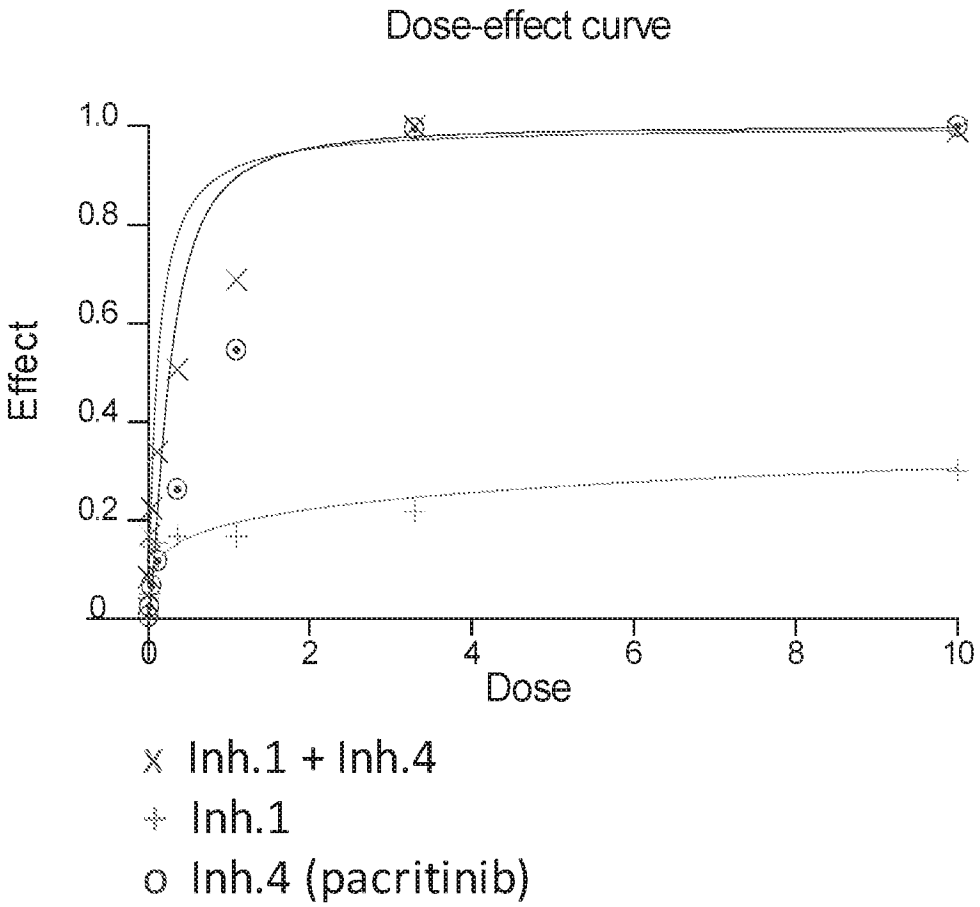

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.1 + Inh.4
Inh.1
Inh.4 (pacritinib)

FIG. 89

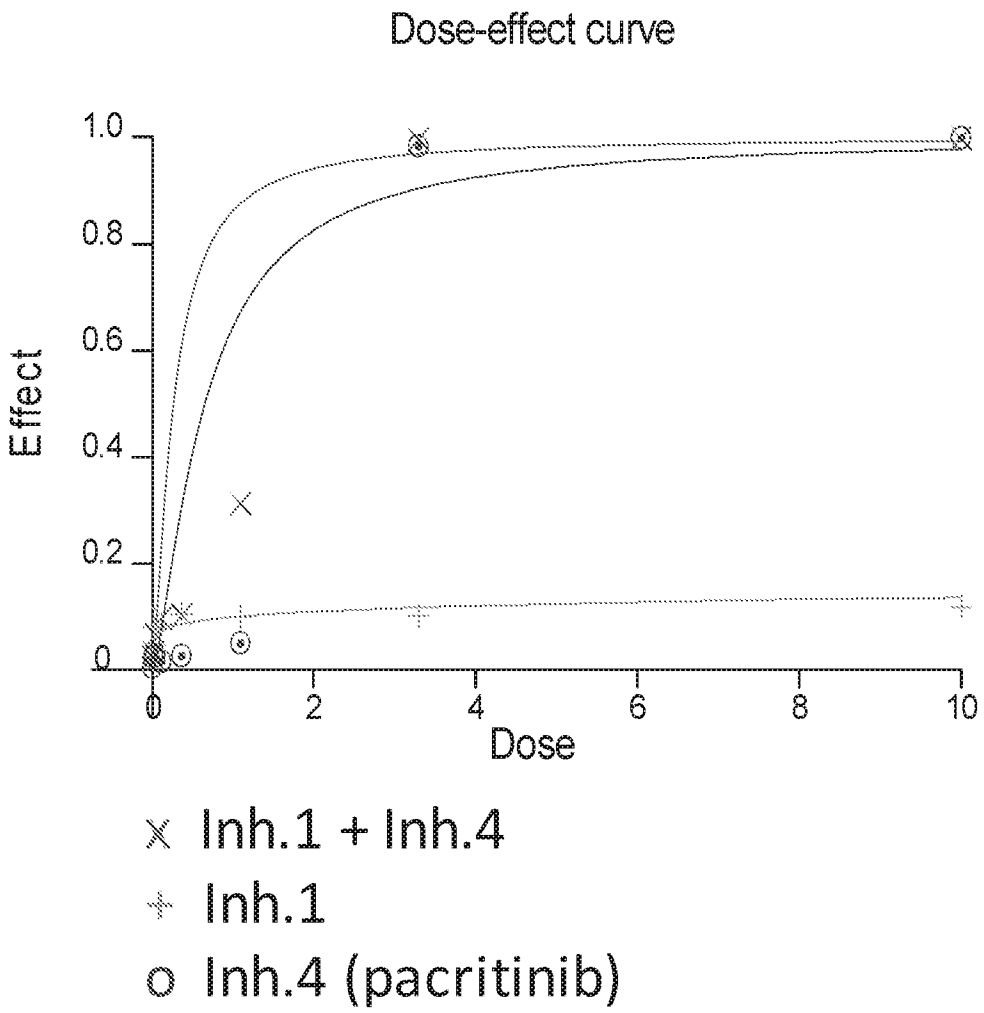

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.1 + Inh.4
Inh.1
Inh.4 (pacritinib)

FIG. 90

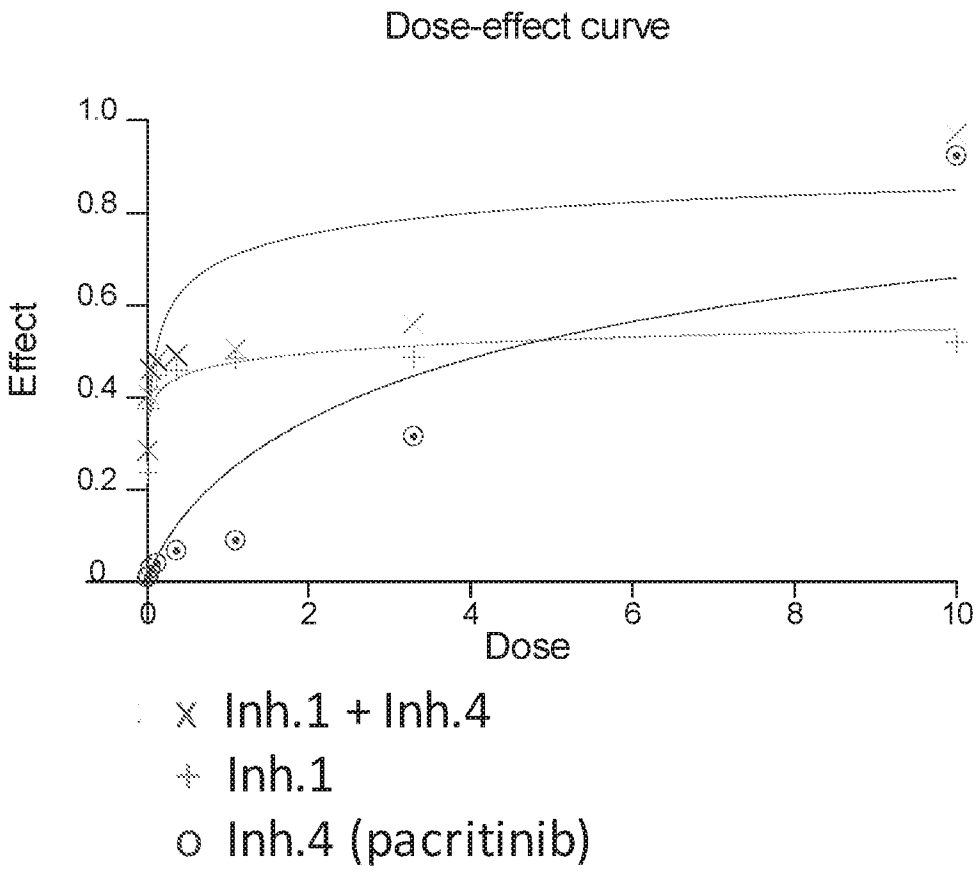

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.1 + Inh.4
Inh.1
Inh.4 (pacritinib)

FIG. 91

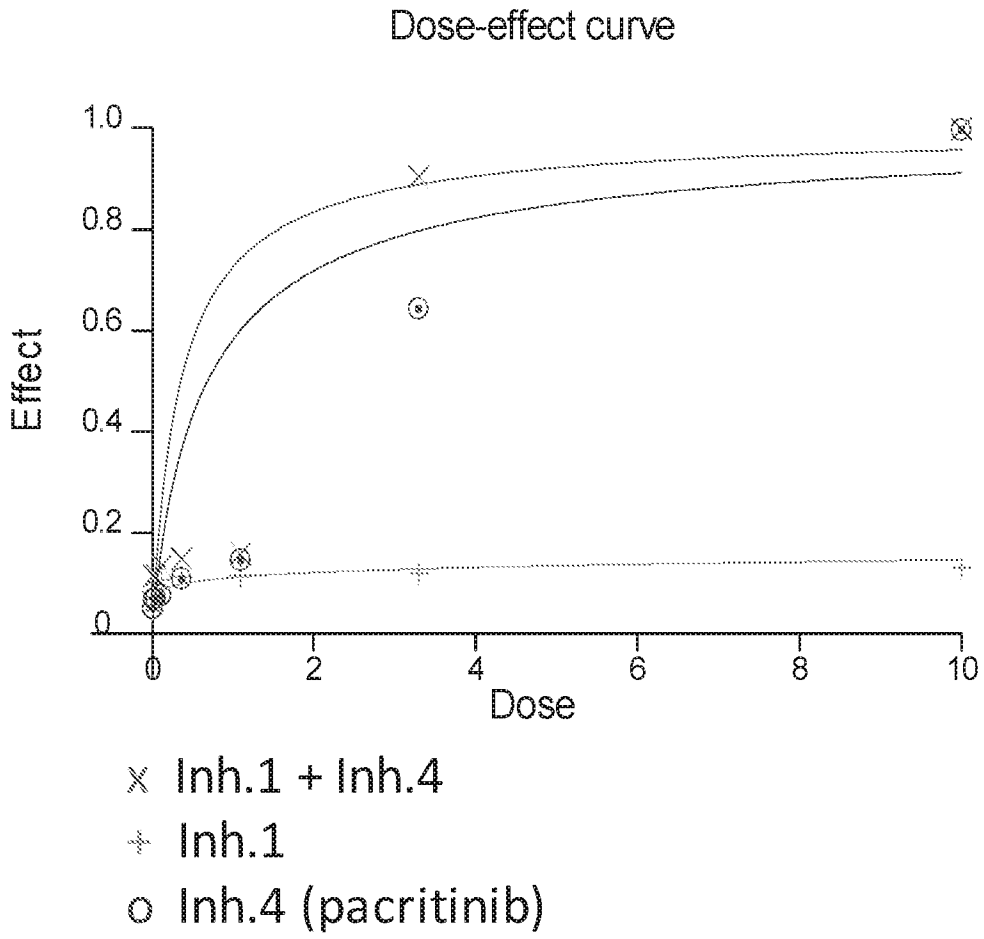

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.1 + Inh.4
Inh.1
Inh.4 (pacritinib)

FIG. 92

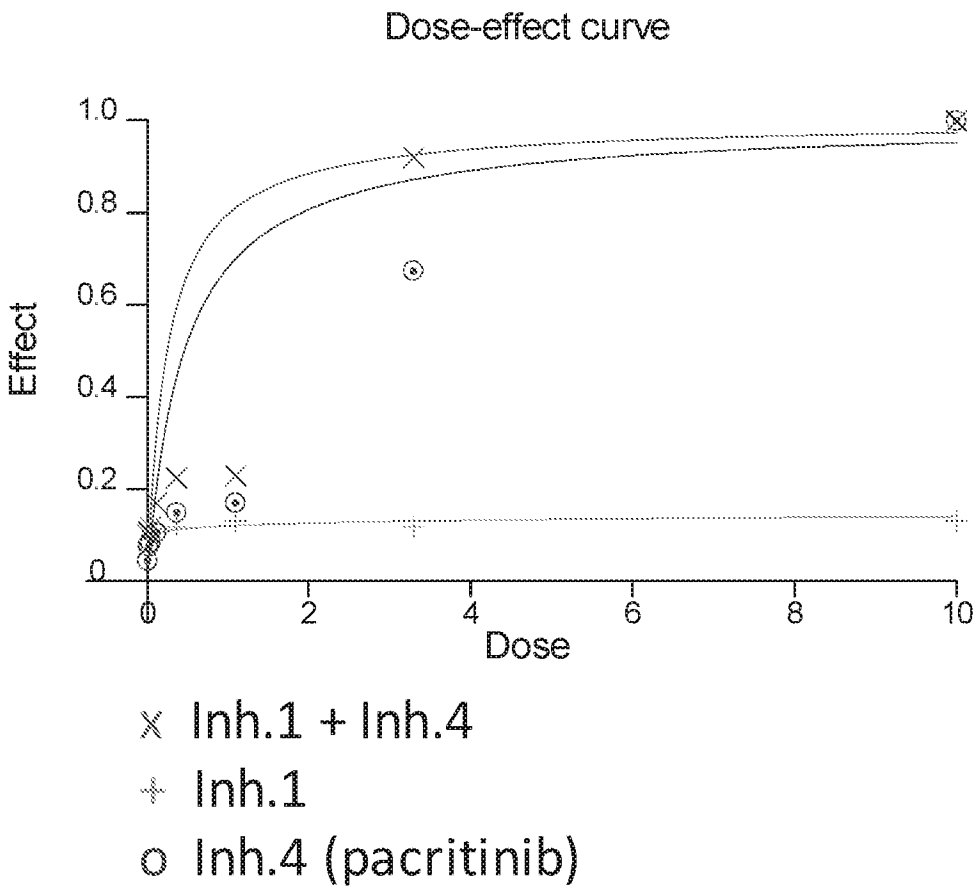

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.1 + Inh.4
Inh.1
Inh.4 (pacritinib)

FIG. 93

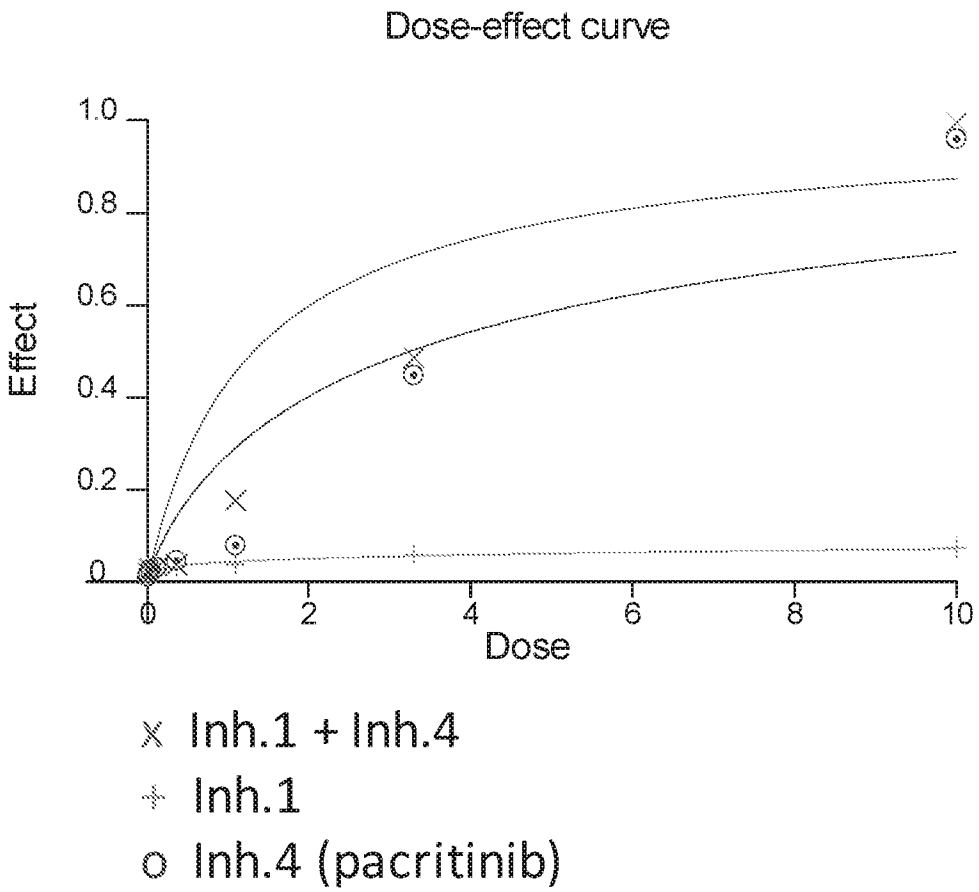

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.1 + Inh.4
Inh.1
Inh.4 (pacritinib)

FIG. 94

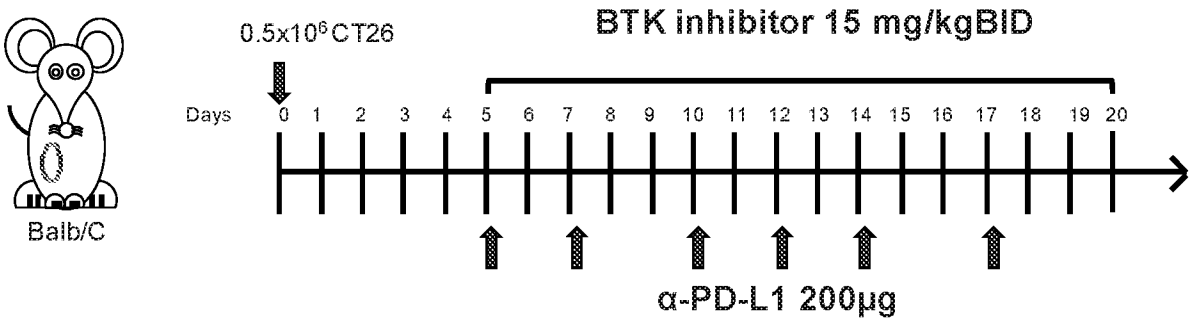

0.5x10⁶CT26
BTK inhibitor 15 mg/kgBID
Days
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Balb/C
α-PD-L1 200μg

FIG. 95

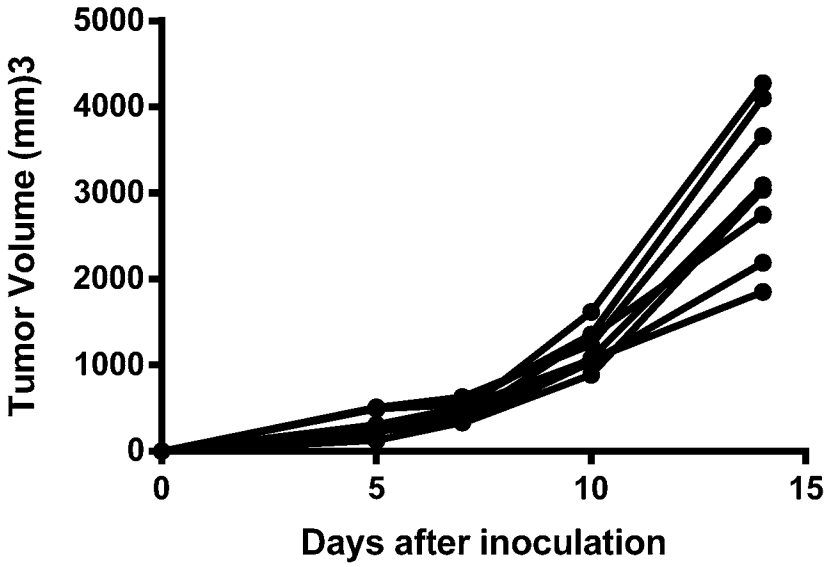

5000
4000
3000
2000
1000
0
Tumor Volume (mm)3
0
5
10
15
Days after inoculation

FIG. 96

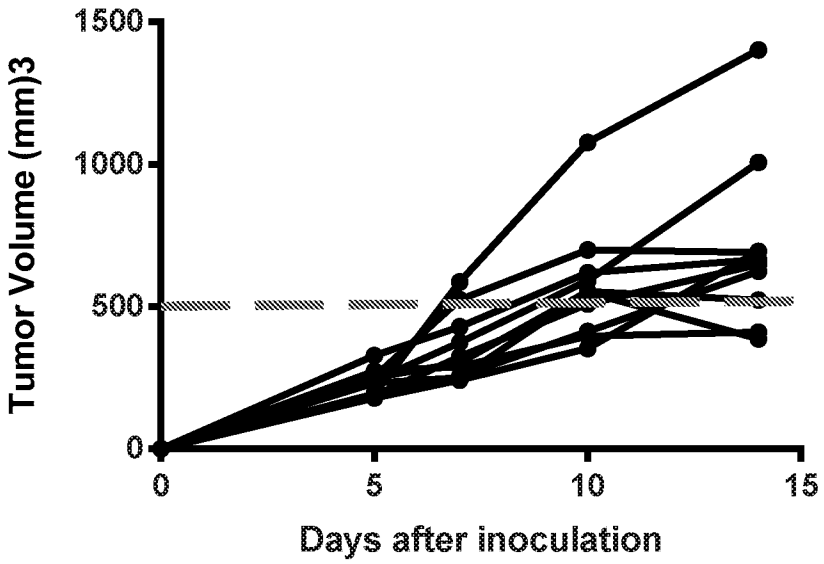

1500
1000
500
0
Tumor Volume (mm)3
0
5
10
15
Days after inoculation

FIG. 97

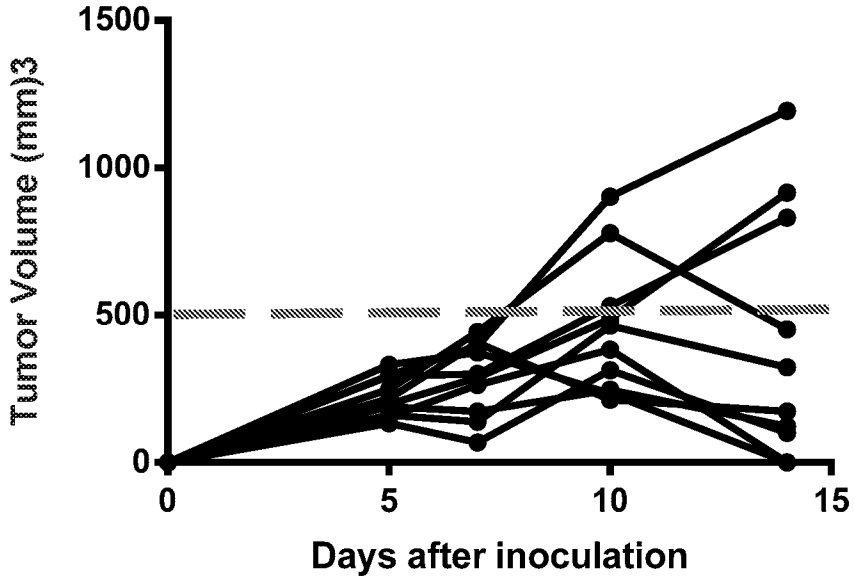

1500
1000
500
0
Tumor Volume (mm)3
0
5
10
15
Days after inoculation

FIG. 98

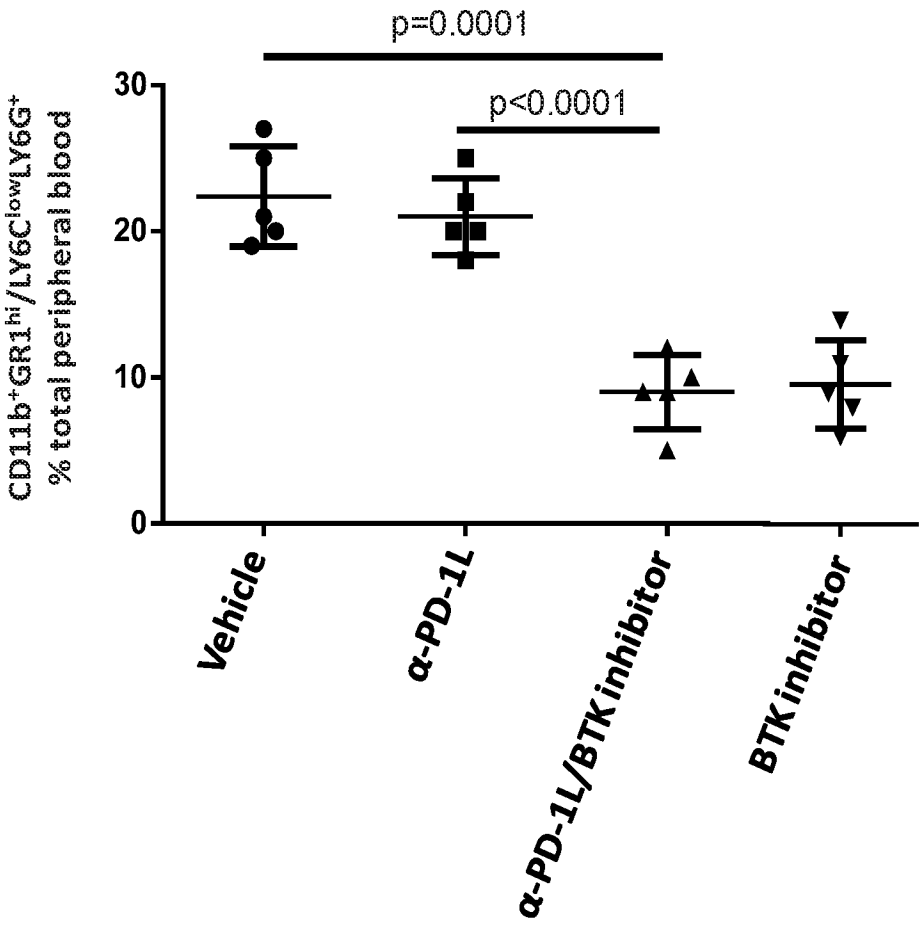

p=0.0001
p<0.0001
30
20
10
0
CD11b+GR1hi/LY6Clow LY6G+
% total peripheral blood
Vehicle
α-PD-1L
α-PD-1L/BTKinhibitor
BTKinhibitor

FIG. 99

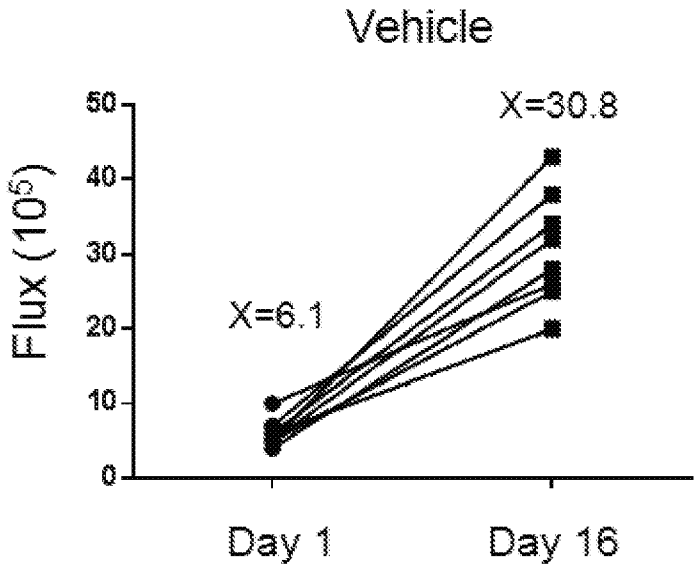



FIG. 100

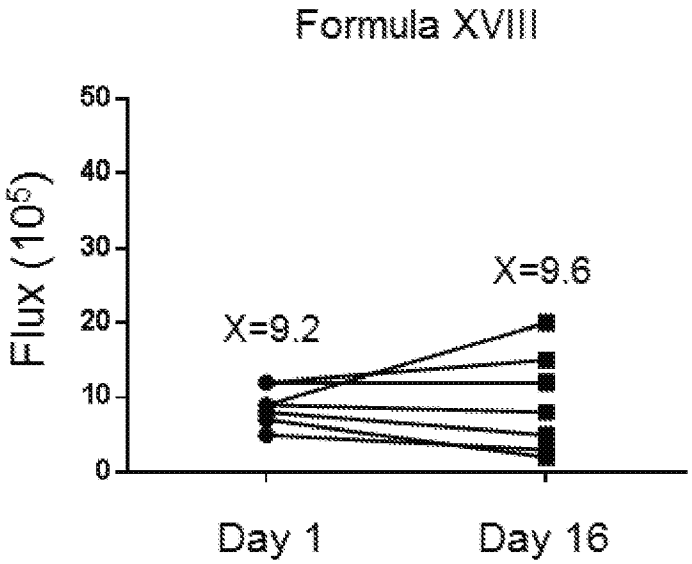



FIG. 101

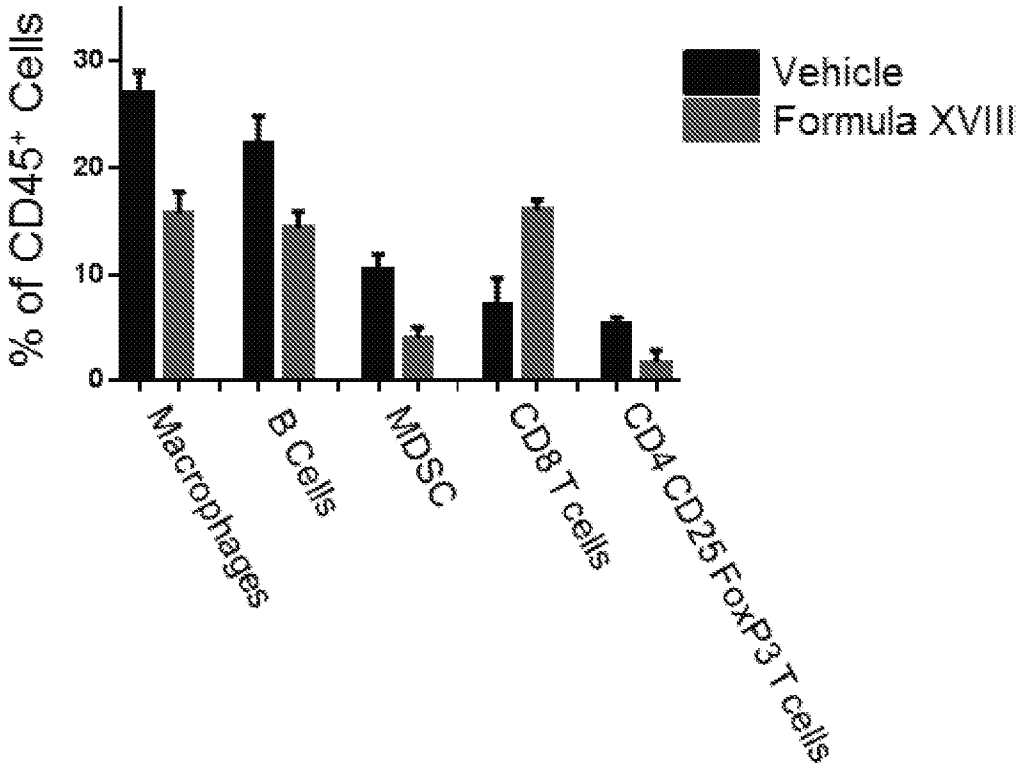

% of CD45+ Cells
30
20
10
0
Vehicle
Formula XVIII
Macrophages
B Cells
MDSC
CD8 T cells
CD4 CD25 FoxP3 T cells

FIG. 102

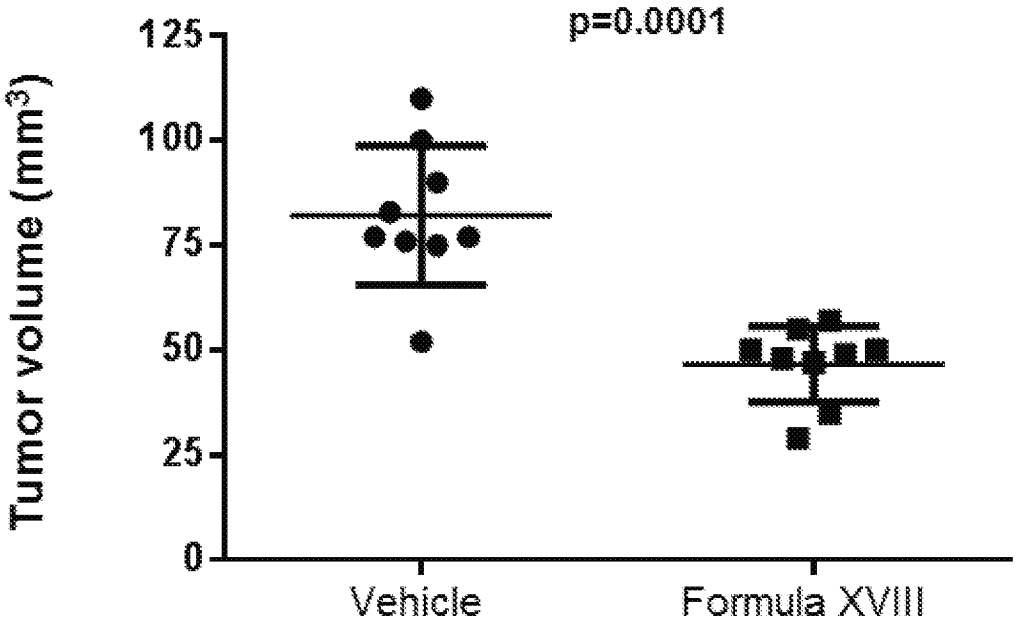

p=0.0001
Tumor volume (mm3)
125
100
75
50
25
0
Vehicle
Formula XVIII

FIG. 103

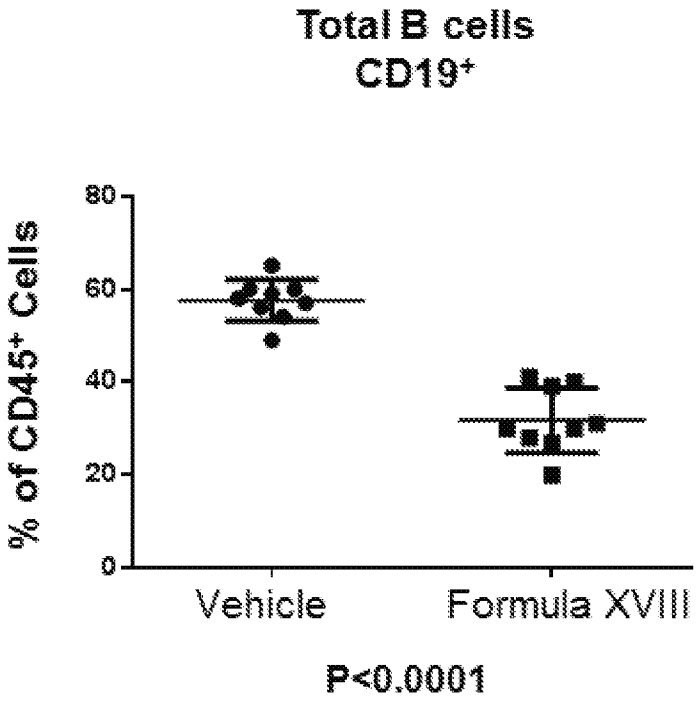

Total B cells
CD19+
% of CD45+ Cells
80
60
40
20
0
Vehicle
Formula XVIII
P<0.0001

FIG. 104

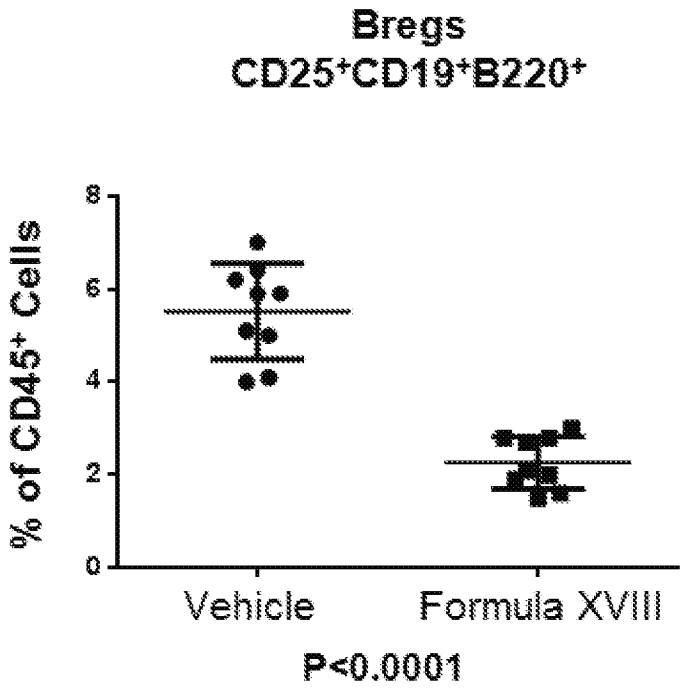

Bregs
CD25+CD19+B220+
% of CD45+ Cells
8
6
4
2
0
Vehicle
Formula XVIII
P<0.0001

FIG. 105

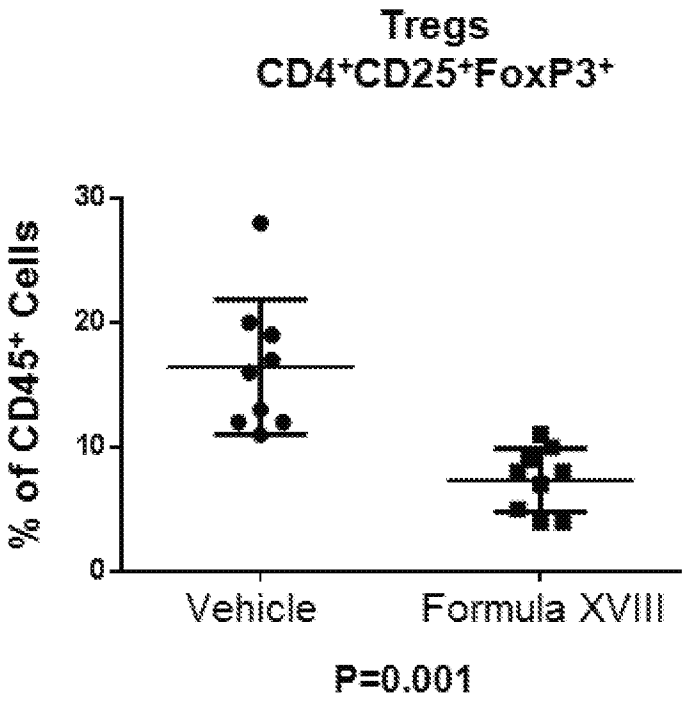

Tregs
CD4+CD25+FoxP3+
% of CD45+ Cells
30
20
10
0
Vehicle
Formula XVIII
P=0.001

FIG. 106

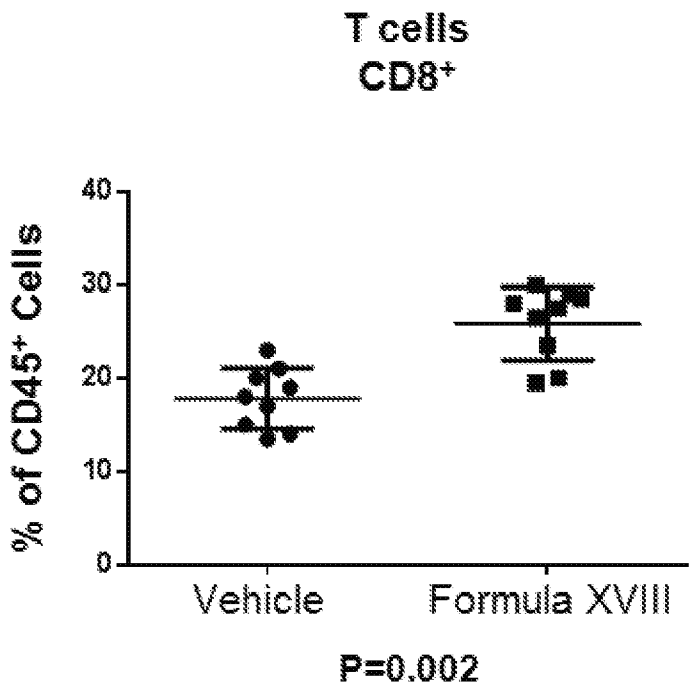

T cells
CD8+
% of CD45+ Cells
40
30
20
10
0
Vehicle
Formula XVIII
P=0.002

FIG. 107

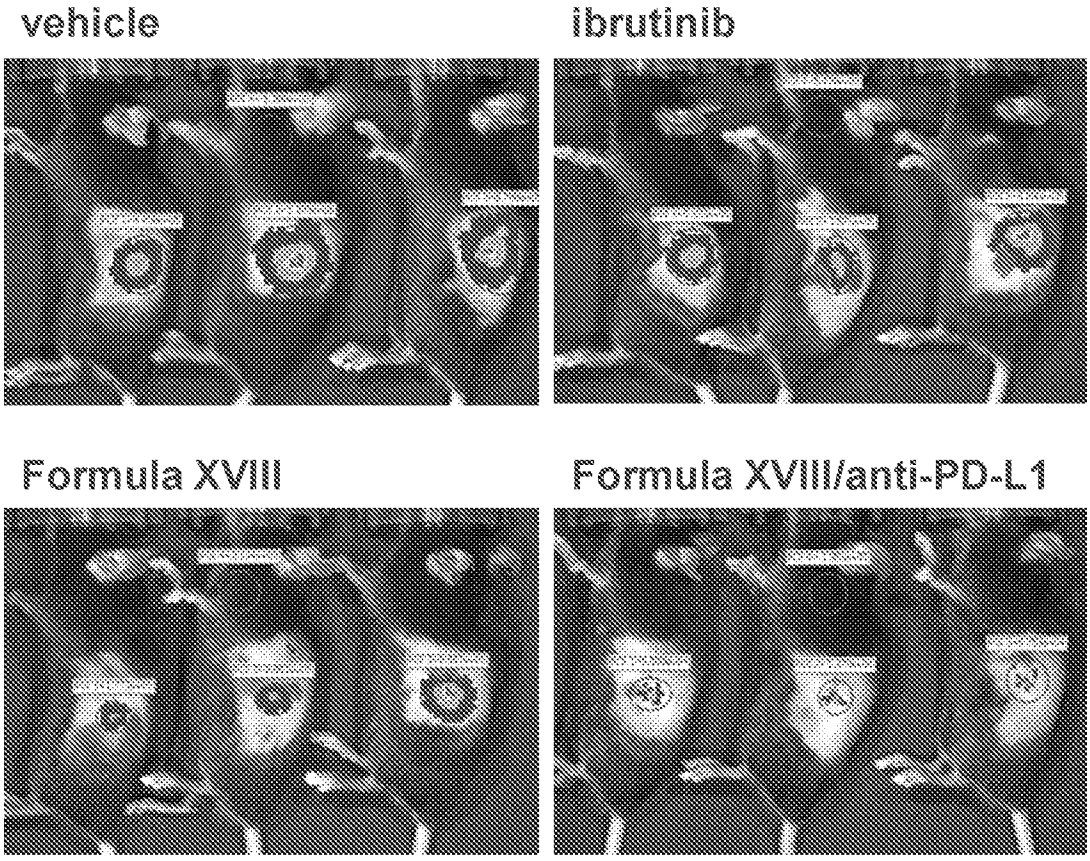



FIG. 108

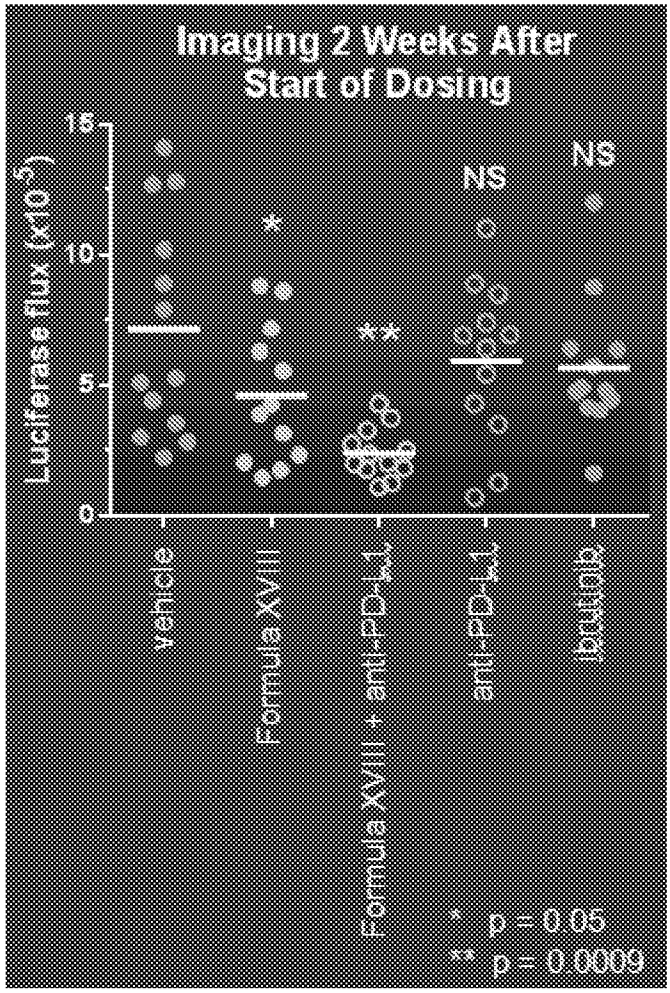

Imaging 2 Weeks After Start of Dosing
Luciferase flux (x10^-2)
15
10
5
0
NS
NS
*
**
vehicle
Formula XVIII
Formula XVIII + anti-PD-L1
anti-PD-L1
ipilimumab
* p = 0.05
** p = 0.0009

FIG. 109

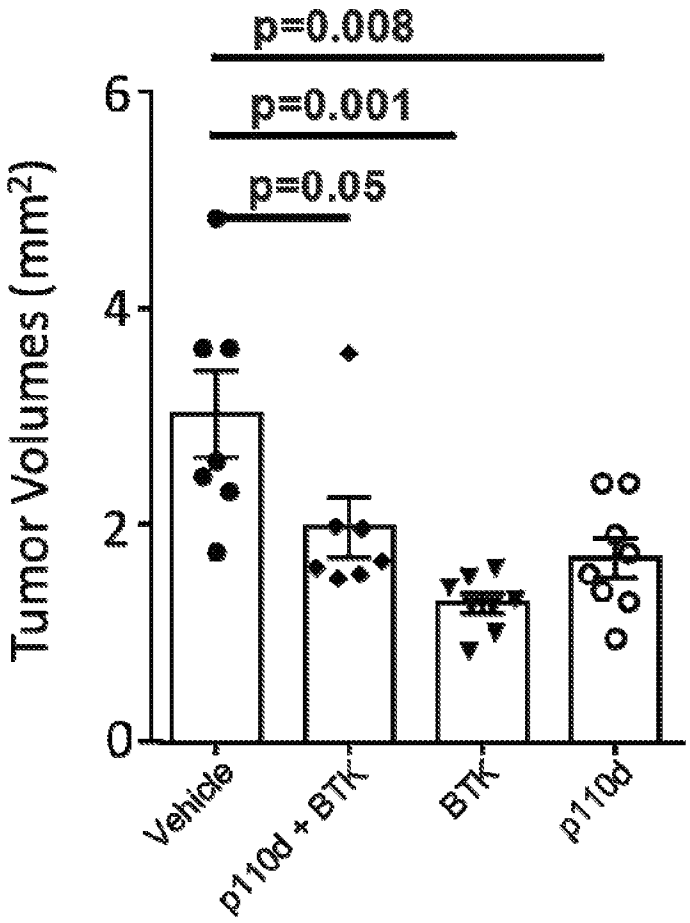

p=0.008
p=0.001
p=0.05
Tumor Volumes (mm2)
6
4
2
0
Vehicle
p110d + BTK
BTK
p110d

FIG. 110

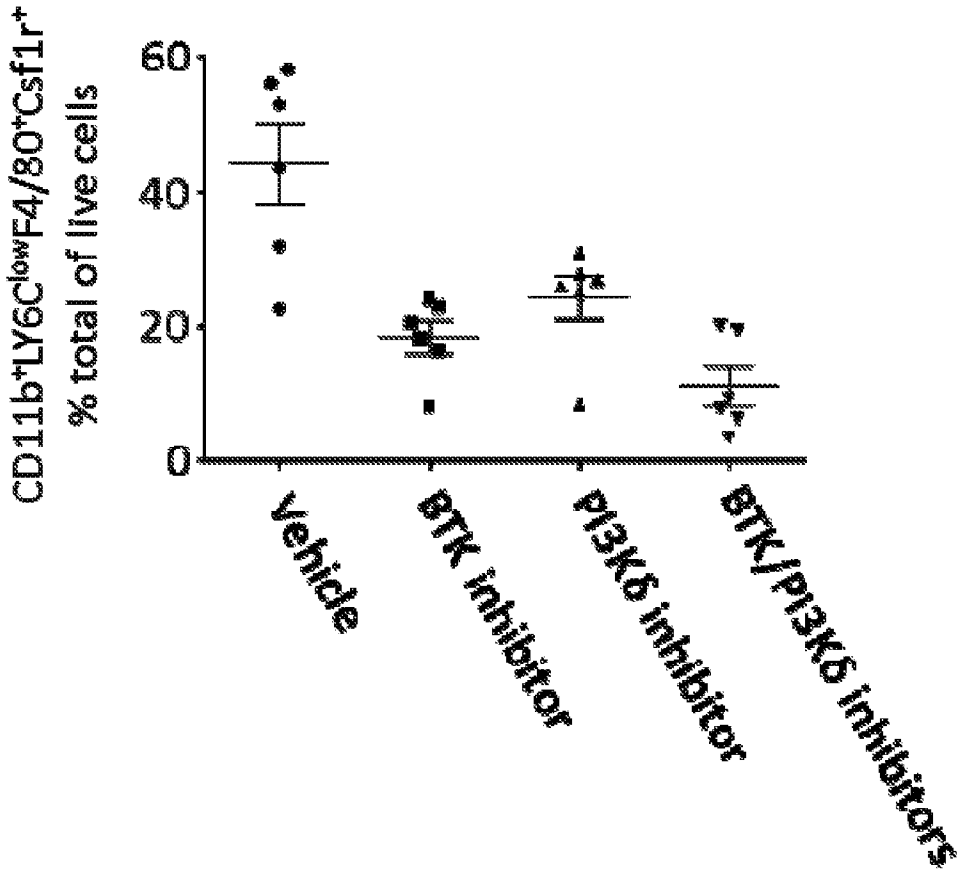

CD11b+LY6Clow F4/80+Csf1r+
% total of live cells
60
40
20
0
vehicle
BTK inhibitor
PI3Kδ inhibitor
BTK/PI3Kδ inhibitors

FIG. 111

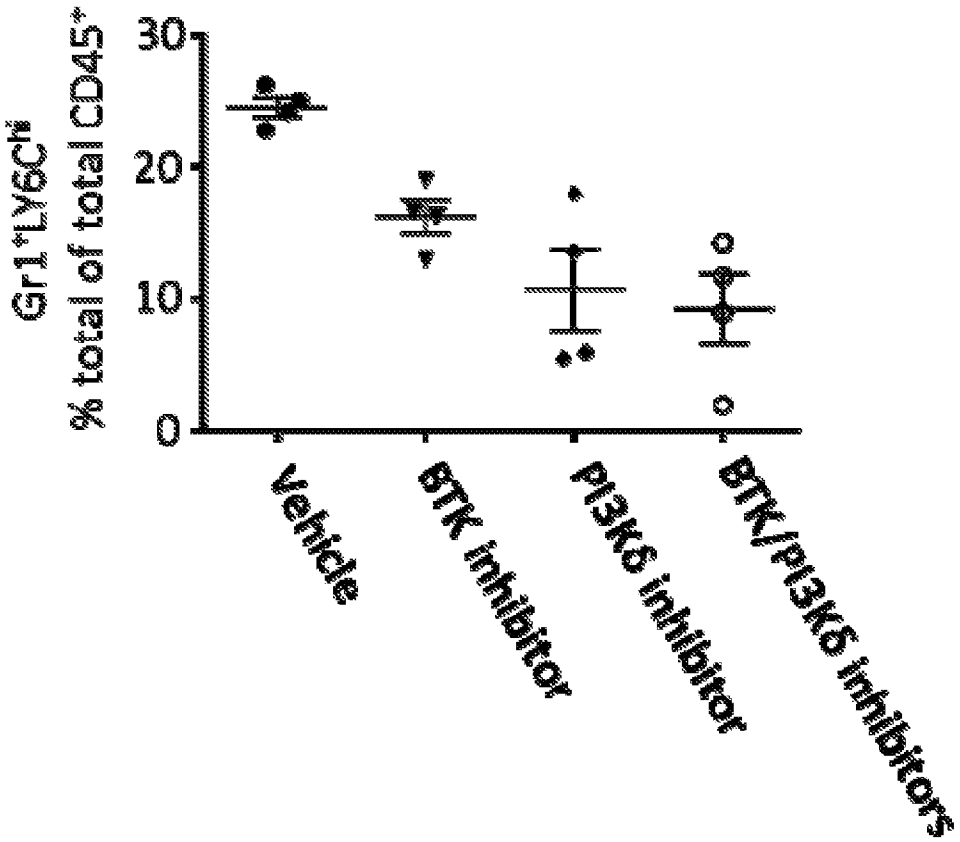

Gr1+LY6Chi
% total of total CD45+
30
20
10
0
Vehicle
BTK inhibitor
PI3Kδ inhibitor
BTK/PI3Kδ inhibitors

FIG. 112

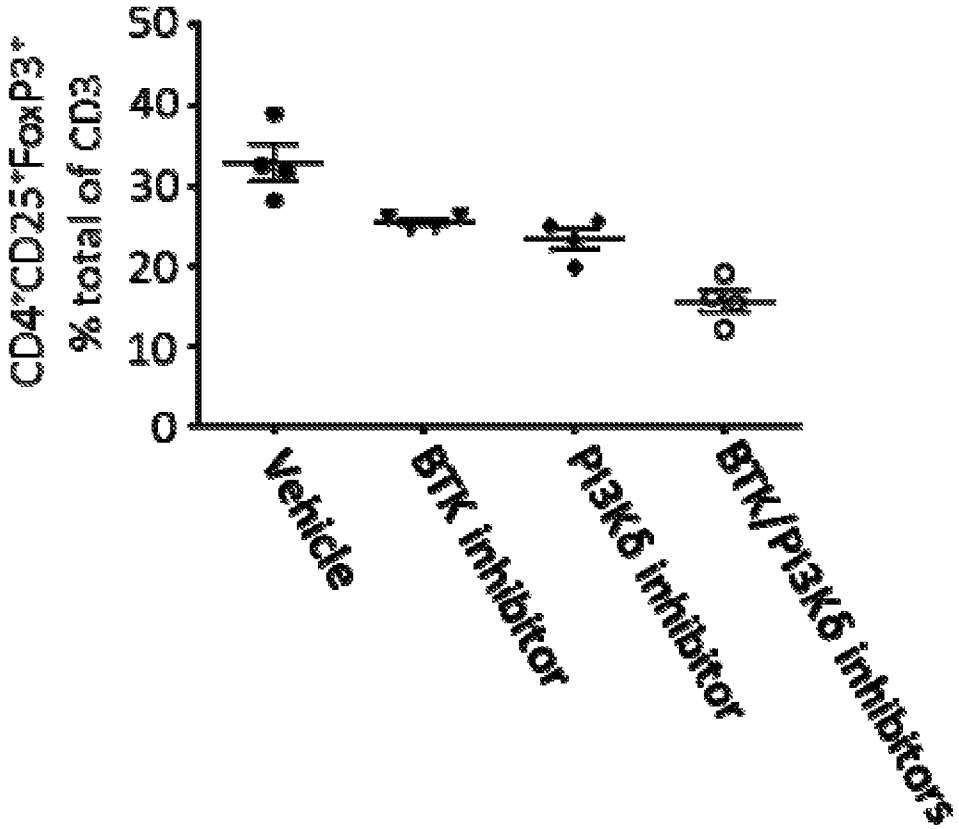

CD4+CD25+FoxP3+
% total of CD3
50
40
30
20
10
0
Vehicle
BTK inhibitor
PI3Kδ inhibitor
BTK/PI3Kδ inhibitors

FIG. 113

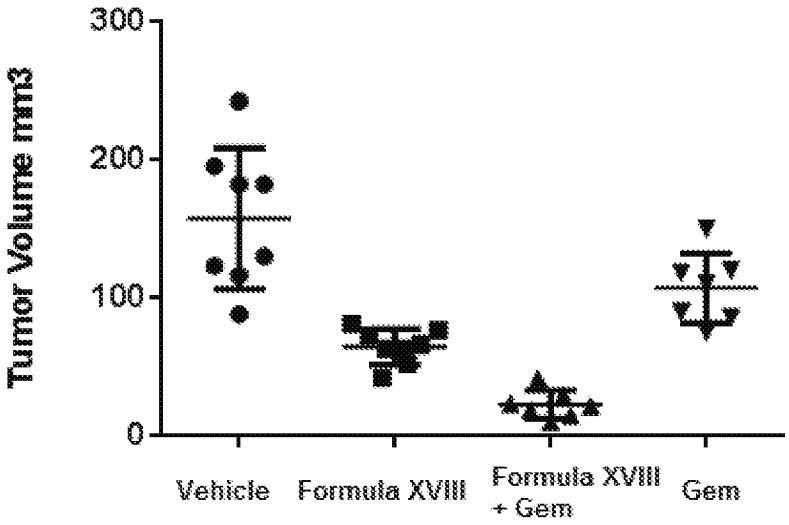

Tumor Volume mm3
300
200
100
0
Vehicle
Formula XVIII
Formula XVIII + Gem
Gem

FIG. 114

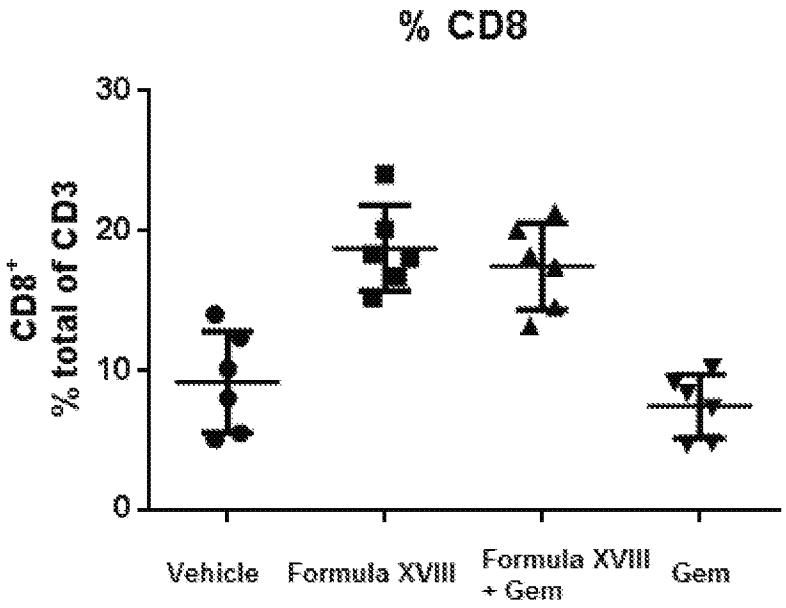

% CD8
CD8+
% total of CD3
30
20
10
0
Vehicle
Formula XVIII
Formula XVIII + Gem
Gem

FIG. 115

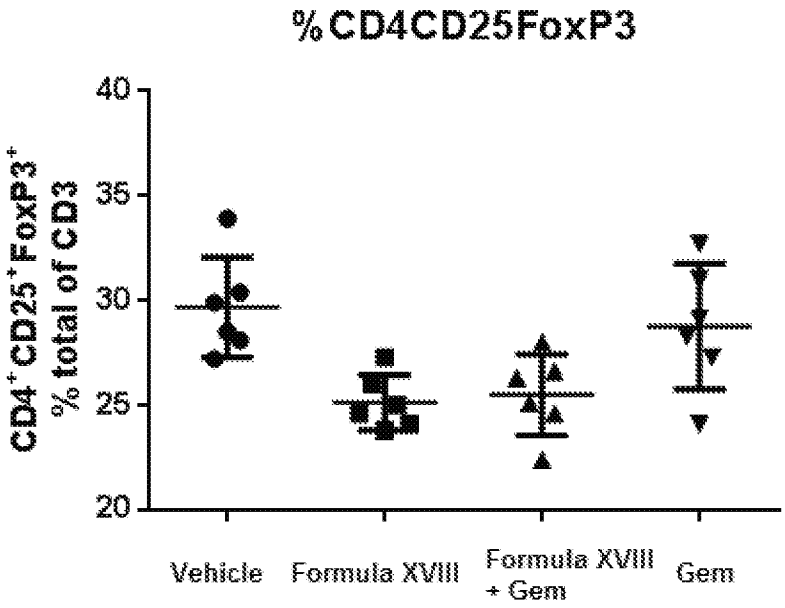

%CD4CD25FoxP3
CD4+CD25+FoxP3+
% total of CD3
40
35
30
25
20
Vehicle
Formula XVIII
Formula XVIII + Gem
Gem

FIG. 116

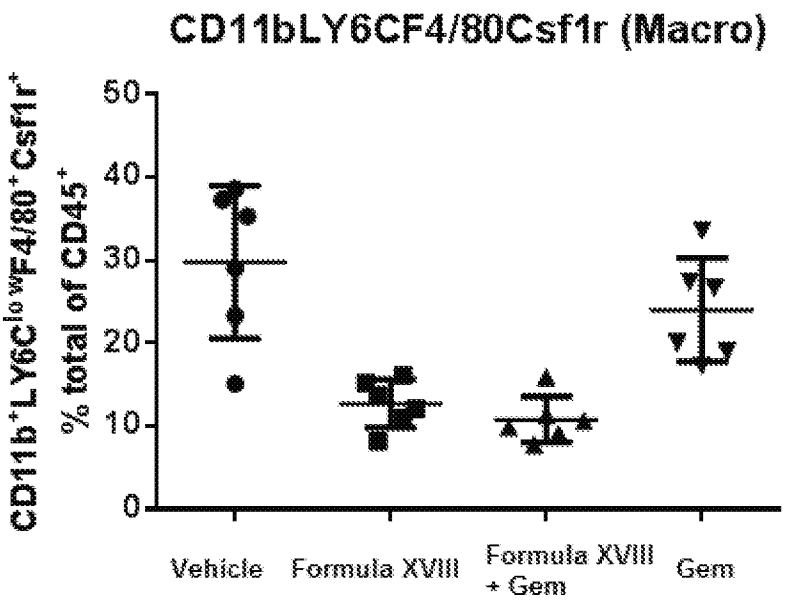

CD11bLY6CF4/80Csf1r (Macro)
CD11b+LY6Clo wF4/80+Csf1r+
% total of CD45+
60
40
30
20
10
0
Vehicle
Formula XVIII
Formula XVIII + Gem
Gem

FIG. 117

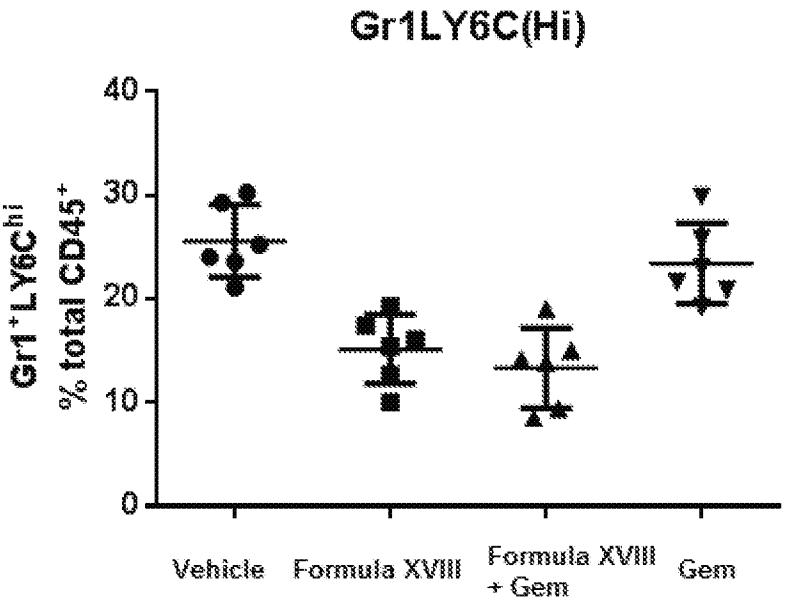

Gr1LY6C(Hi)
Gr1+LY6Chi
% total CD45+
40
30
20
10
0
Vehicle
Formula XVIII
Formula XVIII + Gem
Gem

FIG. 118

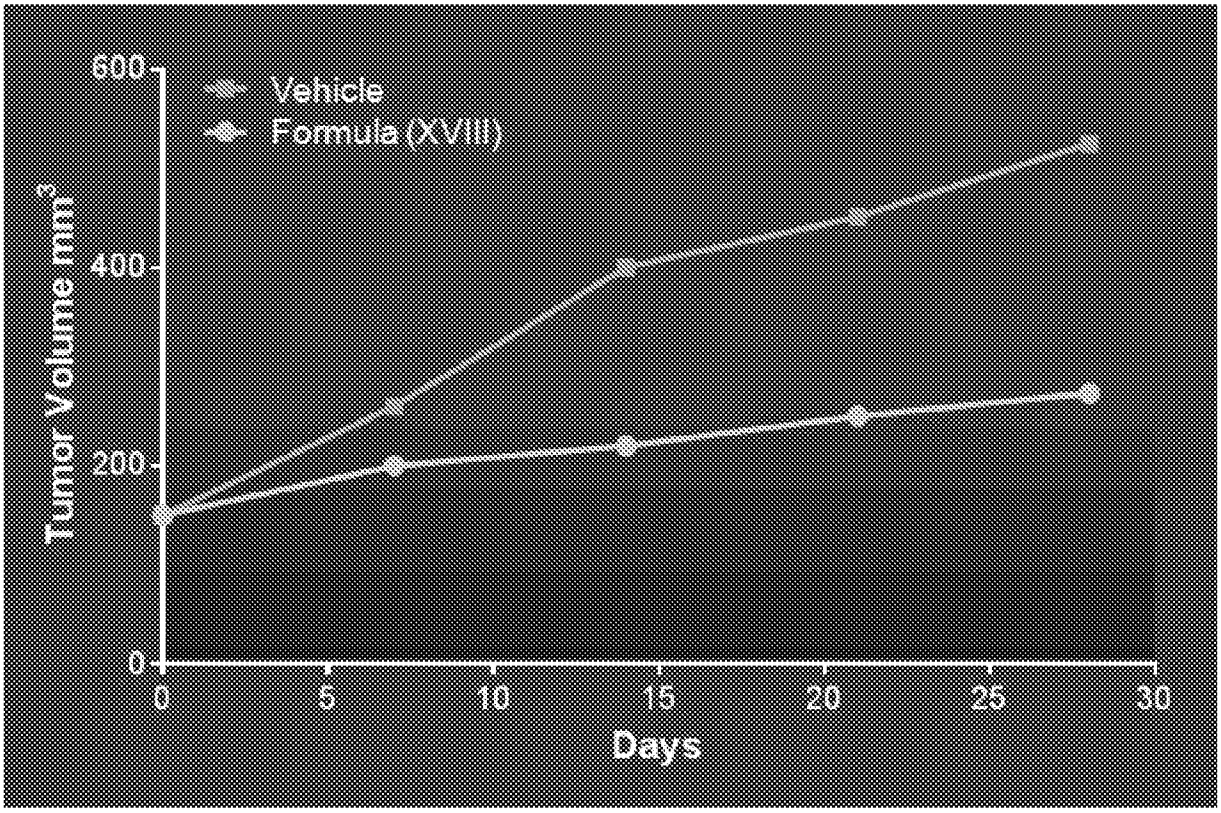

600
400
200
0
Tumor Volume mm3
Vehicle
Formula (XVIII)
0
5
10
15
20
25
30
Days

FIG. 119

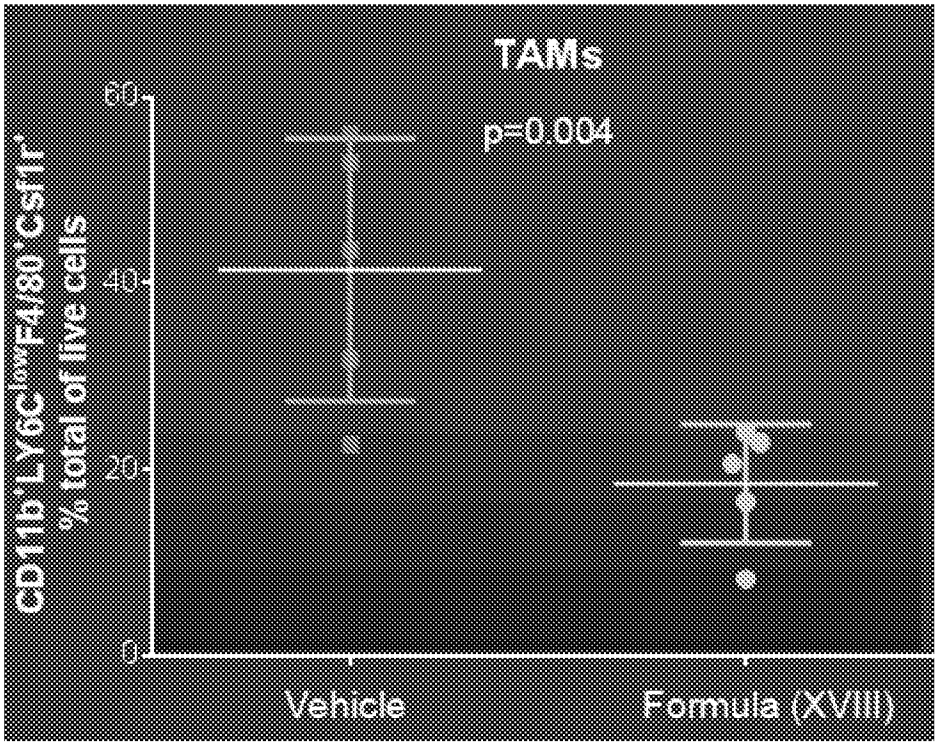

TAMs
p=0.004
CD11b+Ly6C$^{low}$F4/80+Csf1r+
% total of live cells
60
40
20
0
Vehicle
Formula (XVIII)

FIG. 120

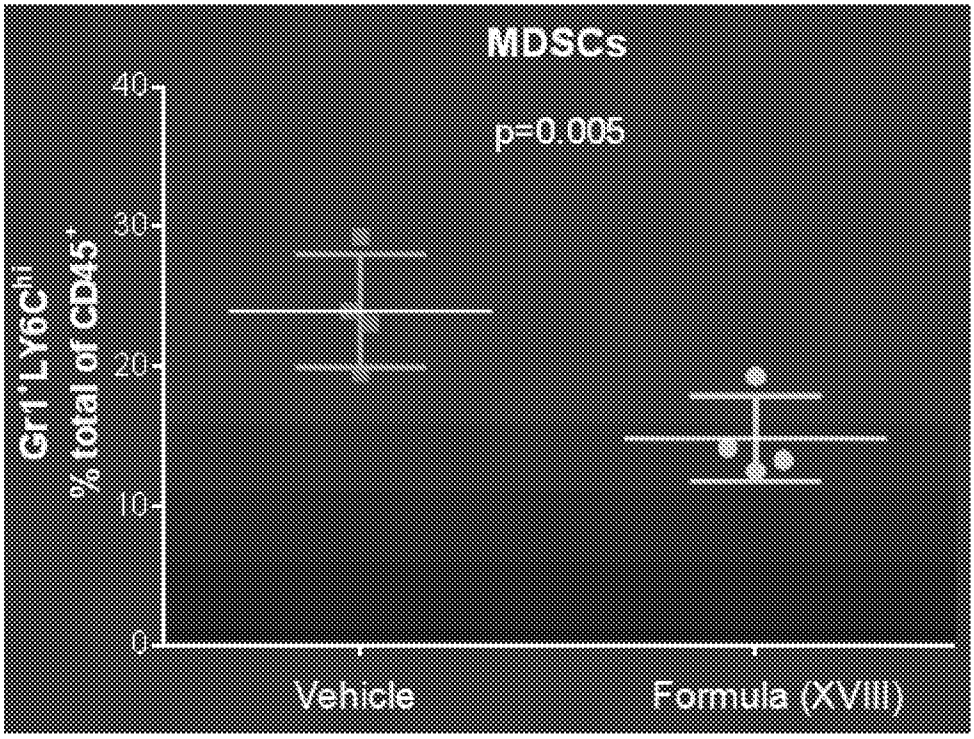

MDSCs
p=0.005
Gr1+Ly6C++
% total of CD45+
40
30
20
10
0
Vehicle
Formula (XVIII)

FIG. 121

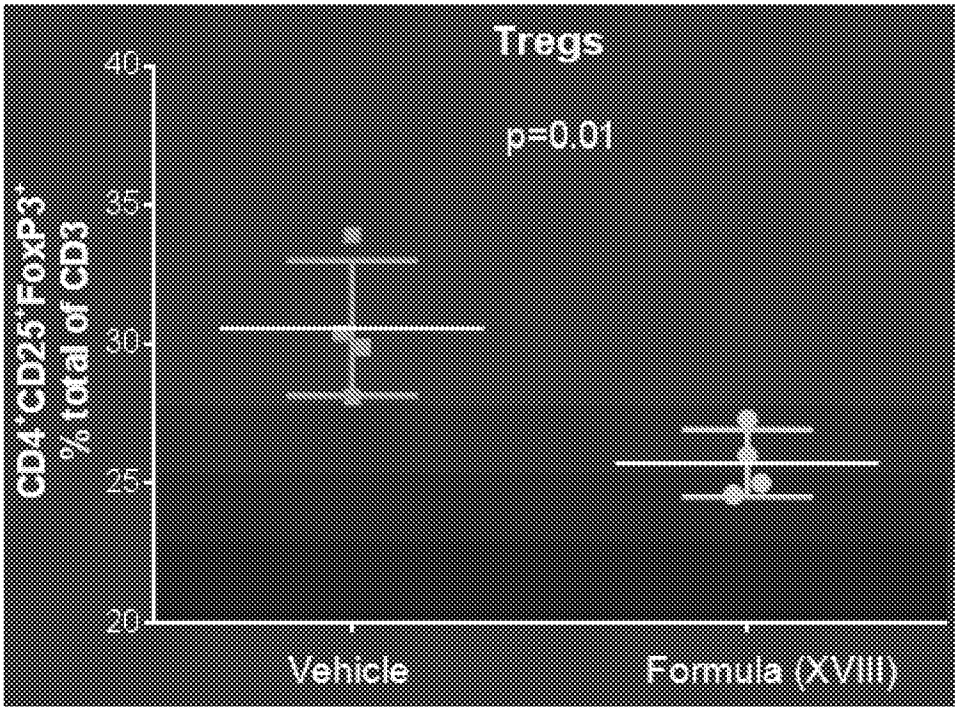

Tregs
p=0.01
CD4+CD25+FoxP3+
% total of CD3
40
35
30
25
20
Vehicle
Formula (XVIII)

FIG. 122

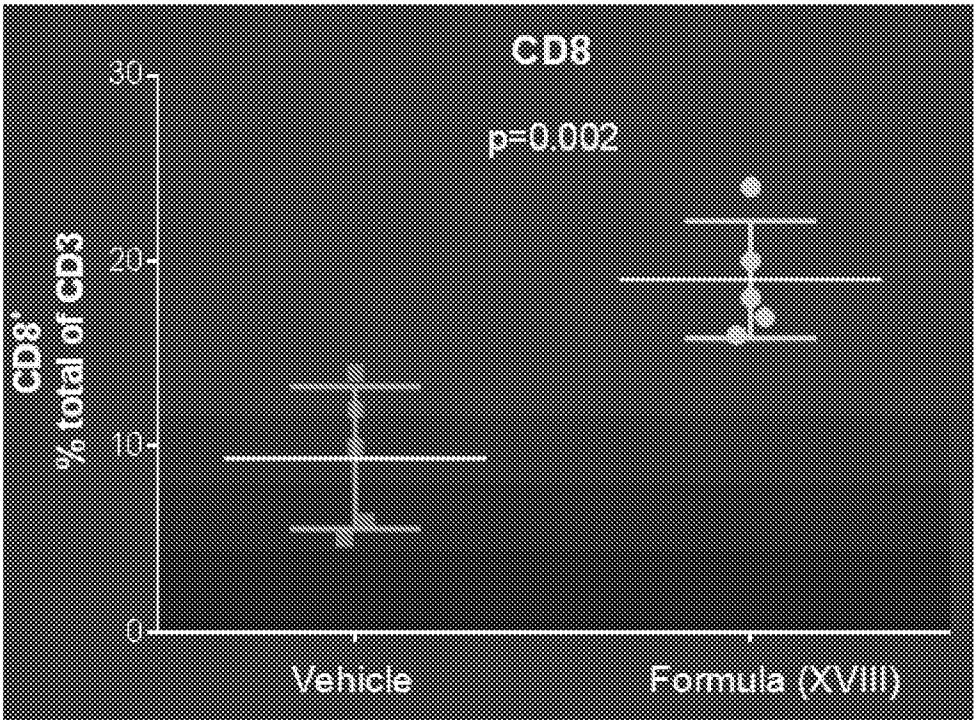



FIG. 123

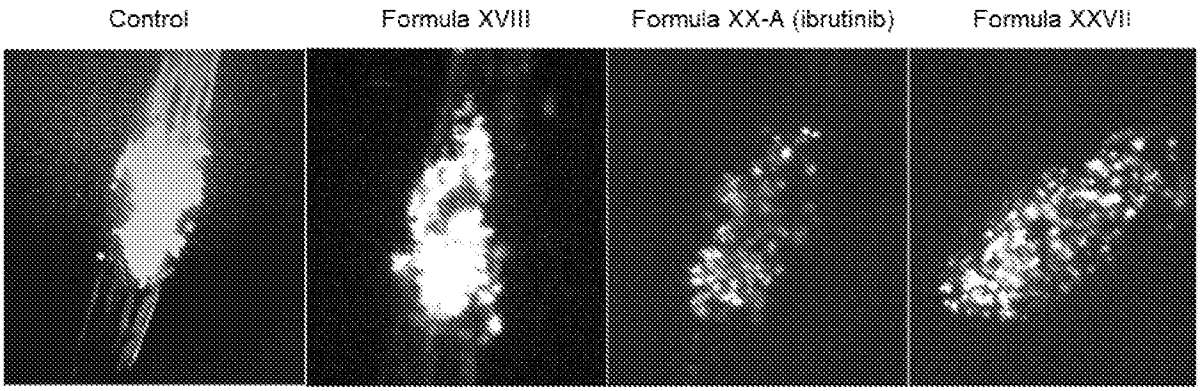

Control
Formula XVIII
Formula XX-A (ibrutinib)
Formula XXVII

FIG. 124

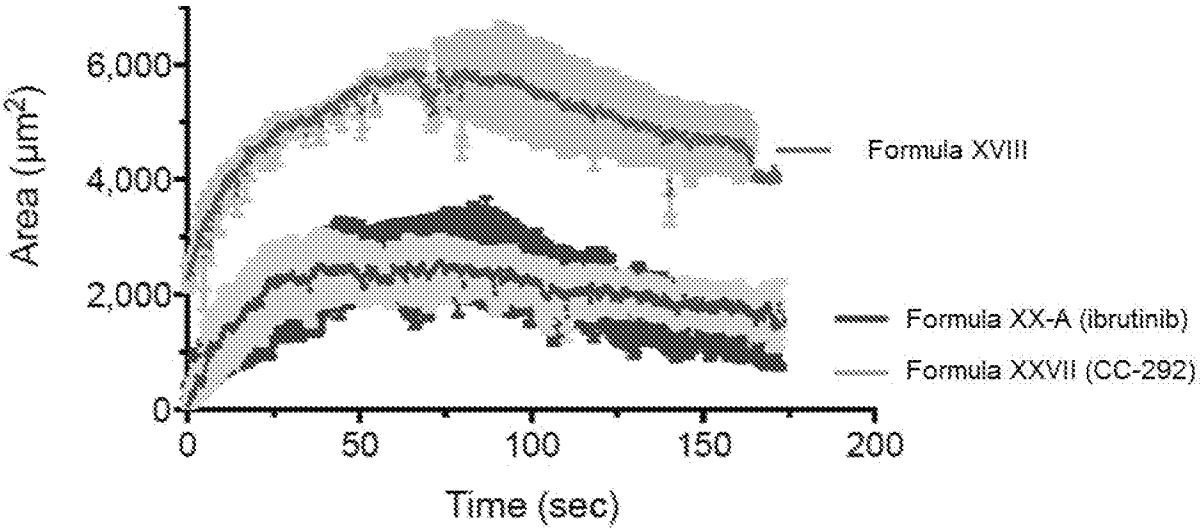

Area (μm²)
6,000
4,000
2,000
0
0
50
100
150
200
Time (sec)
Formula XVIII
Formula XX-A (ibrutinib)
Formula XXVII (CC-292)

FIG. 125

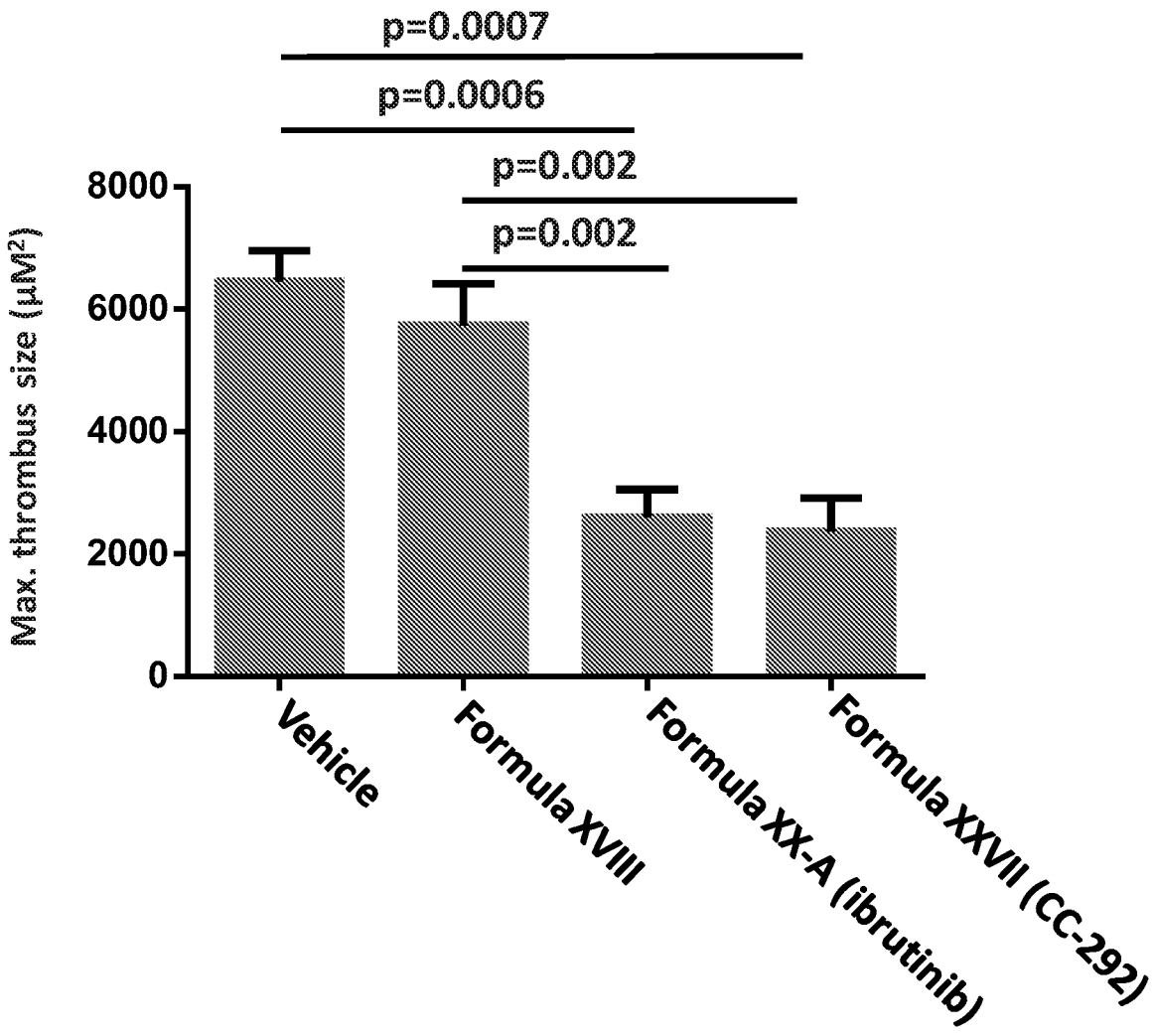

p=0.0007
p=0.0006
p=0.002
p=0.002
8000
6000
4000
2000
0
Max. thrombus size (μM²)
Vehicle
Formula XVIII
Formula XX-A (ibrutinib)
Formula XXVII (CC-292)

FIG. 126

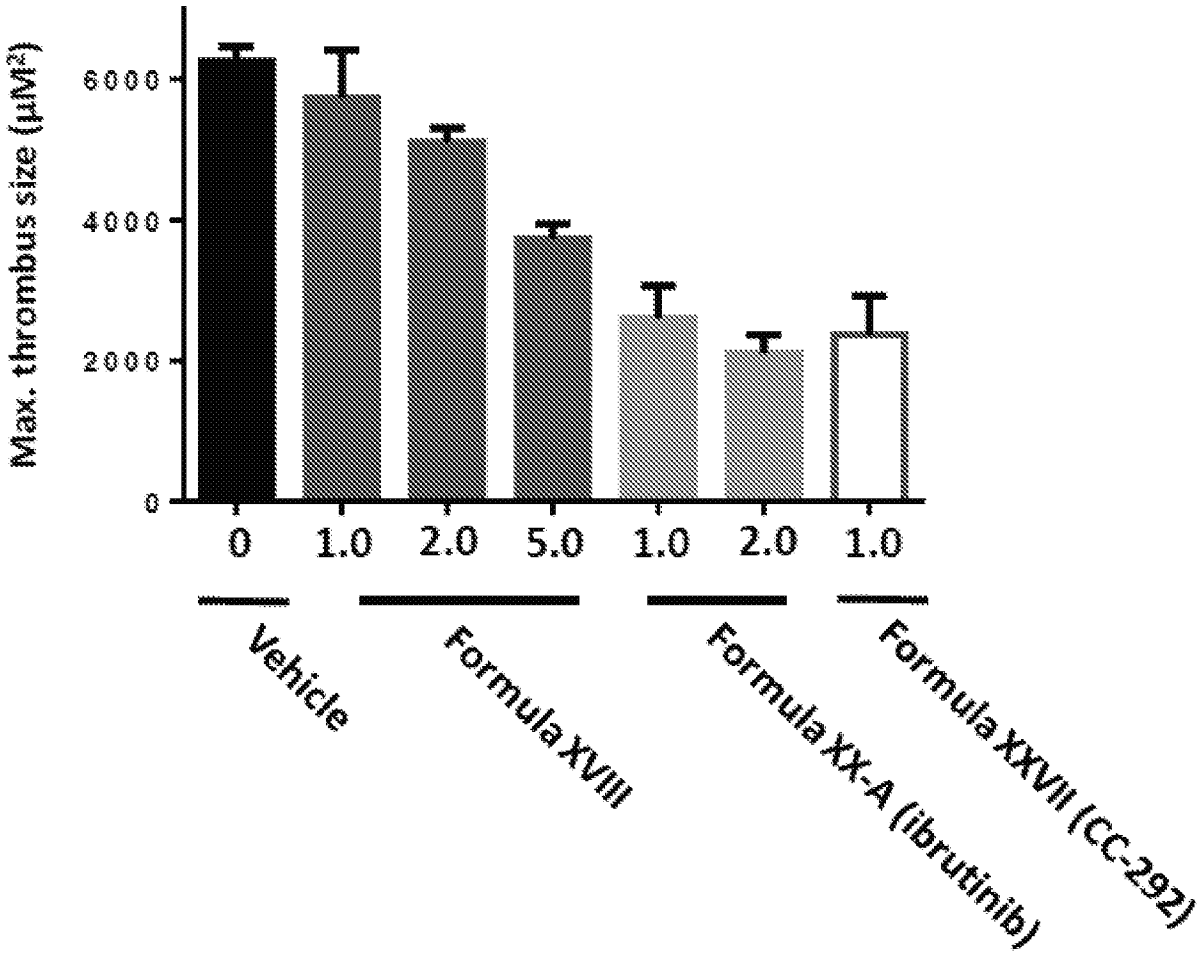

Max. thrombus size (μM²)
6000
4000
2000
0
0
1.0
2.0
5.0
1.0
2.0
1.0
Vehicle
Formula XVIII
Formula XX-A (ibrutinib)
Formula XXVII (CC-292)

FIG. 127

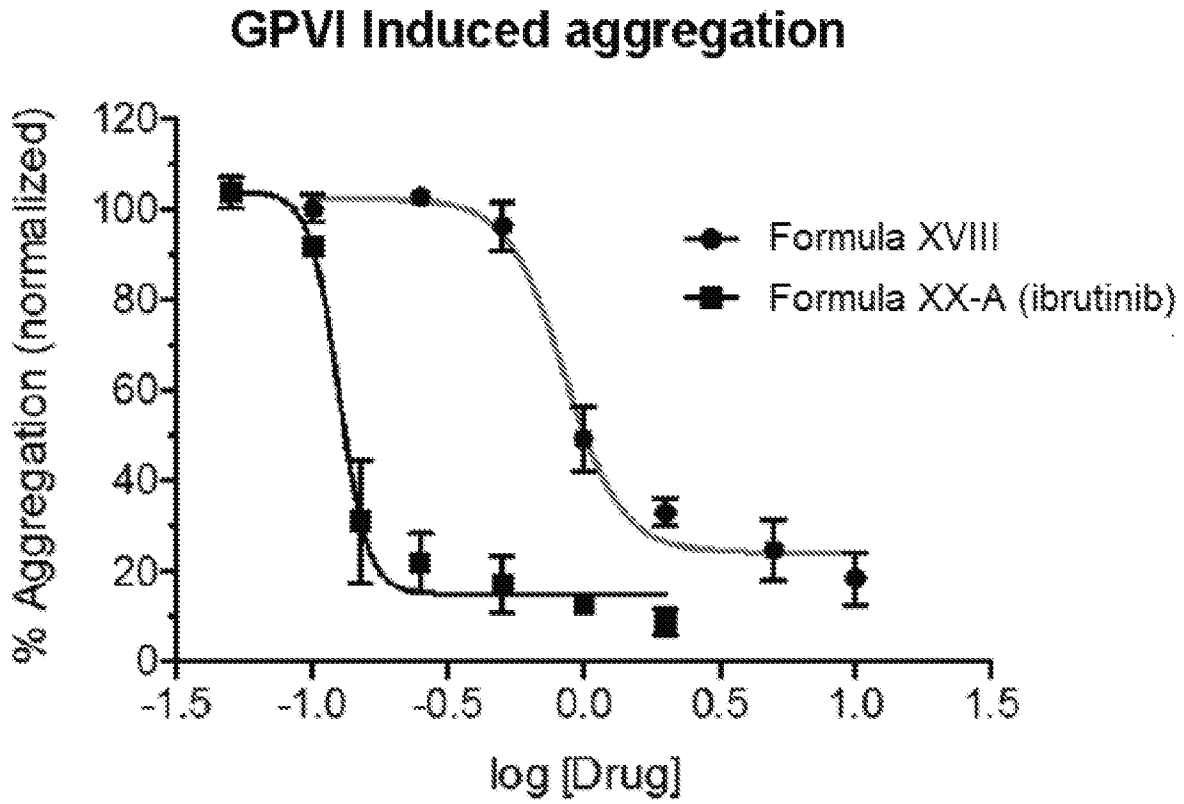

GPVI Induced aggregation
% Aggregation (normalized)
120
100
80
60
40
20
0
-1.5
-1.0
-0.5
0.0
0.5
1.0
1.5
log [Drug]
Formula XVIII
Formula XX-A (ibrutinib)

FIG. 128

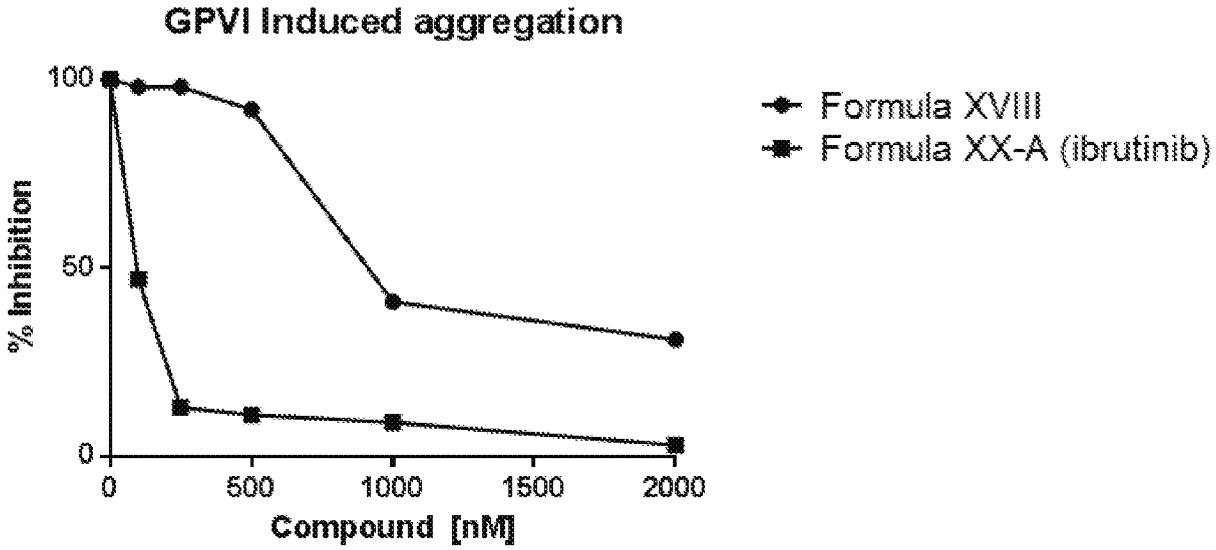

GPVI Induced aggregation
% Inhibition
100
50
0
0
500
1000
1500
2000
Compound [nM]
Formula XVIII
Formula XX-A (ibrutinib)

FIG. 129

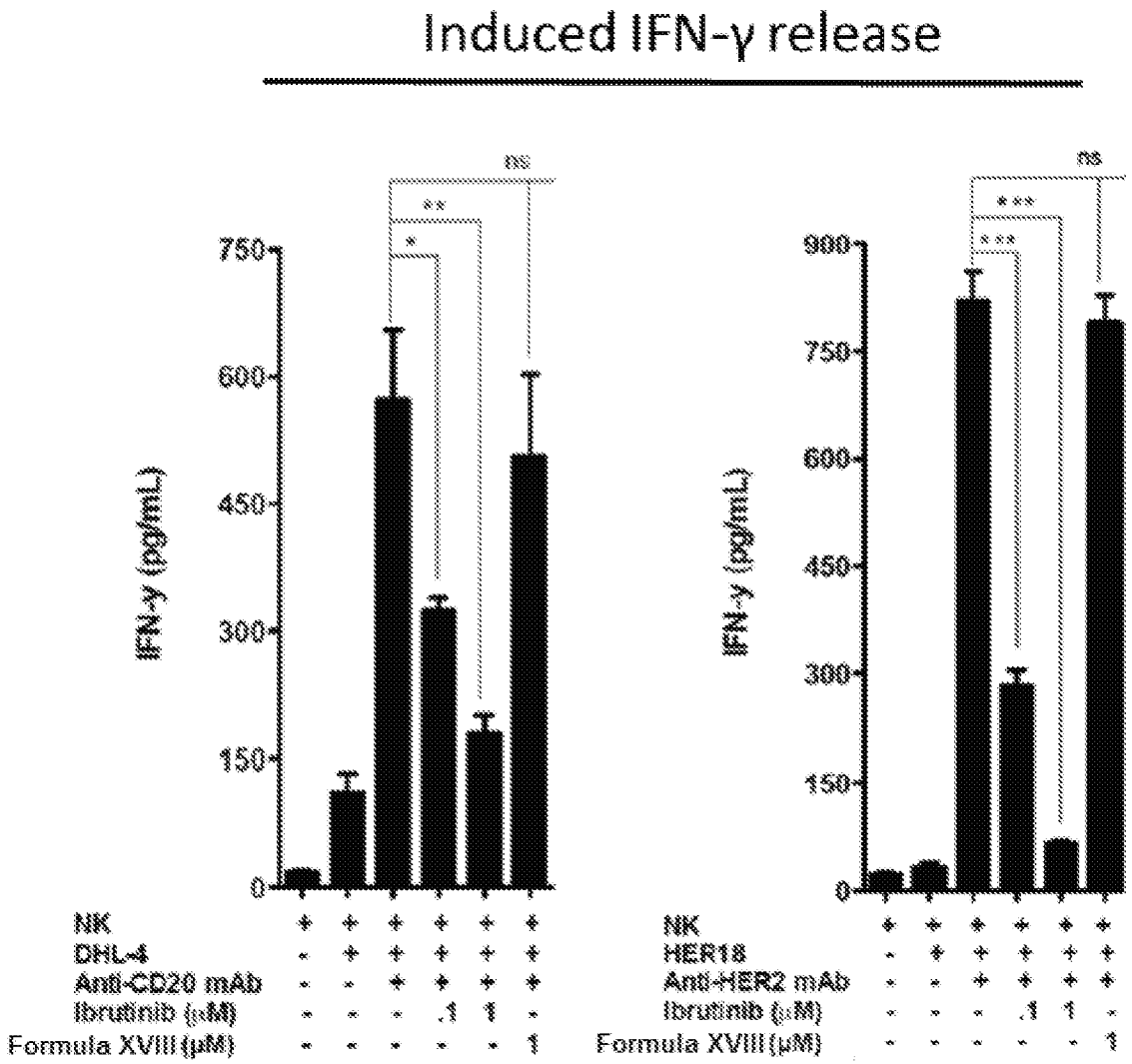

Induced IFN-γ release
IFN-γ (pg/mL)
750
600
450
300
150
0
ns
**
*
NK + + + + + +
DHL-4 - + + + + +
Anti-CD20 mAb - - + + + +
Ibrutinib (μM) - - - .1 1 -
Formula XVIII (μM) - - - - - 1
IFN-γ (pg/mL)
900
750
600
450
300
150
0
ns
***
***
NK + + + + + +
HER18 - + + + + +
Anti-HER2 mAb - - + + + +
Ibrutinib (μM) - - - .1 1 -
Formula XVIII (μM) - - - - - 1

FIG. 130

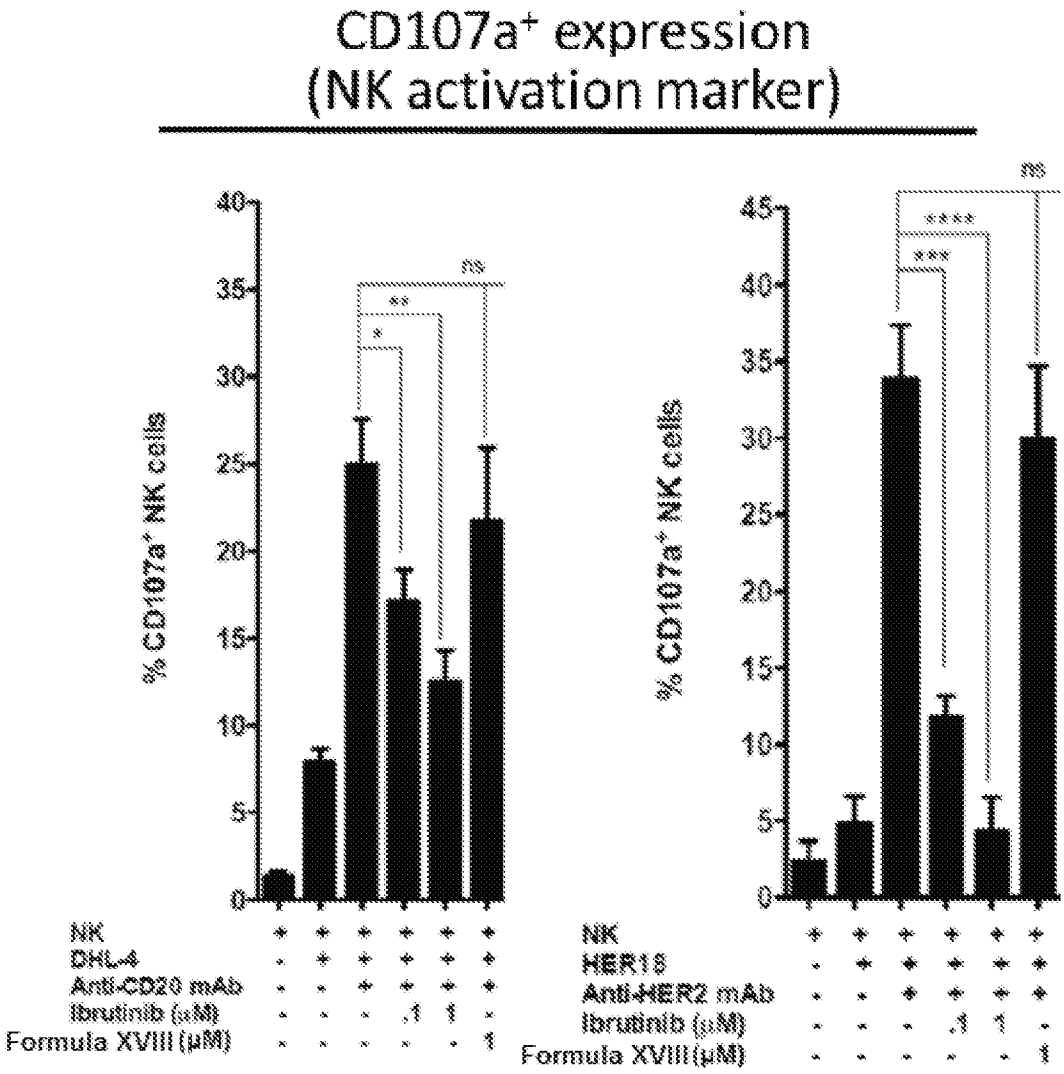

CD107a+ expression
(NK activation marker)
% CD107a+ NK cells
ns
**
*
NK
DHL-4
Anti-CD20 mAb
Ibrutinib (μM)
Formula XVIII (μM)
% CD107a+ NK cells
ns
****
***
NK
HER1/2
Anti-HER2 mAb
Ibrutinib (μM)
Formula XVIII (μM)

FIG. 131

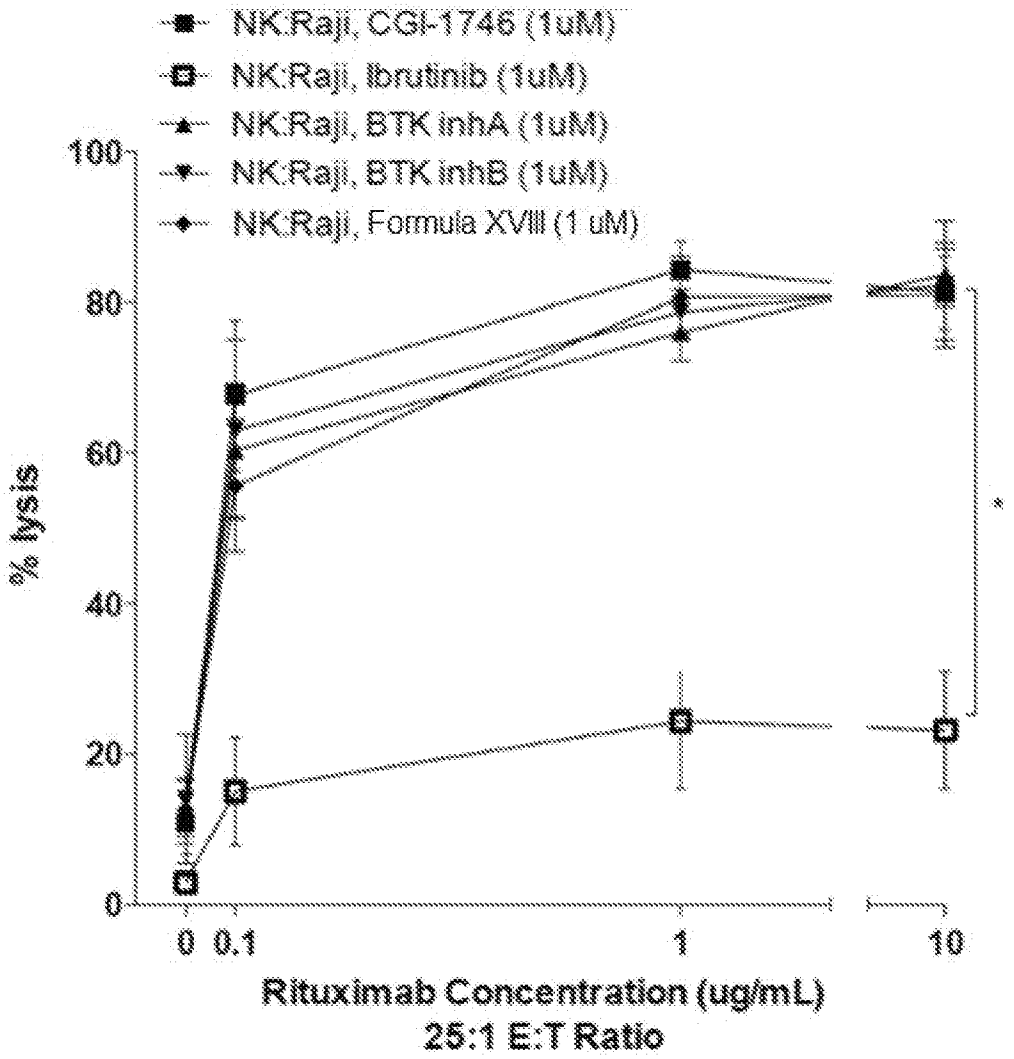

NK:Raji, CGI-1746 (1uM)
NK:Raji, Ibrutinib (1uM)
NK:Raji, BTK inhA (1uM)
NK:Raji, BTK inhB (1uM)
NK:Raji, Formula XVIII (1 uM)
% lysis
100
80
60
40
20
0
0
0.1
1
10
Rituximab Concentration (ug/mL)
25:1 E:T Ratio
*

FIG. 132

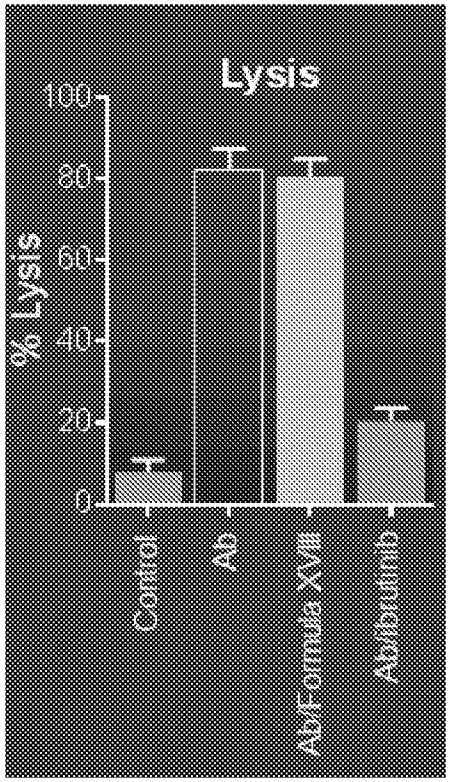

Lysis
% Lysis
100
80
60
40
20
0
Control
Av
Av-Fc mut XVII
Adalimumab

FIG. 133

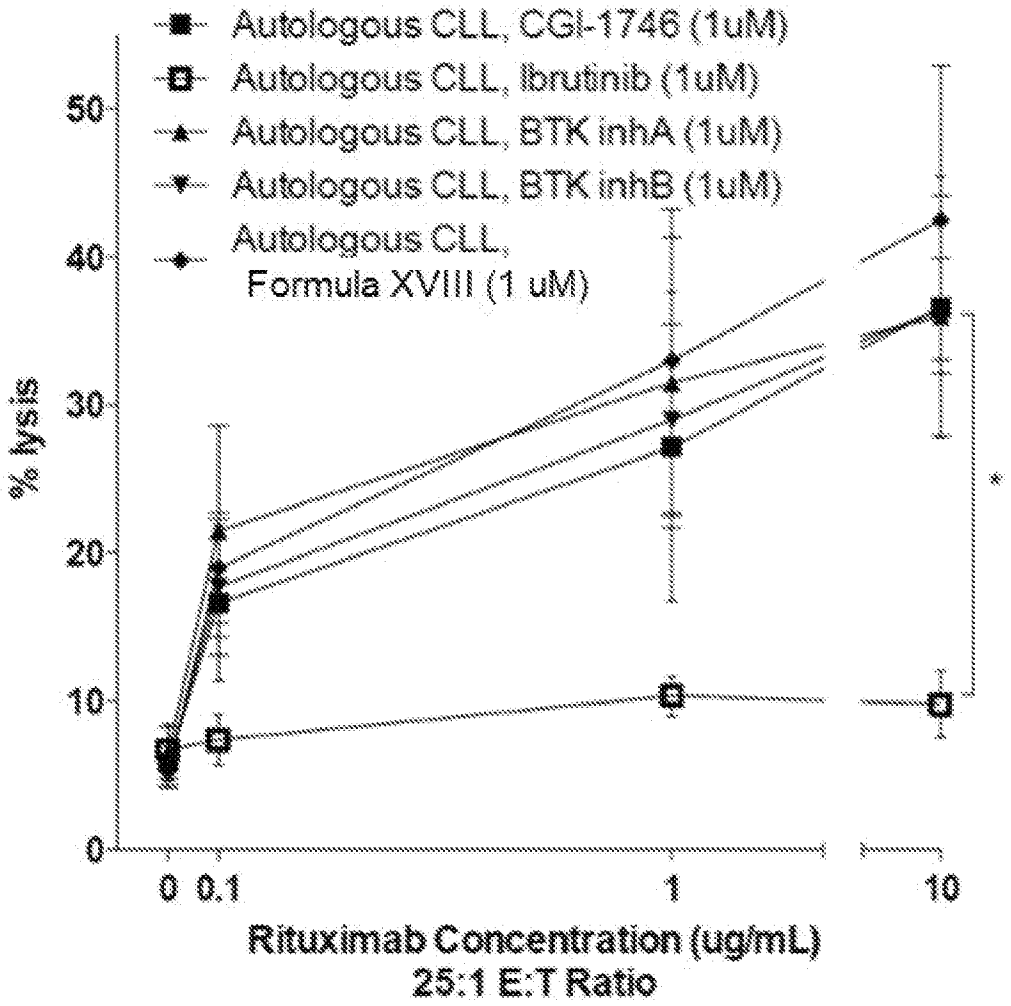

Autologous CLL, CGI-1746 (1uM)
Autologous CLL, Ibrutinib (1uM)
Autologous CLL, BTK inhA (1uM)
Autologous CLL, BTK inhB (1uM)
Autologous CLL, Formula XVIII (1 uM)
% lysis
50
40
30
20
10
0
0
0.1
1
10
*
Rituximab Concentration (ug/mL)
25:1 E:T Ratio

FIG. 134

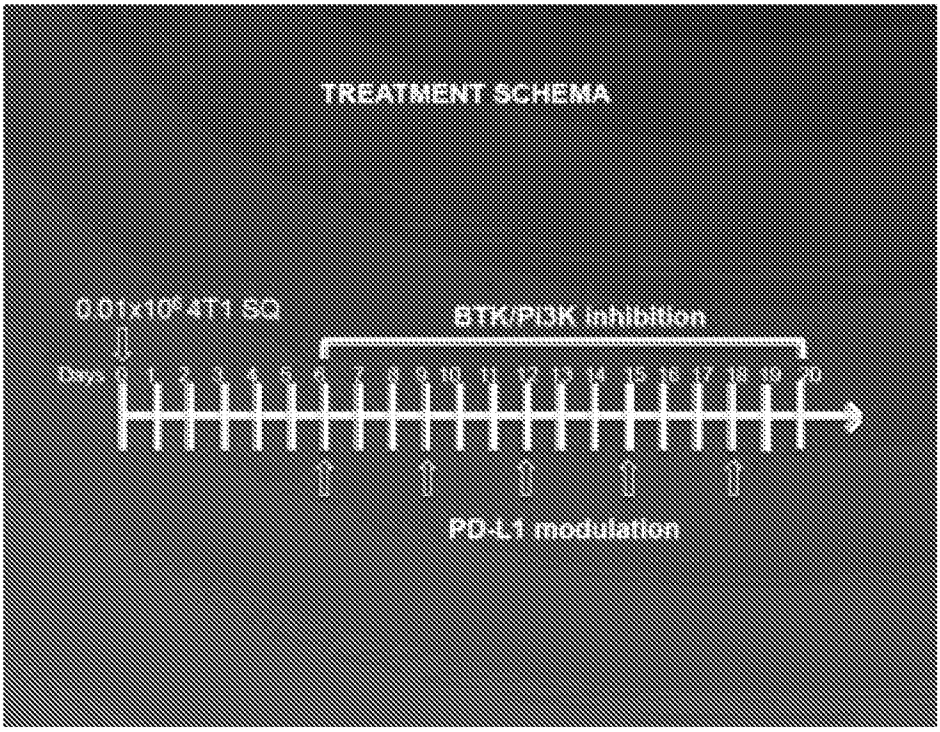

TREATMENT SCHEMA
0.01x10⁶ 4T1 SC
BTK/PI3K inhibition
Days
PD-L1 modulation

FIG. 135

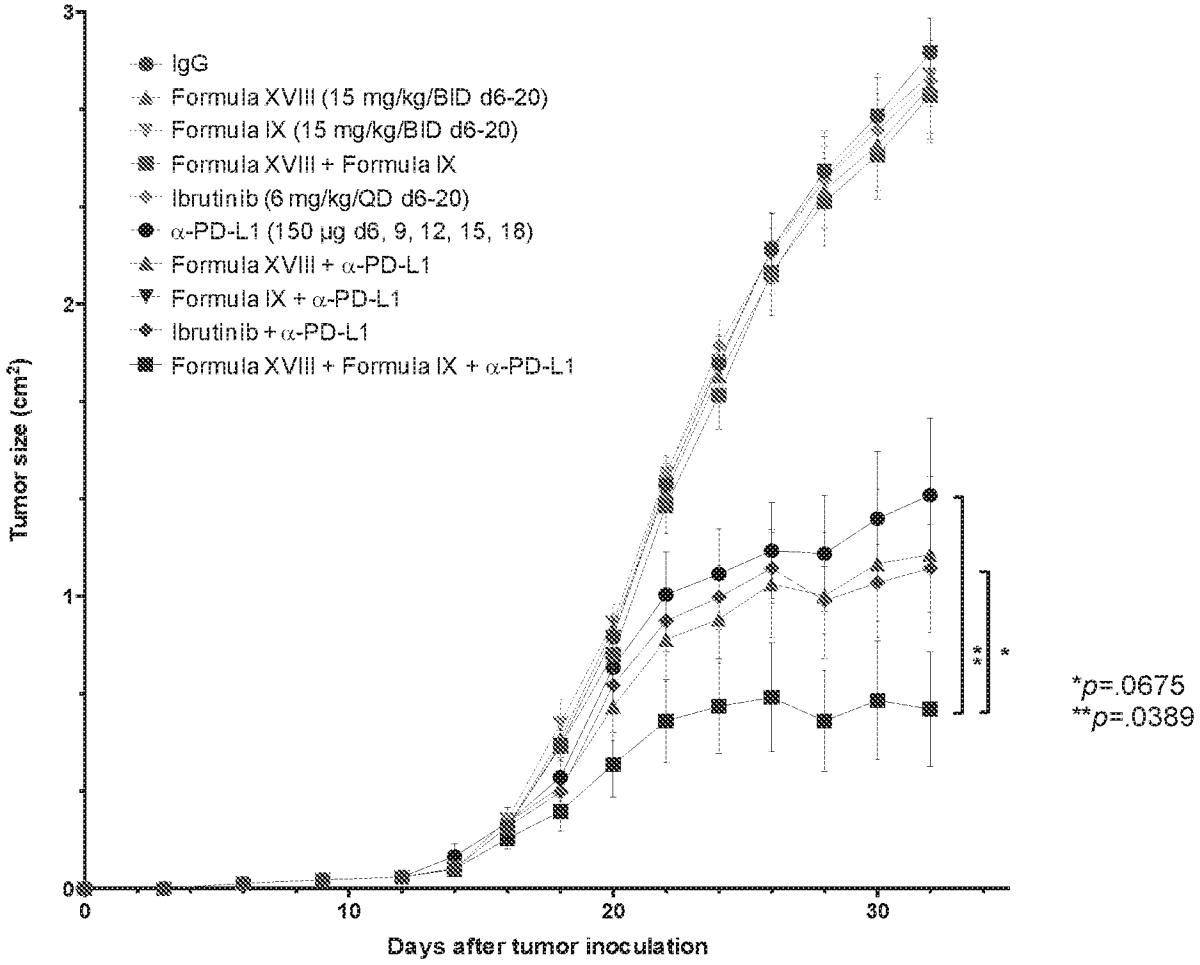

IgG
Formula XVIII (15 mg/kg/BID d6-20)
Formula IX (15 mg/kg/BID d6-20)
Formula XVIII + Formula IX
Ibrutinib (6 mg/kg/QD d6-20)
α-PD-L1 (150 µg d6, 9, 12, 15, 18)
Formula XVIII + α-PD-L1
Formula IX + α-PD-L1
Ibrutinib + α-PD-L1
Formula XVIII + Formula IX + α-PD-L1
Tumor size (cm²)
Days after tumor inoculation
0
1
2
3
0
10
20
30
**
*
*p=.0675
**p=.0389

FIG. 136

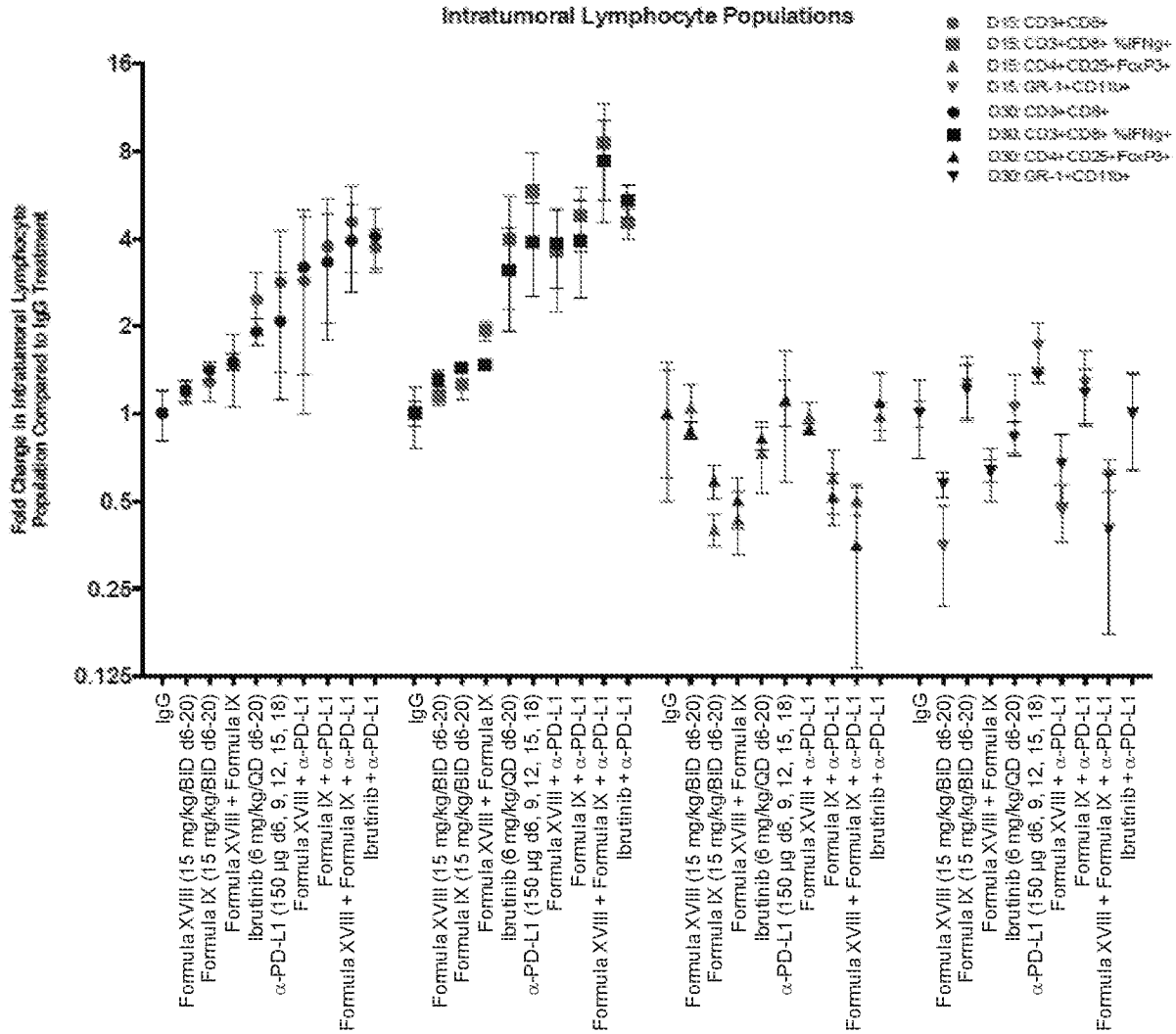

Intratumoral Lymphocyte Populations
Fold Change in Intratumoral Lymphocyte Population Compared to IgG Treatment
16
8
4
2
1
0.5
0.25
0.125
IgG
Formula XVIII (15 mg/kg/BID d6-20)
Formula IX (15 mg/kg/BID d6-20)
Formula XVIII + Formula IX
Ibrutinib (6 mg/kg/QD d6-20)
α-PD-L1 (150 µg d6, 9, 12, 15, 18)
Formula XVIII + α-PD-L1
Formula IX + α-PD-L1
Formula XVIII + Formula IX + α-PD-L1
Ibrutinib + α-PD-L1

FIG. 137

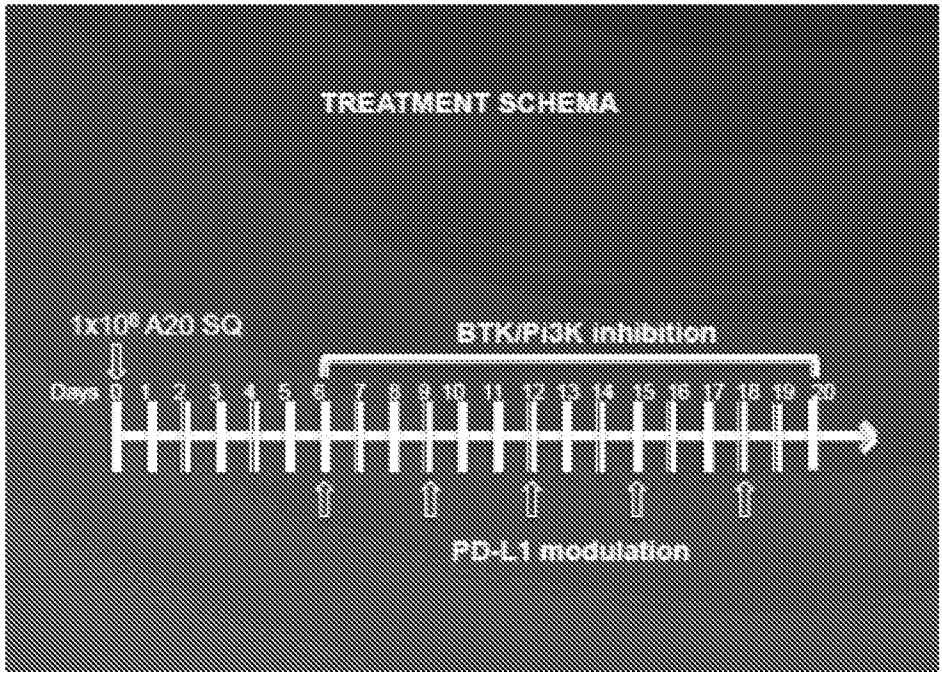
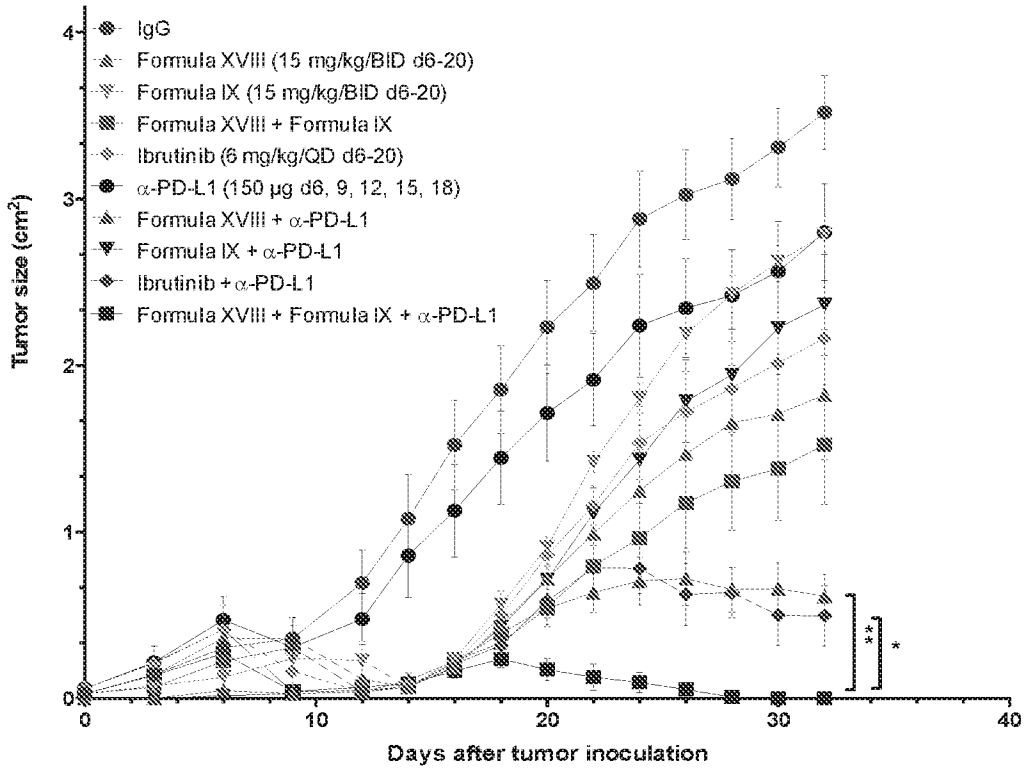

TREATMENT SCHEMA
1x10⁶ A20 SQ
BTK/PI3K inhibition
Days 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
PD-L1 modulation

FIG. 138




*p=.0135
**p=.0637

FIG. 139

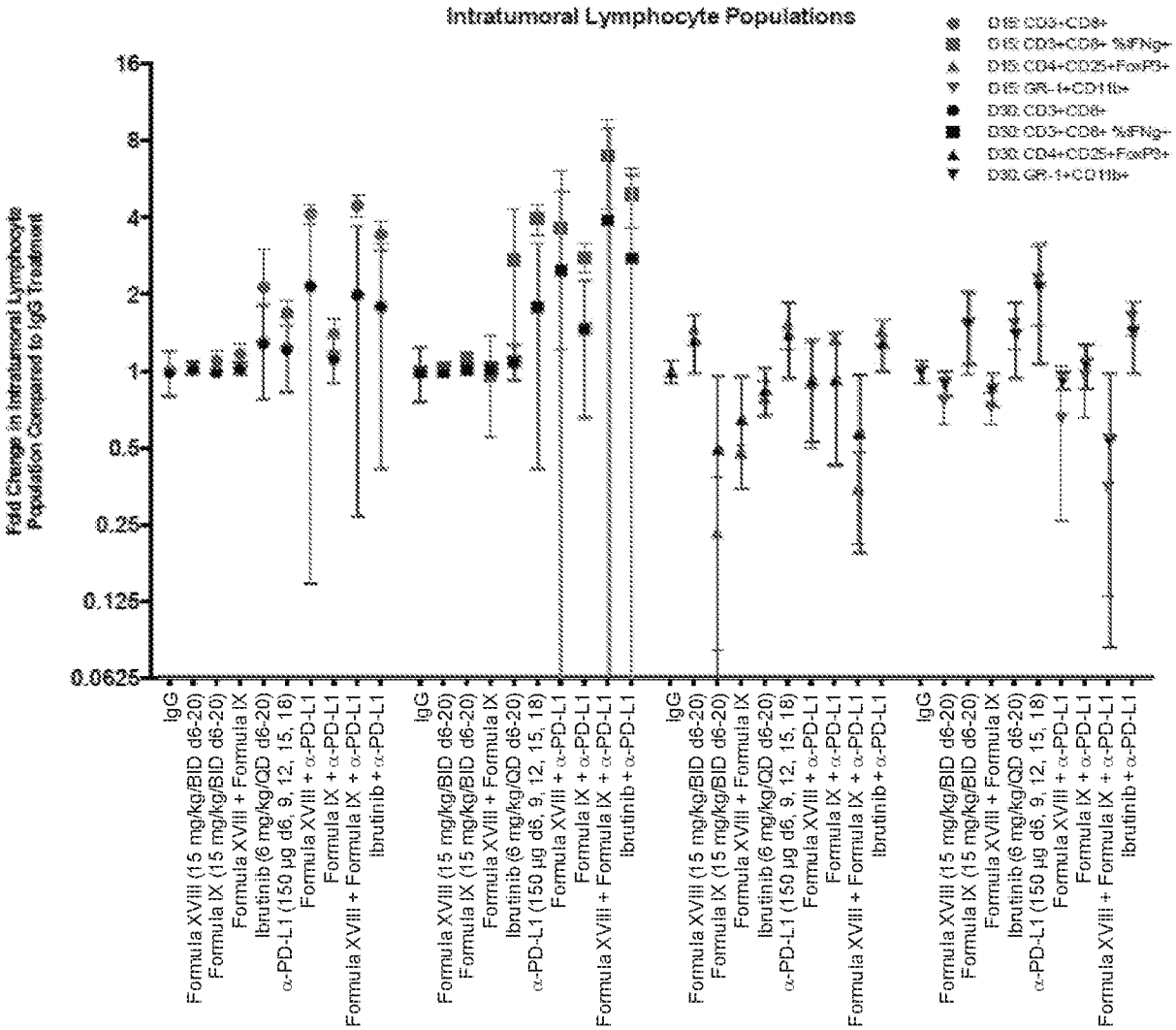

Intratumoral Lymphocyte Populations
Fold Change in Intratumoral Lymphocyte Population Compared to IgG Treatment
16
8
4
2
1
0.5
0.25
0.125
0.0625
D15 CD3+CD8+
D15 CD3+CD8+ %IFNg+
D15 CD4+CD25+FoxP3+
D15 GR-1+CD11b+
D30 CD3+CD8+
D30 CD3+CD8+ %IFNg+
D30 CD4+CD25+FoxP3+
D30 GR-1+CD11b+
IgG
Formula XVIII (15 mg/kg/BID d6-20)
Formula IX (15 mg/kg/BID d6-20)
Formula XVIII + Formula IX
Ibrutinib (6 mg/kg/QD d6-20)
α-PD-L1 (150 µg d6, 9, 12, 15, 18)
Formula XVIII + α-PD-L1
Formula IX + α-PD-L1
Formula XVIII + Formula IX + α-PD-L1
Ibrutinib + α-PD-L1

FIG. 140

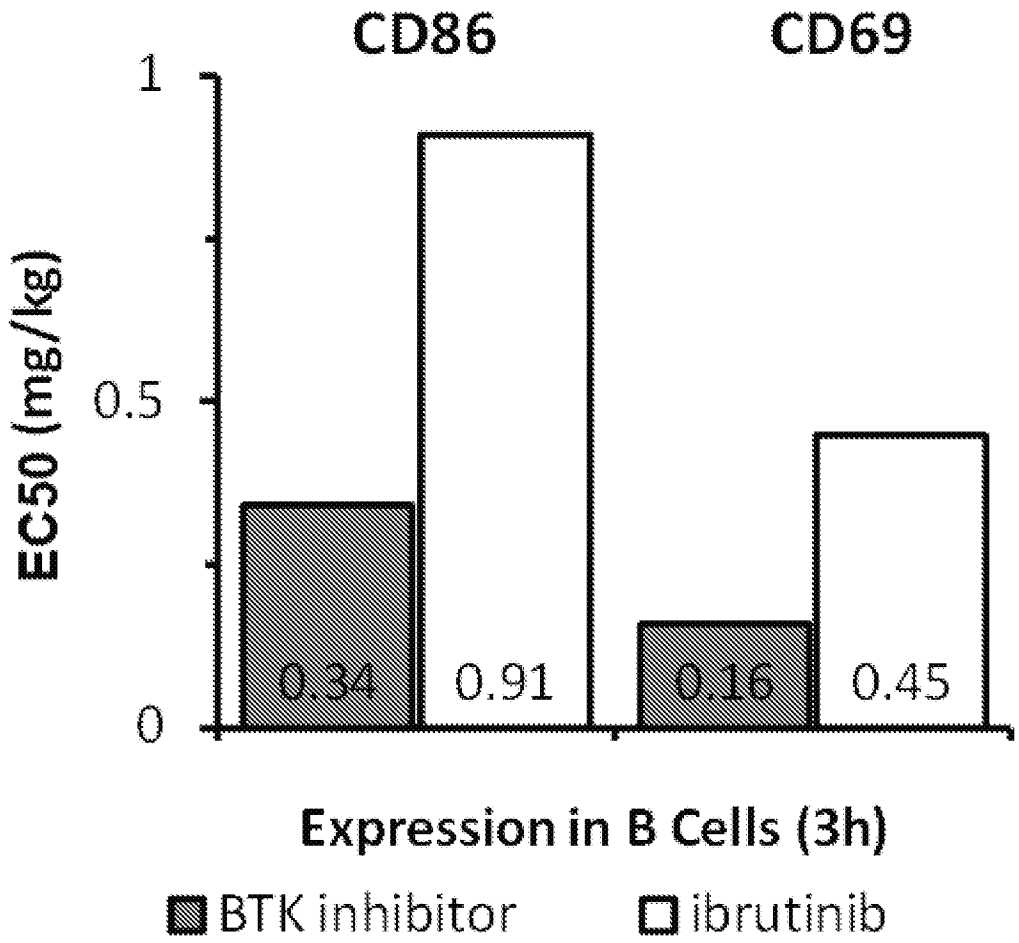

CD86
CD69
1
0.5
0
EC50 (mg/kg)
0.34
0.91
0.16
0.45
Expression in B Cells (3h)
BTK inhibitor
ibrutinib

FIG. 141

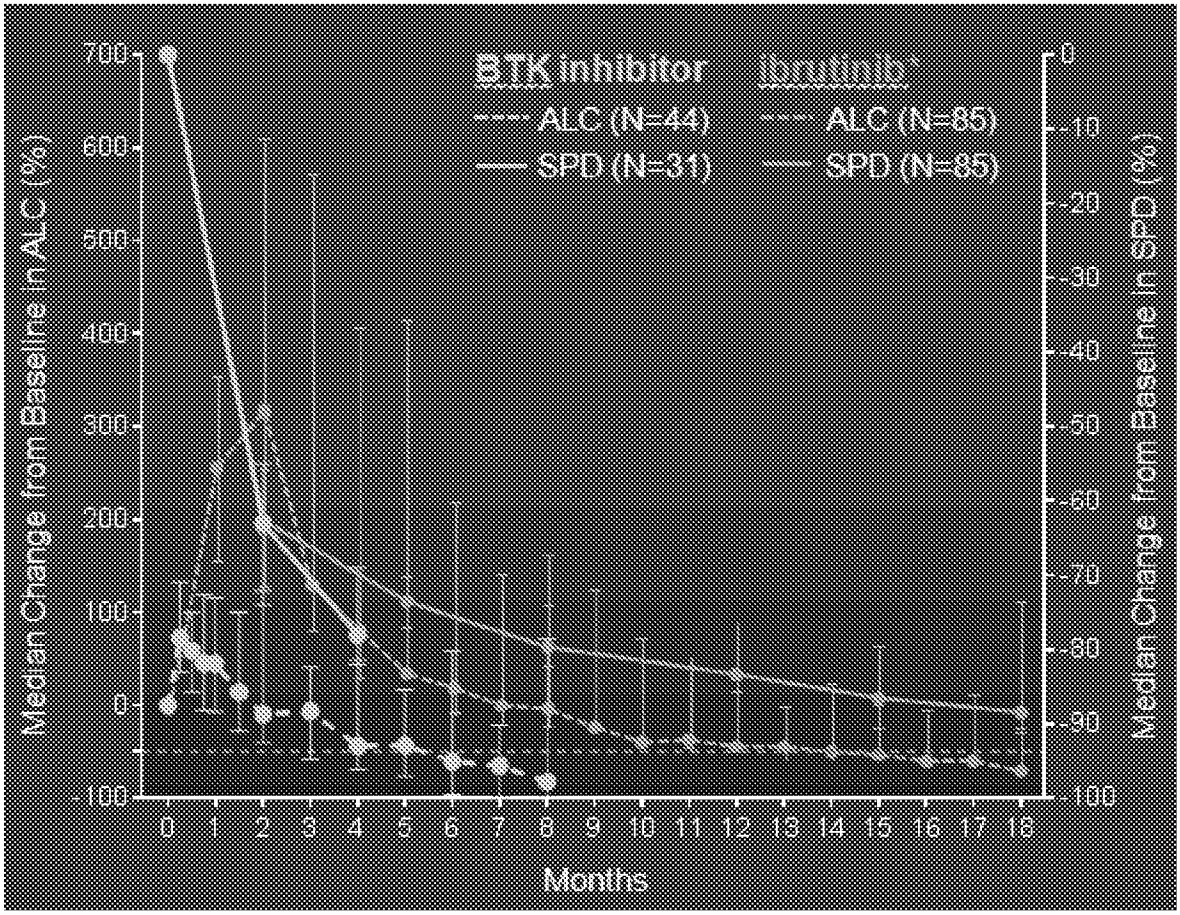

BTK inhibitor
Ibrutinib
ALC (N=44)
SPD (N=31)
ALC (N=85)
SPD (N=85)
Median Change from Baseline in ALC (%)
Median Change from Baseline in SPD (%)
Months
700
600
500
400
300
200
100
0
-100
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

FIG. 142

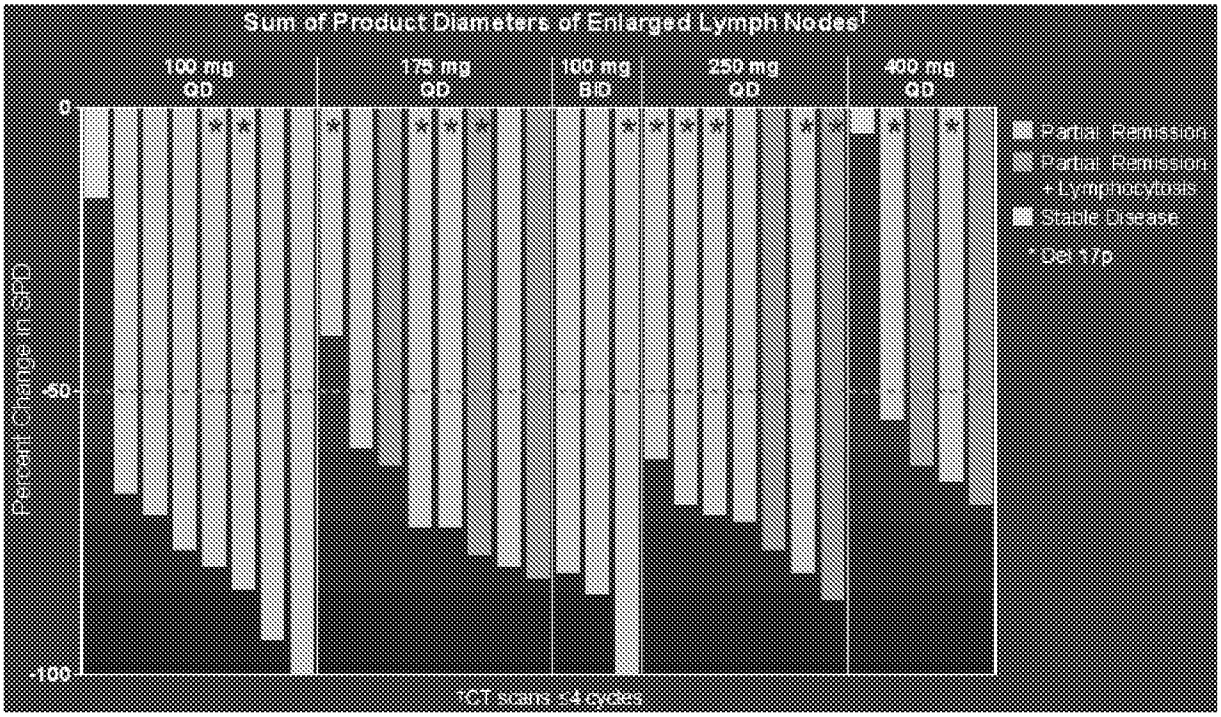

Sum of Product Diameters of Enlarged Lymph Nodes¹
100 mg QD
175 mg QD
100 mg BID
250 mg QD
400 mg QD
0
-50
-100
Percent Change in SPD
Partial Remission
Partial Remission + Lymphocytosis
Stable Disease
*Det. n/p
PCT Scans = 4 cycles

FIG. 143

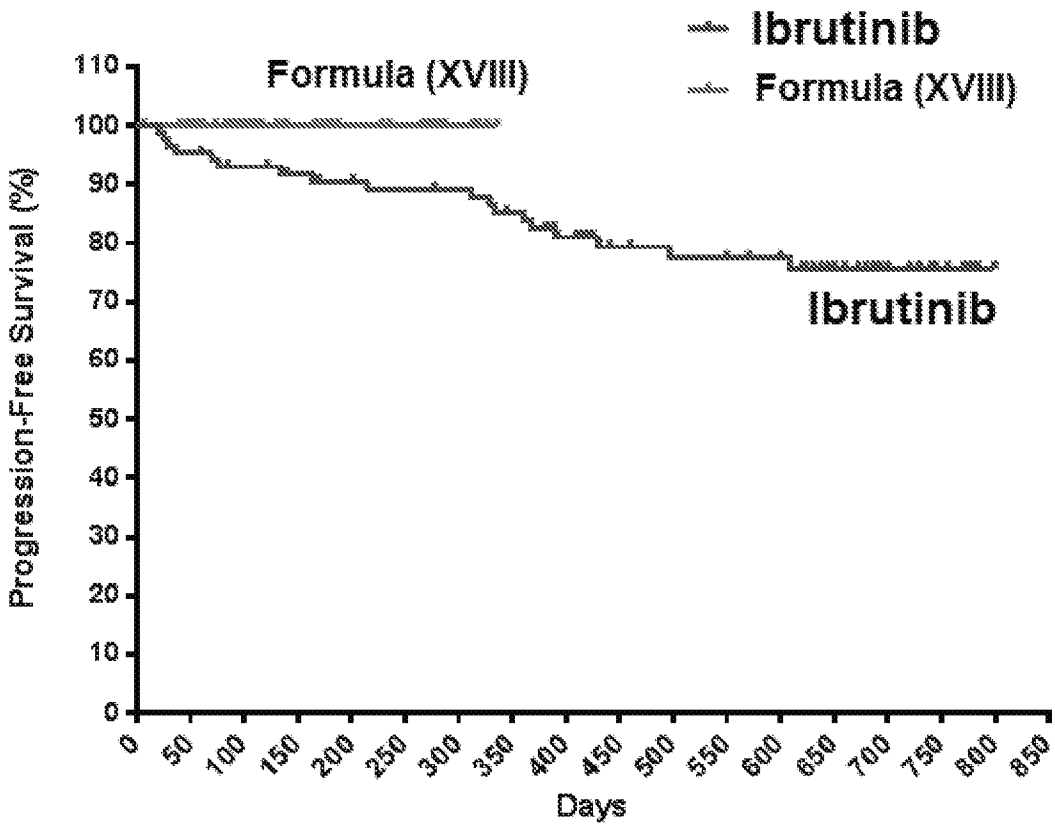

Ibrutinib
Formula (XVIII)
Formula (XVIII)
Ibrutinib
Progression-Free Survival (%)
110
100
90
80
70
60
50
40
30
20
10
0
0
50
100
150
200
250
300
350
400
450
500
550
600
650
700
750
800
850
Days

FIG. 144

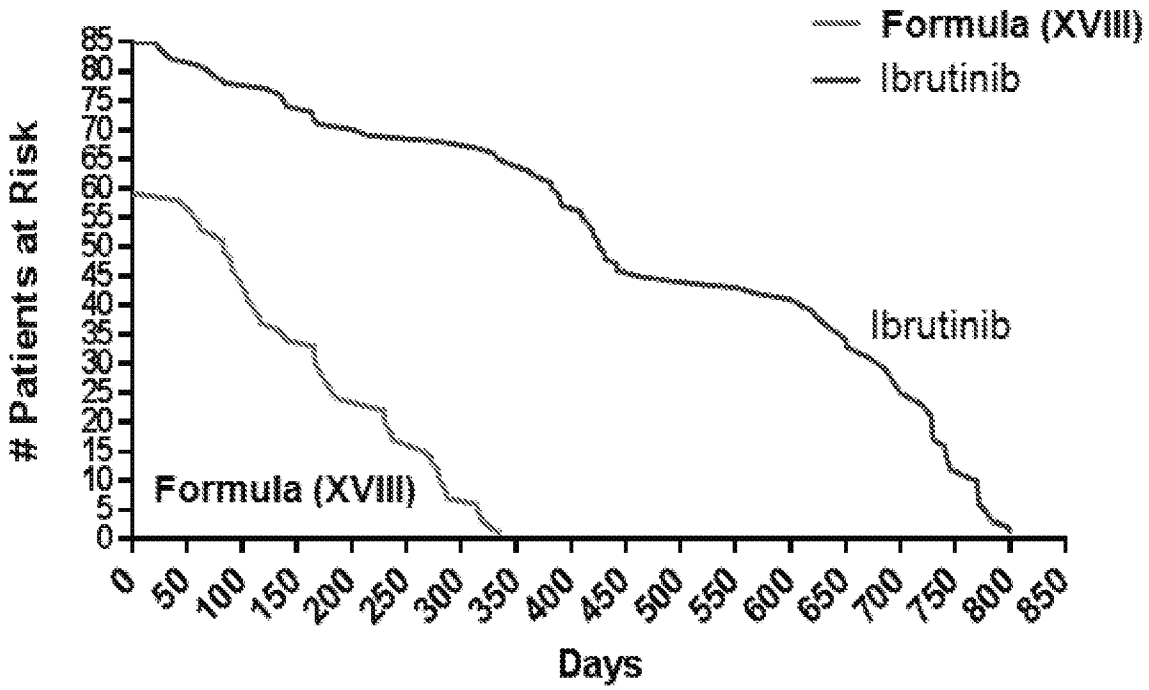

Formula (XVIII)
Ibrutinib
# Patients at Risk
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
Ibrutinib
Formula (XVIII)
0
50
100
150
200
250
300
350
400
450
500
550
600
650
700
750
800
850
Days

FIG. 145

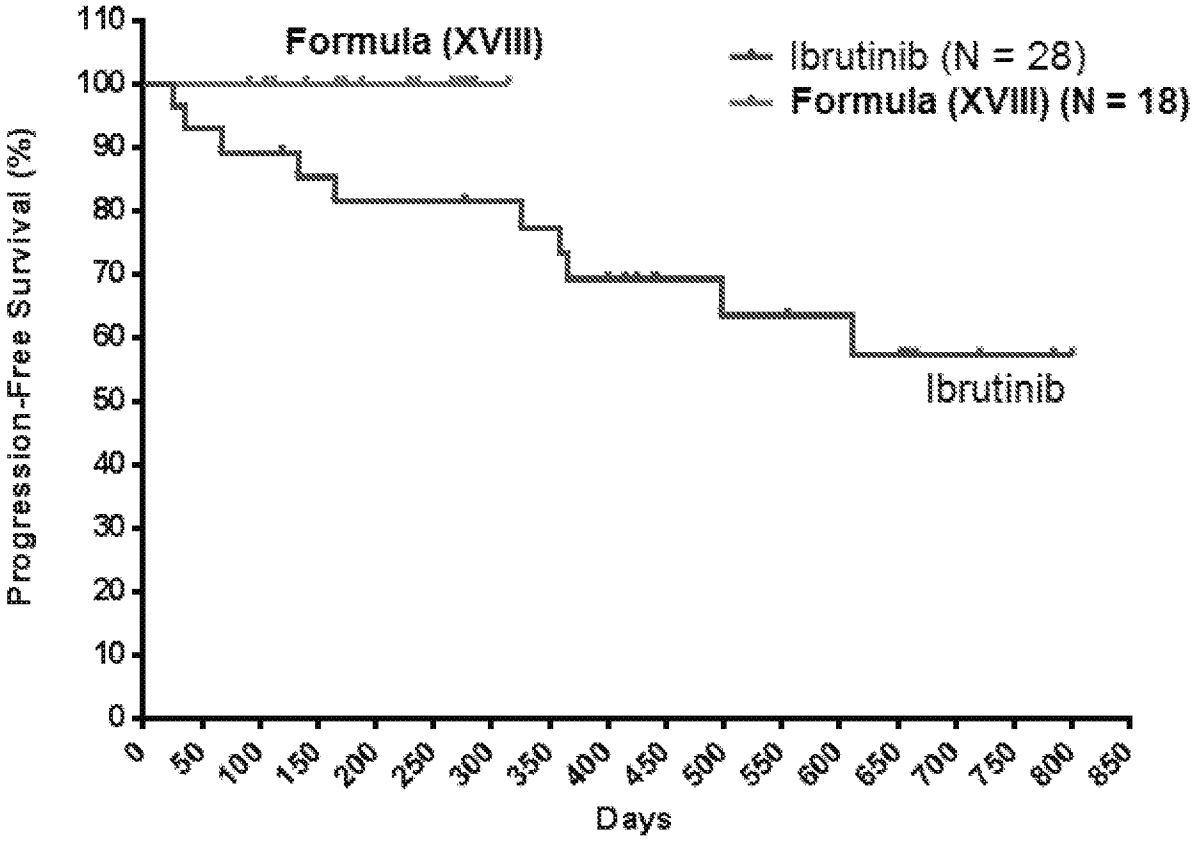

Formula (XVIII)
Ibrutinib (N = 28)
Formula (XVIII) (N = 18)
Ibrutinib
Progression-Free Survival (%)
110
100
90
80
70
60
50
40
30
20
10
0
0
50
100
150
200
250
300
350
400
450
500
550
600
650
700
750
800
850
Days

FIG. 146

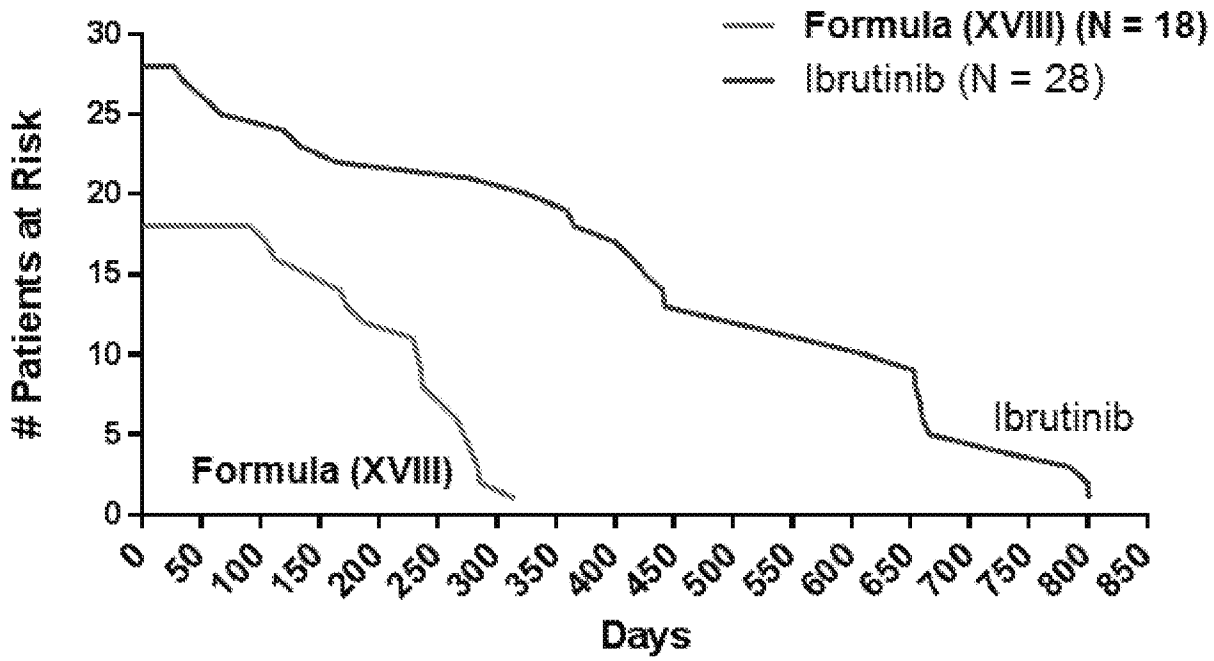

Formula (XVIII) (N = 18)
Ibrutinib (N = 28)
# Patients at Risk
30
25
20
15
10
5
0
Ibrutinib
Formula (XVIII)
0
50
100
150
200
250
300
350
400
450
500
550
600
650
700
750
800
850
Days

FIG. 147

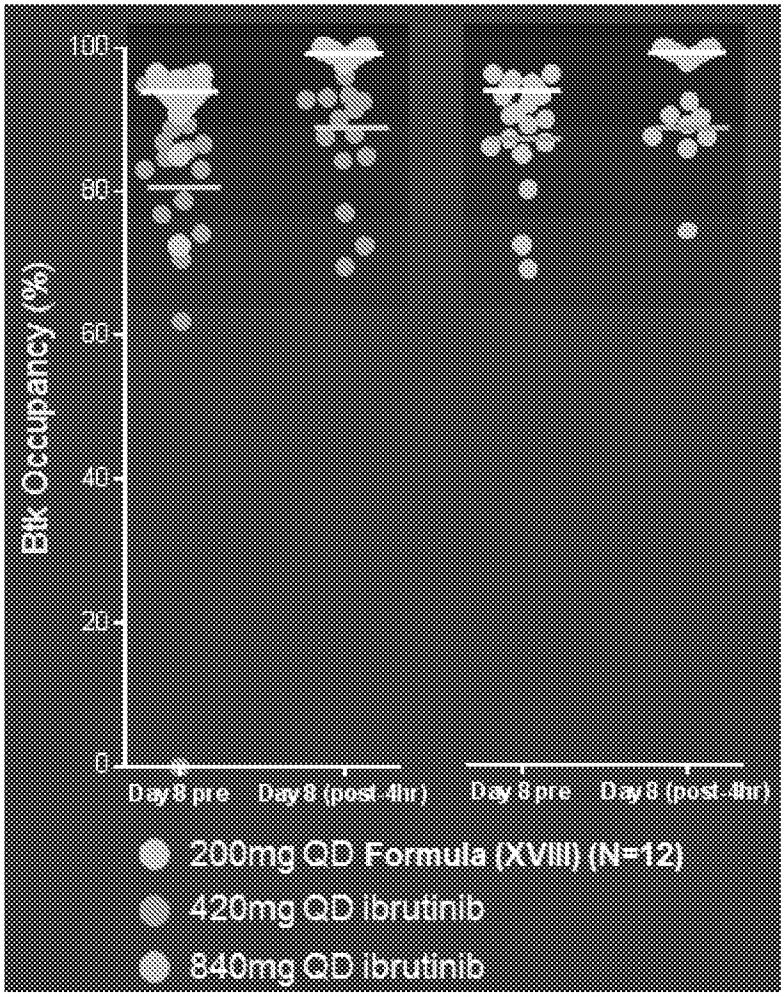

Btk Occupancy (%)
100
80
60
40
20
0
Day8 pre
Day8 (post-4hr)
Day8 pre
Day8 (post-4hr)
200mg QD Formula (XVIII) (N=12)
420mg QD Ibrutinib
840mg QD Ibrutinib

FIG. 148

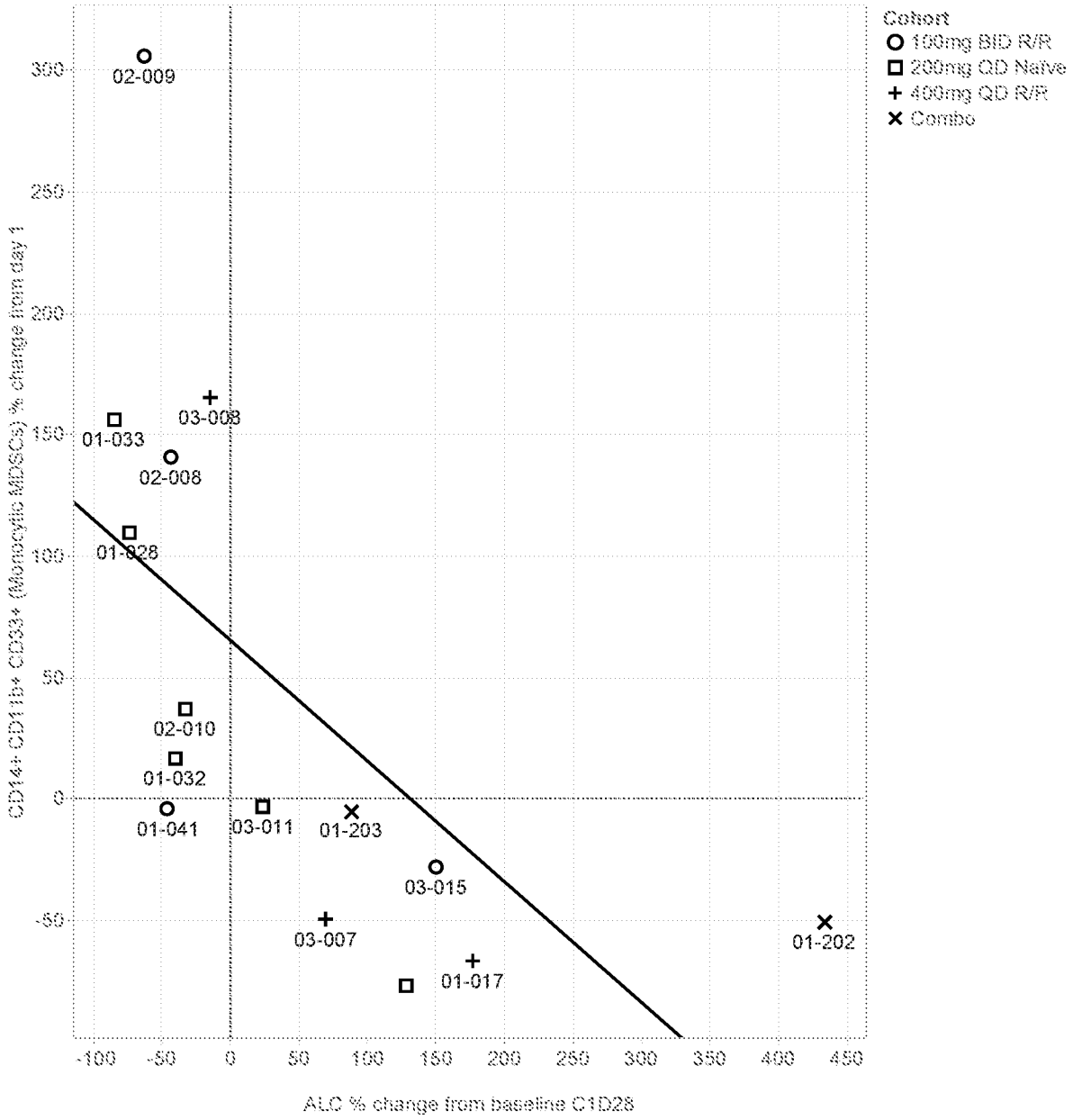

Cohort
100mg BID R/R
200mg QD Naive
400mg QD R/R
Combo
02-009
03-008
01-033
02-008
01-028
02-010
01-032
01-041
03-011
01-203
03-015
03-007
01-017
01-202
CD14+ CD11b+ CD33+ (Monocytic MDSCs) % change from day 1
ALC % change from baseline C1D28
300
250
200
150
100
50
0
-50
-100
-50
0
50
100
150
200
250
300
350
400
450

FIG. 149

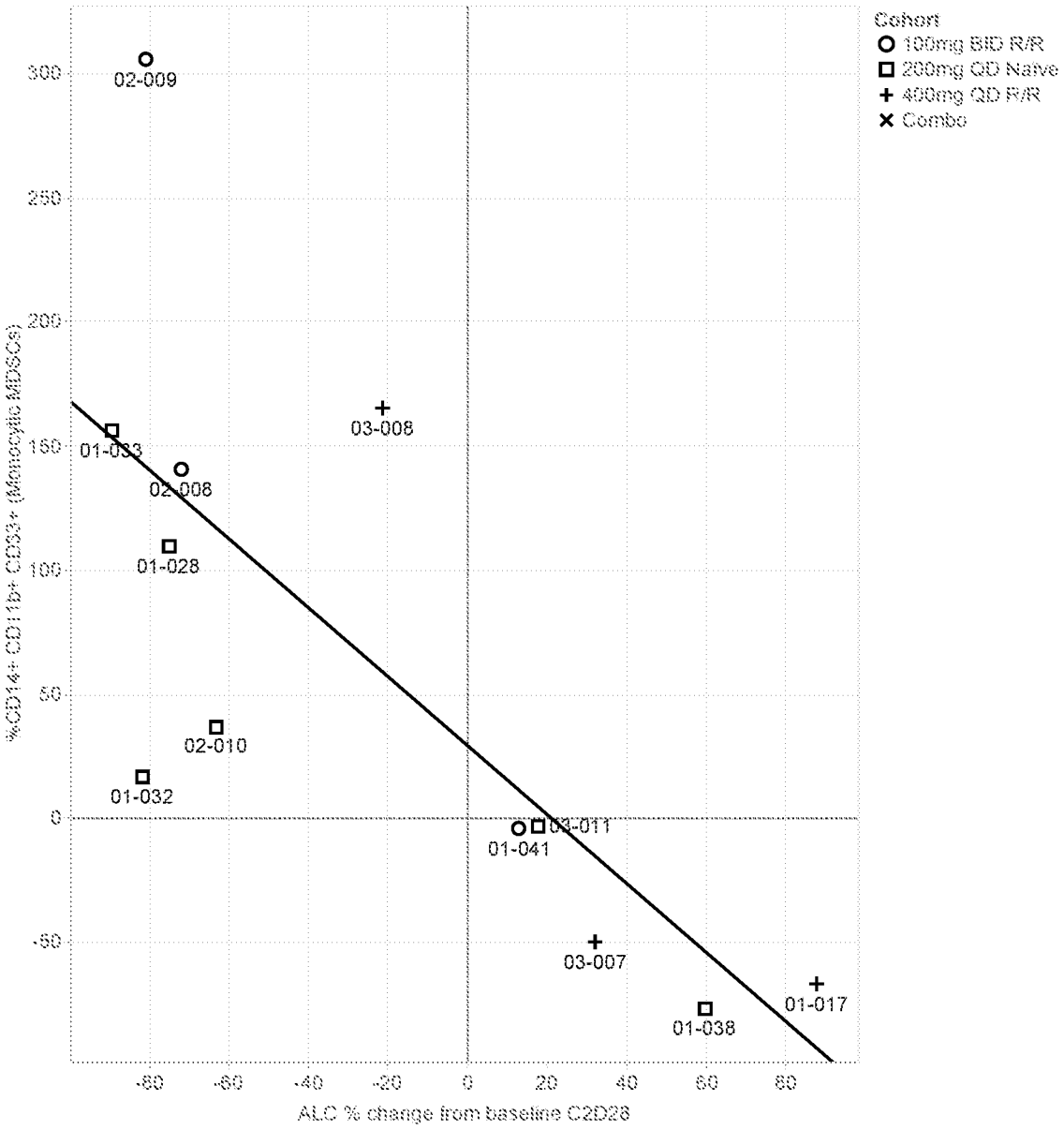

Cohort
100mg BID R/R
200mg QD Naive
400mg QD R/R
Combo
%CD14+ CD11b+ CD33+ (Monocytic MDSCs)
ALC % change from baseline C2D28
300
250
200
150
100
50
0
-50
-80
-60
-40
-20
0
20
40
60
80
02-009
03-008
01-033
02-006
01-028
02-010
01-032
01-041
01-011
03-007
01-017
01-038

FIG. 150

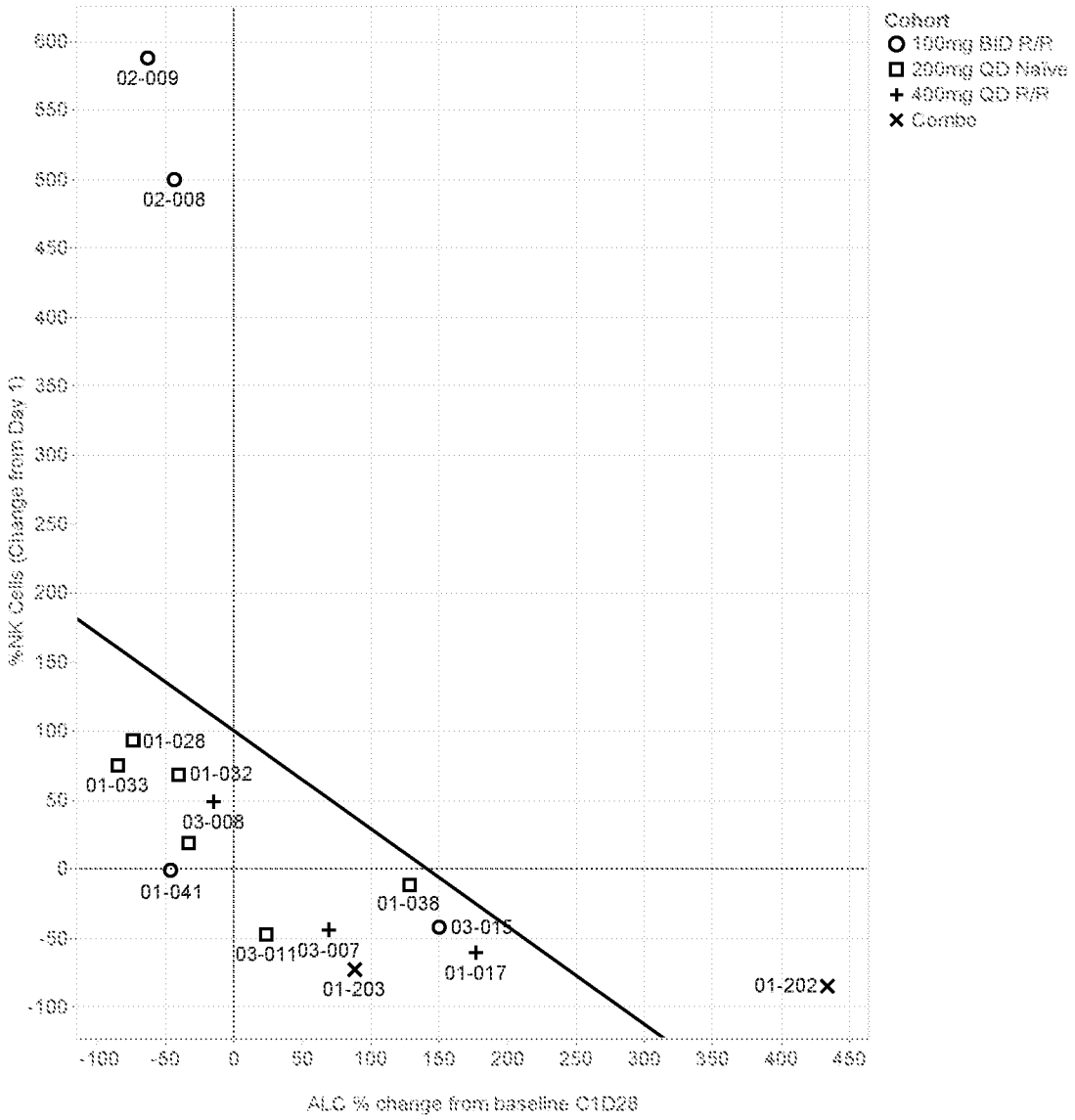

Cohort
100mg BID R/R
200mg QD Naive
400mg QD R/R
Combo
%NK Cells (Change from Day 1)
ALC % change from baseline C1D28
02-009
02-008
01-028
01-033
01-032
03-008
01-041
01-038
03-015
03-011
03-007
01-017
01-203
01-202

FIG. 151

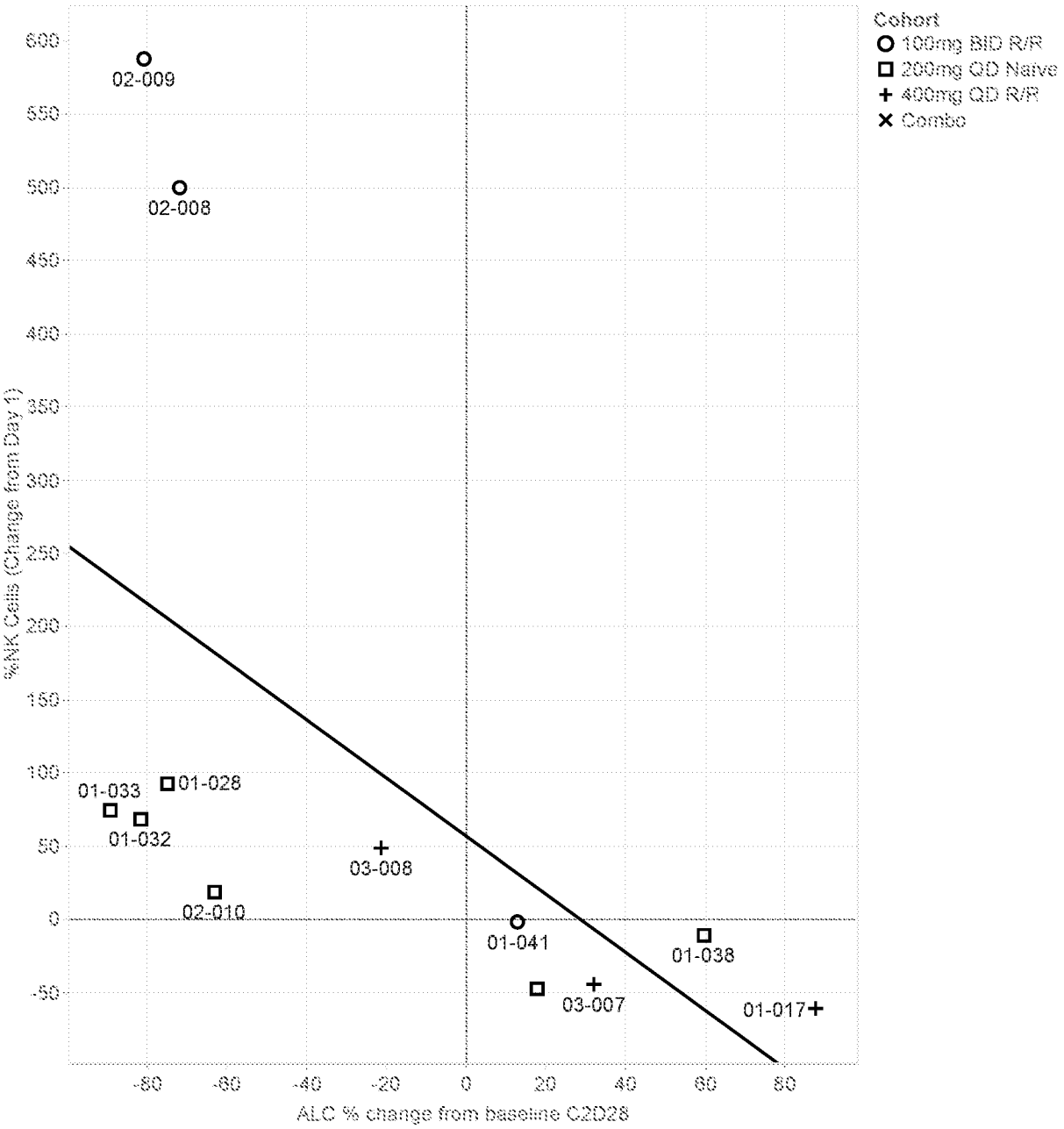

Cohort
100mg BID R/R
200mg QD Naive
400mg QD R/R
Combo
%NK Cells (Change from Day 1)
ALC % change from baseline C2D28
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
-80
-60
-40
-20
0
20
40
60
80
02-009
02-008
01-033
01-028
01-032
03-008
02-010
01-041
01-038
03-007
01-017

FIG. 152

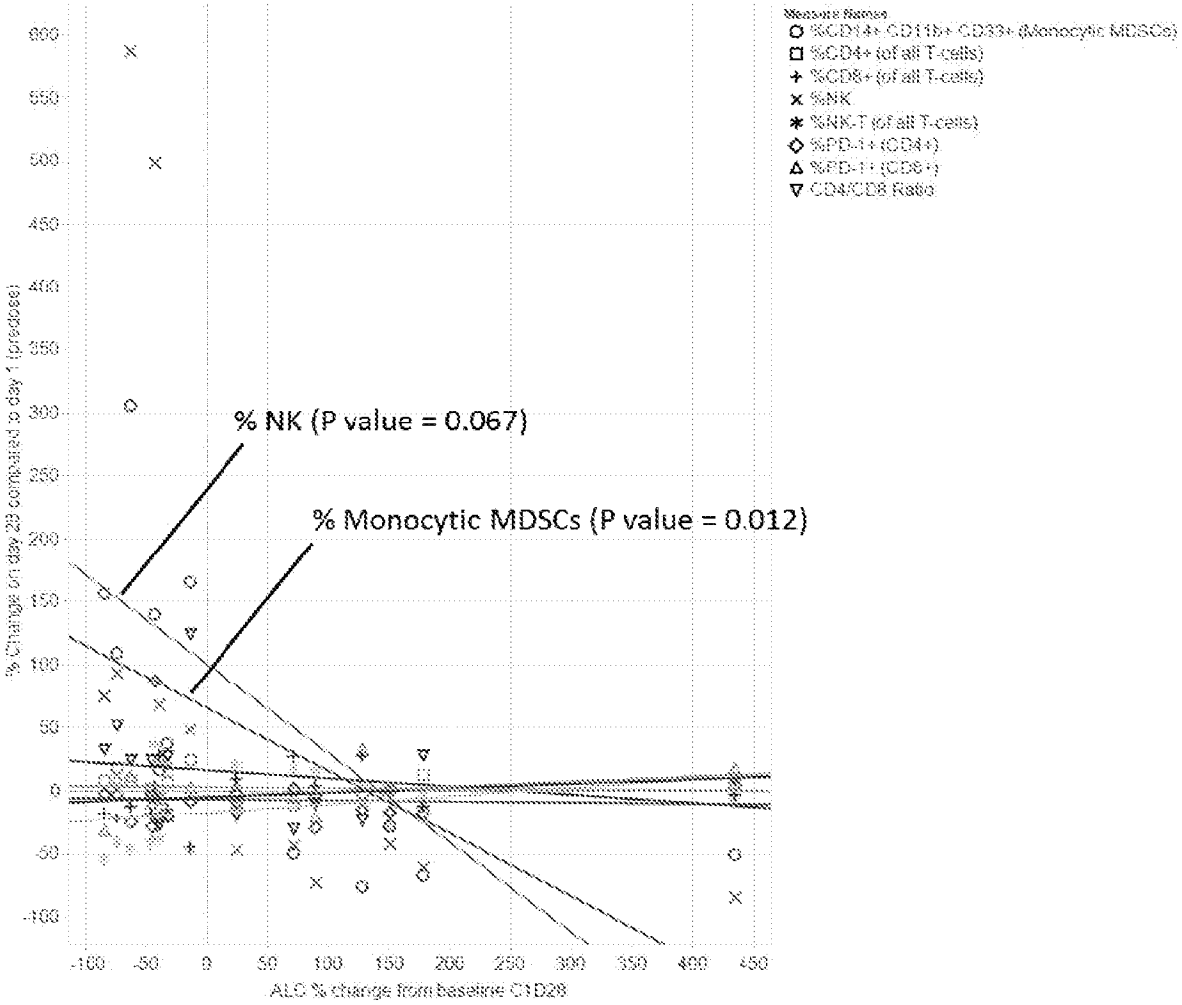

% NK (P value = 0.067)
% Monocytic MDSCs (P value = 0.012)
% Change on day 29 compared to day 1 (pre-dose)
ALC % change from baseline C1D28
%CD14+ CD11b+ CD33+ (Monocytic MDSCs)
%CD4+ (of all T-cells)
%CD8+ (of all T-cells)
%NK
%NK-T (of all T-cells)
%PD-1+ (CD4+)
%PD-1+ (CD8+)
CD4/CD8 Ratio

FIG. 153

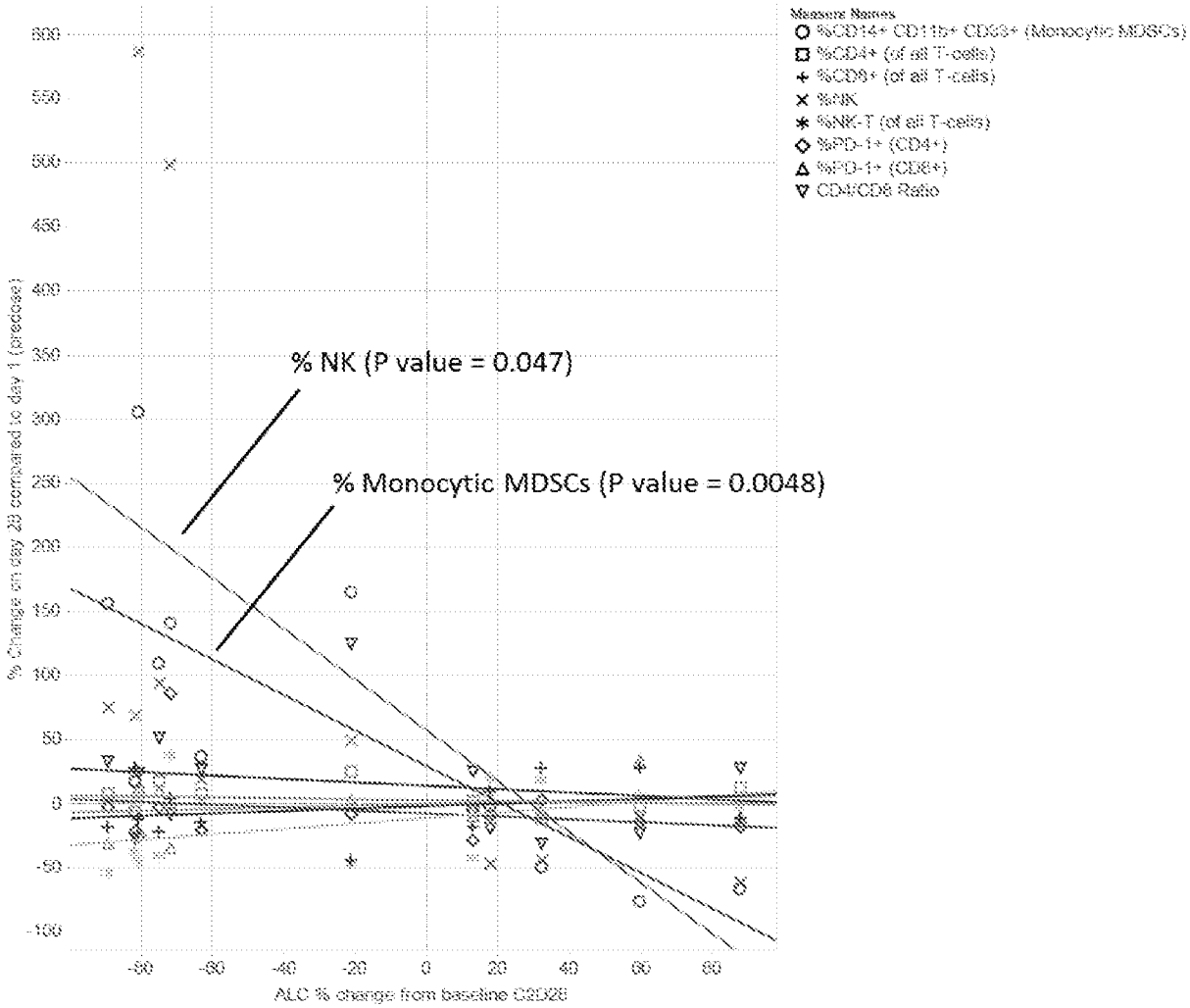

Measure Names
%CD14+ CD11b+ CD33+ (Monocytic MDSCs)
%CD4+ (of all T-cells)
%CD8+ (of all T-cells)
%NK
%NK-T (of all T-cells)
%PD-1+ (CD4+)
%PD-1+ (CD8+)
CD4/CD8 Ratio
% NK (P value = 0.047)
% Monocytic MDSCs (P value = 0.0048)
% Change on day 28 compared to day 1 (increase)
ALC % change from baseline C2D28
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
-100
-60
-40
-20
0
20
40
60

FIG. 154

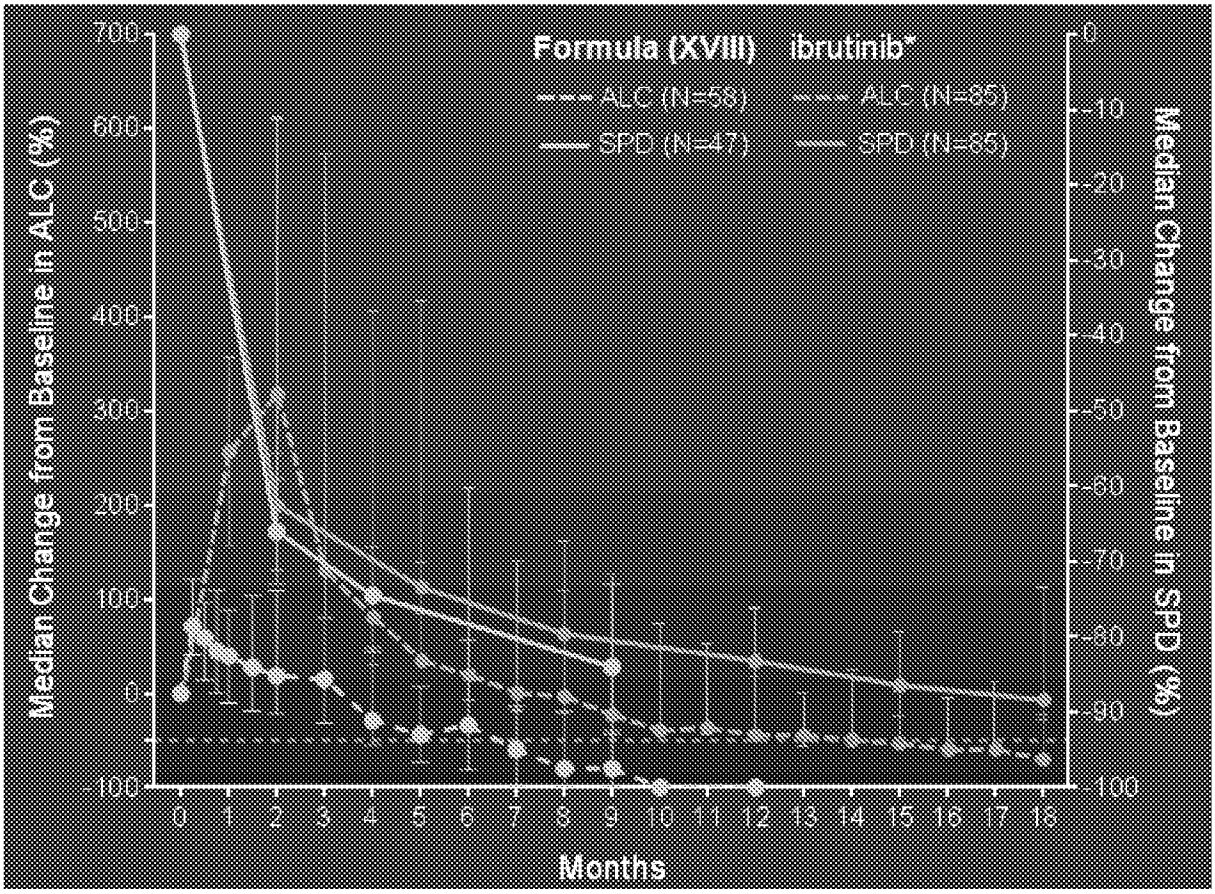

Formula (XVIII) ibrutinib*
ALC (N=58)
ALC (N=85)
SPD (N=47)
SPD (N=85)
Median Change from Baseline in ALC (%)
Median Change from Baseline in SPD (%)
Months
700
600
500
400
300
200
100
0
-100
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

FIG. 155

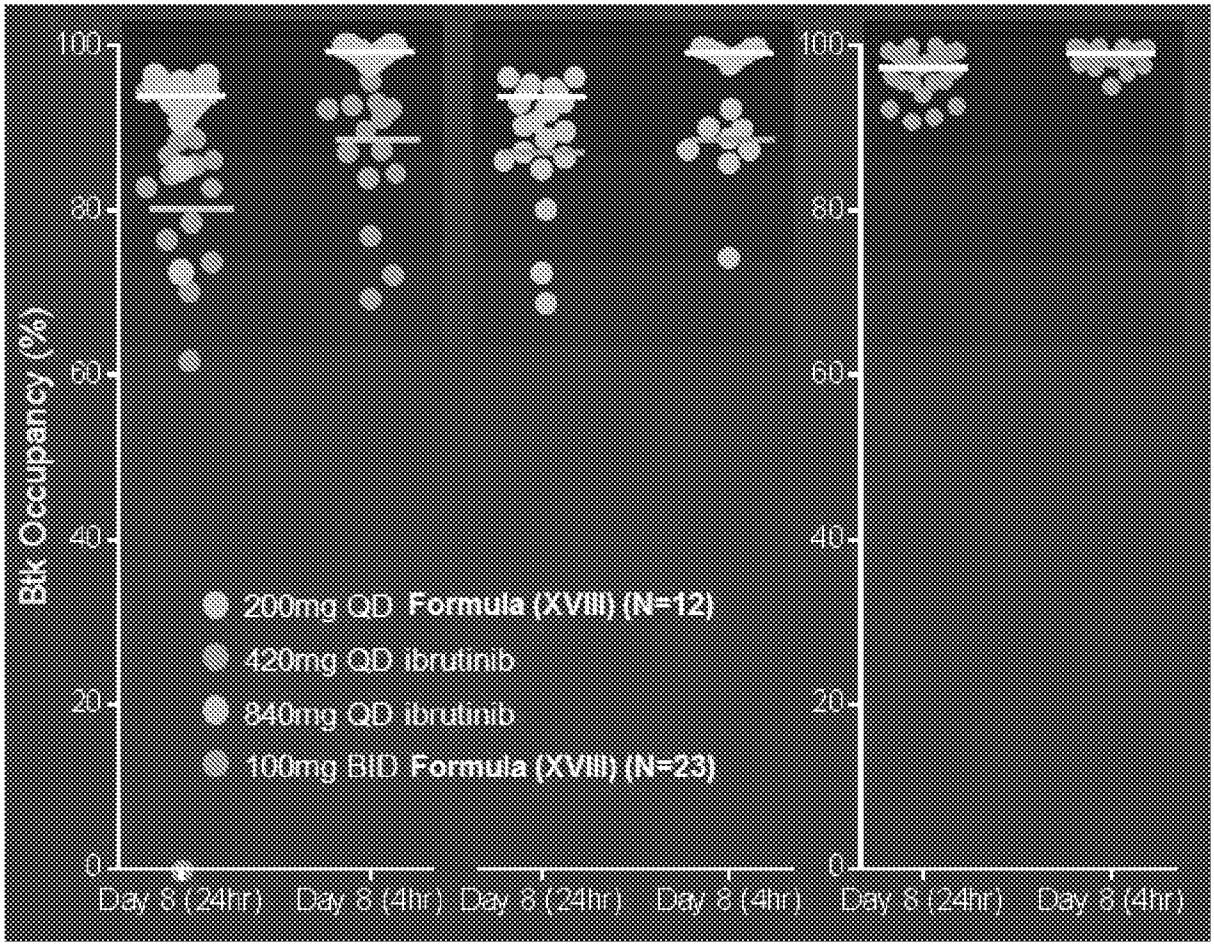
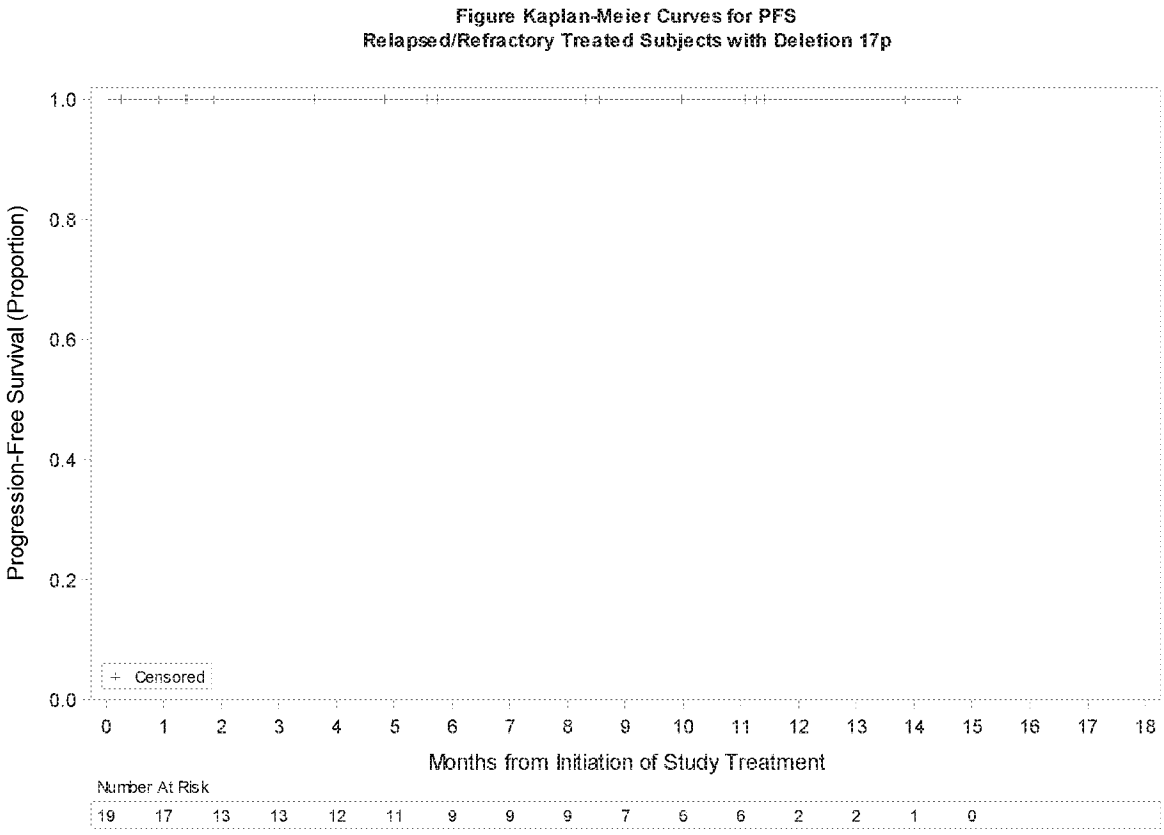

Btk Occupancy (%)
100
80
60
40
20
0
200mg QD Formula (XVIII) (N=12)
420mg QD ibrutinib
840mg QD ibrutinib
100mg BID Formula (XVIII) (N=23)
Day 8 (24hr)
Day 8 (4hr)
Day 8 (24hr)
Day 8 (4hr)
Day 8 (24hr)
Day 8 (4hr)

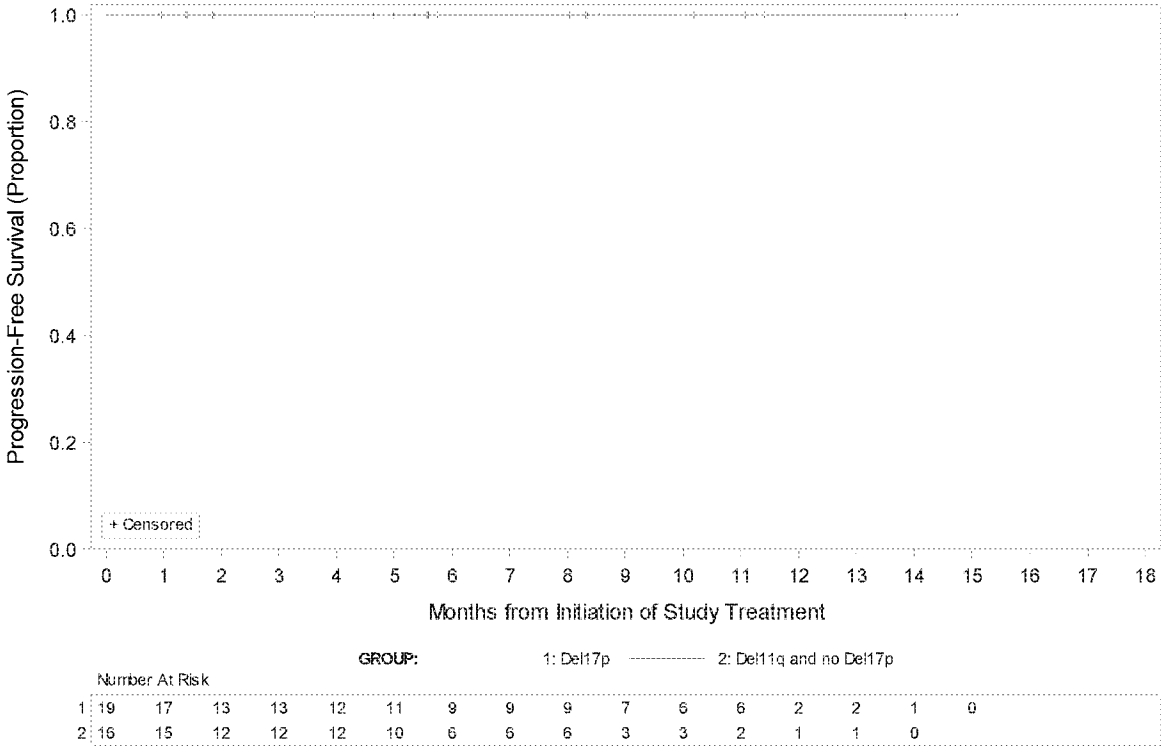
FIG. 156




Note: This figure includes Relapsed/Refractory Cohorts 1, 2a/2b/2c, 3 and 4a/4b.

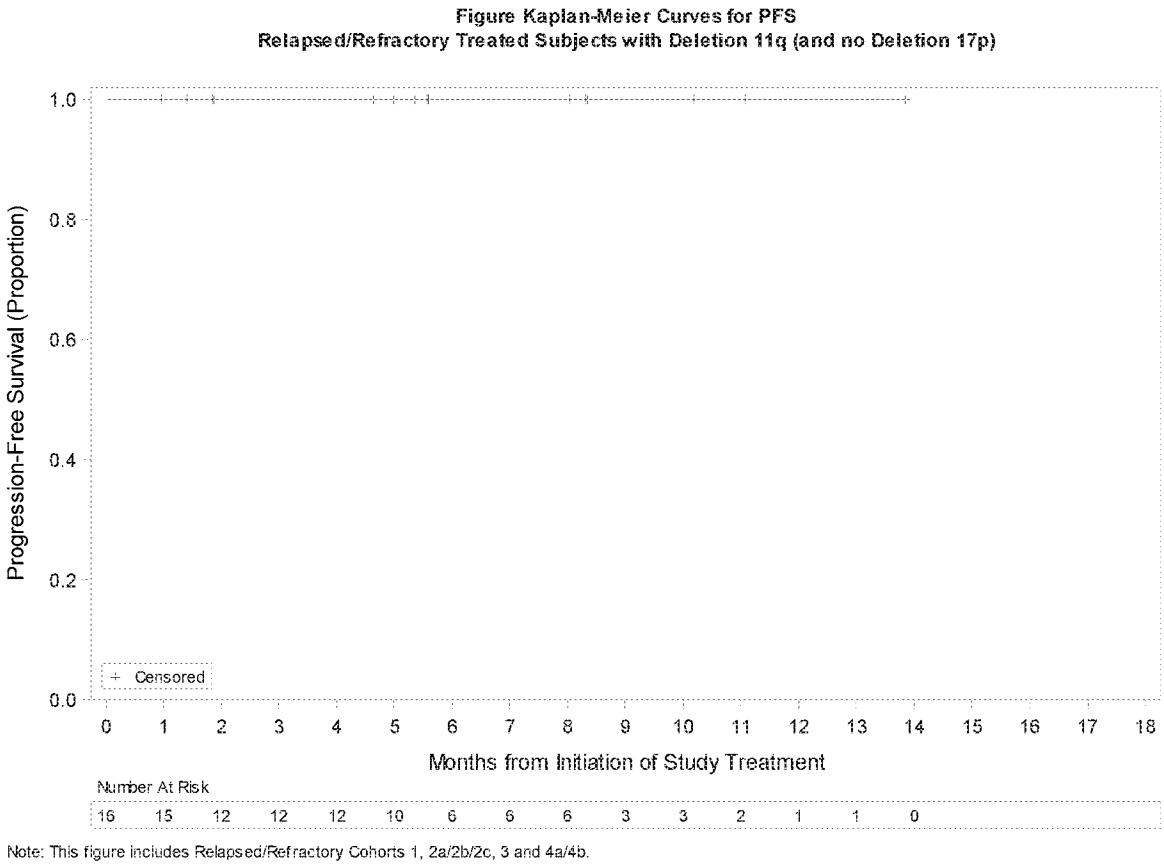
FIG. 157

**Figure Kaplan-Meier Curves for PFS**
**Relapsed/Refractory Treated Subjects**



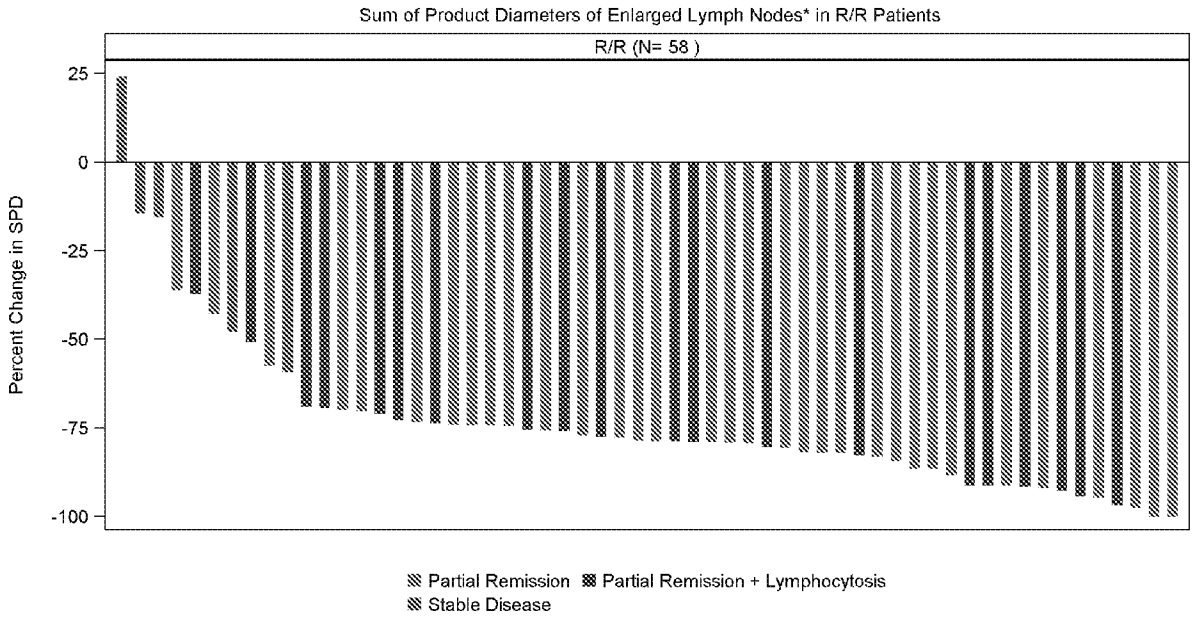

Note: This figure includes Relapsed/Refractory Cohorts 1, 2a/2b/2c, 3 and 4a/4b

FIG. 158




Note: This figure includes Relapsed/Refractory Cohorts 1, 2a/2b/2c, 3 and 4a/4b.

FIG. 159




*Any node with a diameter > 1.5 cm.
N's are subjects with observed Lymphadenopathy and overall response data.
Subjects with overall response but no observed Lymphadenopathy, 01-025 = PR, 06-002 = PR, 06-003 = PR, 03-015 = PRL, 05-001 = PRL, 05-002 = PRL, 25-001 = PRL, 01-026 = SD, 01-035 = SD, 06-004 = SD

FIG. 160

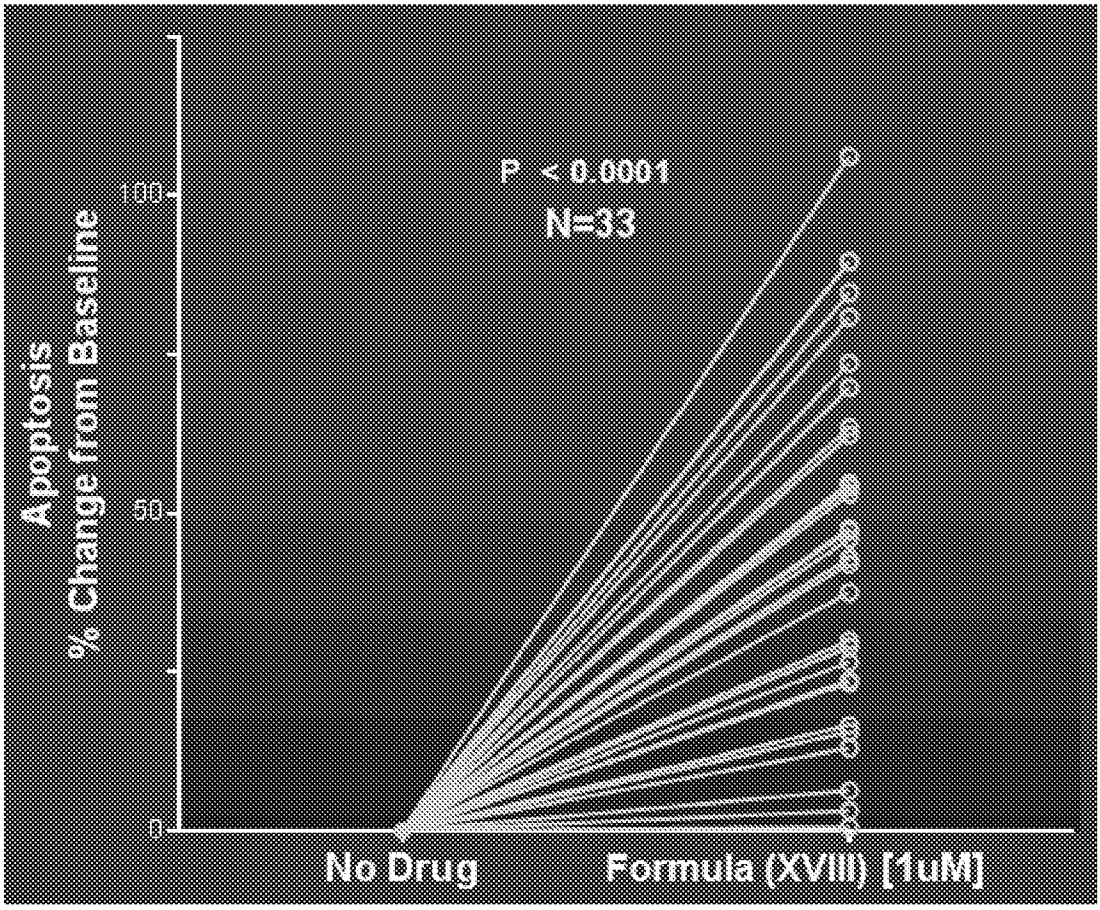

Apoptosis
% Change from Baseline
100
50
0
P < 0.0001
N=33
No Drug
Formula (XVIII) [1uM]

FIG. 161

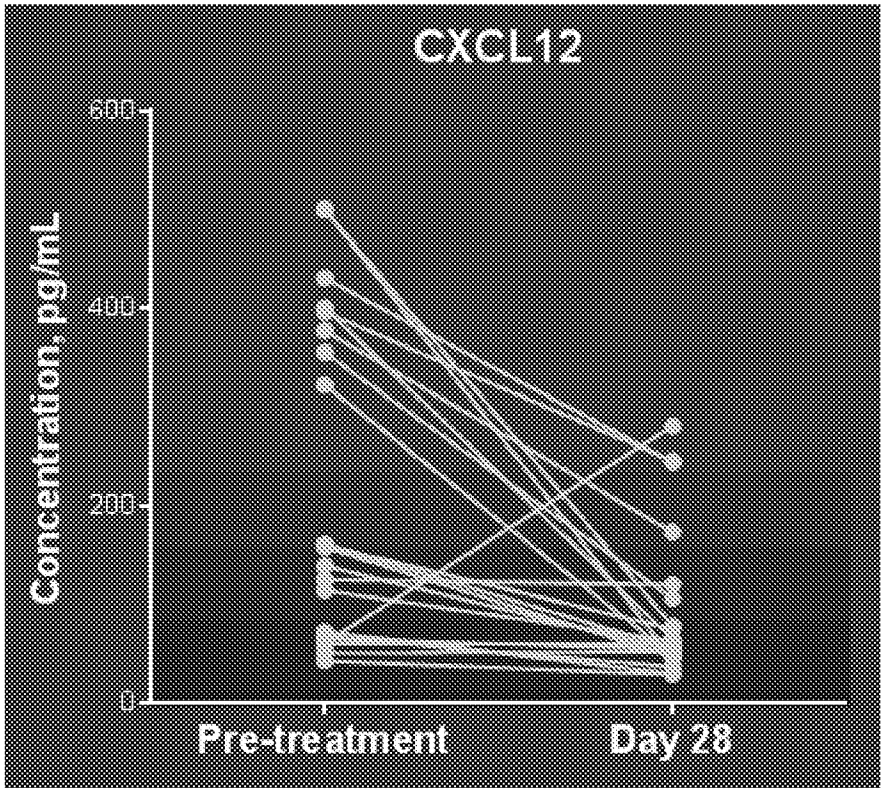

CXCL12
Concentration, pg/mL
600
400
200
0
Pre-treatment
Day 28

FIG. 162

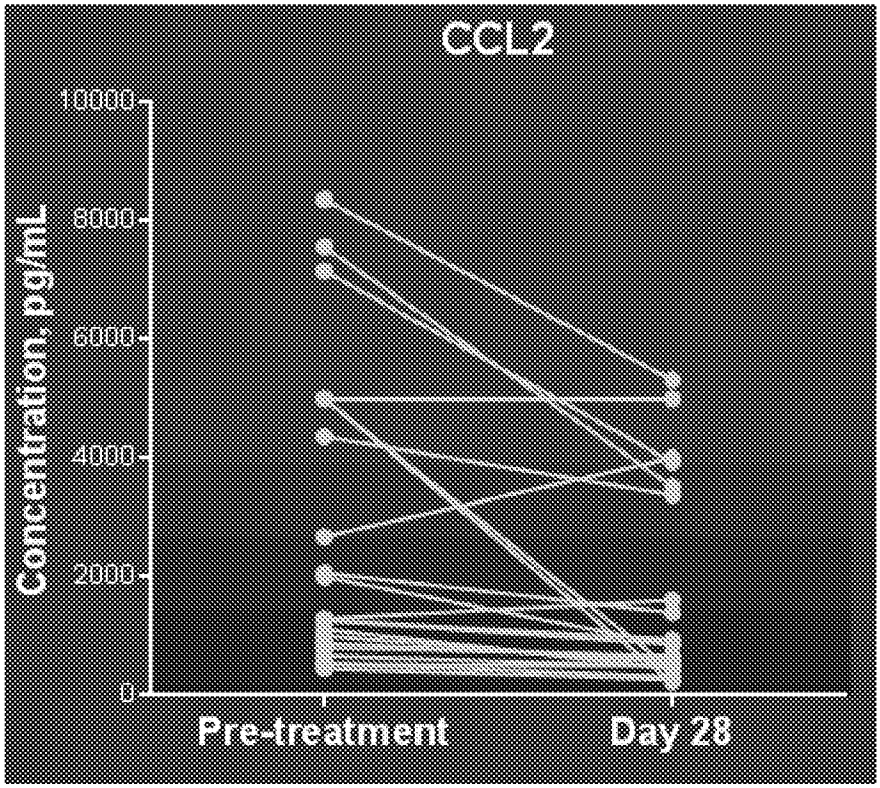

CCL2
Concentration, pg/mL
10000
8000
6000
4000
2000
0
Pre-treatment
Day 28

FIG. 163

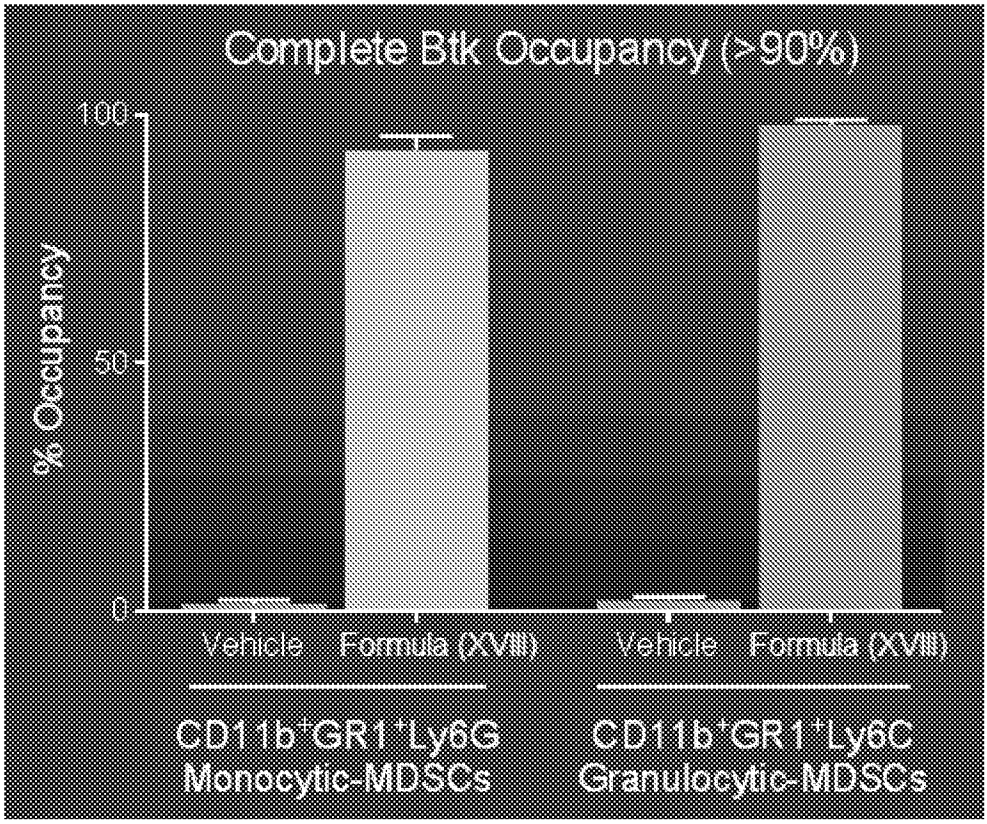

Complete Btk Occupancy (>90%)
100
50
0
% Occupancy
Vehicle
Formula (XVIII)
Vehicle
Formula (XVIII)
CD11b+GR1+Ly6G
Monocytic-MDSCs
CD11b+GR1+Ly6C
Granulocytic-MDSCs

FIG. 164

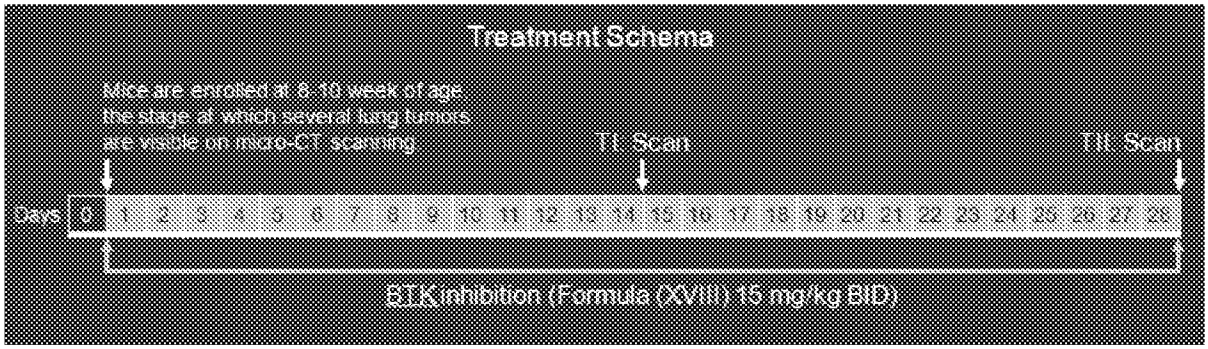

Treatment Schema
Mice are enrolled at 8-10 week of age
the stage at which several lung tumors
are visible on micro-CT scanning
T1 Scan
T2 Scan
Days
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28
BTK inhibition (Formula (XVIII) 15 mg/kg BID)

FIG. 165

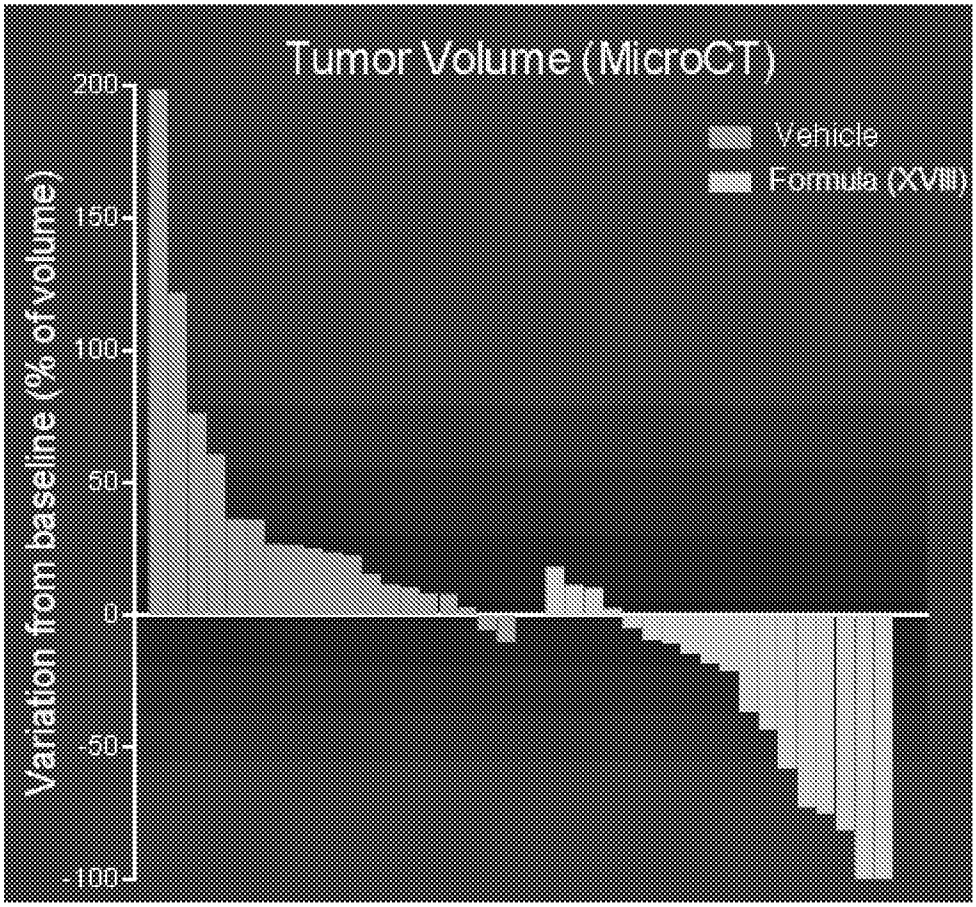

Tumor Volume (MicroCT)
Vehicle
Formula (XVIII)
Variation from baseline (% of volume)
200
150
100
50
0
-50
-100

FIG. 166

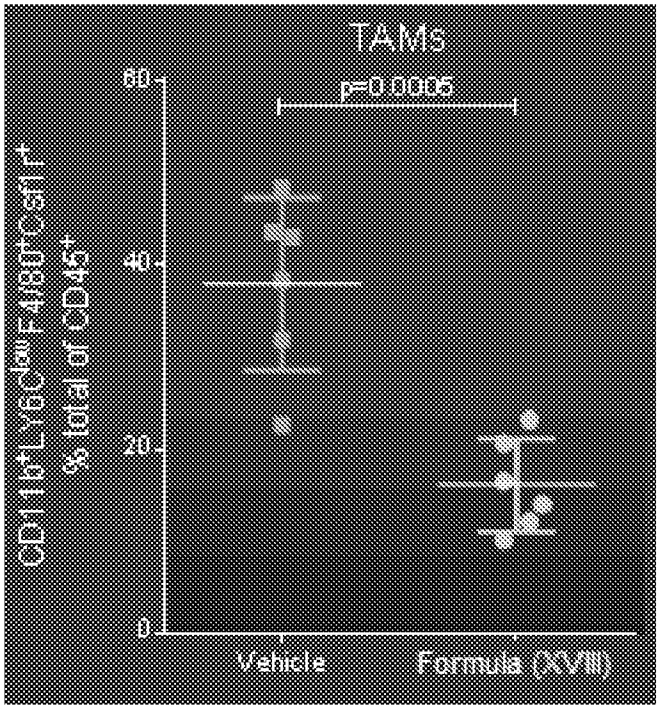

TAMs
p=0.0005
CD11b+Ly6C-/lowF4/80hiCsf1r+
% total of CD45+
60
40
20
0
Vehicle
Formula (XVIII)

FIG. 167

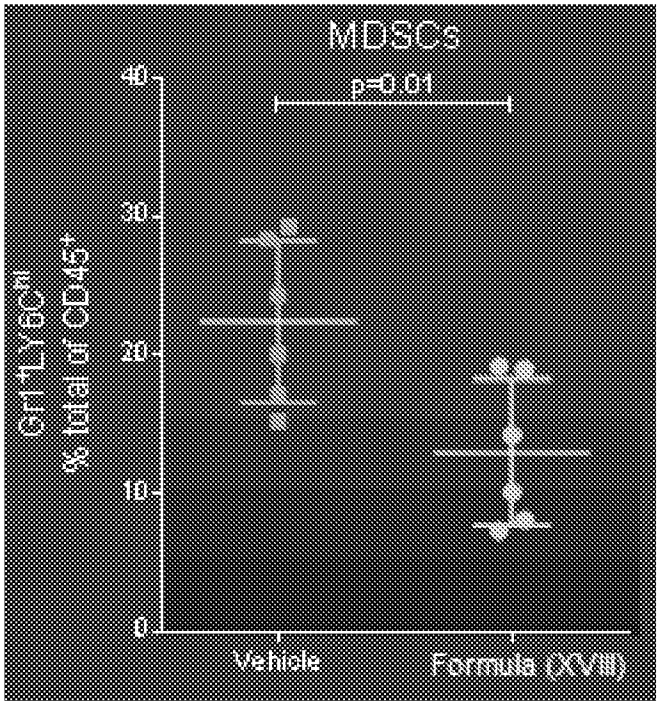

MDSCs
p=0.01
40
30
20
10
0
Gr1+Ly6C+ % total of CD45+
Vehicle
Formula (XVIII)

FIG. 168

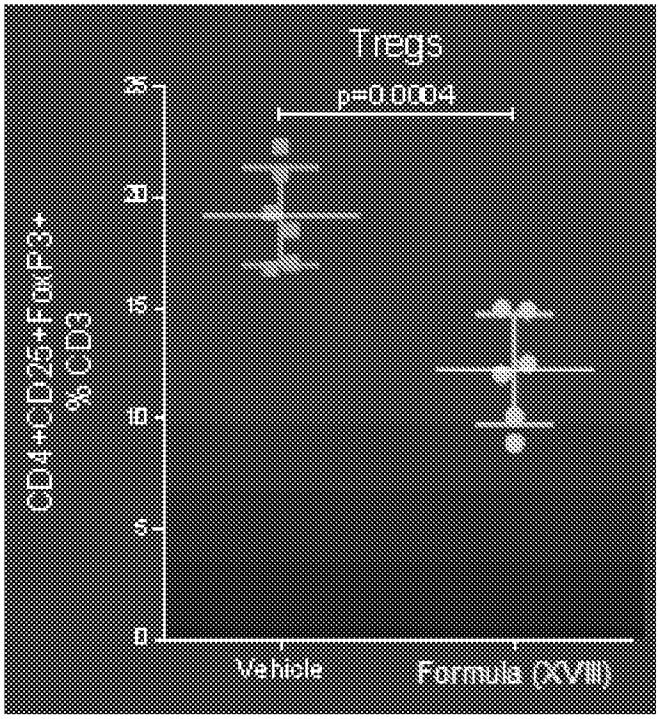

Tregs
p=0.0004
CD4+CD25+FoxP3+
% CD3
0
5
10
15
20
Vehicle
Formula (XVIII)

FIG. 169

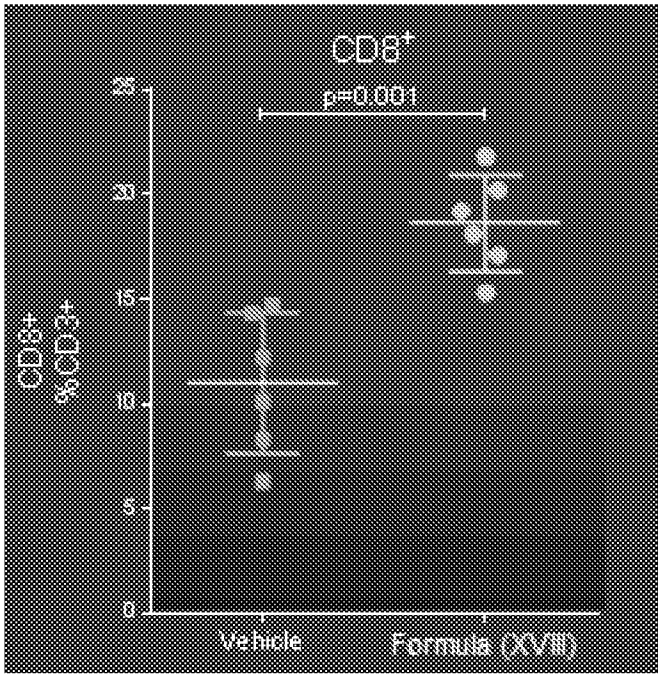



FIG. 170

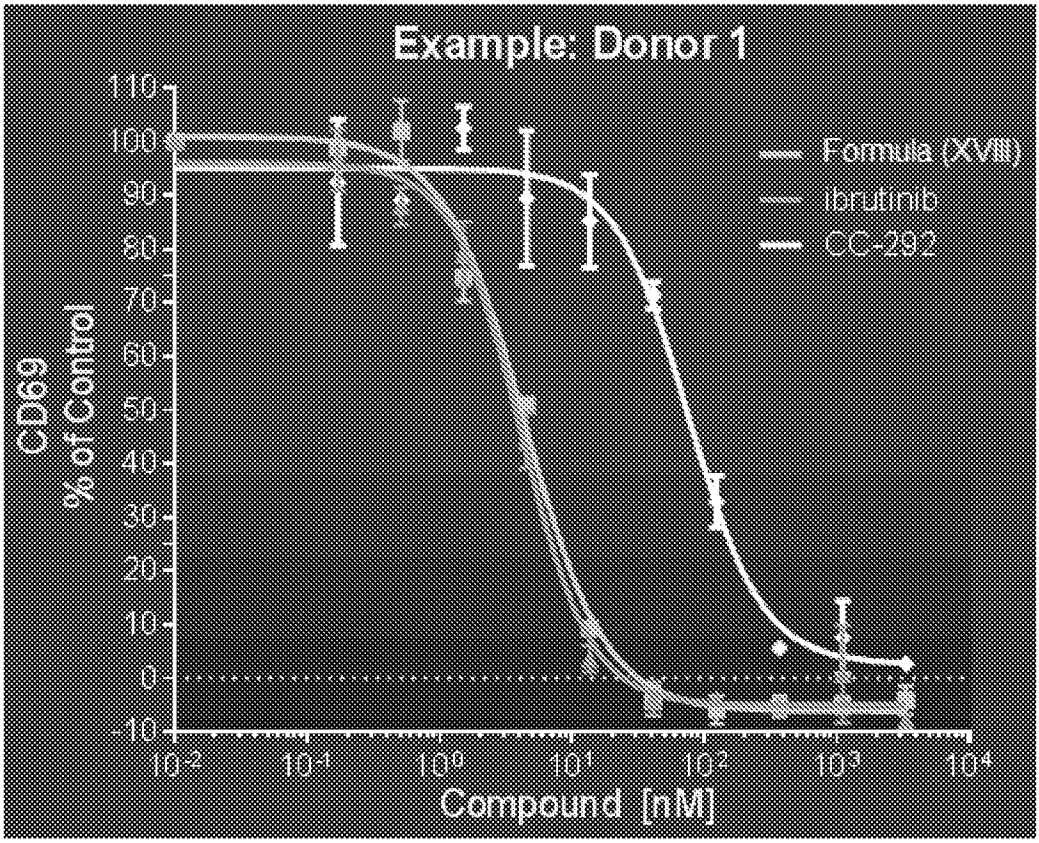

Example: Donor 1
Formula (XVIII)
ibrutinib
CC-292
CD69
% of Control
110
100
90
80
70
60
50
40
30
20
10
0
-10
$10^{-2}$
$10^{-1}$
$10^{0}$
$10^{1}$
$10^{2}$
$10^{3}$
$10^{4}$
Compound [nM]

FIG. 171

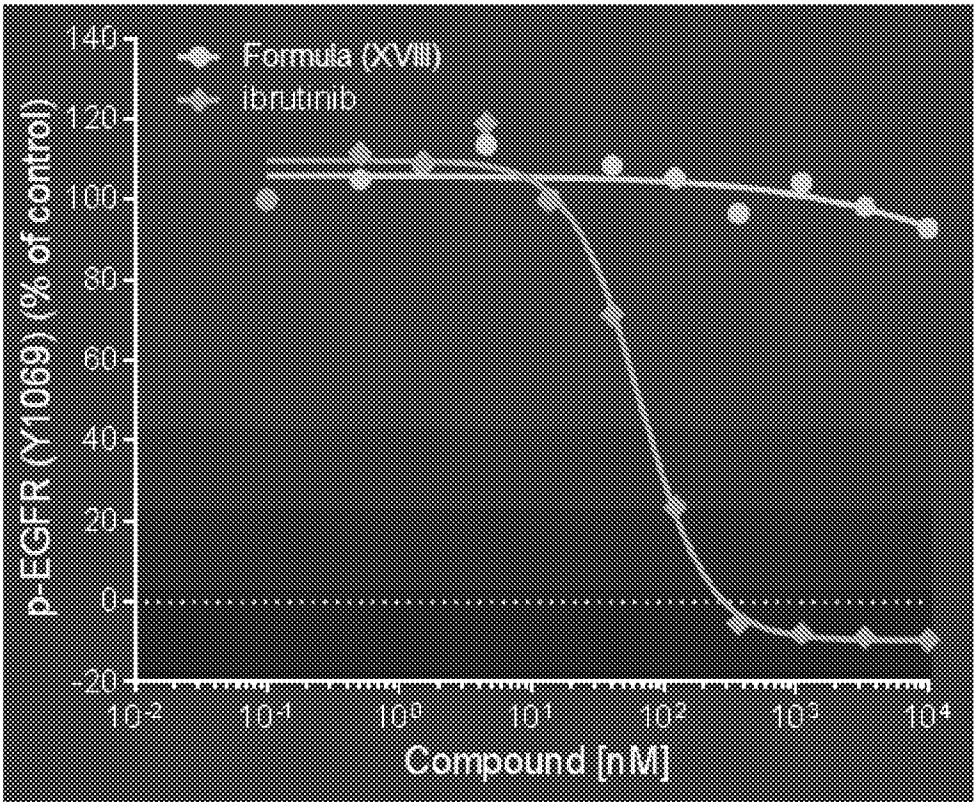

Formula (XVIII)
ibrutinib
p-EGFR (Y1069) (% of control)
140
120
100
80
60
40
20
0
-20
$10^{-2}$
$10^{-1}$
$10^{0}$
$10^{1}$
$10^{2}$
$10^{3}$
$10^{4}$
Compound [nM]

FIG. 172

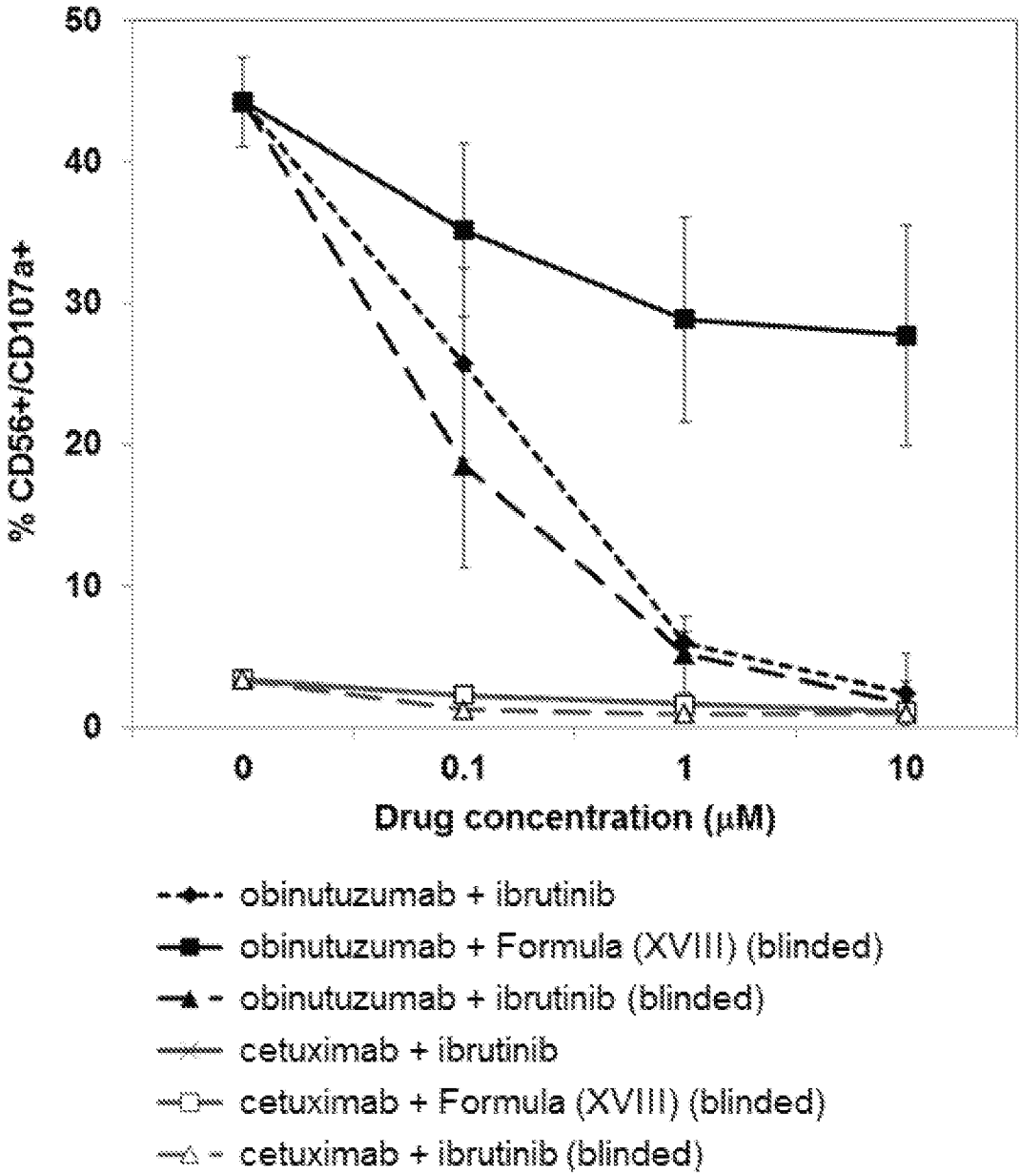

50
40
30
20
10
0
% CD56+/CD107a+
0
0.1
1
10
Drug concentration (μM)
obinutuzumab + ibrutinib
obinutuzumab + Formula (XVIII) (blinded)
obinutuzumab + ibrutinib (blinded)
cetuximab + ibrutinib
cetuximab + Formula (XVIII) (blinded)
cetuximab + ibrutinib (blinded)

FIG. 173

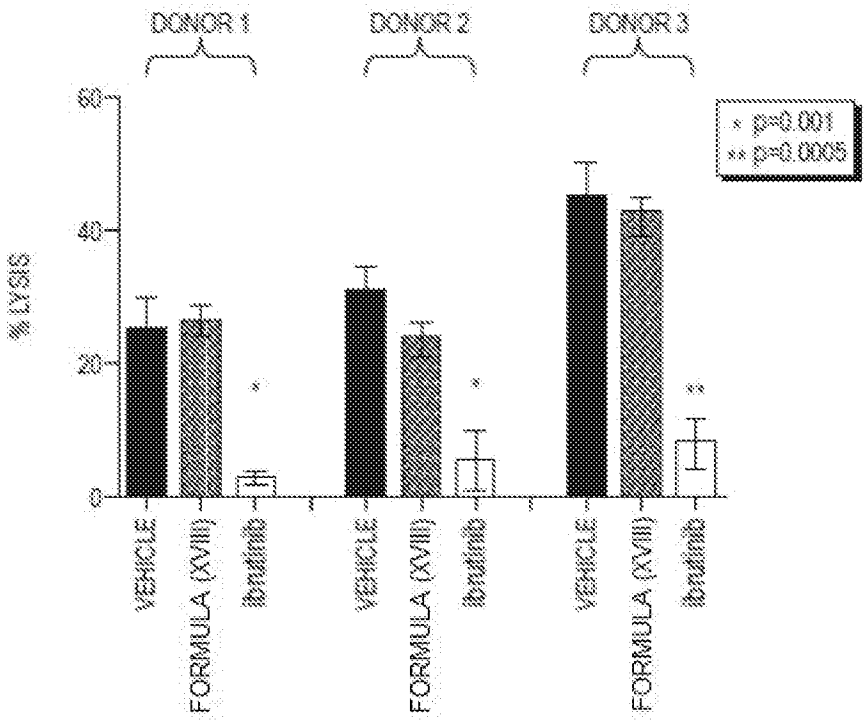

DONOR 1
DONOR 2
DONOR 3
* p<0.001
** p<0.005
% LYSIS
60
40
20
0
VEHICLE
FORMULA (XVIII)
Ibrutinib
VEHICLE
FORMULA (XVIII)
Ibrutinib
VEHICLE
FORMULA (XVIII)
Ibrutinib

FIG. 174

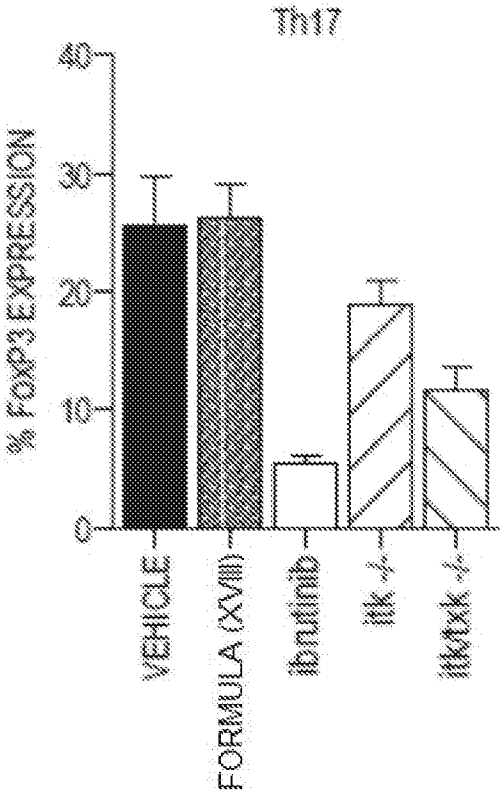

Th17
% FoxP3 EXPRESSION
0
10
20
30
40
VEHICLE
FORMULA (XVIII)
ibrutinib
Itk -/-
Itk/Rlk -/-

FIG. 175

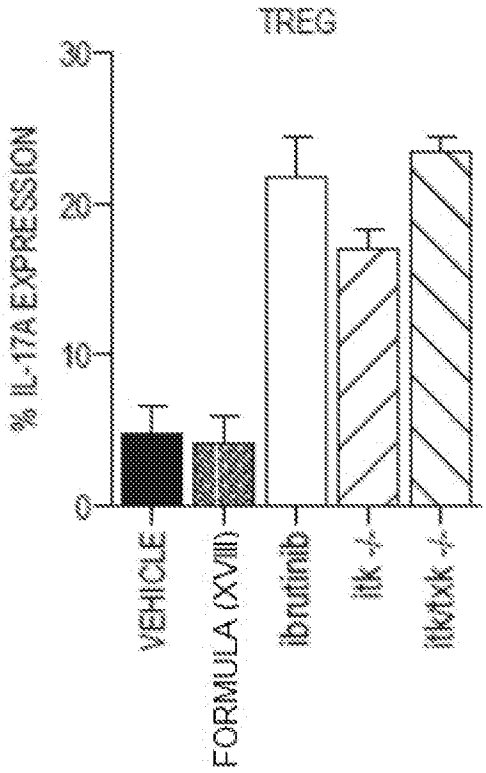

TREG
% IL-17A EXPRESSION
30
20
10
0
VEHICLE
FORMULA (XVIII)
ibrutinib
itk -/-
itk/rlk -/-

FIG. 176

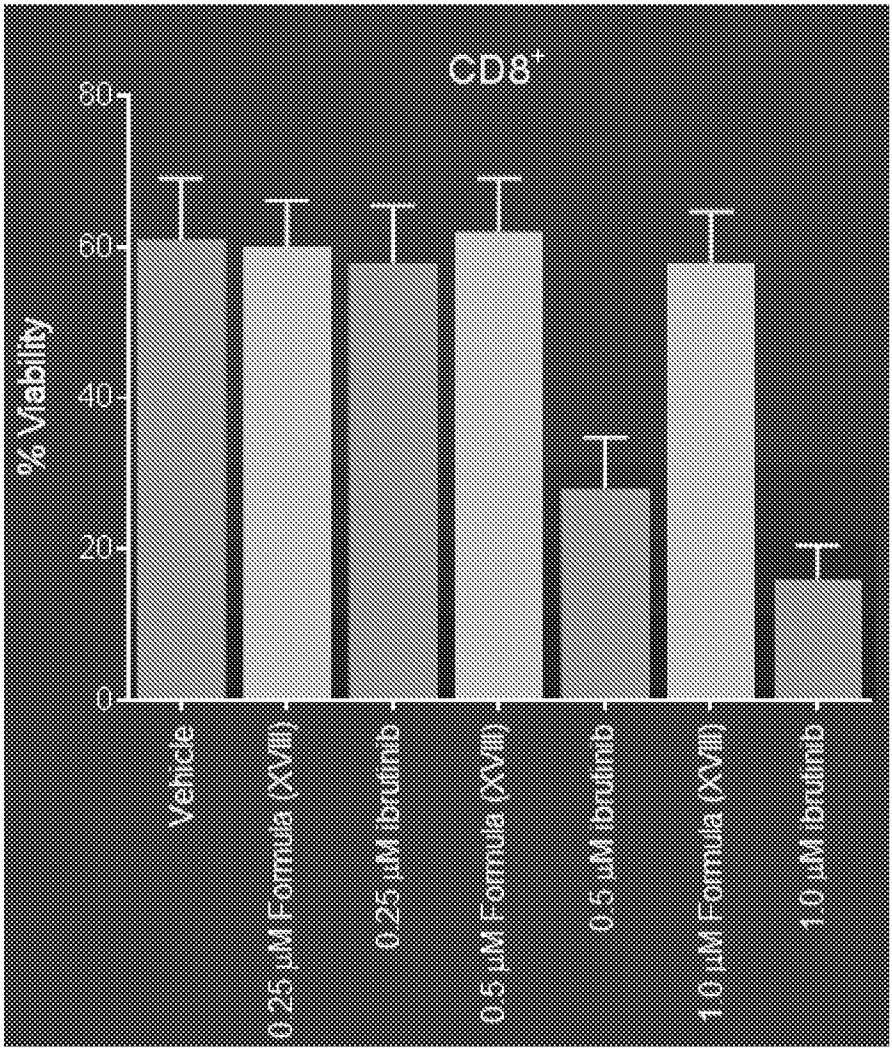

CD8+
% Viability
80
60
40
20
0
Vehicle
0.25 μM Formula (VIII)
0.25 μM Ibrutinib
0.5 μM Formula (VIII)
0.5 μM Ibrutinib
1.0 μM Formula (VIII)
1.0 μM Ibrutinib

FIG. 177

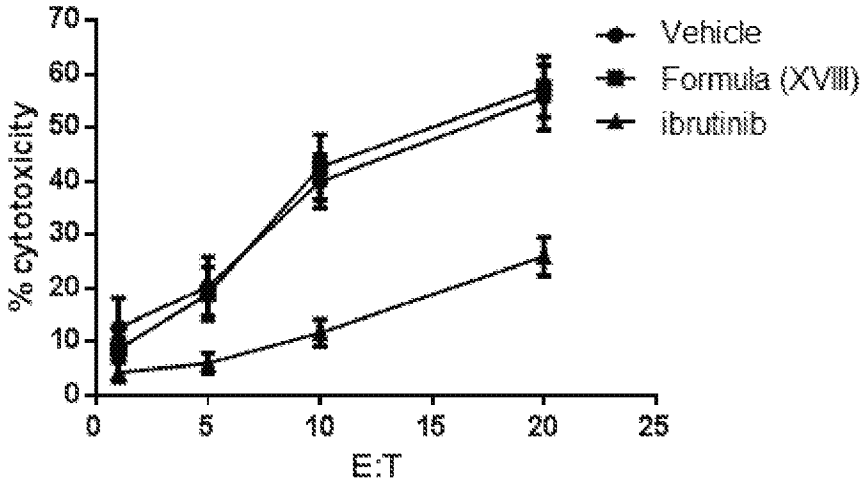

70
60
50
40
30
20
10
0
% cytotoxicity
0
5
10
15
20
25
E:T
Vehicle
Formula (XVIII)
ibrutinib

FIG. 178

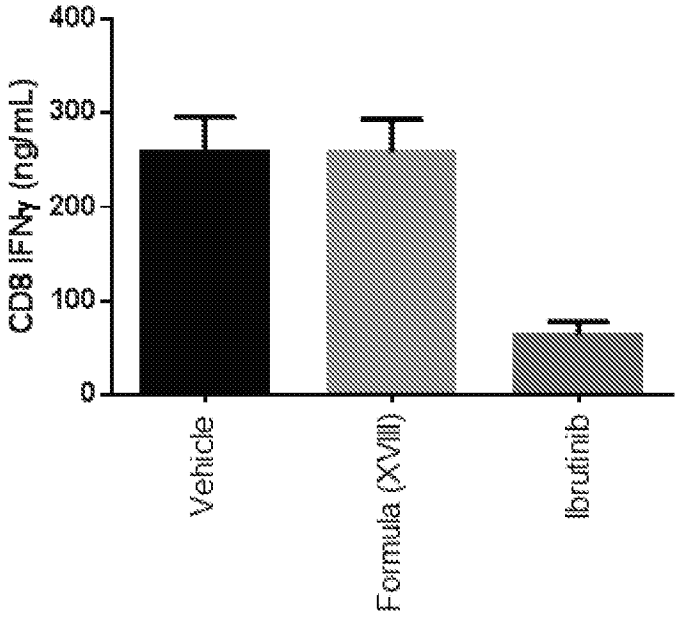

400
300
200
100
0
CD8 IFNγ (ng/mL)
Vehicle
Formula (XVIII)
Ibrutinib

FIG. 179

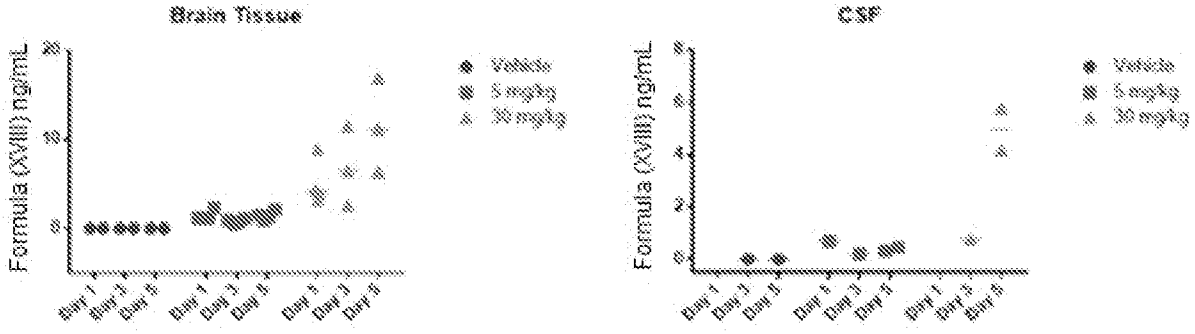



FIG. 180

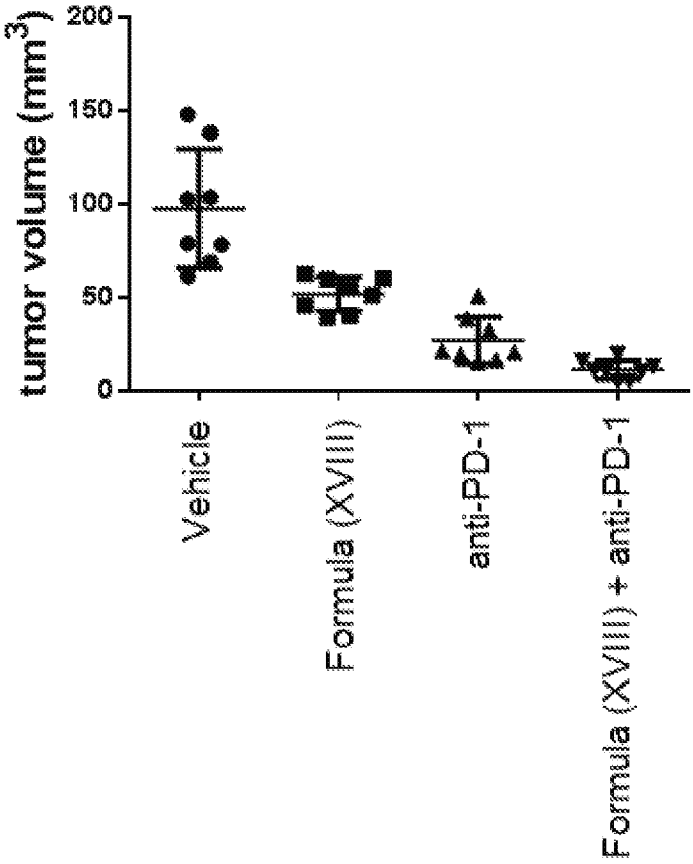

tumor volume (mm3)
200
150
100
50
0
Vehicle
Formula (XVIIII)
anti-PD-1
Formula (XVIIII) + anti-PD-1

FIG. 181

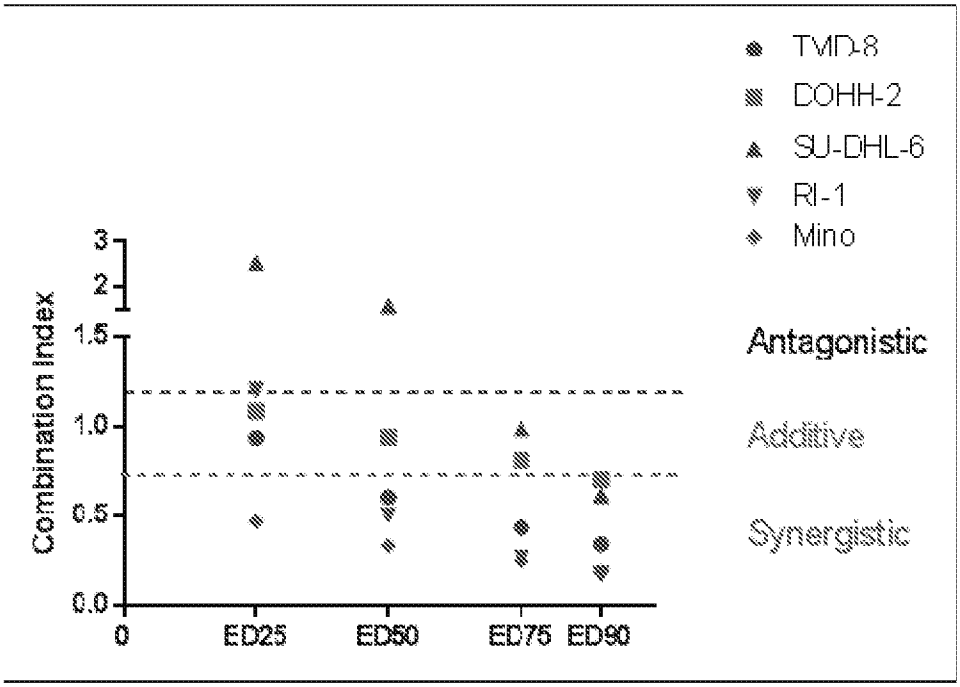

TMD-8
DOHH-2
SU-DHL-6
RI-1
Mino
Antagonistic
Additive
Synergistic
Combination Index
3
2
1.5
1.0
0.5
0.0
0
ED25
ED50
ED75
ED90

FIG. 182

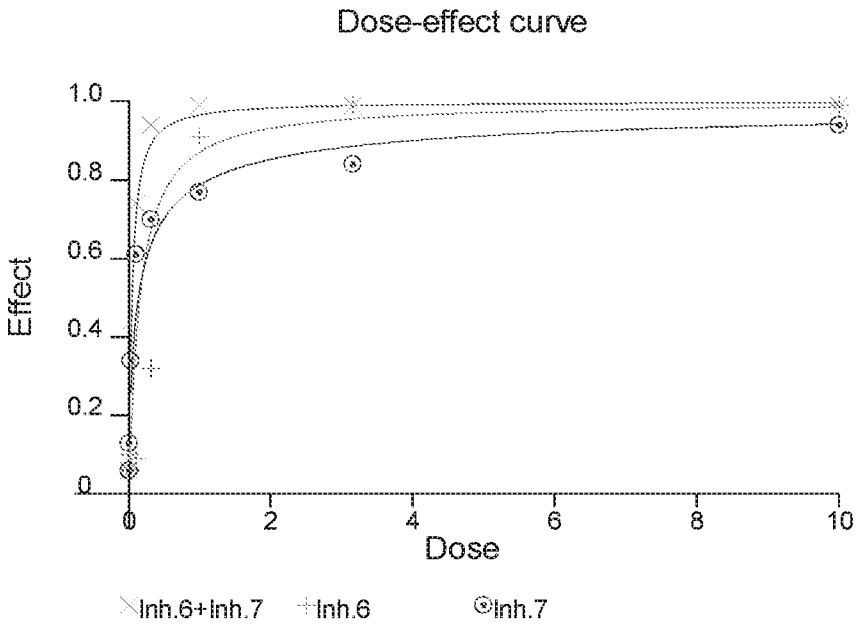

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.6+Inh.7
Inh.6
Inh.7

FIG. 183

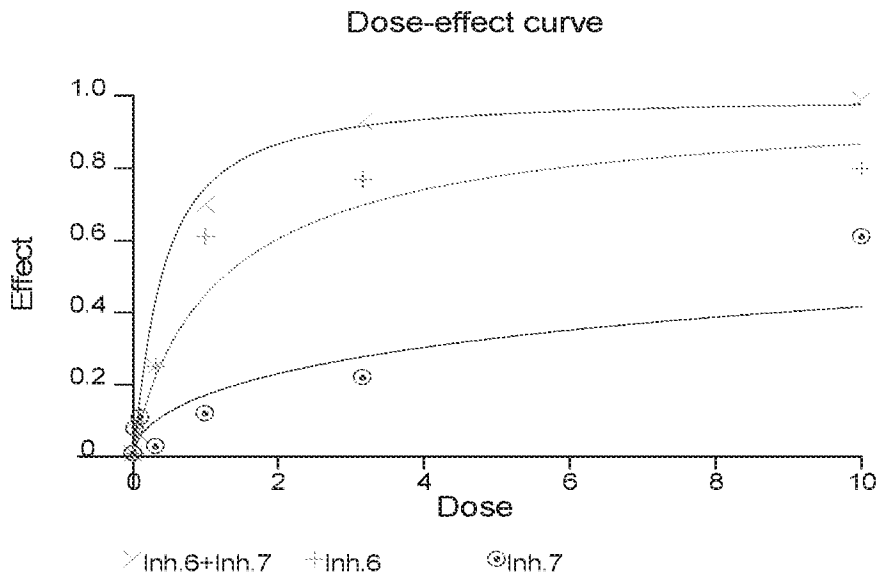

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.6+Inh.7
Inh.6
Inh.7

FIG. 184

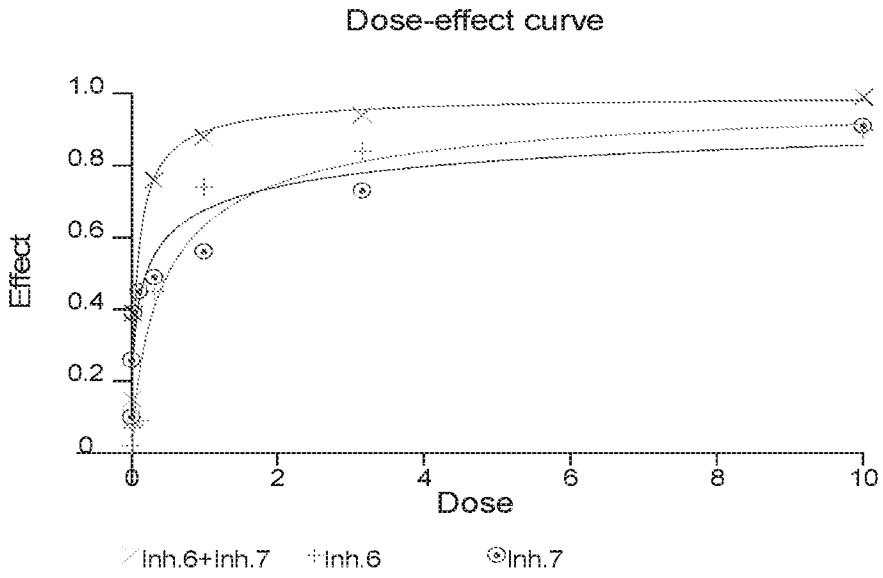

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.6+Inh.7
Inh.6
Inh.7

FIG. 185

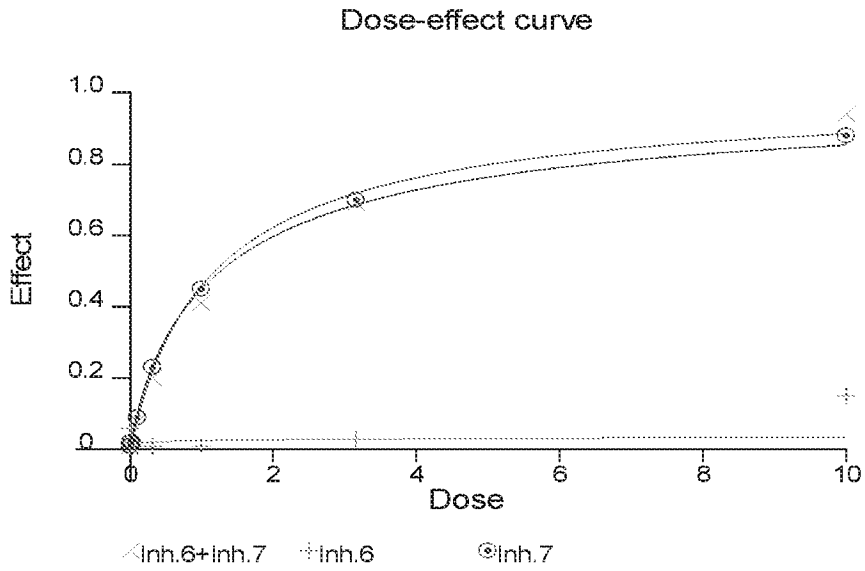

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.6+Inh.7
Inh.6
Inh.7

FIG. 186

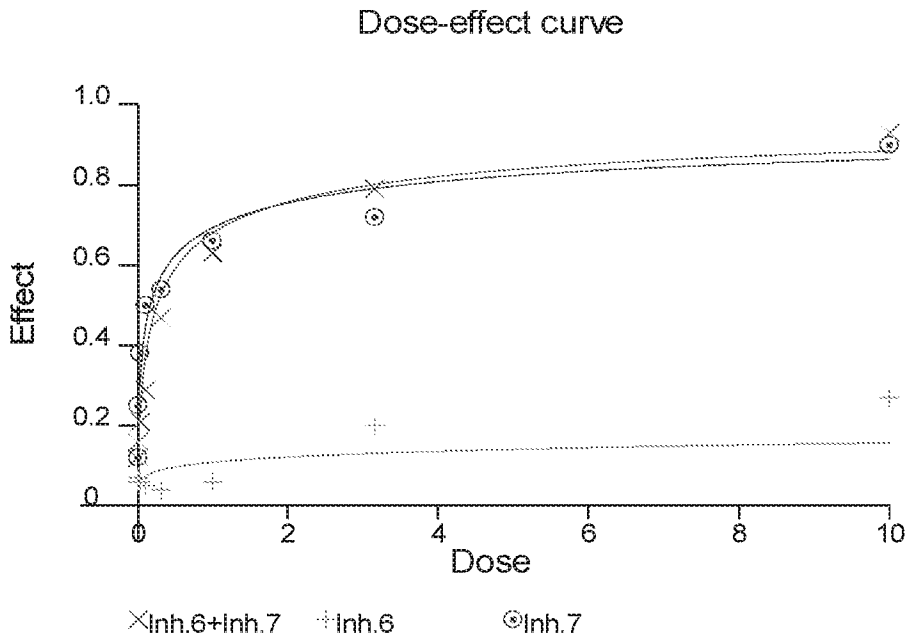

Dose-effect curve
1.0
0.8
0.6
0.4
0.2
0
Effect
0
2
4
6
8
10
Dose
Inh.6+Inh.7
Inh.6
Inh.7

FIG. 187

# INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/056127

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/00 A61K31/4155 A61K31/416 A61K31/454 A61K31/519
A61K39/395 A61K45/06
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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|---|---|
| 2 November 2015 | 06/11/2015 |

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

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