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PD-L1 inhibitor
BTK inhibitor
PI3K-δ inhibitor

Abstract:

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PD-L1 inhibitor
BTK inhibitor
PI3K-δ inhibitor

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

FIG. 1

Btki + PI3K (1000nM)
Btki + PI3K (300nM)
Btki + PI3K (100nM)
Btki + PI3K (30nM)
Btki + PI3K (10nM)
Btki + PI3K (3nM)

(57) Abstract: Therapeutic compositions and methods of using the compositions, including combinations of a Bruton's tyrosine kinase (BTK) inhibitor, a phosphomositide 3-kinase (PI3K) inhibitor, a PI3K inhibitors selective for the γ- and δ-isomers and selective for both γ- and δ-isomers (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-L1 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.
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 agammaglobulinaemia) 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.

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
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.

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 SDF1 (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-SDF1 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 (p110 toutes, p110, p110, and p110) 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- and PI3K- isoforms are preferentially expressed in normal and malignant leukocytes.

[009] The delta isoform of class I PI3K (PI3K-) 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- 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 isoform of class I PI3K (PI3K-) 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-α inhibitors, PI3K-β inhibitors and those that are PI3K-γ,δ,ε 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 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 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 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, 131I-tositumomab, ibritumomab, 90Y-ibritumomab, 111In-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, 131I-tositumomab, ibritumomab, 90Y-ibritumomab, 111In-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 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 inhibit or 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-L1 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-γ 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, alopixprin, antithrombin, apixaban, argatroban, aspirin, aspirin with extended-release dipyridamole, beraprost, betrixaban, bivalirudin, carbasalate calcium, cilostazol, clopidogrel, clopidogrel bisulfate, cloriricmen, 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-L1 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-L1 inhibitor and a BTK inhibitor, either simultaneously or separately.
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.

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 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.

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.

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-į 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-į 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-į 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

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.

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.
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.

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.

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.

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**

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.

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.

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-į 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-į 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-į 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-į 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-į 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-į 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-į 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-į 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.
FIG. 13 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula XVIII and the PI3K-\textsuperscript{i} 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.

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-\textsuperscript{i} 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 \( \mu \text{M} \).

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-\textsuperscript{i} 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 \( \mu \text{M} \).

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-\textsuperscript{i} 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 \( \mu \text{M} \).

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-\textsuperscript{i} 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 \( \mu \text{M} \).

FIG. 18 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula XVIII and the PI3K-\textsuperscript{i} 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-į 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-į 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-į 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-į 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 lymphoma, 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-į 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-į 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-į 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-į 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-į 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-į 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-į 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-į 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-į 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-į 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-į 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-į 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.
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-ι inhibitor of Formula IX (“Inh.3”). The y-axis (“Effect”) is given in units of Fα (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

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-ι inhibitor of Formula IX (“Inh.3”). The y-axis (“Effect”) is given in units of Fα (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

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.

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 Fα (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

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 Fα (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.

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 Fα (fraction affected) and the x-axis (“Dose”) is given in linear units of µM.
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.

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).

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.

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.

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.

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 \( \mu \text{M} \).

[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 \( \mu \text{M} \).

[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 \( \mu \text{M} \).

[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 \( \mu \text{M} \).

[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.

[0100] 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’)

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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 lymphoma), 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 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.

[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 \( \mu \text{M} \).

**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 \( \mu \text{M} \).

**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 \( \mu \text{M} \).

**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 \( \mu \text{M} \).

**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 \( \mu \text{M} \).

**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 \( \mu \text{M} \).

**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)

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(“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.

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.
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.

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.

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.

FIG. 95 illustrates the dosing schema used for the |-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.

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

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

FIG. 98 illustrates the effect of |-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 |-PD-L1 inhibitor and a BTK inhibitor in a syngeneic CT26 colon cancer model in mice.

FIG. 99 illustrates the synergistic effect of |-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.
FIG. 109 illustrates bioluminescence imaging results 2 weeks after start of dosing in the ID8 ovarian cancer model study.

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.

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.

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.

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.

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.

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<sub>low</sub>, 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<sub>hi</sub>, 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 μM². 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, inhibitA (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 l-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 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) l-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 l-PD-L1 antibody at 150 µg, on days 6, 9, 12, 15, and 18; (8) the PI3K inhibitor of Formula (IX) at 15 mg/kg, BID, on days 6 to 20, combined with l-PD-L1 antibody at 150 µg, on days 6, 9, 12, 15, and 18; (9) the PI3K inhibitor ibrutinib at 6 mg/kg, QD, on days 6 to 20, combined with l-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 [·]-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 [·]-PD-L1 inhibitor (BioXcell In Vivo MAb 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-· 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) [·]-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 [·]-PD-L1 antibody at 150 μg, on days 6, 9, 12, 15, and 18; (8) the PI3K-· inhibitor of Formula (IX) at 15 mg/kg, BID, on days 6 to 20, combined with [·]-PD-L1 antibody at 150 μg, on days 6, 9, 12, 15, and 18; (9) the PI3K-· inhibitor ibrutinib at 6 mg/kg, QD, on days 6 to 20, combined with [·]-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 [·]-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
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.

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

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

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

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

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

FIG. 164 illustrates BTK inhibitory effects on MDSCs.

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

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

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.

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.

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.

FIG. 170 illustrates CD8^+ T cells in the KrasL2 NSCLC model.
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.

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

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.

FIG. 174 shows the effects of BTK inhibition on generalized NK cell mediated cytotoxicity.

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.

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

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.

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.

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

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

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-і 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-і 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-і 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-і 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-і 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.
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

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).

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).

SEQ ID NO:3 is the heavy chain variable region (V\textsubscript{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).

SEQ ID NO:4 is the light chain variable region (V\textsubscript{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).

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).

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).

SEQ ID NO:7 is the heavy chain CDR3 amino acid sequence of the PD-1 inhibitor nivolumab (corresponding to SEQ ID NO:25 in WO 2014/055648 A1).

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


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


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

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

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

[00247] SEQ I.D. 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).
SEQ ID NO:31 is the light chain of the anti-PD-L1 antibody durvalumab (MEDI4736).


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).


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).


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).


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

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

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).

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).

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).

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).

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).

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).
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).

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).

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

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


SEQ ID NO:81 is the HVR-L1 region of the anti-PD-L1 antibody avelumab (MSB0010718C) (corresponding to SEQ ID NO:19 in U.S. Patent Application

[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 “pharmacologically acceptable salt” refers to salts derived from a variety of organic and inorganic counter ions known in the art. Pharmacologically 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. Pharmacologically 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.
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.

The term “in vivo” refers to an event that takes place in a subject's body.

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.

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 $^{15}$C-enriched carbons, are within the scope of this invention.

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.

“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, -SR, -OC(O)-R', -N(R')_2, -C(O)R', -C(O)OR, -OC(O)N(R')_2, -C(O)N(R')_2, -N(R')C(O)OR, -N(R')C(O)R', -N(R')C(O)N(R')_2, N(R')C(NR')_2N(R')_2, -N(R')SO_2R' (where t is 1 or 2), -S(O) OR (where t is 1 or 2), -S(O)OR' (where t is 1 or 2), or PO_2R' (where each R' is independently hydrogen, alkyl, fluoroalkyl, carbocycyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroarylalkylalkyl, 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] “Alkylhetarylalkyl” 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.
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.

“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 \(C_{2-10}\)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 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, trimethylsilyl, -OR\(^{-}\), -SR\(^{\prime}\), -OC(O)-R\(^{\prime}\), -N(R\(^{\prime}\))\(_{2}\), -C(O)R\(^{\prime}\), -C(O)OR\(^{\prime}\), -OC(O)N(R\(^{\prime}\))\(_{2}\), -C(O)N(R\(^{\prime}\))\(_{2}\), -N(R\(^{\prime}\))C(O)OR\(^{\prime}\), -N(R\(^{\prime}\))C(O)R\(^{\prime}\), -N(R\(^{\prime}\))C(NO\(^{\prime}\))N(R\(^{\prime}\))\(_{2}\), -N(R\(^{\prime}\))S(O)\(_{2}\)R\(^{\prime}\) (where t is 1 or 2), -S(O)\(_{2}\)OR\(^{\prime}\) (where t is 1 or 2), -S(O)\(_{2}\)N(R\(^{\prime}\))\(_{2}\) (where t is 1 or 2), or PO\(_{3}\)(R\(^{\prime}\))\(_{2}\), where each R\(^{\prime}\) is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

“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.

“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, trimethylsilyl, -OR’, -SR’, -OC(O)-R’, -N(R’)_2, -C(O)R’,
-C(O)OR’, -OC(O)N(R’)_2, -C(O)N(R’)_2, -N(R’)(C(O)OR’, -N(R’)(C(O)R’,
-N(R’)(C(O)N(R’)_2, N(R’)(C(NR’))N(R’)_2, -N(R’)(S(O)R’)(where t is 1 or 2), -S(O)’R’
(where t is 1 or 2), -S(O)’N(R’)_2 (where t is 1 or 2), or PO’(R’)_2, where each R’ 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, trimethylsilyl, -OR', -SR', -OC(O)-R', -N(R')_2, -C(O)R', -C(O)OR', -OC(O)N(R')_2, -C(O)N(R')_2, -N(R')_2C(O)OR', -N(R')_2C(O)R', -N(R')_2C(O)N(R')_2, N(R')_2C(NR')_2N(R')_2, -N(R')_2S(O)R', -S(O)OR' (where t is 1 or 2), -S(O)OR' (where t is 1 or 2), -S(O)OR' (where t is 1 or 2), or PO_3(O)R', where each R' is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, 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', -SR', -OC(O)-R',
-N(R')_2, -C(O)R', -C(O)OR', -OC(O)N(R')_2, -C(O)N(R')_2, -N(R')C(O)OR',
-N(R')C(O)R', -N(R')C(O)N(R')_2, N(R')C(NR')_2N(R')_2, -N(R')S(O)R' (where t is 1 or 2),
-S(O)_2OR' (where t is 1 or 2), -S(O)_2N(R')_2 (where t is 1 or 2), or PO_3(R')_2, where each R'
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 alkoxy carbonyl”
refers to an alkoxy carbonyl group wherein the alkoxy group is a lower alkoxy group.

[00358] The term “substituted alkoxy carbonyl” 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
alkoxy carbonyl 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', -SR', -OC(O)-R', -N(R')_2, -C(O)R',
-C(O)OR', -OC(O)N(R')_2, -C(O)N(R')_2, -N(R')C(O)OR', -N(R')C(O)R',
-N(R')C(O)N(R')_2, N(R')C(NR')_2N(R')_2, -N(R')S(O)R' (where t is 1 or 2), -S(O)_2OR'
(where t is 1 or 2), -S(O)_2N(R')_2 (where t is 1 or 2), or PO_3(R')_2, where each R'
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, -SR, -OC(O)-R, -N(R)₂, -C(O)R, -C(O)OR, -OC(O)N(R)₂, -C(O)N(R)₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)N(R)₂, -N(R)C(NR)N(R)₂, -N(R)S(O)R (where t is 1 or 2), -S(O)OR (where t is 1 or 2), -S(O)N(R)₂ (where t is 1 or 2), or PO₃(R'), where each R' 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, -SR, -OC(O)-R, -N(R)₂, -C(O)R, -C(O)OR, -OC(O)N(R)₂, -C(O)N(R)₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)N(R)₂, -N(R)C(NR)N(R)₂, -N(R)S(O)R (where t is 1 or 2), -S(O)OR (where t is 1 or 2), -S(O)N(R)₂ (where t is 1 or 2), or PO₃(R'), where each R' is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00361] “Amino” or “amine” refers to a -N(R')₂ radical group, where each R' 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')₂ group has two R' 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')₂ is intended to include, but is not limited to, 1-pyrroolidinyl 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, trimethylsilyl, -OR, -SR, -OC(O)-R', -N(R')_2, -C(O)R, -C(O)OR, -OC(O)N(R), -C(NR)OR, -C(NR)R, -N(R')C(O)R, -N(R')C(O)OR, -N(R')C(O)N(R')_2, N(R')C(NR')N(R')_2, -N(R')S(O)R' (where t is 1 or 2), -S(O)OR' (where t is 1 or 2), -S(O)N(R')_2 (where t is 1 or 2), or PO(R')_2, where each R' 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, and NR'R'' 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), 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, of -N(R), 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, -SR, -OC(O)-R', -N(R')_2, -C(O)R', -C(O)OR', -OC(O)N(R')_2, -C(O)N(R')_2, -N(R')C(O)OR', -N(R')C(O)N(R')_2, -N(R')C(NR')_2, -N(R')S(O)R', -S(O)R', -(OR)R' (where t is 1 or 2), -S(O)N(R')_2, -(OR)N(R')_2, -(OR)R' (where t is 1 or 2), or PO_3R', where each R' is independently hydrogen, alkyl, fluoroalkyl, carbocyclic, 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, -SR, -OC(O)-R, -N(R)\(^2\), -C(O)R, -C(O)OR, -OC(O)N(R)\(^2\),
N(R\(^t\))C(NR\(^i\))N(R\(^t\)), -N(R\(^t\))S(O)\(^r\)\(_2\) (where \(t\) is 1 or 2), -S(O)\(^r\)OR (where \(t\) is 1 or 2),
-S(O)\(^r\)N(R\(^t\)) (where \(t\) is 1 or 2), or PO\(^r\)\(_2\) where each R\(^t\) 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,
heteroaryl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl,
heteroarylalkyl, hydroxy, halo, cyano, nitro, oxo, thioxo, trimethylsilyl, -OR, -SR,
-OC(O)-R, -N(R\(^t\))\(^r\), -C(O)R, -C(O)OR, -OC(O)N(R\(^t\))\(^r\), -C(O)N(R\(^t\))\(^r\),
-N(R\(^t\))C(O)OR, -N(R\(^t\))C(O)R, -N(R\(^t\))C(NR\(^i\))N(R\(^t\))\(^r\) (where \(t\) is 1 or 2),
-S(O)\(^r\)OR (where \(t\) is 1 or 2), or PO\(^r\)\(_2\) where each R\(^t\) is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl,
heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.
“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.

“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.

“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.

“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.

“Heteroaryl” or “heteroaromatic” or “HetAr” refers to a 5- to 18-membered aromatic radical (e.g., C$_4$-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 pyridyldiene. 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, benzo[c][1,2,4]oxadiazolyl, benzo[d][1,3]thiazolyl, benzo[d][1,3]thiazolyl, benzofuranyl, benzopyranyl, benzopyranonyl, 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-5H-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]pyrazinyl, 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, isoiazolyl, indazolyl, indolyl, indazolyl, indazolyl, indolyl, indoliny1, isoindoliny1, isoquinoliny1, indolizinyl, isoxazolyl, 5,8-methano-5,6,7,8-tetrahydroquinazolinyl, naphthyridinyl, 1,6-naphthyridinonyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranonyl, 5,6,6a,7,8,9,10,10a-octahydrobenzo[h]quinazolinyl, 1-phenyl-1H-pyrrolyl, phenazinyl, phenothiazinyl, phenoazinyl, 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, quinolinony1, isoquinoliny1, tetrahydroquinoliny1, 5,6,7,8-tetrahydroquinoliny1, 5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidinyl, 6,7,8,9-tetrahydro-5H-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. thiényl). 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, trimethylsilyl, -OR, -SR, -OC(O)-R, -N(R')_2, -C(O)R, -C(O)OR, -OC(O)N(R')_2, -C(O)N(R')_2, -N(R')C(O)OR, -N(R')C(O)R, -N(R')C(O)N(R')_2, N(R')C(NR')N(R')_2, -N(R')S(O)R' (where t is 1 or 2).
-S(OR)\textsuperscript{t} (where t is 1 or 2), -S(OR')\textsuperscript{t}N(R'\textsuperscript{2}) (where t is 1 or 2), or PO\textsuperscript{t}(R'\textsuperscript{2}), where each R' is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkalkyl, 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] “Heterocycloalkyl” 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, thiényl[1,3]dithianyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydrosoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuranyl, 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, heteroaryalkyl, hydroxy, halo, cyano, nitro, oxo, thioxo,
trimethylsilanyl, -OR, -SR, -OC(O)-R, -N(R)\textsubscript{2}, -C(O)R, -C(O)OR, -OC(O)N(R)\textsubscript{2}, -C(O)N(R)\textsubscript{2}, -N(R)\textsubscript{2}C(O)R, -N(R)\textsubscript{2}C(O)OR, -N(R)\textsubscript{2}C(O)N(R)\textsubscript{2}, N(R)\textsubscript{2}C(NR)\textsubscript{2}N(R)\textsubscript{2}, -N(R)\textsubscript{2}S(O)\textsubscript{2}R (where \(t\) is 1 or 2), -S(O)\textsubscript{2}OR (where \(t\) is 1 or 2), -S(O)\textsubscript{2}N(R)\textsubscript{2} (where \(t\) is 1 or 2), or PO\textsubscript{2}(R)\textsubscript{2}, where each R\textsuperscript{*} is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroaryalkyl.

[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\textsubscript{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\textsubscript{2})-H, -S(O\textsubscript{2})-(optionally substituted alkyl), -S(O\textsubscript{2})-(optionally substituted amino), -S(O\textsubscript{2})-(optionally substituted aryl), -S(O\textsubscript{2})-(optionally substituted heteroaryl), and -S(O\textsubscript{2})-(optionally substituted heterocycloalkyl).

[00385] “Sulfonamidyl” or “sulfonamido” refers to a -S(=O)\textsubscript{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)\textsubscript{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)₂OR 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 synths 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,

[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(1H)-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 tosloxy 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).
“Solvate” refers to a compound in physical association with one or more molecules of a pharmaceutically acceptable solvent.

“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, alkyaryl, 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, sulfanyl, 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.

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.

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.

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 Vₕ) 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 Vₙ) and a light chain constant region. The light chain constant region is comprised of one domain, Cₙ. The Vₕ and Vₙ 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 Vₕ and Vₙ 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.

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
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.
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.

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.

The term “glycosylation” refers to a modified derivative of an antibody. An aglycosylated 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 Fe 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 alklylation 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 (C₁-C₁₀) 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 $1 \times 10^{-7}$ M or less, more preferably $5 \times 10^{-8}$ M or less, more preferably $1 \times 10^{-8}$ M or less, more preferably $5 \times 10^{-9}$ 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 $1 \times 10^{-7}$ M or less, more preferably $5 \times 10^{-8}$ M or less, more preferably $1 \times 10^{-8}$ M or less, more preferably $5 \times 10^{-9}$ 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 $1 \times 10^{-7}$ M or less, more preferably $5 \times 10^{-8}$ M or less, more preferably $1 \times 10^{-8}$ M or less, more preferably $5 \times 10^{-9}$ 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 $1 \times 10^{-7}$ M or less, more preferably $5 \times 10^{-8}$ M or less, more preferably $1 \times 10^{-8}$ M or less, more preferably $5 \times 10^{-9}$ M or less.

[00417] The term “radioisotope-labeled complex” refers to both non-covalent and covalent attachment of a radioactive isotope, such as $^{89}$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 inhibitor.

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

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

[00426] In an embodiment, the PI3K inhibitor is a PI3K-ʔi inhibitor.

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

[00428] In an embodiment, the combination of the PI3K inhibitor, PI3K-ήinhibitor, PI3K-ϊ inhibitor, or PI3K-ʔi inhibitor with the BTK inhibitor is administered by oral,
intravenous, intramuscular, intraperitoneal, subcutaneous or transdermal means.

[00429] In an embodiment, the PI3K inhibitor, PI3K-Ö inhibitör, PI3K-į inhibitör, or PI3K-Ų inhibitör 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-Ö inhibitör, PI3K-į inhibitör, or PI3K-Ų inhibitör is administered to the subject before administration of the BTK inhibitor.

[00432] In an embodiment, the PI3K inhibitor, PI3K-Ö inhibitör, PI3K-į inhibitör, or PI3K-Ų inhibitör is administered concurrently with the administration of the BTK inhibitor.

[00433] In an embodiment, the PI3K inhibitor, PI3K-Ö inhibitör, PI3K-į inhibitör, PI3K-Ų inhibitör 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
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-\( \mu \)-inhibitor, a PI3K-\( \iota \)-inhibitor, and a PI3K-\( \bar{\iota} \)-inhibitor. In one specific embodiment, it is a PI3K-\( \iota \)-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.

In an embodiment, the PI3K inhibitor, which is preferably selected from the group consisting of a PI3K-\( \mu \)-inhibitor, a PI3K-\( \iota \)-inhibitor, and a PI3K-\( \bar{\iota} \)-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-\( \mu \)-inhibitor, PI3K-\( \iota \)-inhibitor, or PI3K-\( \bar{\iota} \)-inhibitor) is a compound of Formula (I):

\[
\text{Cy} \quad \begin{array}{c} \text{O} \\ \text{W}_b^5 \end{array} \quad \begin{array}{c} \text{N} \\ \text{B} \end{array} \quad \begin{array}{c} \text{Y} \\ \text{W}_d \end{array} \quad \text{X}
\]

\text{Formula (I)}

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

\text{Cy} \text{ is aryl or heteroaryl substituted by 0 or 1 occurrences of } R^3 \text{ and 0, 1, 2, or 3 occurrences of } R^5; \\
\text{W}_b^5 \text{ is } CR^8, \text{CHR}^8, \text{ or } N; \\
\text{R}^5 \text{ is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, alkoxy, amidino, amino, acyl, acyloxy, sulfonamido, halo, cyano, hydroxy, or nitro; } \\
\text{B} \text{ 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; \\
\text{each } R^2 \text{ is independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, }


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

X is -(CH(R₉))ₙ⁻;

Y is -N(R₉)-C(=O)-, -C(=O)-N(R₉)-, -C(=O)-N(CH(R₉))ₙ⁻, -N(R₉)-S(=O)-, -S(=O)⁻, -S(=O)₂⁻;

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

R₃ 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 Rᵢ is independently alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, heteroalkyl, alkoxy, amido, amino, acyl, acyloxy, sulfinyl, sulfonyl, sulfoxide, sulfone, sulfonamido, halo, cyano, aryl, heteroaryl, hydroxyl, or nitro;

each R₉ is independently hydrogen, alkyl, cycloalkyl, heterocyclyl, or heteroalkyl; or two adjacent occurrences of R₉ together with the atoms to which they are attached form a 4- to 7-membered ring;

Wₜ is heterocyclyl, aryl, cycloalkyl, or heteroaryl, each of which is substituted with one or more R₁⁰, R₁¹, R₁² or R₁³, and

R₁⁰, R₁¹, R₁² and R₁³ are each independently hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, heterocyclyloxy, amido, amino, acyl, acyloxy, alkoxy carbonyl, 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-Ȗinhibitor, PI3K-į-inhibitor, or PI3K-Ȗ,į inhibitor) is a compound of Formula (I-1):

![Formula (II)](image-url)
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof,
wherein:

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

\[ \text{Formula (II-A)} \]

\( W_c \) is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl;
q is an integer of 0, 1, 2, 3, or 4;
X is a bond or \(-(\text{CH(R}^9))_z-\), and z is an integer of 1, 2, 3 or 4;
Y is a bond, \(-\text{N(R}^9)-\), \(-\text{O}-\), \(-\text{S}-\), \(-\text{S(=O)}-\), \(-\text{S(=O)}_2-\), \(-\text{C(=O)}-\), \(-\text{C(=O)(CHR}^9)_z-\), \(-\text{N(R}^9)-\text{C(=O)-}\), \(-\text{N(R}^9-\text{C(=O)NH}-\) or \(-\text{N(R}^9-C(\text{R}^9)_2-\);
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;

R³ is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkoxy, amido, amino, alkoxy carbonyl sulfonamido, halo, cyano, hydroxy or nitro; and each instance of R⁹ is independently hydrogen, alkyl, or heterocycloalkyl.

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

![Formula (III)](image)

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

R² is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl,

heteroarylalkyl, alkoxy, amino, halo, cyano, hydroxy or nitro; and R² is hydrogen, alkyl, or heterocycloalkyl.

[00443] In a preferred embodiment, the PI3K-Ųį inhibitor is a compound of 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):

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

[00445] In a preferred embodiment, the PI3K inhibitor is (S)-3-((9H-purin-6-yl)amino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-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.
In an embodiment, the PI3K inhibitor (which may be a PI3K-δ inhibitor, PI3K-į inhibitor, or PI3K-ų 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-į inhibitor is a compound of Formula (V):

\[
\begin{align*}
&X^1 \text{ is } C(R^9) \text{ or } N; \\
&X^2 \text{ is } C(R^9_{10}) \text{ or } N; \\
&Y \text{ is } N(R^1), O \text{ or } S; \\
&Z \text{ is } CR^8 \text{ or } N; \\
&n \text{ is } 0, 1, 2 \text{ or } 3; \\
&R^1 \text{ is a direct-bonded or oxygen-linked saturated, partially saturated or unsaturated } 5-, 6- \text{ or } 7\text{-membered monocyclic ring containing } 0, 1, 2, 3 \text{ or } 4 \text{ atoms selected from } N, O \text{ and } S, \text{ but containing no more than one } 0 \text{ or } S, \text{ wherein the available carbon atoms of the ring are substituted by } 0, 1 \text{ or } 2 \text{ oxo or thioxo groups, wherein the ring is substituted by } 0 \text{ or } 1 \text{ R}^2 \text{ substituents, and the ring is additionally substituted by } 0, 1, 2 \text{ or } 3 \text{ substituents independently selected from halo, nitro, cyano, } (C_{1-4})\text{alkyl, } O(C_{1-4})\text{alkyl, } O(C_{1-4})\text{haloalkyl, NH C}_{1-4}, N((C_{1-4})\text{alkyl})(C_{1-4})\text{alkyl and } (C_{1-4})\text{haloalkyl; } \\
&R^2 \text{ is selected from halo, } (C_{1-4})\text{haloalkyl, cyano, nitro, } —C(\delta-O)R^9, —C(\delta-O)OR^9, —C(\delta-O)NR^9R^9, —C(\delta-O)NR^9NR^9, —OR^9, —OC(\delta-O)R^9, —OC(\delta-O)NR^9R^9, —OC(\delta-O)NR^9NR^9, —OC(\delta-O)N(R^9)S(\delta-O)R^9, —O(C_{2-6})\text{alkyl}NR^9R^9, —O(C_{2-6})\text{alkyl}OR^9, —SR^9.
\end{align*}
\]
OS(◊O)R', —S(◊O)₂R', —S(◊O)₂NR'R', —S(◊O)₂N(R')C(◊O)R', —
S(◊O)₂N(R')C(◊O)OR', —S(◊O)₂N(R')C(◊O)NR'R', —NR'R', —N(R')C(◊O)R',
—N(R')C(◊O)OR', —N(R')C(◊O)NR'R', —N(R')C(◊O)NR'R', —N(R')S(◊O)₂R',
—N(R')S(◊O)₂NR'R', —NR'(C₆₋₆ alkyl)NR'R' and —NR'(C₂₋₂ alkyl)OR'; or R² is selected from (C₁₋₆ alkyl, phenyl, benzyl, heteroaryl, heterocycle,
—(C₁₋₆ alkyl)heteroaryl, —((C₁₋₆ alkyl)heterocycle, —O((C₁₋₆)alkyl)heteroaryl, —
O((C₁₋₆)alkyl)heterocycle, —NR²((C₁₋₆)alkyl)heteroaryl, —NR²(C₁₋₆)
heteroaryl)phenyl, —O((C₁₋₆)alkyl)phenyl and —NR²((C₁₋₆)alkyl)phenyl all of which are substituted by 0, 1, 2 or 3 substituents selected from
(C₁₋₆)haloalkyl, O(C₁₋₆)alkyl, Br, Cl, F, I and (C₁₋₆)alkyl;
R¹ is selected from H, halo, (C₁₋₆)haloalkyl, cyano, nitro, —C(◊O)R', —C(◊O)R', —
C(◊O)NR'R', —C(◊O)NR'R', —OR', —OC(◊O)R', —OC(◊O)NR'R', —
OC(◊O)N(R')S(◊O)₂R', —O(C₁₋₆ alkyl)NR'R', —O(C₁₋₆)alkylOR', —SR', —
S(◊O)R', —S(◊O)₂R', —S(◊O)₂NR'R', —S(◊O)₂N(R')C(◊O)R', —
S(◊O)₂N(R')C(◊O)OR', —S(◊O)₂N(R')C(◊O)NR'R', —NR'R', —N(R')C(◊O)R',
—N(R')C(◊O)OR', —N(R')C(◊O)NR'R', —N(R')C(◊O)NR'R', —N(R')S(◊O)₂R',
—N(R')S(◊O)₂NR'R', —NR'(C₁₋₆)alkylOR', (C₁₋₆)alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the (C₁₋₆)alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from (C₁₋₆)haloalkyl, O(C₁₋₆)alkyl, Br, Cl, F, I and (C₁₋₆)alkyl;
R² is, independently, in each instance, halo, nitro, cyano, (C₁₋₆)alkyl, O(C₁₋₆)alkyl, O(C₁₋₆)
haloalkyl, NH(C₁₋₆)alkyl, N((C₁₋₆)alkyl)(C₁₋₆)alkyl or (C₁₋₆)haloalkyl;
R³ is, independently, in each instance, H, halo, (C₁₋₆)alkyl, (C₁₋₆)haloalkyl, or (C₁₋₆)alkyl
substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, O(C₁₋₆)alkyl, (C₁₋₆)
alkyl, (C₁₋₆)haloalkyl, O(C₁₋₆)alkyl, NH₂, NHC₆₋₆alkyl, N(C₁₋₆)alkyl(C₁₋₆)alkyl; or both R² groups together form a (C₃₋₆)spiroalkyl substituted by 0, 1, 2 or 3 substituents selected from halo, cyano, OH, O(C₁₋₆)alkyl, (C₁₋₆)alkyl, (C₁₋₆)haloalkyl, O(C₁₋₆)
alkyl, NH₂, NHC₆₋₆alkyl, N((C₁₋₆)alkyl)(C₁₋₆)alkyl;
R⁴ is selected from H, halo, (C₁₋₆)alkyl, (C₁₋₆)haloalkyl, cyano, nitro, —C(◊O)R¹, —
C(◊O)OR¹, —C(◊O)NR'R¹, —C(◊O)NR'R¹, —S(◊O)R¹, —S(◊O)₂R¹, —
S(◊O)₂NR'R¹, —S(◊O)₂N(R¹)C(◊O)R¹, —S(◊O)₂N(R¹)C(◊O)OR¹, —
R' is selected from H, halo, (C\textsubscript{1-6})alkyl, (C\textsubscript{1-6})haloalkyl, cyano, nitro, —C(\d-O)R', —
C(\d-O)OR', —C(\d-O)N\textsubscript{R'}R', —C(\d-O)NR\textsubscript{R'}R', —S(\d-O)R', —S(\d-O)\textsubscript{2}R', —
S(\d-O)\textsubscript{2}N\textsubscript{R'}R', —S(\d-O)\textsubscript{2}N(R')(\d-O)R', —S(\d-O)\textsubscript{2}N(\d-O)OR', —
S(\d-O)\textsubscript{2}N(R')(\d-O)OR';

R' is selected from H, (C\textsubscript{1-6})haloalkyl, Br, Cl, F, I, OR', NR'R', (C\textsubscript{1-6})alkyl, phenyl,
benzyl, heteroaryl and heterocycle, wherein the (C\textsubscript{1-6})alkyl, phenyl, benzyl, heteroaryl
and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from (C\textsubscript{1-6})haloalkyl, O(C\textsubscript{1-6})alkyl, Br, Cl, F, I and (C\textsubscript{1-6})alkyl;

R' is selected from H, halo, (C\textsubscript{1-6})haloalkyl, cyano, nitro, —C(\d-O)R', —C(\d-O)OR', —
C(\d-O)NR'R'C(\d-O)NR'R', —OR', —OC(\d-O)R', —OC(\d-O)NR'R', —
OC(\d-O)N(R')(\d-O)S(\d-O)R', —O(C\textsubscript{2-6})alkylOR', —SR', —S(\d-O)R', —S(\d-O)\textsubscript{2}R', —
S(\d-O)\textsubscript{2}NR'R', —S(\d-O)\textsubscript{2}N(R')(\d-O)R', —S(\d-O)\textsubscript{2}N(\d-O)C(\d-O)OR', —
S(\d-O)\textsubscript{2}N(R')(\d-O)C(\d-O)OR', —N(R')(\d-O)C(\d-O)OR', —N(R'(\d-O)C(\d-O)OR', —
N(R')(\d-O)NR'R'N(R')(\d-O)NR'R', —N(R')(\d-O)NR'R'NR'R', —N(R')(\d-O)NR'R'NR'R', —
N(R')(\d-O)NR'R'NR'R', —N(R')(\d-O)NR'R'NR'R', —NR'(\d-O)NR'R', —NR'(\d-O)NR'R', —
NR'(\d-O)alkylnR'R', —NR'(\d-O)alkylnR', —NR'(\d-O)alkylnR'; or R' 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\textsubscript{1-6})haloalkyl, cyano, nitro, —C(\d-O)R', —C(\d-O)OR', —C(\d-O)NR'R', —
C(\d-O)NR'R', —OR', —OC(\d-O)R', —OC(\d-O)NR'R', —
OC(\(\delta\)O)NR\(\alpha\)R, —O(C\(_{2-6}\)alkyl)NR\(\alpha\)R, —SR, —S(\(\delta\)O)R, —S(\(\delta\)O)\(_2\)NR\(\alpha\)R, —C(\(\delta\)O)OR, —C(\(\delta\)O)NR\(\alpha\)R, —C(\(\delta\)O)OR, —S(\(\delta\)O)\(_2\)NR\(\alpha\)R, —S(\(\delta\)O)\(_2\)NR\(\alpha\)R, —N(R\(\alpha\)C(\(\delta\)O)OR, —N(R\(\alpha\)C(\(\delta\)O)OR, —N(R\(\alpha\)C(\(\delta\)O)OR, —N(R\(\alpha\)C(\(\delta\)O)OR, —N(R\(\alpha\)C(\(\delta\)O)OR, —N(R\(\alpha\)C(\(\delta\)O)OR, —N(R\(\alpha\)C(\(\delta\)O)OR, —N(R\(\alpha\)C(\(\delta\)O)OR, —N(R\(\alpha\)C(\(\delta\)O)OR,

\[00448\] In another embodiment, the PI3K inhibitor (which may be a PI3K-\(\bar{\gamma}\) inhibitor, PI3K-\(\bar{\iota}\) inhibitor, or PI3K-\(\bar{\iota}\) inhibitor) is a compound of Formula (VI):

![Formula (VI)](image_url)

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 CR₈ or N;
R¹ 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 R² substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, (C₁₋₄)alkyl, O(C₁₋₄)
haloalkyl, (NHC₁₋₄)alkyl, N(C₁₋₄ alkyl)(C₁₋₄)alkyl and (C₁₋₄)haloalkyl;
R² is selected from halo, (C₁₋₄)haloalkyl, cyano, nitro, —C(Ọ-O)R¹, —C(Ọ-O)OR¹, —
C(Ọ-O)N(Ọ-N(R³))NR³R¹, —OR¹, —OC(Ọ-O)R¹, —OC(Ọ-O)NR³R¹, —
OC(Ọ-O)N(R³)S(Ọ-O)₂R¹, —O(C₂₋₆)alkylNR³R¹, —O(C₂₋₆)alkylOR¹, —S(Ọ-O)R¹, —S(Ọ-O)NR³R¹, —S(Ọ-O)₂N(R³)(Ọ-O)R¹, —S(Ọ-O)₂N(R³)C(Ọ-O)OR¹, —
S(Ọ-O)₂N(R³)C(Ọ-O)NR³R¹, —NR³R¹, —N(R³)C(Ọ-O)R¹, —N(R³)C(Ọ-O)OR¹, —
N(R³)C(Ọ-O)NR³R¹, —N(R³)S(Ọ-O)₂R¹, —
N(R³)S(Ọ-O)₂NR³R¹, —NR³(C₂₋₆)alkylNR³R¹ and —NR³(C₂₋₆)alkylOR¹; or R² is selected from (C₁₋₆)alkyl, phenyl, benzyl, heteroaryl, heterocycle, —((C₁₋₃)
alkyl)heteroaryl, —((C₁₋₃)alkyl)heterocycle, —O((C₁₋₃)alkyl)heteroaryl, —O((C₁₋₃)
alkyl)heterocycle, —NR³((C₁₋₃)alkyl)heteroaryl, —NR³((C₁₋₃)alkyl)heterocycle, —
((C₁₋₃)alkyl)phenyl, —O((C₁₋₃)alkyl)phenyl and —NR³((C₁₋₃)alkyl)phenyl all of which are substituted by 0, 1, 2 or 3 substituents selected from (C₁₋₄)haloalkyl, O(C₁₋₄)alkyl, Br, Cl, F, I and (C₁₋₄)alkyl;
R¹ is selected from H, halo, (C₁₋₄)haloalkyl, cyano, nitro, —C(Ọ-O)R¹, —C(Ọ-O)OR¹,
C(Ọ-O)NR³R¹C(Ọ-NR³)NR³R¹, —OR¹, —OC(Ọ-O)R¹, —OC(Ọ-O)NR³R¹, —
OC(Ọ-O)N(R³)S(Ọ-O)₂R¹, —O(C₂₋₆)alkylNR³R¹, —O(C₂₋₆)alkylOR¹, —SR¹, —
S(Ọ-O)R¹, —S(Ọ-O)₂R¹, —S(Ọ-O)NR³R¹, —S(Ọ-O)₂N(R³)(Ọ-O)R¹, —
S(Ọ-O)₂N(R³)C(Ọ-O)OR¹, —S(Ọ-O)₂N(R³)(Ọ-O)NR³R¹, NR³R¹, —N(R³)C(Ọ-O)R¹, —
N(R³)C(Ọ-O)OR¹, —N(R³)C(Ọ-O)NR³R¹, —N(R³)C(Ọ-NR³)NR³R¹, —N(R³)S(Ọ-O)₂R¹,
—N(R³)S(Ọ-O)₂NR³R¹, —NR³(C₂₋₆)alkylOR¹, (C₁₋₆)alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the (C₁₋₆)alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from (C₁₋₆)haloalkyl, O(C₁₋₆)alkyl, Br, Cl, F, I and (C₁₋₆)alkyl;
R is, independently, in each instance, H, halo, (C₁⁻₆)alkyl, (C₁⁻₄)haloalkyl, or (C₁⁻₆)alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, O(C₁⁻₄)alkyl, (C₁⁻₄)alkyl, (C₁⁻₄)haloalkyl, NH₂, (NHC₁⁻₄)alkyl, N(C₁⁻₄)alkyl(C₁⁻₄)alkyl; or both R groups together form a C₃⁻₆-spiroalkyl substituted by 0, 1, 2 or 3 substituents selected from halo, cyano, OH, O(C₁⁻₄)alkyl, (C₁⁻₄)alkyl, (C₁⁻₄)haloalkyl, O(C₁⁻₄)alkyl, NH₂, (NHC₁⁻₄)alkyl, N((C₁⁻₄)alkyl)(C₁⁻₄)alkyl;

R is selected from H, halo, (C₁⁻₆)alkyl, (C₁⁻₄)haloalkyl, cyano, nitro, —C(δ-O)R, —C(δ-O)OR, —C(δ-O)NR R', —C(δ-NR')NR R', —S(δ-O)R, —S(δ-O)₂R, —S(δ-O)₂NR R', —S(δ-O)₂N(R')C(δ-O)R', —S(δ-O)₂N(R')C(δ-O)OR, —S(δ-O)₂N(R')C(δ-O)NR R';

R is selected from H, halo, (C₁⁻₆)alkyl, (C₁⁻₄)haloalkyl, cyano, nitro, —C(δ-O)R, —C(δ-O)OR, —C(δ-O)NR R', —C(δ-NR')NR R', —S(δ-O)R, —S(δ-O)₂R, —S(δ-O)₂NR R', —S(δ-O)₂N(R')C(δ-O)R', —S(δ-O)₂N(R')C(δ-O)OR, —S(δ-O)₂N(R')C(δ-O)NR R';

R is selected from H, (C₁⁻₆)haloalkyl, Br, Cl, F, I, OR, NR R', (C₁⁻₆)alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the (C₁⁻₆)alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from (C₁⁻₆)haloalkyl, O(C₁⁻₆)alkyl, Br, Cl, F, I and (C₁⁻₆)alkyl;

R is selected from H, halo, (C₁⁻₄)haloalkyl, cyano, nitro, —C(δ-O)R, —C(δ-O)OR, —C(δ-O)NR R', —C(δ-NR')NR R', —OR, —OC(δ-O)R, OC(δ-O)NR R', —OC(δ-O)N(R')S(δ-O)R, —O(C₂₋₆)alkylNR R', —O(C₂₋₆)alkylOR, —SR, —S(δ-O)R, —S(δ-O)₂R, —S(δ-O)₂NR R', —S(δ-O)₂N(R')C(δ-O)R', —S(δ-O)₂N(R')C(δ-O)OR, —S(δ-O)₂N(R')C(δ-O)NR R';

R is selected from H, halo, (C₁⁻₄)haloalkyl, cyano, nitro, —C(δ-O)R, —C(δ-O)OR, —C(δ-O)NR R', —C(δ-NR')NR R', —OR, —OC(δ-O)R, —OC(δ-O)NR R', —OC(δ-O)N(R')S(δ-O)R, —O(C₂₋₆)alkylOR, —SR, —S(δ-O)R, —S(δ-O)₂R, —S(δ-O)₂NR R', —S(δ-O)₂N(R')C(δ-O)R', —S(δ-O)₂N(R')C(δ-O)OR, —S(δ-O)₂N(R')C(δ-O)NR R', —S(δ-O)₂N(R')C(δ-O)OR.
—S(δO)₂N(R')C(δO)NR'R', NR'R', —N(R')C(δO)R', —N(R')C(δO)OR', —N(R')C(δO)NR'R', —N(R')C(δO)NR'NR', —N(R')S(δO)₂R', —N(R')S(δO)₂NR'R', —NR'(C₂₋₆)alkylNR'R', —NR'(C₂₋₆)alkylOR'; or R" 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, (C₁₋₄)haloalkyl, cyano, nitro, —C(δO)R', —C(δO)OR', —C(δO)NR'R', —C(δO)NR'R', —OR', —OC(δO)R', —OC(δO)NR'R', —OC(δO)NR'R', —OC(δO)NR'R', —O(C₂₋₆)alkylOR', —SR', —S(δO)R', —S(δO)₂R', —S(δO)₂NR'R', —S(δO)₂NR'R', —S(δO)₂N(R')C(δO)R', —S(δO)₂N(R')C(δO)OR', —S(δO)₂N(R')C(δO)NR'R', —S(δO)₂N(R')C(δO)NR'R', —N(R')C(δO)OR', —N(R')C(δO)OR', —N(R')C(δO)OR', —N(R')C(δO)OR', —N(R')C(δO)OR', —N(R')C(δO)OR', —N(R')C(δO)OR', —N(R')C(δO)OR', —N(R')C(δO)OR', —N(R')C(δO)OR', —NR'(C₂₋₆)alkylNR'R' and —NR'(C₂₋₆)alkylOR';

R¹₀ is H, (C₁₋₃)alkyl, (C₁₋₄)haloalkyl, cyano, nitro, CO₂R', C(δO)NR'R', —C(δO)NR'R', —S(δO)₂N(R')C(δO)R', —S(δO)₂N(R')C(δO)OR', —S(δO)₂N(R')C(δO)NR'R', —S(δO)₂N(R')C(δO)NR'R', —S(δO)₂N(R')C(δO)NR'R', —S(δO)₂N(R')C(δO)NR'R', —S(δO)₂N(R')C(δO)NR'R', —S(δO)₂N(R')C(δO)NR'R', R' is independently, at each instance, H or R;b; and

R;b is independently, at each instance, phenyl, benzyl or (C₁₋₄)alkyl being substituted by 0, 1, 2 or 3 substituents selected from halo, (C₁₋₄)alkyl, (C₁₋₄)haloalkyl, —O(C₁₋₄)alkyl, —NH₂, —NH(C₁₋₄)alkyl, —N(C₁₋₄)alkyl(C₁₋₄)alkyl.

[00449] In another embodiment, the PI3K inhibitor (which may be a PI3K-Į inhibitor, PI3K-į inhibitor, or PI3K-Ųį inhibitor) is a compound of 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$_{1-4}$)$_2$alkyl, O(C$_{1-4}$)$_3$haloalkyl, NH(C$_{1-4}$)$_2$alkyl, N(C$_{1-4}$)$_2$alkyl(C$_{1-4}$)$_2$alkyl and (C$_{1-4}$)haloalkyl;
- R$^2$ is selected from halo, (C$_{1-4}$)haloalkyl, cyano, nitro, —C(δ-O)R$^*$, —C(δ-O)OR$^*$, —C(δ-O)NR$^*$R$^*$, —C(δ-O)NR$^*$R$^*$NR$^*$, —C(δ-O)NR$^*$R$^*$, —OR$^*$, —OC(δ-O)R$^*$, —OC(δ-O)NR$^*$R$^*$, —OC(δ-O)N(R$^*$)S(δ-O)$_2$ R$^*$, —OC(δ-O)$_2$alkylNR$^*$R$^*$, —OC(δ-O)$_2$alkylOR$^*$, —SR$^*$, —SR$^*$, —SR$^*$, —S(δ-O)$_2$ R$^*$, —S(δ-O)$_2$NR$^*$R$^*$, —S(δ-O)$_2$N(R$^*$)C(δ-O)R$^*$, —S(δ-O)$_2$N(R$^*$)C(δ-O)OR$^*$, —S(δ-O)$_2$N(R$^*$)C(δ-O)NR$^*$R$^*$, —NR$^*$R$^*$, —N(R$^*$)C(δ-O)NR$^*$R$^*$, —N(R$^*$)C(δ-O)NR$^*$R$^*$, —N(R$^*$)S(δ-O)$_2$ R$^*$, —N(R$^*$)S(δ-O)$_2$NR$^*$R$^*$, —NR$^*$C(2-6 alkyl)NR$^*$R$^*$ and —NR$^*$C(2-6 alkyl)OR$^*$; or R$^2$ is selected from (C$_{1-4}$)alkyl, phenyl, benzyl, heteroaryl, heterocycle, —(C$_{1-3}$)
alkyl)heteroaryl, —(C1-3 alkyl)heterocycle, —O(C1-3 alkyl)heteroaryl, —O((C1 a

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)alkyl)heterocycle, —NR (C1-3 alkyl)heteroaryl, —NR (C1-3 alkyl)heterocycle, —(C1 a

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alkyl)phenyl, —O(C1-3 alkyl)phenyl and —NR (C1-3 alkyl)phenyl all of which are

substituted by 0, 1, 2 or 3 substituents selected from (C1-4 )haloalkyl, O(C1-4 )alkyl, Br,
Cl, F, I and (C1-4 )alkyl;
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R is selected from H, halo, (C1-4 )haloalkyl, cyano, nitro, —C(ő O)R , —C(ő O)OR , —
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C(ő O)NR R , —C(ő NR )NR R , —OR , —OC(ő O)R , —OC(ő O)NR R , —
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OC(ő O)N(R )S(ő O)2 R , —OC2-6 )alkylNR R , —OC2-6 )alkylOR , —SR , —
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S(ő O)R , —S(ő O)2 R , —S(ő O)2 NR R , —S(ő O)2 N(R )C(ő O)R , —
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S(ő O)2 N(R )C(ő O)OR , —S(ő O)2 N(R )C(ő O)NR R , —NR R , —N(R )C(ő O)R ,
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—N(R )C(ő O)OR , —N(R )C(ő O)NR R , —N(R )C(ő NR )NR R , —
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N(R )S(ő O)2 R , —N(R )S(ő O)2 NR R , —NR (C2-6 )alkylNR R , —NR (C2 a

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)alkylOR , (C1-6 )alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the (C1 )alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1,

2 or 3 substituents selected from (C1-6 )haloalkyl, O(C1-6 )alkyl, Br, Cl, F, I and (C1 6

)alkyl;

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R is, independently, in each instance, H, halo, (C1-6 )alkyl, (C1-4 )haloalkyl, or (C1-6 )alkyl
substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, O(C1-4 )alkyl, (C1 4

)alkyl, (C1-3 )haloalkyl, O(C1-4 )alkyl, NH2 , NHC1-4 )alkyl, N(C1-4 )alkyl(C1-4 )alkyl; or
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both R groups together form a C3-6 -spiroalkyl substituted by 0, 1, 2 or 3 substituents

selected from halo, cyano, OH, O(C1-4 )alkyl, (C1-4 )alkyl, (C1-3 )haloalkyl, O(C1 4

)alkyl, NH2 , NHC1-4 )alkyl, N(C1-4 )alkyl)C1-4 )alkyl;

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R is selected from H, halo, (C1-6 )alkyl, (C1-4 haloalkyl, cyano, nitro, —C(ő O)R , —
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C(ő O)OR , —C(ő O)NR R , —C(ő NR )NR R , —S(ő O)R S(ő O)2 R , —
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S(ő O)2 NR R , —S(ő O)2 N(R )C(ő O)R , —S(ő O)2 N(R )C(ő O)OR , —
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S(ő O)2 N(R )C(ő O)NR R ;
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R is selected from H, halo, (C1-6 )alkyl, (C1-4 haloalkyl, cyano, nitro, —C(ő O)R , —
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C(ő O)OR , —C(ő O)NR R , —C(ő NR )NR R , —S(ő O)R S(ő O)2 R , —
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S(ő O)2 NR R , —S(ő O)2 N(R )C(ő O)R , —S(ő O)2 N(R )C(ő O)OR , —
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S(ő O)2 N(R )C(ő O)NR R ;
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R is selected from H, (C1-6 )haloalkyl, Br, Cl, F, I, OR , NR R , (C1-6 )alkyl, phenyl,


benzyl, heteroaryl and heterocycle, wherein the (C<sub>1-6</sub>)alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from (C<sub>1-6</sub>)heteroaryl, O(C<sub>1-6</sub>)alkyl, Br, Cl, F, I and (C<sub>1-6</sub>)alkyl;

R<sup>+</sup> is selected from H, halo, (C<sub>1-4</sub>)heteroaryl, cyano, nitro, —C(δ-O)R<sup>a</sup>, —C(δ-O)OR<sup>a</sup>, —C(δ-O)NR<sup>a</sup>R<sup>b</sup>, —C(δ-O)NO<sub>2</sub>R<sup>a</sup>, —OR<sup>a</sup>, —OC(δ-O)R<sup>a</sup>, —OC(δ-O)NR<sup>a</sup>R<sup>b</sup>, —OC(δ-O)NO<sub>2</sub>R<sup>a</sup>, —OC(δ-O)N(R’)<sub>2</sub> —OC<sub>2</sub>-alkylNR<sup>a</sup>R<sup>b</sup>, —OC<sub>2</sub>-alkylOR<sup>a</sup>, —SR<sup>a</sup>, —S(δ-O)R<sup>a</sup>, —S(δ-O)R<sup>a</sup> —S(δ-O)<sub>2</sub>NR<sup>a</sup>R<sup>b</sup>, —S(δ-O)<sub>2</sub>N(R’)<sub>2</sub>C(δ-O)R<sup>a</sup>, —S(δ-O)<sub>2</sub>N(R’)<sub>2</sub> —S(δ-O)<sub>2</sub>NR<sup>a</sup>R<sup>b</sup>, —S(δ-O)<sub>2</sub>N(R’)<sub>2</sub>C(δ-O)R<sup>a</sup>, —S(δ-O)<sub>2</sub>N(R’)<sub>2</sub> —S(δ-O)<sub>2</sub>NR<sup>a</sup>R<sup>b</sup>, —S(δ-O)<sub>2</sub>N(R’)<sub>2</sub>C(δ-O)R<sup>a</sup>, —S(δ-O)<sub>2</sub>N(R’)<sub>2</sub> —S(δ-O)<sub>2</sub>NR<sup>a</sup>R<sup>b</sup>, —S(δ-O)<sub>2</sub>N(R’)<sub>2</sub>C(δ-O)R<sup>a</sup>, —S(δ-O)<sub>2</sub>N(R’)<sub>2</sub> —S(δ-O)<sub>2</sub>NR<sup>a</sup>R<sup>b</sup>, —S(δ-O)<sub>2</sub>N(R’)<sub>2</sub>C(δ-O)R<sup>a</sup>, —S(δ-O)<sub>2</sub>N(R’)<sub>2</sub>
R^{10} is H, (C_{1-3} alkyl, (C_{1-3})haloalkyl, cyano, nitro, CO_{2}R', C(\delta-O)NR'R', —
C(\delta-NR')NR'R', —S(\delta-O)_{2}N(R')C(\delta-O)R', —S(\delta-O)_{2}N(\delta-O)OR', —
S(\delta-O)_{2}N(R')C(\delta-O)NR', —S(\delta-O)R', S(\delta-O)_{2}R' or S(\delta-O)_{2}NR'R';
R^{11} is H or (C_{1-4})alkyl;
R' is independently, at each instance, H or R^{b}; and
R^{2} 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_{1-4})haloalkyl, —O(C_{1-4})alkyl, —NH_{2}, —NHC(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-\bar{U} inhibitor,
PI3K-\bar{I} inhibitor, or PI3K-\bar{I}; inhibitor) is a compound of Formula (VIII):

![Formula (VIII)](image)

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

wherein:
X^{1} is C(R^{a}) or N;
X^{2} is C(R^{b}) or N;
Y is N(R^{11}), O or S;
Z is CR^{s} 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^{s} substituents, and the ring is additionally substituted by 0, 1, 2
or 3 substituents independently selected from halo, nitro, cyano, (C₁-₄)alkyl, O(C₁-
₄)alkyl, O(C₁-₄)haloalkyl, NH(C₁-₄)alkyl, N(C₁-₄)alkyl(C₁-₄)alkyl and (C₁-₄)haloalkyl;

R³ is selected from halo, (C₁-₄)haloalkyl, cyano, nitro, —C(ıt-O)R³, —C(ıt-O)OR³, —
C(ıt-O)NR'R³—C(ıt-NR')NR'R³, —OR³, —OC(ıt-O)R³, —OC(ıt-O)NR'R³, —
OC(ıt-O)N(R')S(ıt-O)₂R³, —OC₂₆ alkylOR³, —SR³, —S(ıt-O)R³, —S(ıt-O)₂R³, —
S(ıt-O)₂NR'R³, —S(ıt-O)₂N(R')C(ıt-O)R³, —S(ıt-O)₂N(R')C(ıt-O)OR³, —
S(ıt-O)₂N(R')C(ıt-O)NR'R³, —N(ıt-R')C(ıt-O)R³, —N(ıt-R')C(ıt-O)OR³, —
N(ıt-R')S(ıt-O)₂NR'R³, —N(ıt-R')C(ıt-NR')NR'R³, —N(ıt-R')S(ıt-O)₂R³, —
N(ıt-R')S(ıt-O)₂NR'R³, —N(ıt-R')C(ıt-NR')NR'R³, —N(ıt-R')C(ıt-O)R³, —N(ıt-R')C(ıt-O)OR³, —
N(ıt-R')C(ıt-NR')NR'R³, —N(ıt-R')S(ıt-O)₂R³, —

R³ is selected from H, halo, (C₁-₄)haloalkyl, cyano, nitro, —C(ıt-O)R³, —C(ıt-O)OR³, —
C(ıt-O)NR'R³—C(ıt-NR')NR'R³, —OR³, —OC(ıt-O)R³, —OC(ıt-O)NR'R³, —
OC(ıt-O)N(R')S(ıt-O)₂R³, —OC₂₆ alkylOR³, —SR³, —S(ıt-O)R³, —S(ıt-O)₂R³, —
S(ıt-O)₂NR'R³, —S(ıt-O)₂N(R')C(ıt-O)R³, —S(ıt-O)₂N(R')C(ıt-O)OR³, —
S(ıt-O)₂N(R')C(ıt-O)NR'R³, —N(ıt-R')C(ıt-O)R³, —N(ıt-R')C(ıt-O)OR³, —
N(ıt-R')C(ıt-NR')NR'R³, —N(ıt-R')S(ıt-O)₂R³, —

R³ is, independently, in each instance, H, halo, (C₁-₄)alkyl, (C₁-₄)haloalkyl, or (C₁-₆)
alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, O(C₁-₄)alkyl, (C₁-
₄)alkyl, (C₁-₃)haloalkyl, O(C₁-₄)alkyl, NH₂, NH(C₁-₄)alkyl, N(C₁-₄)alkyl(C₁-₄)alkyl; or
both R³ groups together form a C₅₋₆-spiroalkyl substituted by 0, 1, 2 or 3 substituents
selected from halo, cyano, OH, O(C₁-₄)alkyl, (C₁-₄)alkyl, (C₁-₃)haloalkyl, O(C₁-
₄)alkyl, NH₂, NH(C₁-₄)alkyl, N(C₁-₄)alkyl(C₁-₄)alkyl;
R is selected from H, halo, (C₁₋₆)alkyl, (C₁₋₆)haloalkyl, cyano, nitro, —C(óO)R', —
C(óO)OR', —C(óO)NR'R', —C(óO)NR'R', —S(óO)R', —S(óO)₂R', —
S(óO)₂NR'R', —S(óO)₂N(R'R)C(óO)R', —S(óO)₂N(R'R)ₐC(óO)OR', —
S(óO)₂N(R'R)ₐC(óO)NR'R'ₐ;
R' is selected from H, halo, (C₁₋₆)alkyl, (C₁₋₆)haloalkyl, cyano, nitro, —C(óO)R', —
C(óO)OR', —C(óO)NR'R', —C(óO)NR'R', —S(óO)R', —S(óO)₂R', —
S(óO)₂NR'R', —S(óO)₂N(R'R)C(óO)R', —S(óO)₂N(R'R)ₐC(óO)OR', —
S(óO)₂N(R'R)ₐC(óO)NR'R'ₐ;
R'' is selected from H, (C₁₋₆)haloalkyl, Br, Cl, F, I, OR', NR'ₐR', (C₁₋₆)alkyl, phenyl,
benzyl, heteroaryl and heterocycle, wherein the (C₁₋₆)alkyl, phenyl, benzyl, heteroaryl
and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from
(C₁₋₆)haloalkyl, OC₁₋₆alkyl, Br, Cl, F, I and (C₁₋₆)alkyl;
R is selected from H, halo, (C₁₋₆)haloalkyl, cyano, nitro, —C(óO)R', —C(óO)OR', —
OC(óO)N(R')S(óO)₂R', —OC₁₋₆alkylNR'R', —OC₁₋₆alkylOR', —SR', —S(óO)R',
—S(óO)₂R', —S(óO)₂NR'R', —S(óO)₂N(R')C(óO)R', —S(óO)₂N(R')ₐC(óO)OR', —
S(óO)₂N(R')ₐC(óO)NR'R', —NR'R', —N(R')C(óO)R', —N(R')ₐC(óO)OR', —
N(R')ₐC(óO)NR'R', —N(R')ₐC(óO)NR'R', —N(R')ₐS(óO)₂R', —
N(R')ₐS(óO)₂NR'R', —NR'(C₁₋₆)alkylNR'R', —NR'(C₁₋₆)alkylOR', (C₁₋₆)alkyl,
phenyl, benzyl, heteroaryl and heterocycle, wherein the (C₁₋₆)alkyl, phenyl, benzyl,
heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents
selected from halo, (C₁₋₆)haloalkyl, cyano, nitro, —C(óO)R', —C(óO)OR', —
C(óO)NR'R', —C(óO)NR'R', —OR', —OC(óO)R', OC(óO)NR'R', —
OC(óO)N(R')S(óO)₂R', —OC₁₋₆alkylOR', —SR', —S(óO)R', —S(óO)₂R', —
S(óO)₂R', —S(óO)₂NR'R', —S(óO)₂N(R')C(óO)R', —S(óO)₂N(R')ₐC(óO)OR', —
S(óO)₂N(R')ₐC(óO)NR'R', —N(R')C(óO)R', —N(R')C(óO)OR', —
N(R')C(óO)NR'R', —N(R')C(óO)NR'R', —N(R')S(óO)₂R', —
N(R')₂S(óO)₂NR'R', —NR'(C₁₋₆)alkylNR'R', —NR'(C₁₋₆)alkylOR'; or R 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, (C₆H₅)haloalkyl, cyano, nitro, —C(O)R₁, —
C(ś-O)OR₁, —C(ś-O)NR₁R₂, —C(ś-O)NR₁R₂O, —OR₁, —OC(ś-O)R₂, —
OC(ś-O)NR₁R₂, —OC(ś-O)NR₁R₂O, —OC₂₋₆ alkylNR₁R₂, —OC₂₋₆ alkylOR₁,
—SR₁, —S(ś-O)R₂, —S(ś-O)₂ R₂, —S(ś-O)₂ NR₁R₂, —S(ś-O)₂ N(R')₃ C(ś-O)R₁, —
S(ś-O)₂ N(R')₃ C(ś-O)OR₁, —S(ś-O)₂ N(R')₃ C(ś-O)NR₁R₂, —NR₁R₂, —N(R')₃ C(ś-O)R₁,
—N(R')₃ C(ś-O)OR₁, —N(R')₃ C(ś-O)NR₁R₂, —N(R')₃ C(ś-O)NR₁R₂O, —
N(R')₃ S(ś-O)₂ R₂, —N(R')₃ S(ś-O)₂ NR₁R₂, —NR₁(₂₋₆) alkylNR₁R₂ and —NR₁R₂(₂₋₆)
alkylOR₁.

R₁₀ is H, (C₆H₅) alkyl, (C₆H₅) haloalkyl, cyano, nitro, CO₂ R₁, C(ś-O)NR₁R₂, —
C(ś-O)NR₁R₂O, —C(ś-O)NR₁R₂O, —C(ś-O)NR₁R₂O, —C(ś-O)NR₁R₂O, —OR₁, —OC(ś-O)R₂, —
OC(ś-O)NR₁R₂, —OC(ś-O)NR₁R₂O, —OC₂₋₆ alkylNR₁R₂, —OC₂₋₆ alkylOR₁,
—SR₁, —S(ś-O)R₂, —S(ś-O)₂ R₂, —S(ś-O)₂ NR₁R₂, —S(ś-O)₂ N(R')₃ C(ś-O)R₁, —
S(ś-O)₂ N(R')₃ C(ś-O)OR₁, —S(ś-O)₂ N(R')₃ C(ś-O)NR₁R₂, —NR₁R₂, —N(R')₃ C(ś-O)R₁,
—N(R')₃ C(ś-O)OR₁, —N(R')₃ C(ś-O)NR₁R₂, —N(R')₃ C(ś-O)NR₁R₂O, —
N(R')₃ S(ś-O)₂ R₂, —N(R')₃ S(ś-O)₂ NR₁R₂, —NR₁(₂₋₆) alkylNR₁R₂ and —NR₁R₂(₂₋₆)
alkylOR₁.

[00451] In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-Ô
inhibitor, PI3K-į inhibitor, or PI3K-û inhibitor) is a compound of Formula (VIII)
wherein X₁ is C(R₁) and X₂ is N.

[00452] In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-Ô
inhibitor, PI3K-į inhibitor, or PI3K-û inhibitor) is a compound of Formula (VIII)
wherein X₁ is C(R₁) and X₂ is C(R₁₀).

[00453] In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-Ô
inhibitor, PI3K-į inhibitor, or PI3K-û inhibitor) is a compound of Formula (VIII)
wherein R₁ is phenyl substituted by 0, 1, 2, or 3 independently selected R₂ substituents.

[00454] In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-Ô
inhibitor, PI3K-į inhibitor, or PI3K-û inhibitor) is a compound of Formula (VIII)
wherein R₁ is phenyl.
In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-α inhibitor, PI3K-β inhibitor, or PI3K-γ inhibitor) is a compound of Formula (VIII) wherein R¹ is selected from 2-methylphenyl, 2-chlorophenyl, 2-trifluoromethylphenyl, 2-fluorophenyl and 2-methoxyphenyl.

In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-α inhibitor, PI3K-β inhibitor, or PI3K-γ inhibitor) is a compound of Formula (VIII) wherein R¹ is phenoxy.

In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-α inhibitor, PI3K-β inhibitor, or PI3K-γ inhibitor) is a compound of Formula (VIII) wherein R¹ 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 R² substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C₁₋₄ alkyl, OC₁₋₄ alkyl, OC₁₋₄ haloalkyl, NHC₁₋₄ alkyl, N(C₁₋₄ alkyl)C₁₋₄ alkyl and C₁₋₄ haloalkyl.

In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-α inhibitor, PI3K-β inhibitor, or PI3K-γ inhibitor) is a compound of Formula (VIII) wherein R¹ 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 R² substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C₁₋₄ alkyl, OC₁₋₄ haloalkyl, NHC₁₋₄ alkyl, N(C₁₋₄ alkyl)C₁₋₄ alkyl and C₁₋₄ haloalkyl.

In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-α inhibitor, PI3K-β inhibitor, or PI3K-γ inhibitor) is a compound of Formula (VIII) wherein R¹ 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 R² substituents, and the ring is additionally substituted by 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C₁₋₄ alkyl, OC₁₋₄ alkyl, OC₁₋₄ haloalkyl, NHC₁₋₄ alkyl, N(C₁₋₄ alkyl)C₁₋₄ alkyl and C₁₋₄ haloalkyl.
In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-subclass inhibitor, PI3K-δ inhibitor, or PI3K-ζ 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.

In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-subclass inhibitor, PI3K-δ inhibitor, or PI3K-ζ inhibitor) is a compound of Formula (VIII) wherein R^1 is selected from pyridyl and pyrimidinyl.

In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-subclass inhibitor, PI3K-δ inhibitor, or PI3K-ζ inhibitor) is a compound of Formula (VIII) wherein R^3 is selected from halo, C\textsubscript{1-6} haloalkyl, cyano, nitro, —C(O)R^2, —C(δ-O)OR^2, —C(δ-O)NR^2R^3, —C(NR^2)NR^3R^4, —OR^2, —OC(δ-O)R^2, —OC(δ-O)NR^2R^3, —OC(δ-O)NR^3R^4, —OC(δ-O)NR^2R^3 —OC(δ-O)NR^3R^4, —OC(δ-O)NR^2R^3 —OC(δ-O)NR^3R^4, —OC(δ-O)N(R')(S(δ-O))R^2, —OC\textsubscript{2-6} alkylNR^2R^3, —OC\textsubscript{2-6} alkylOR^2, —SR^3, —S(δ-O)R^4, —S(δ-O)OR^2, —S(δ-O)N(R')(C(δ-O))R^2, —S(δ-O)N(R')(C(δ-O))OR^2, —S(δ-O)N(R')(C(δ-O))OR^2, —S(δ-O)N(R')(C(δ-O))OR^2, —N(R')(C(δ-O)NR^2R^3, —N(R')(C(δ-O)NR^3R^4, —N(R')(C(δ-O)NR^2R^3, —N(R')(C(δ-O)NR^3R^4, —N(R')(S(δ-O))R^2, —N(R')(S(δ-O))R^2, —NR^2(C\textsubscript{2-6} alkylNR^2R^3, —NR^2, C\textsubscript{1-6} alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C\textsubscript{1-6} alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C\textsubscript{1-6} haloalkyl, OC\textsubscript{1-6} alkyl, Br, Cl, F, I and C\textsubscript{1-6} alkyl.

In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-subclass inhibitor, PI3K-δ inhibitor, or PI3K-ζ inhibitor) is a compound of Formula (VIII) wherein R^3 is H.

In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-subclass inhibitor, PI3K-δ inhibitor, or PI3K-ζ inhibitor) is a compound of Formula (VIII) wherein R^3 is selected from F, Cl, C\textsubscript{1-6} alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C\textsubscript{1-6} alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C\textsubscript{1-6} haloalkyl, OC\textsubscript{1-6} alkyl, Br, Cl, F, I and C\textsubscript{1-6} alkyl.

In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-subclass inhibitor, PI3K-δ inhibitor, or PI3K-ζ inhibitor) is a compound of Formula (VIII)
wherein R^5 is, independently, in each instance, H, halo, C₁₆ alkyl, C₁₄ haloalkyl, or C₁₄ alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, OC₁₄ alkyl, C₁₄ haloalkyl, C₁₄ alkyl, NH₂, NHC₁₄ alkyl, N(C₁₄ alkyl)C₁₄ alkyl; or both R^5 groups together form a C₆ spiroalkyl substituted by 0, 1, 2 or 3 substituents selected from halo, cyano, OH, OC₁₄ alkyl, C₁₄ alkyl, C₁₃ haloalkyl, OC₁₄ alkyl, NH₂, NHC₁₄ alkyl, N(C₁₄ alkyl)C₁₄ alkyl.

[00466] In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-Į inhibitor, PI3K-į inhibitor, or PI3K-Ų 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-Į inhibitor, PI3K-į inhibitor, or PI3K-Ų 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-Į inhibitor, PI3K-į inhibitor, or PI3K-Ų inhibitor) is a compound of Formula (VIII) wherein at least one R^5 is halo, C₁₆ alkyl, C₁₄ haloalkyl, or C₁₆ alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, OC₁₄ alkyl, C₁₄ alkyl, C₁₃ haloalkyl, OC₁₄ alkyl, NH₂, NHC₁₄ alkyl, N(C₁₄ alkyl)C₁₄ alkyl.

[00469] In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-Į inhibitor, PI3K-į inhibitor, or PI3K-Ų inhibitor) is a compound of Formula (VIII) wherein R^5 is H.

[00470] In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-Į inhibitor, PI3K-į inhibitor, or PI3K-Ų inhibitor) is a compound of Formula (VIII) wherein R^5 is F, Cl, cyano or nitro.

[00471] In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-Į inhibitor, PI3K-į inhibitor, or PI3K-Ų 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-Į inhibitor, PI3K-į inhibitor, or PI3K-Ų inhibitor) is a compound of Formula (VIII) wherein R^7 is F, Cl, cyano or nitro.
In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-ï inhibitor, PI3K-Ȗ inhibitor, or PI3K-ű inhibito...) wherein \( R^8 \) is selected from H, CF\(_3\), C\(_{1-3}\) alkyl, Br, Cl and F.

In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-û inhibitor, PI3K-į inhibitor, or PI3K-į inhibit...) wherein \( R^8 \) is selected from H.

In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-û inhibitor, PI3K-į inhibitor, or PI3K-į inhibit...) wherein \( R^8 \) is selected from CF\(_3\), C\(_{1-3}\) alkyl, Br, Cl and F.

In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-û inhibitor, PI3K-į inhibitor, or PI3K-į inhibit...) wherein \( R^8 \) is H.

In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-\( \tilde{\text{\textit{U}}} \) inhibitor, PI3K-\( \tilde{\text{\textit{I}}} \) inhibitor, or PI3K-\( \tilde{\text{\textit{L}}} \) inhibitor) is a compound of Formula (VIII) wherein \( R^g \) 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, \( -C(\tilde{\text{\textit{O}}})R^a, -C(\tilde{\text{\textit{O}}})OR^a, \)
\( -C(\tilde{\text{\textit{O}}})NR^aR^b, -C(\tilde{\text{\textit{O}}})NR^aR^b, -OR^a, -OC(\tilde{\text{\textit{O}}})R^a, -OC(\tilde{\text{\textit{O}}})NR^aR^b, \)
\( -OC(\tilde{\text{\textit{O}}})N(R^e)S(\tilde{\text{\textit{O}}})_2R^b, -OC_{2-6} alkylNR^aR^b, -OC_{2-6} alkylOR^a, -SR^a, -S(\tilde{\text{\textit{O}}})R^a, \)
\( -S(\tilde{\text{\textit{O}}})_2R^b, -S(\tilde{\text{\textit{O}}})_2NR^aR^b, -S(\tilde{\text{\textit{O}}})_2N(R^e)C(\tilde{\text{\textit{O}}})OR^a, -S(\tilde{\text{\textit{O}}})_2C(\tilde{\text{\textit{O}}})NR^aR^b, \)
\( -NR^aR^b, -N(R^e)C(\tilde{\text{\textit{O}}})R^a, -N(R^e)C(\tilde{\text{\textit{O}}})OR^a, -N(R^e)C(\tilde{\text{\textit{O}}})NR^aR^b, \)
\( -N(R^e)C(\tilde{\text{\textit{O}}})NR^aR^b, -NR^aC(\tilde{\text{\textit{O}}})NR^aR^b, -N(R^e)S(\tilde{\text{\textit{O}}})_2R^b, -N(R^e)S(\tilde{\text{\textit{O}}})_2NR^aR^b, \)
\( -NR^aC_{2-6} alkylNR^aR^b \) and \( -NR^aC_{2-6} alkylOR^a \).

In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-\( \tilde{\text{\textit{U}}} \) inhibitor, PI3K-\( \tilde{\text{\textit{I}}} \) inhibitor, or PI3K-\( \tilde{\text{\textit{L}}} \) inhibitor) is a compound of Formula (IX) wherein \( R^{10} \) is H.

In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-\( \tilde{\text{\textit{U}}} \) inhibitor, PI3K-\( \tilde{\text{\textit{I}}} \) inhibitor, or PI3K-\( \tilde{\text{\textit{L}}} \) inhibitor) is a compound of Formula (VIII) wherein \( R^{11} \) is H.

In a preferred embodiment, the PI3K-\( \tilde{\text{\textit{I}}} \) inhibitor is a compound of Formula (IX):
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

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

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

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

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

[00486] In a preferred embodiment, the PI3K-į inhibitor is a compound of Formula (XI):
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00487] In a preferred embodiment, the PI3K-\(\gamma\) 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-\(\gamma\) inhibitor is a compound of Formula (XII):

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

[00489] In a preferred embodiment, the PI3K-\(\gamma\) 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.
In a preferred embodiment, the PI3K-į inhibitor is a compound of Formula (XIII):

![Formula (XIII)](image)

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

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

In an embodiment, the PI3K inhibitor or PI3K-į 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-į inhibitor is a compound of Formula (XIV):

![Formula (XIV)](image)

wherein
X and Y, independently, are N or CH;
Z is N—R or O;
R¹ are the same and are hydrogen, halo, or C₁-₃ alkyl;
R² and R³, independently, are hydrogen, halo, or C₁-₃ alkyl;
R⁴ is hydrogen, halo, OR, CN, C₂₆ alkynyI, C(6-O)R₈, C(6-O)NR'R, C₃ heterocycloalkyl, C₁-₃ alkyleneC₅₆ heterocycloalkyl, O(C₁-₃)alkyleneOR, O(C₁-₃)alkyleneNR'R, O(C₁-₃)alkyleneNR'R, O(C₁-₃)alkyleneC₅₆ cycloalkyl, OC₅₆ heterocycloalkyl, O(C₁-₃)alkyleneC₅₆ CH, or O(C₁-₃)alkylene(6-O)NR'R;
R⁵ is (C₁-₃)alkyl, CH₂CF₃, phenyl, CH₂ClCH, (C₁-₃)alkyleneOR, (C₁-₃)alkyleneNR'R, or C₁-₃ alkyleneNHC(6-O)OR;
R⁶ is hydrogen, halo, or NR'R;
R⁷ is hydrogen or R⁵ and R⁶ are taken together with the atoms to which they are attached to form a five- or six-membered saturated ring;
R¹ is C₁-₃ alkyl, halo, CF₃, or CH₂C₆H₅;
n is 0, 1, or 2;
R³ is hydrogen, (C₁-₃)alkyl, or CH₂C₆H₅;
R⁴ is hydrogen or C₁-₃ alkyl; and
R₈ is hydrogen, C₁-₃ alkyl, or halo,
wherein when the R¹ groups are different from hydrogen, R² and R⁴ are the same; or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00493] In a preferred embodiment, the PI3K inhibitor or PI3K-į inhibitor is an enantiomer of Formula (XIV), as shown in Formula (XV):
wherein X, Y, Z, R\textsubscript{1} through R\textsubscript{8}, R\textsubscript{a}, R\textsubscript{b}, R\textsubscript{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\textsubscript{8} is C\textsubscript{1,3} alkyl, F, Cl, or CF\textsubscript{3}. Alternatively, in such embodiments, n is 0 (such that there is no R\textsubscript{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\textsubscript{6} is hydrogen, halo, or NH\textsubscript{2}. Preferably, R\textsubscript{6} is hydrogen.

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

[00498] Unexpectedly, potency against PI3K-\textgamma is conserved when R\textsubscript{1} is the same. In structural formulae (I) and (II), R\textsubscript{2} and R\textsubscript{4} may differ provided that R\textsubscript{1} is H. When R\textsubscript{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\textsubscript{2} and R\textsubscript{4} can be the same such that the compounds advantageously do not exhibit atropisomerism.

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In preferred embodiments, Z is N—R	extsuperscript{7}, and the bicyclic ring system containing X and Y is:

\[ \text{R}^{5} \text{ is methyl, trifluoromethyl, chloro, or fluoro; R}^{4} \text{ is hydrogen, fluoro, chloro, OH, OCH}_{3}, \text{ OCH}_{2} \text{ClCH}, \text{ O(CH}_{2}\text{)}_{2} \text{N(CH}_{3}\text{)}_{2}, \text{ C(OH)}\text{CH}_{3}, \text{ ClCH}, \text{ CN, C(\text{oH})NH}_{2}, \text{ OCH}_{2} \text{C(OH)}\text{NH}_{2}, \text{ O(CH}_{2}\text{)}_{2} \text{OCH}_{3}, \text{ O(CH}_{2}\text{)}_{2} \text{N(CH}_{3}\text{)}_{2}, \]

and R	extsuperscript{5} is hydrogen, methyl, chloro, or fluoro; R	extsuperscript{4} is hydrogen or fluoro; R	extsuperscript{5} is NH\textsubscript{2}, hydroxyl, or fluoro; R	extsuperscript{7} is hydrogen or R	extsuperscript{5} and R	extsuperscript{7} are taken together to form

and R	extsuperscript{6} is hydrogen, methyl, chloro, or fluoro; R	extsuperscript{6} is hydrogen or fluoro; R	extsuperscript{6} is NH\textsubscript{2}, hydroxyl, or fluoro; R	extsuperscript{7} is hydrogen or R	extsuperscript{5} and R	extsuperscript{7} are taken together to form

R	extsuperscript{2} is hydrogen, methyl, chloro, or fluoro; R	extsuperscript{1} is hydrogen, fluoro, chloro, OH, OCH\textsubscript{3}, OCH\textsubscript{2}ClCH, O(CH\textsubscript{2})\textsubscript{2}N(CH\textsubscript{3})\textsubscript{2}, C(OH)CH\textsubscript{3}, ClCH, CN, C(OH)NH\textsubscript{2}, OCH\textsubscript{2}C(OH)NH\textsubscript{2}, O(CH\textsubscript{2})\textsubscript{2}OCH\textsubscript{3}, O(CH\textsubscript{2})\textsubscript{2}N(CH\textsubscript{3})\textsubscript{2},

and R	extsuperscript{3} is methyl, ethyl, propyl, phenyl, CH\textsubscript{2}OH, CH\textsubscript{2}OCH\textsubscript{2}CH\textsubscript{3}, CH\textsubscript{2}CF\textsubscript{3}, CH\textsubscript{2}OC(CH\textsubscript{3})\textsubscript{3}, CH\textsubscript{2}ClCH, (CH\textsubscript{2})\textsubscript{3}N(CH\textsubscript{2})\textsubscript{2}, (CH\textsubscript{2})\textsubscript{3}NH\textsubscript{2}, (CH\textsubscript{2})\textsubscript{3}NH\textsubscript{2}, (CH\textsubscript{2})\textsubscript{3}NHC(\text{oH})OCH\textsubscript{2}CH\textsubscript{3}, or (CH\textsubscript{2})\textsubscript{4}NHC(\text{oH})OCH\textsubscript{2}CH\textsubscript{3}; R	extsuperscript{2} is hydrogen, methyl, fluoro, or bromo; and n is 0 or 1.
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, and S. The term “halo” is defined as fluoro, bromo, chloro, and iodo.

In a preferred embodiment, the PI3K inhibitor (which may be a PI3K-Ȗ inhibitor, PI3K-į inhibitor, or PI3K-Ȗ,į inhibitor) is (S)-2-(1-((9H-purin-6-
yl)amino)propyl)-5-fluoro-3-phenylquinazolin-4(3\text{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-\text{\textregistered}-inhibitor, PI3K-ï€-inhibitor, or PI3K-\text{\textregistered}-inhibitor) is 4(3\text{H})-quazalinone, 5-fluoro-3-phenyl-2-\{(1\text{S})-1-(9\text{H}-purin-6-ylamino)propyl\}-5-fluoro-3-phenyl-2-\{(1\text{S})-1-\{(7\text{H}-purin-6-yl)amino\}propyl\}quazolin-4(3\text{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-\text{\textregistered}-inhibitor, PI3K-ï€-inhibitor, or PI3K-\text{\textregistered}-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):
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof,
wherein:
X is CH, N, O or S;
Y is C(R₆), N, O or S;
Z is CH, N or bond;
A is CH or N;
B₁ is N or C(R₆);
B₂ is N or C(R₆);
B₃ is N or C(R₆);
B₄ is N or C(R₆);
R₁ is R₁₁C(=O), R₁₂S(=O), R₁₃S(=O)₂ or (C₁₄,₆)alkyl optionally substituted with R₁₄;
R₂ is H, (C₃₃)alkyl or (C₃₇)cycloalkyl;
R₃ is H, (C₄₈)alkyl or (C₃₇)cycloalkyl; or
R₂ and R₃ form, together with the N and C atom they are attached to, a (C₃₇,₈)heterocycloalkyl optionally substituted with one or more fluorine, hydroxyl, (C₁,₃)alkyl, (C₁,₃)alkoxy or oxo;
R₄ is H or (C₁₃)alkyl;
R₅ is H, halogen, cyano, (C₁₄)alkyl, (C₁₃)alkoxy, (C₁₆,₆)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;

\( R_8 \) is H or (C\(_{1-3}\))alkyl; or

\( R_3 \) and \( R_5 \) 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

\( R_3 \) 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\(_3\))cycloalkoxy, (C\(_{6-10}\))aryl and (C\(_{3-7}\))heterocycloalkyl; or \( R_{12} \) 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(Rₖ) or N and X is C or N;
0 to 2 atoms of B₁, B₂, B₃ and B₄ are N;
with the terms used having the following meanings:
(Cᵢ₋₂) alkyl means an alkyl group having 1 to 2 carbon atoms, being methyl or ethyl,
(Cᵢ₋₁₋₃) alkyl means a branched or unbranched alkyl group having 1-3 carbon atoms, being
methyl, ethyl, propyl or isopropyl;
(Cᵢ₋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, (Cᵢ₋₃) alkyl
groups being preferred;
(Cᵢ₋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, (Cᵢ₋₅) alkyl groups being preferred. (Cᵢ₋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. (Cᵢ₋₁₋₅) alkyl groups are preferred,
(Cᵢ₋₁₋₁₋₄) alkyl being most preferred;
(Cᵢ₋₁₋₂₋₃) alkoxy means an alkoxy group having 1-2 carbon atoms, the alkyl moiety having
the same meaning as previously defined;
(Cᵢ₋₁₋₁₋₃) alkoxy means an alkoxy group having 1-3 carbon atoms, the alkyl moiety having
the same meaning as previously defined. (Cᵢ₋₁₋₂) alkoxy groups are preferred;
(Cᵢ₋₁₋₁₋₄) alkoxy means an alkoxy group having 1-4 carbon atoms, the alkyl moiety having
the same meaning as previously defined. (Cᵢ₋₁₋₁₋₃) alkoxy groups are preferred, (Cᵢ₋₁₋₂₋₂) alkoxy
groups being most preferred;
(Cᵢ₋₂₋₄) alkenyl means a branched or unbranched alkenyl group having 2-4 carbon atoms,
such as ethenyl, 2-propenyl, isobutenyl or 2-butenyl;
(Cᵢ₋₂₋₆) alkenyl means a branched or unbranched alkenyl group having 2-6 carbon atoms,
such as ethenyl, 2-butenyl, and n-pentenyl, (Cᵢ₋₂₋₄) alkenyl groups being most preferred;
(Cᵢ₋₂₋₄) alkynyl means a branched or unbranched alkynyl group having 2-4 carbon atoms,
such as ethynyl, 2-propynyl or 2-butyln;
(C\textsubscript{2-6})alkynyl means a branched or unbranched alkynyl group having 2-6 carbon atoms, such as ethynyl, propynyl, n-butyln, n-pentynyl, isopentynyl, iso-hexynyl. (C\textsubscript{2-4})alkynyl groups are preferred; (C\textsubscript{3-6})cycloalkyl means a cycloalkyl group having 3-6 carbon atoms, being cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl;

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

(C\textsubscript{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\textsubscript{2-6})heterocycloalkyl being pyrrolidine; the heterocycloalkyl group may be attached via a heteroatom if feasible;

(C\textsubscript{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\textsubscript{3-7}) heterocycloalkyl groups are azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl; more preferred (C\textsubscript{3-7}) heterocycloalkyl groups are piperidine, morpholine and pyrrolidine; and the heterocycloalkyl group may be attached via a heteroatom if feasible;

(C\textsubscript{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\textsubscript{6-10})aryl means an aromatic hydrocarbon group having 6-10 carbon atoms, such as phenyl, naphthyl, tetrahydro-naphthyl or indenyl; the preferred (C\textsubscript{6-10})aryl group is phenyl;

(C\textsubscript{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\textsubscript{1-5})heteroaryl may optionally be substituted; preferred (C\textsubscript{1-5})heteroaryl groups are tetrazolyl, imidazolyl, thiazolyl, pyridyl, pyrimidyl, triazinyl, thiényl or furyl, a more preferred (C\textsubscript{1-5})heteroaryl is pyrimidyl;

(C\textsubscript{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\textsubscript{1-9}) heteroaryl may optionally be substituted; preferred (C\textsubscript{1-9}) heteroaryl groups are quinoline, isoquinoline and indole;

[(C\textsubscript{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\textsubscript{1-4})alkyl]amino group is methylamino;

di[(C\textsubscript{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\textsubscript{1-4})alkyl]amino group is dimethylamino;

halogen means fluorine, chlorine, bromine or iodine;

(C\textsubscript{1-3})alkyl-C(O)-S-(C\textsubscript{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\textsubscript{3-7})cycloalkenyl means a cycloalkenyl group having 3-7 carbon atoms, preferably 5-7 carbon atoms; preferred (C\textsubscript{3-7}) cycloalkenyl groups are cyclopentenyl or cyclohexenyl; cyclohexenyl groups are most preferred;

(C\textsubscript{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\textsubscript{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\textsubscript{n});

Z is CH or bond;
A is CH;
B₁ is N or C(R₇);
B₂ is N or C(R₈);
B₃ is N or CH;
B₄ is N or CH;
R₁ is R₁₁ C(=O),
R₂ is (C₁₋₃)alkyl;
R₃ is (C₁₋₃)alkyl; or
R₂ and R₃ form, together with the N and C atom they are attached to, a (C₃₋₇)heterocycloalkyl ring selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, and morpholinyl, optionally substituted with one or more fluorine, hydroxyl, (C₁₋₃)alkyl, or (C₁₋₃)alkoxy;
R₄ is H;
R₅ is H, halogen, cyano, (C₁₋₄)alkyl, (C₁₋₃)alkoxy, (C₃₋₆)cycloalkyl, or an alkyll group which is optionally substituted with one or more halogen;
R₆ is H or (C₁₋₃)alkyl;
R₇ is H, halogen or (C₁₋₃)alkoxy;
R₈ is H or (C₁₋₃)alkyl; or
R₇ and R₈ form, together with the carbon atom they are attached to a (C₆₋₁₀)aryl or (C₁₋₉)heteroaryl;
R₉ and R₁₀ together may form a (C₃₋₇)cycloalkenyl or (C₆₋₁₀)heterocycloalkenyl, each optionally substituted with (C₁₋₃)alkyl or one or more halogen;
R₁₁ is independently selected from the group consisting of (C₂₋₆)alkenyl and (C₂₋₆)alkynyl, where each alkenyl or alkynyl is optionally substituted with one or more substituents selected from the group consisting of hydroxyl, (C₁₋₄)alkyl, (C₃₋₇)cycloalkyl, [(C₁₋₄)alkyl]amino, di[(C₁₋₄)alkyl]amino, (C₁₋₃)alkoxy, (C₁₋₃)cycloalkoxy, (C₆₋₁₀)aryl and (C₃₋₇)heterocycloalkyl;
with the proviso that 0 to 2 atoms of B₁, B₂, B₃ and B₄ are N.

[00509] In an embodiment of Formula (XVII), B₁ is C(R₇); B₂ is C(R₈); B₃ is C(R₉); B₄ is C(R₁₀); R₇, R₉, and R₁₀ are each H; and R₈ is hydrogen or methyl.
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.

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

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

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

In an embodiment of Formula (XVII), R₂ is selected from the group consisting of hydrogen, fluorine, methyl, methoxy and trifluoromethyl.

In an embodiment of Formula (XVII), R₃ is hydrogen.

In an embodiment of Formula (XVII), R₂ and R₃ 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, (C₁₋₃)alkyl and (C₁₋₃)alkoxy.

In an embodiment of Formula (XVII), R₂ and R₃ together form a heterocycloalkyl ring selected from the group consisting of azetidinyl, pyrrolidinyl and piperidinyl.

In an embodiment of Formula (XVII), R₂ and R₃ together form a pyrrolidinyl ring.

In an embodiment of Formula (XVII), R₁ is independently selected from the group consisting of (C₁₋₆)alkyl, (C₂₋₆)alkenyl or (C₂₋₆)alkynyl, each optionally substituted with one or more substituents selected from the group consisting of hydroxyl, (C₁₋₄)alkyl, (C₃₋₇)cycloalkyl, [(C₁₋₄)alkyl]amino, di[(C₁₋₄)alkyl] amino, (C₁₋₃)alkoxy, (C₃₋₁₀)cycloalkoxy, (C₆₋₁₀)aryl and (C₃₋₇)heterocycloalkyl.

In an embodiment of Formula (XVII), B₁, B₂, B₃ and B₄ are CH; X is N; Y and Z are CH; R₅ is CH₃; A is N; R₂, R₃ and R₄ are H; and R₁ is CO-CH₃.
In an embodiment of Formula (XVII), B₁, B₂, B₃ and B₄ are CH; X and Y are N; Z is CH; R₅ is CH₃; A is N; R₂, R₃ and R₄ are H; and R₁ is CO-CH₃.

In an embodiment of Formula (XVII), B₁, B₂, B₃ and B₄ are CH; X and Y are N; Z is CH; R₅ is CH₃; A is CH; R₂ and R₃ together form a piperidinyl ring; R₄ is H; and R₁ is CO-ethenyl.

In an embodiment of Formula (XVII), B₁, B₂, B₃ and B₄ are CH; X, Y and Z are CH; R₅ is H; A is CH; R₂ and R₃ together form a piperidinyl ring; R₄ is H; and R₁ is CO-propynyl.

In an embodiment of Formula (XVII), B₁, B₂, B₃ and B₄ are CH; X, Y and Z are CH; R₅ is CH₃; A is CH; R₂ and R₃ together form a morpholinyl ring; R₄ is H; and R₁ is CO-propynyl.

In a preferred embodiment, the BTK inhibitor is a compound of 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 overnight. 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)-Benzyg 2-(8-chloroimidazo[1,5- α]pyrazin-3-yl)pyrrolidine-1-carboxylate was prepared as follows. (S)-Benzyg 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 pooled (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 110 °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-a]pyrazin-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 (1.26 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%).
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 thereof.

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

![Formula (XVIII-A)](image)


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

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

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

![Chemical Structure Diagram]

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

[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):
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof,
wherein:
X is CH, N, O or S;
Y is C(Rᵢ), N, O or S;
Z is CH, N or bond;
A is CH or N;
B₁ is N or C(Rᵢ);
B₂ is N or C(Rᵢ);
B₃ is N or C(Rᵢ);
B₄ is N or C(Rᵢ);
R₁ is R₁₁C(O), R₁₂S(O), R₁₃SO₂ or (C₁₋₆)alkyl optionally substituted with R₁₄;
R₂ is H, (C₁₋₆)alkyl or (C₃₋₇)cycloalkyl;
R₃ is H, (C₁₋₆)alkyl or (C₃₋₇)cycloalkyl; or
R₂ and R₃ form, together with the N and C atom they are attached to, a (C₃₋₇)heterocycloalkyl optionally substituted with one or more fluorine, hydroxyl, (C₁₋₆)alkyl, (C₁₋₆)alkoxy or oxo;
R₄ is H or (C₁₋₆)alkyl;
R₅ is H, halogen, cyano, (C₁₋₄)alkyl, (C₁₋₆)alkoxy, (C₃₋₆)cycloalkyl; all alkyl groups of R₅ are optionally substituted with one or more halogen; or R₅ is (C₆₋₁₀)aryl or (C₂₋₆)alkyl;
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_{3-7})cycloalkoxy, (C_{6-10})aryl or (C_{3-7})heterocycloalkyl, or
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_{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_{3-7})cycloalkoxy, (C_{6-10})aryl 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(R₆) or N and X is C or N;
- 0 to 2 atoms of B₁, B₂, B₃ and B₄ are N;

with the terms used having the following meanings:

(C₁-₃)alkyl means a branched or unbranched alkyl group having 1-3 carbon atoms, being methyl, ethyl, propyl or isopropyl;

(C₁-₄)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, (C₁-₃)alkyl groups being preferred;

(C₁-₆)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. (C₁, s)alkyl groups are preferred, (C₁-₄)alkyl being most preferred;

(C₁-₂)alkoxy means an alkoxy group having 1-2 carbon atoms, the alkyl moiety having the same meaning as previously defined;

(C₁-₃)alkoxy means an alkoxy group having 1-3 carbon atoms, the alkyl moiety having the same meaning as previously defined, with (C₁-₂)alkoxy groups preferred;

(C₂-₃)alkenyl means an alkenyl group having 2-3 carbon atoms, such as ethenyl or 2-propenyl;

(C₂-₄)alkenyl means a branched or unbranched alkenyl group having 2-4 carbon atoms, such as ethenyl, 2-propenyl, isobutenyl or 2-butenyl;

(C₂-₆)alkenyl means a branched or unbranched alkenyl group having 2-6 carbon atoms, such as ethenyl, 2-butenyl, and n-pentenyl, with (C₂-₄)alkenyl groups preferred, and (C₂-₃)alkenyl groups even more preferred;

(C₂-₄)alkynyl means a branched or unbranched alkynyl group having 2-4 carbon atoms, such as ethynyl, 2-propynyl or 2-butynyl;

(C₂-₃)alkynyl means an alkynyl group having 2-3 carbon atoms, such as ethynyl or 2-propynyl;

(C₂-₆)alkynyl means a branched or unbranched alkynyl group having 2-6 carbon atoms, such as ethynyl, propynyl, n-butyln, n-pentynyl, isopentynyl, isohexynyl or n-hexynyl, with (C₂-₄)alkynyl groups preferred, and (C₂-₃)alkynyl groups more...
preferred;

(C\textsubscript{3-6})cycloalkyl means a cycloalkyl group having 3-6 carbon atoms, being cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl;

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

(C\textsubscript{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\textsubscript{2-6})heterocycloalkyl is pyrrolidinyl; and the heterocycloalkyl group may be attached via a heteroatom if feasible;

(C\textsubscript{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\textsubscript{3-7})heterocycloalkyl groups are azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl; more preferred (C\textsubscript{3-7})heterocycloalkyl groups are piperidine, morpholine and pyrrolodine; and the heterocycloalkyl group may be attached via a heteroatom if feasible;

(C\textsubscript{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\textsubscript{6-10})aryl means an aromatic hydrocarbon group having 6-10 carbon atoms, such as phenyl, naphthyl, tetrahydroanthryptyl or indenyl; the preferred (C\textsubscript{6-10})aryl group is phenyl;

(C\textsubscript{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\textsubscript{1-5})heteroaryl may optionally be substituted.; preferred (C\textsubscript{1-5})heteroaryl groups are tetrazolyl, imidazolyl, thiadiazolyl, pyridyl, pyrimidyl, triazinyl, thienyl or furyl, and the more preferred (C\textsubscript{1-5})heteroaryl is pyrimidyl;

[(C\textsubscript{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 \([(C_{1-4})\text{alkyl}]\text{amino}\) group is methylamino;
di\([(C_{1-4})\text{alkyl}]\text{amino}\) 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\([(C_{1-4})\text{alkyl}]\text{amino}\) group is dimethylamino;
halogen means fluorine, chlorine, bromine or iodine;
\((C_{1-3})\text{alkyl-C(O)-S-}(C_{1-3})\text{alkyl}\) 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;
\((C_{3-7})\text{cycloalkenyl}\) means a cycloalkenyl group having 3-7 carbon atoms, preferably 5-7 carbon atoms; preferred \((C_{3-7})\text{cycloalkenyl}\) groups are cyclopentenyl or cyclohexenyl; and cyclohexenyl groups are most preferred;
\((C_{2-6})\text{heterocycloalkenyl}\) 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 \((C_{2-6})\text{heterocycloalkenyl}\) 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):
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof,
wherein:
Lₜ is CH₂, 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), OS(=O)ₓ, or NRS(=O)ₓ, where x is 1 or 2;
R₇ and R₈ are each independently H; or R₇ and R₈ taken together form a bond;
R₆ is H; and
R is H or (C₁₋₆)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)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one. In a preferred embodiment, the BTK inhibitor is 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-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)-1H-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.

[00550] In a preferred embodiment, the BTK inhibitor is a compound of Formula (XXI):

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

$L_2$ 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 \( \text{C}(=\text{O}), \text{OC}(=\text{O}), \text{NRC}(=\text{O}), \text{C}(=\text{S}), \text{S}(=\text{O})_{\text{x}}, \text{OS}(=\text{O})_{\text{x}} \) or \( \text{NRS}(=\text{O})_{\text{x}} \), where \( \text{x} \) is 1 or 2;

\( \text{R}_7^\text{'} \) and \( \text{R}_8^\text{'} \) are each \( \text{H} \); or \( \text{R}_7^\text{'} \) and \( \text{R}_8^\text{'} \) taken together form a bond;

\( \text{R}_7^\text{'} \) is \( \text{H} \); and

\( \text{R} \) is \( \text{H} \) or \( (\text{C}_{\text{1-6}})\text{alkyl} \).

[00551] In an embodiment, the BTK inhibitor is a compound of Formula (XXII):

\[
\begin{align*}
\text{NH}_2 & \\
\text{N} & \\
\text{N} & \\
\text{Y} & \\
\text{Z} & \\
\text{R}_7 & \\
\text{R}_8 &
\end{align*}
\]

Formula (XXII)

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

\( \text{L}_1 \) is \( \text{CH}_2, \text{O}, \text{NH} \) or \( \text{S} \);

\( \text{Ar} \) 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;

\( \text{Z} \) is \( \text{C}(=\text{O}), \text{OC}(=\text{O}), \text{NRC}(=\text{O}), \text{C}(=\text{S}), \text{S}(=\text{O})_{\text{x}}, \text{OS}(=\text{O})_{\text{x}} \) or \( \text{NRS}(=\text{O})_{\text{x}} \), where \( \text{x} \) is 1 or 2;

\( \text{R}_7^\text{'} \) and \( \text{R}_8^\text{'} \) are each \( \text{H} \); or \( \text{R}_7^\text{'} \) and \( \text{R}_8^\text{'} \) taken together form a bond;

\( \text{R}_7^\text{'} \) is \( \text{H} \); and

\( \text{R} \) is \( \text{H} \) or \( (\text{C}_{\text{1-6}})\text{alkyl} \).

[00552] In an embodiment, the BTK inhibitor is a compound of Formula (XXIII):
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof,
wherein:

Lₐ is CH₂, 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;

R₇ and R₈ are each H; or R₇ and R₈ taken together form a bond;

R₆ is H; and

R is H or (Cᵢ₋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):
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof,
wherein:

Q₁ is aryl₁, heteroaryl₁, cycloalkyl, heterocyclyl, cycloalkenyl, or heterocycloalkenyl, any
of which is optionally substituted by one to five independent G₁ substituents;

R₁ is alkyl, cycloalkyl, bicycloalkyl, aryl, heteroaryl, aralkyl, heterocyclyl, or
heterobicycloalkyl, any of which is optionally substituted by one or more
independent G₁ substituents;

G₁ and G₁₁ are each independently halo, oxo, -CF₃, -OCF₃, -OR₂, -NR₂R' (R₃₃a), -
C(O)R₂, -CO₂R₂, -CONR₃R₄, -NO₂, -CN, -S(O)₂R₀₁, -SO₂NR₂R₃, NR₂(C=O)R₂, 
NR₂(C=O)OR₂, NR₂(C=O)NR₂R₃, NR₂S(O)₂R₀₁, -(C=S)OR₂, -(C=O)SR₂, -
NR₂(C=NR₃)NR₂R₄, -NR₂(C=NR₃)OR₂, -NR₂(C=NR₃)SR₂, -O(C=O)OR₂, -
O(C=O)NR₂R₂, -O(C=O)SR₂, -S(C=O)OR₂, -S(C=O)NR₂R₃, (C₀₋₁₀)alkyl, (C₂₋₁₀)
alkenyl, (C₋₁₀)alkynyl, (C₋₁₀₋₁₅)alkoxy(C₋₁₀₋₁₅)alkyl, (C₋₁₀₋₁₅)alkoxy(C₋₁₀₋₁₅)alkenyl, (C₋₁₀₋₁₅)
alkoxy(C₋₁₀₋₁₅)alkynyl, (C₋₁₀₋₁₅₋₁₁₀)alkylthio(C₋₁₀₋₁₅₋₁₁₀)alkyl, (C₋₁₀₋₁₅₋₁₁₀)alkylthio(C₋₁₀₋₁₅₋₁₁₀)alkenyl,
(C₋₁₀₋₁₅₋₁₁₀)alkylthio(C₋₁₀₋₁₅₋₁₁₀)alkynyl, cyclo(C₋₁₀₋₁₅₋₁₁₀)alkyl, cyclo(C₋₁₀₋₁₅₋₁₁₀)alkenyl, cyclo(C₋₁₀₋₁₅₋₁₁₀)
alkynyl, cyclo(C₋₁₀₋₁₅₋₁₃₋₁₀)alkenyl(c-C₋₁₀₋₁₃₋₁₀)alkenyl, cyclo(C₋₁₀₋₁₅₋₁₃₋₁₀)alkenyl(c-C₋₁₀₋₁₃₋₁₀)alkenyl,
(cyclo(C₋₁₀₋₁₅₋₁₃₋₁₀)alkenyl(c-C₋₁₀₋₁₃₋₁₀)alkenyl, cyclo(C₋₁₀₋₁₅₋₁₃₋₁₀)alkenyl(c-C₋₁₀₋₁₃₋₁₀)alkenyl,
(cyclo(C₋₁₀₋₁₅₋₁₃₋₁₀)alkenyl(c-C₋₁₀₋₁₃₋₁₀)alkenyl, heterocyclyl-(C₋₁₀₋₁₅₋₁₁₀)alkyl, heterocyclyl-(C₋₁₀₋₁₅₋₁₁₀)
alkenyl, or heterocyclyl-(C₋₁₀₋₁₅₋₁₁₀)alkynyl, any of which is optionally substituted with one or more
independent halo, oxo, -CF₃, -OCF₃, -OR₂, -NR₂R' (R₃₃a), -C(O)R₂, -
CO₂R₂, -CONR₃R₄, -NO₂, -CN, -S(O)₂R₀₁, -SO₂NR₂R₃, NR₂(C=O)R₂, 
NR₂(C=O)OR₂, NR₂(C=O)NR₂R₃, NR₂S(O)₂R₀₁, -(C=S)OR₂, -(C=O)SR₂, -
NR₂(C=NR₃)NR₂R₄, -NR₂(C=NR₃)OR₂, -NR₂(C=NR₃)SR₂, -O(C=O)OR₂, -
O(C=O)SR₂, -S(C=O)OR₂, or -S(C=O)NR₂R₃ substituents; or -(Xₙ₊₁₋₁₀)R₄; or arylo-(C₀₋₁₀).
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$_{333a}$)$_{ja}$, -C(O)R$_{222}$, -CO$_2$R$_{222}$, -CONR$_{222}$ R$_{333}$, -NO$_2$, -CN, -S(O)$_{ja}$ R$_{222}$, -
SO$_2$NR$_{222}$ 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)$_{ja}$ 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$_0$.

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$_{333a}$)$_{ja}$, -C(O)R$_{222}$, -CO$_2$R$_{222}$, -CONR$_{222}$ R$_{333}$, -NO$_2$, -CN, -S(O)$_{ja}$ R$_{222}$, -
SO$_2$NR$_{222}$ 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)$_{ja}$ 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)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$_{222}$, -NR$_{222}$, -NO$_2$, -CN, -S(O)$_{ja}$ R$_{222}$, -SO$_2$NR$_{222}$ R$_{333}$, NR$_{221}$ (C=O)R$_{331}$, NR$_{221}$ (C=O)OR$_{331}$,
NR$_{21}$ (C=O)NR$_{21}$ R$_{31}^1$, NR$_{21}$ S(O)$_{ja}$ R$_{31}^1$, -(C=S)OR$_{21}^1$, -(C=O)SR$_{21}^1$, -NR$_{21}^1$
(C=NR$_{31}$)NR$_{21}$ R$_{31}^1$, -NR$_{21}^1$ (C=NR$_{31}$)OR$_{21}^1$, -NR$_{21}^1$ (C=NR$_{31}$)SR$_{31}^1$, -O(C=O)OR$_{21}^1$,
-O(C=O)NR$_{21}$ R$_{31}^1$, -O(C=O)SR$_{21}^1$, -S(C=O)OR$_{21}^1$, -S(C=O)NR$_{21}$ R$_{31}^1$, -P(O)OR$_{21}^1$, -
(C$_{0-10}$)alkyl, (C$_{-10}$)alkenyl, (C$_{-10}$)alkynyl, (C$_{-10}$)alkoxy(C$_{-10}$)alkyl, (C$_{-10}$)
alkoxy(C$_{-10}$)alkenyl, (C$_{-10}$)alkoxy(C$_{-10}$)alkynyl, (C$_{-10}$)alkylthio(C$_{-10}$)alkyl,
(C$_{-10}$)alkylthio(C$_{-10}$)alkenyl, (C$_{-10}$)alkylthio(C$_{-10}$)alkynyl, cyclo(C$_{-10}$)alkyl,
cyclo(C$_{-10}$)alkenyl, cyclo(C$_{-10}$)alkynyl, cyclo(C$_{-10}$)alkenyl, cyclo(C$_{-10}$)alkynyl, cyclo(C$_{-10}$)
alkenyl(C$_{-10}$)alkenyl, cyclo(C$_{-10}$)alkynyl(C$_{-10}$)alkenyl, heterocyclyl-(C$_{-10}$)alkyl,
heterocyclyl-(C$_{-10}$)alkenyl, or heterocyclyl-(C$_{-10}$)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$_{333a}$)$_{ja}$, -C(O)R$_{222}$, -CO$_2$R$_{222}$, -CONR$_{222}$ R$_{333}$, -NO$_2$, -CN,
S(O)$_{ja}$ R$_{222}$, -SO$_2$NR$_{222}$ 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)$_{ja}$ R$_{333}$, -(C=S)OR$_{222}$, -(C=O)SR$_{222}$,
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\(_2\) R\(^{2221}\), -CONR\(^{2221}\) R\(^{3331}\), -NO\(_2\), -CN, -S(O)\(_{j5a}\), -SO\(_2\) NR\(^{2221}\) 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\(_{-10}\)) alkyl, hetaryl-(C\(_{-10}\))alkenyl, or hetaryl-(C\(_{-10}\))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\(_2\) R\(^{2221}\), -CONR\(^{2221}\) R\(^{3331}\), -NO\(_2\), -CN, -S(O)\(_{j5a}\), -SO\(_2\) NR\(^{2221}\) 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\(^{2221}\) 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\(^{11}\);

R\(^2\), R\(^2\), R\(^3\), R\(^3\), R\(^3\), R\(^3\), a, R\(^3\), R\(^3\), R\(^2\), R\(^2\), R\(^2\), R\(^2\), R\(^2\), R\(^{22a1}\), R\(^{33a1}\), R\(^{33a1}\), R\(^{33a1}\), R\(^{33a1}\), R\(^{33a1}\), R\(^{33a1}\), and R\(^{33a1}\) are each independently equal to (C\(_{-10}\))alkyl, (C\(_{-10}\))alkenyl, (C\(_{-10}\))alkynyl, (C\(_{-10}\))alkoxy(C\(_{-10}\))alkyl, (C\(_{-10}\))alkoxy(C\(_{-10}\))alkenyl, (C\(_{-10}\))alkoxy(C\(_{-10}\))alkynyl, (C\(_{-10}\))alkylthio(C\(_{-10}\))alkyl, (C\(_{-10}\))alkylthio(C\(_{-10}\))alkenyl, (C\(_{-10}\))alkylthio(C\(_{-10}\))alkynyl, cyclo(C\(_{-8}\))alkyl, cyclo(C\(_{-8}\))alkylthio(C\(_{-8}\))alkyl, cyclo(C\(_{-8}\))alkylthio(C\(_{-8}\))alkenyl, cyclo(C\(_{-8}\))alkylthio(C\(_{-8}\))alkynyl, cyclo(C\(_{-8}\))alkyl(C\(_{-8}\))alkenyl, cyclo(C\(_{-8}\))alkyl(C\(_{-8}\))alkynyl, cyclo(C\(_{-8}\))alkenyl(C\(_{-8}\))alkenyl, cyclo(C\(_{-8}\))alkenyl(C\(_{-8}\))alkynyl, cyclo(C\(_{-8}\))alkenyl(C\(_{-8}\))alkenyl, heterocyclyl-(C\(_{-10}\))alkyl, heterocyclyl-(C\(_{-10}\))alkenyl, or heterocyclyl-(C\(_{-10}\))alkynyl, any of which is optionally substituted by one or more G\(^{11}\) substituents; or aryl-(C\(_{-10}\))alkyl, aryl-(C\(_{-10}\))alkenyl, aryl-(C\(_{-10}\))alkenyl, or aryl-(C\(_{-10}\))alkynyl, heteraryl-(C\(_{-10}\))alkyl, heteraryl-(C\(_{-10}\))alkenyl, or
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hetaryl-(C2 -1 0 )alkynyl, any of which is optionally substituted by one or more G
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substituents; or in the case of -NR R (R )j1 or -NR R (R a)j1a or
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-NR R (R a)j2a or -NR
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NR

and R

R

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3331

(R

333a1

R

2221

)j5a or -NR

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R

(R

3331

333a1

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)j3a or -NR

333a1

(R

R

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333a1

(R

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)j6a , R and R or R

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)j4a or 333

and R 3 or R

2221

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
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more G
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substituents;

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X and Y are each independently -O-, -NR -, -S(O)j7 -, -CR R -, -N(C(O)OR )-, 7

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N(C(O)R )-, -N(SO2 R )-, -CH2 O-, -CH2 S-, -CH2 N(R )-, -CH(NR )-, 7

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CH2 N(C(O)R )-, -CH2 N(C(O)OR )-, -CH2 N(SO2 R )-, -CH(NHR )-, 7

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CH(NHC(O)R )-, -CH(NHSO2 R )-, -CH(NHC(O)OR )-, -CH(OC(O)R )-, 7

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CH(OC(O)NHR )-, -CH=CH-, -C.ident.C-, -C(=NOR )-, -C(O)-, -CH(OR )-,
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-C(O)N(R )-, -N(R )C(O)-, -N(R )S(O)-, -N(R )S(O)2 - -OC(O)N(R )-, 7

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N(R )C(O)N(R )-, -NR C(O)O-, -S(O)N(R )-, -S(O)2 N(R )-, -N(C(O)R )S(O)-, 7

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N(C(O)R )S(O)2 -, -N(R )S(O)N(R )-, -N(R )S(O)2 N(R )-, -C(O)N(R )C(O)-, 7

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S(O)N(R )C(O)-, -S(O)2 N(R )C(O)-, -OS(O)N(R )-, -OS(O)2 N(R )-, -N(R )S(O)O-, 7

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N(R )S(O)2 O-, -N(R )S(O)C(O)-, -N(R )S(O)2 C(O)-, -SON(C(O)R )-, 7

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SO2 N(C(O)R )-, -N(R )SON(R )-, -N(R )SO2 N(R )-, -C(O)O-, -N(R )P(OR )O-, 7

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N(R )P(OR )-, -N(R )P(O)(OR )O-, -N(R )P(O)(OR )-, -N(C(O)R )P(OR )O-, 7

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N(C(O)R )P(OR )-, -N(C(O)R )P(O)(OR )O-, -N(C(O)R )P(OR )-, -CH(R )S(O)-, 7

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CH(R )S(O)2 -, -CH(R )N(C(O)OR )-, -CH(R )N(C(O)R )-, -CH(R )N(SO2 R )-, 7

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CH(R )O-, -CH(R )S-, -CH(R )N(R )-, -CH(R )N(C(O)R )-, -CH(R )N(C(O)OR )-,
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-CH(R )N(SO2 R )-, -CH(R )C(=NOR )-, -CH(R )C(O)-, -CH(R )CH(OR )-,
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-CH(R )C(O)N(R )-, -CH(R )N(R )C(O)-, -CH(R )N(R )S(O)-, -CH(R )N(R )S(O)2 7

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, -CH(R )OC(O)N(R )-, -CH(R )N(R )C(O)N(R )-, -CH(R )NR C(O)O-, 7

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CH(R )S(O)N(R )-, -CH(R )S(O)2 N(R )-, -CH(R )N(C(O)R )S(O)-, 7

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CH(R )N(C(O)R )S(O)-, -CH(R )N(R )S(O)N(R )-, -CH(R )N(R )S(O)2 N(R )-, 7

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CH(R )C(O)N(R )C(O)-, -CH(R )S(O)N(R )C(O)-, -CH(R )S(O)2 N(R )C(O)-, 7

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CH(R )OS(O)N(R )-, -CH(R )OS(O)2 N(R )-, -CH(R )N(R )S(O)O-, 7

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CH(R )N(R )S(O)2 O-, -CH(R )N(R )S(O)C(O)-, -CH(R )N(R )S(O)2 C(O)-, -


CH(R\textsuperscript{7})SON(C(O)R\textsuperscript{7})-, -CH(R\textsuperscript{7})SO\textsubscript{2}N(C(O)R\textsuperscript{7})-, -CH(R\textsuperscript{7})N(R\textsuperscript{7})SON(R\textsuperscript{7})-, -CH(R\textsuperscript{7})N(R\textsuperscript{7})SO\textsubscript{2}N(R\textsuperscript{7})-, -CH(R\textsuperscript{7})C(O)O-, -CH(R\textsuperscript{7})N(R\textsuperscript{7})P(OR\textsuperscript{8})O-, -CH(R\textsuperscript{7})N(C(O)R\textsuperscript{7})P(OR\textsuperscript{8})O-, -CH(R\textsuperscript{7})N(C(O)R\textsuperscript{7})P(OR\textsuperscript{8})O-, -CH(R\textsuperscript{7})N(C(O)R\textsuperscript{7})P(OR\textsuperscript{8})O-, -CH(R\textsuperscript{7})N(C(O)R\textsuperscript{7})P(OR\textsuperscript{8})O-.

or X\textsuperscript{1} and Y\textsuperscript{1} are each independently represented by one of the following structural formulas:

\[
\text{R}^{10}, \text{ taken together with the phosphinamide or phosphonamide, is a 5-, 6-, or 7-membered aryl, heteroaryl or heterocyclyl ring system;}
\]

R\textsuperscript{5}, R\textsuperscript{6}, and G\textsuperscript{111} are each independently a (C\textsubscript{0}-\textsuperscript{10})alkyl, (C\textsubscript{2}-\textsuperscript{10})alkenyl, (C\textsubscript{2}-\textsuperscript{10})alkynyl, (C\textsubscript{1}-\textsuperscript{10})alkoxy(C\textsubscript{1}-\textsuperscript{10})alkyl, (C\textsubscript{1}-\textsuperscript{10})alkoxy(C\textsubscript{2}-\textsuperscript{10})alkenyl, (C\textsubscript{1}-\textsuperscript{10})alkoxy(C\textsubscript{2}-\textsuperscript{10})alkynyl, (C\textsubscript{1}-\textsuperscript{10})alkylthio(C\textsubscript{1}-\textsuperscript{10})alkyl, (C\textsubscript{1}-\textsuperscript{10})alkylthio(C\textsubscript{2}-\textsuperscript{10})alkenyl, (C\textsubscript{1}-\textsuperscript{10})alkylthio(C\textsubscript{2}-\textsuperscript{10})alkynyl, cyclo(C\textsubscript{3}-\textsuperscript{8})alkyl, cyclo(C\textsubscript{3}-\textsuperscript{8})alkenyl, cyclo(C\textsubscript{3}-\textsuperscript{8})alkynyl, cyclo(C\textsubscript{5}-\textsuperscript{8})alkenyl, cyclo(C\textsubscript{5}-\textsuperscript{8})alkynyl, heterocyclyl-(C\textsubscript{0}-\textsuperscript{10})alkyl, heterocyclyl-(C\textsubscript{2}-\textsuperscript{10})alkenyl, or heterocyclyl-(C\textsubscript{2}-\textsuperscript{10})alkynyl, any of which is optionally substituted with one or more independent halo, -CF\textsubscript{3}, -OCF\textsubscript{3}, -OR\textsuperscript{77}, -NR\textsuperscript{77}R\textsuperscript{87}, -C(O)R\textsuperscript{77}, -CO\textsubscript{2}R\textsuperscript{77}, -CONR\textsuperscript{77}R\textsuperscript{87}, -NO\textsubscript{2}, -CN, -S(O)\textsubscript{5a}R\textsuperscript{77}, -SO\textsubscript{2}NR\textsuperscript{77}R\textsuperscript{87}, NR\textsuperscript{77}(C=O)R\textsuperscript{87}, NR\textsuperscript{77}(C=O)OR\textsuperscript{87}, NR\textsuperscript{77}(C=O)NR\textsuperscript{77}R\textsuperscript{87}, NR\textsuperscript{77}S(O)\textsubscript{5a}R\textsuperscript{87}. 

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-(C=S)OR 7, -(C=O)SR 7, -NR 7 (C=NR 8)NR 8 OR 8, -NR 7 (C=NR 8)SR 7, -O(C=O)OR 7, -O(C=O)SR 7, -S(C=O)OR 7, -P(O)OR 7, OR 7, or -S(C=O)NR 8 R 7 substituents; or aryl-(C 10)alkynyl, aryl-(C 10)alkynyl, any of which is optionally substituted with one or more independent halo, -CF 3, -OCF 3, -OR 7, -NR 7 R 8, -C(O)R 7, -CO 2 R 7, -CONR 7 R 7, -NO 2, -CN, -S(O) 3 R 7, -SO 2 NR 7 R 8, NR 7 (C=O)R 7, NR 7 (C=O)OR 7, NR 7 (C=O)SR 7, -O(C=O)OR 7, -S(C=O)OR 7, or -S(C=O)NR 8 R 7 substituents; or hetaryl-(C 10)alkynyl, hetaryl-(C 10)alkynyl, or hetaryl-(C 10)alkynyl, any of which is optionally substituted with one or more independent halo, -CF 3, -OCF 3, -OR 7, -NR 7 R 8, -C(O)R 7, -CO 2 R 7, -CONR 7 R 7, -NO 2, -CN, -S(O) 3 R 7, -SO 2 NR 7 R 8, NR 7 (C=O)R 7, NR 7 (C=O)OR 7, NR 7 (C=O)SR 7, -O(C=O)OR 7, -S(C=O)OR 7, or -S(C=O)NR 8 R 7 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, alky, alkenyl, aryl, heteroaryl, heterocyclyl or cycloalkyl, any of which is optionally substituted by one or more G 41 substituents; R 9 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 49 is equal to halo, -OR 7, -SH, -NR 7 R 8, -CO 2 R 7, -CONR 7 R 8, -NO 2, -CN, -S(O) 3 j 8, -SO 2 NR 7 R 8, -(C 10)alkyl, -(C 10)alkenyl, -(C 10)alkynyl, -(C 10)alkoxy(C 10)alkyl, -(C 10)alkoxy(C 10)alkenyl, -(C 10)alkoxy(C 10)alkynyl, -(C 10)alkylthio(C 10)alkyl, -(C 10)alkylthio(C 10)alkenyl, -(C 10)alkylthio(C 10)alkynyl, cyclo(C 3 8)alkyl, cyclo(C 3 8)alkenyl, cyclo(C 3 8)alkynyl, cyclo(C 3 8)alkoxy(C 3 8)alkyl, cyclo(C 3 8)alkoxy(C 3 8)alkenyl, cyclo(C 3 8)alkoxy(C 3 8)alkynyl, cyclo(C 3 8)alkylthio(C 3 8)alkyl, cyclo(C 3 8)alkylthio(C 3 8)alkenyl, cyclo(C 3 8)alkylthio(C 3 8)alkynyl.
alkenyl(C\textsubscript{1-10})alkyl, cyclo(C\textsubscript{3-8})alkyl(C\textsubscript{2-10})alkenyl, cyclo(C\textsubscript{3-8})alkenyl(C\textsubscript{2-10})alkenyl, cyclo(C\textsubscript{3-8})alkenyl(C\textsubscript{2-10})alkynyl, heterocyclyl-(C\textsubscript{0-10})alkyl, heterocyclyl-(C\textsubscript{2-10})alkenyl, or heterocyclyl-(C\textsubscript{2-10})alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, -OR\textsuperscript{778}, -SO\textsubscript{2}NR\textsuperscript{778} R\textsuperscript{888}, or -NR\textsuperscript{778} R\textsuperscript{888} substituents; or aryI-(C\textsubscript{2-10})alkenyl, aryI-(C\textsubscript{2-10})alkynyl, or aryI-(C\textsubscript{2-10})alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, -OR\textsuperscript{778}, (C\textsubscript{1-10})alkyl, (C\textsubscript{2-10})alkenyl, (C\textsubscript{2-10})alkynyl, halo(C\textsubscript{1-10})alkyl, halo(C\textsubscript{2-10})alkenyl, halo(C\textsubscript{2-10})alkynyl, -COOH, (C\textsubscript{1-4})alkoxycarbonyl, -CONR\textsuperscript{778} R\textsuperscript{888}, -SO\textsubscript{2}NR\textsuperscript{778} R\textsuperscript{888}, or -NR\textsuperscript{778} R\textsuperscript{888} substituents; or hetaryl-(C\textsubscript{0-10})alkyl, hetaryl-(C\textsubscript{2-10})alkenyl, or hetaryl-(C\textsubscript{2-10})alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, -OR\textsuperscript{778}, (C\textsubscript{1-10})alkyl, (C\textsubscript{2-10})alkenyl, (C\textsubscript{2-10})alkynyl, halo(C\textsubscript{1-10})alkyl, halo(C\textsubscript{2-10})alkenyl, halo(C\textsubscript{2-10})alkynyl, -COOH, (C\textsubscript{1-4})alkoxycarbonyl, -CONR\textsuperscript{778} R\textsuperscript{888}, -SO\textsubscript{2}NR\textsuperscript{778} R\textsuperscript{888}, or -NR\textsuperscript{778} R\textsuperscript{888} substituents; or in the case of -NR\textsuperscript{778} R\textsuperscript{888}, R\textsuperscript{878} and R\textsuperscript{888} 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\textsubscript{1-10})alkoxy, -SO\textsubscript{2}NR\textsuperscript{778} R\textsuperscript{888}, or -NR\textsuperscript{778} R\textsuperscript{888} substituents; R\textsuperscript{778}, R\textsuperscript{878}, R\textsuperscript{888}, and R\textsuperscript{888} are each independently (C\textsubscript{0-10})alkyl, (C\textsubscript{2-10})alkenyl, (C\textsubscript{2-10})alkynyl, (C\textsubscript{1-10})alkoxy(C\textsubscript{1-10})alkyl, (C\textsubscript{1-10})alkoxy(C\textsubscript{2-10})alkenyl, (C\textsubscript{1-10})alkoxy(C\textsubscript{2-10})alkynyl, (C\textsubscript{1-10})alkylthio(C\textsubscript{1-10})alkyl, (C\textsubscript{1-10})alkylthio(C\textsubscript{2-10})alkenyl, (C\textsubscript{1-10})alkylthio(C\textsubscript{2-10})alkynyl, cyclo(C\textsubscript{3-8})alkyl, cyclo(C\textsubscript{3-8})alkenyl, cyclo(C\textsubscript{3-8})alkynyl, heterocyclyl-(C\textsubscript{0-10})alkyl, heterocyclyl-(C\textsubscript{2-10})alkenyl, heterocyclyl-(C\textsubscript{2-10})alkynyl, heterocyclyl-(C\textsubscript{3-8})alkyl, heterocyclyl-(C\textsubscript{3-8})alkenyl, heterocyclyl-(C\textsubscript{3-8})alkynyl.
alkynyl, (C<sub>1</sub>-<sub>10</sub>)alkylcarbonyl, (C<sub>2</sub>-<sub>10</sub>)alkenylcarbonyl, (C<sub>2</sub>-<sub>10</sub>)alkynylcarbonyl, (C<sub>1</sub>-<sub>4</sub>)alkoxy carbonyl, (C<sub>1</sub>-<sub>4</sub>)alkoxy carbonyl(C<sub>1</sub>-<sub>10</sub>)alkyl, mono(C<sub>1</sub>-
alkylaminocarbonyl, di(C<sub>1</sub>-)alkylaminocarbonyl, mono(aryl)aminocarbonyl, di(aryl)aminocarbonyl, or (C<sub>1</sub>-<sub>4</sub>)alkyl(aryl)aminocarbonyl, any of which is optionally substituted with one or more independent halo, cyano, hydroxy, nitro, (C<sub>1</sub>-<sub>4</sub>)alkoxy, -SO<sub>2</sub>N((C<sub>0</sub>-<sub>4</sub>)alkyl)((C<sub>0</sub>-<sub>4</sub>)alkyl), or -N((C<sub>0</sub>-<sub>4</sub>)alkyl)((C<sub>0</sub>-<sub>4</sub>)alkyl) substituents; or aryl-(C<sub>1</sub>-<sub>4</sub>)alkyl, aryl-(C<sub>2</sub>-<sub>10</sub>)alkenyl, or aryl-(C<sub>2</sub>-<sub>10</sub>)alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, -O((C<sub>0</sub>-<sub>4</sub>)alkyl), (C<sub>1</sub>-
aldehydic), (C<sub>1</sub>-<sub>4</sub>)alkyl, (C<sub>1</sub>-<sub>4</sub>)alkenyl, (C<sub>2</sub>-<sub>10</sub>)alkynyl, halo(C<sub>1</sub>-<sub>4</sub>)alkyl, halo(C<sub>1</sub>-<sub>4</sub>)alkenyl, halo(C<sub>2</sub>-
aldehydic), (C<sub>2</sub>-<sub>10</sub>)alkynyl, -COOH, (C<sub>1</sub>-<sub>4</sub>)alkoxy carbonyl, -CON((C<sub>0</sub>-<sub>4</sub>)alkyl)((C<sub>0</sub>-<sub>4</sub>)alkyl), -SO<sub>2</sub>N((C<sub>0</sub>-<sub>4</sub>)alkyl)((C<sub>0</sub>-<sub>4</sub>)alkyl), or -N((C<sub>0</sub>-<sub>4</sub>)alkyl)((C<sub>0</sub>-<sub>4</sub>)alkyl) substituents; or hetaryl-(C<sub>1</sub>-<sub>4</sub>)alkyl, hetaryl-(C<sub>2</sub>-<sub>10</sub>)alkenyl, or hetaryl-(C<sub>2</sub>-<sub>10</sub>)alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, -O((C<sub>0</sub>-
aldehydic), (C<sub>1</sub>-<sub>10</sub>)alkyl, (C<sub>1</sub>-<sub>10</sub>)alkenyl, (C<sub>2</sub>-<sub>10</sub>)alkynyl, halo(C<sub>1</sub>-<sub>10</sub>)alkyl, halo(C<sub>1</sub>-<sub>10</sub>)alkenyl, halo(C<sub>2</sub>-
aldehydic), (C<sub>2</sub>-<sub>10</sub>)alkynyl, -COOH, (C<sub>1</sub>-<sub>4</sub>)alkoxy carbonyl, -CON((C<sub>0</sub>-<sub>4</sub>)alkyl)((C<sub>0</sub>-<sub>4</sub>)alkyl), -SO<sub>2</sub>N((C<sub>0</sub>-<sub>4</sub>)alkyl)((C<sub>0</sub>-<sub>4</sub>)alkyl), or -N((C<sub>0</sub>-<sub>4</sub>)alkyl)((C<sub>0</sub>-<sub>4</sub>)alkyl) substituents; or mono((C<sub>1</sub>-<sub>6</sub>)alkyl)amino(C<sub>1</sub>-<sub>6</sub>)alkyl, di((C<sub>1</sub>-<sub>6</sub>)alkyl)amino(C<sub>1</sub>-<sub>6</sub>)alkyl, mono(aryl)aminocarbonyl(C<sub>1</sub>-<sub>6</sub>)alkyl, or -N((C<sub>1</sub>-<sub>6</sub>)alkyl)-(C<sub>1</sub>-<sub>6</sub>)alkyl-aryl, any of which is optionally substituted with one or more independent halo, cyano, nitro, -O((C<sub>0</sub>-<sub>4</sub>)alkyl), (C<sub>1</sub>-<sub>4</sub>)alkyl, (C<sub>1</sub>-<sub>4</sub>)alkenyl, (C<sub>2</sub>-<sub>10</sub>)alkynyl, halo(C<sub>1</sub>-<sub>4</sub>)alkyl, halo(C<sub>1</sub>-<sub>4</sub>)alkenyl, halo(C<sub>2</sub>-
aldehydic), (C<sub>2</sub>-<sub>10</sub>)alkynyl, -COOH, (C<sub>1</sub>-<sub>4</sub>)alkoxy carbonyl, -CON((C<sub>0</sub>-<sub>4</sub>)alkyl)((C<sub>0</sub>-<sub>4</sub>)alkyl), -SO<sub>2</sub>N((C<sub>0</sub>-<sub>4</sub>)alkyl)((C<sub>0</sub>-<sub>4</sub>)alkyl), or -N((C<sub>0</sub>-<sub>4</sub>)alkyl)((C<sub>0</sub>-<sub>4</sub>)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):
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\(^2\) is hydrogen, halogen, \(\text{—CN, —CF}_{3}, \text{C}_{1-6} \text{ aliphatic, C}_{1-4} \text{ haloaliphatic, —OR, —C(O)R, or —C(O)N(R)}_{2} \text{;}

each R group is independently hydrogen or an optionally substituted group selected from \(\text{C}_{1-6} \text{ 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 \(\text{C}_{1-3} \text{ alkyline chain wherein one methylene unit of W}\(^1\) or W\(^2\) is optionally replaced by —NR\(^2\)—, —N(R\(^1\))C(O)—, —C(O)N(R\(^1\))—, —N(R\(^1\))SO\(_2\)—, —SO\(_2\)N(R\(^1\))—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —SO— or —SO\(_2\)—;

R\(^3\) is hydrogen, optionally substituted \(\text{C}_{1-6} \text{ 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\(^1\) 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\(^3\) and R\(^1\) are independently selected from —R, halogen, —OR, —O(CH\(_3\))\(_q\) OR, —CN, —NO\(_2\), —SO\(_2\) R, —SO\(_2\) N(R\(^1\))\(_2\), —SOR, —C(O)R, —CO\(_2\) R, —C(O)N(R\(^1\))\(_2\), —NRC(O)R, —NRC(O)NR\(_2\), —NRSO\(_2\) R, or —N(R\(^1\))\(_2\), wherein q is 1-4; or:

R\(^2\) 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<sub>1-6</sub> aliphatic; or
R’ and R’ 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<sub>1-6</sub> 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’ is -L-Y, wherein:
L is a covalent bond or a bivalent C<sub>1-8</sub> 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_2N(R)-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -SO-, -SO_2-, -C(I\(\delta\)-S)-, -C(I\(\delta\)-NR)-, -N\(\delta\)N-; or \(-C(I\(\delta\)-N)-; \)

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 \(-Q-Z, \text{ oxo, } \text{ NO}_2, \text{ halogen, CN, or } C_{1-6} \text{ aliphatic, wherein:} \)

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;

\(R'\) is hydrogen, halogen, \(-CN, -CF_3, C_{1-4} \text{ aliphatic, } C_{1-4} \text{ haloaliphatic, } -OR, -C(O)R, \) or \(-C(O)N(R)_2; \)

each R group is independently hydrogen or an optionally substituted group selected from \(C_{1-6} \text{ aliphatic, phenyl, an optionally substituted } 4-7 \text{ membered heterocyclic ring having } 1-2 \text{ heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a } 5-6 \text{ membered monocyclic heteroaryl ring having } 1-4 \text{ heteroatoms independently selected from nitrogen, oxygen, or sulfur;} \)

\(W^1\) and \(W^2\) are each independently a covalent bond or a bivalent \(C_{1-3} \text{ 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 \(C_{1-6} \text{ aliphatic, or } -C(O)R, \) 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 \(R'\) 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

\(R'\) and \(R'\) are independently selected from \(-R, \text{ halogen, } -OR, -O(CH_3)_q OR, -CN,
—NO₂, —SO₂ R, —SO₂ N(R)₂, —SOR, —C(O)R, —CO₂ R, —C(O)N(R)₂, —NRC(O)R, —NRC(O)NR₂, —NRSO₂ R, or —N(R) ... carbocyclic ring. In yet other embodiments, Ring A is an optionally substituted 4-7 membered heterocyclic ring having 1-3 heteroatoms independently selected from the group consisting of hydrogen, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, and heterocyclic; or:

R¹ and R¹ 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 C₁₋₆ aliphatic; or

R² and R² 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 C₁₋₆ 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°, or —(CH₂)ₙ OR°, or —O(CH₂)ₙ OR°, wherein each R° 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, —CF₃, —ClCH, —OCH₂phenyl, —OCH₂(fluorophenyl), or —OCH₂pyridyl.

[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)](image)

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):
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} alkenylene, (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} alkylnyl 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^3R^4, (4) CO_2R^5, and (5) OR^6;

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^i’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):
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 $C_{1-4}$ alkenylene, (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$^3$R$^4$, (2) halogen atoms, (3) CONR$^5$R$^6$, (4) CO$_2$R$^7$, 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\(^i\)'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):

\[
\text{Formula (XXVIII-B)}
\]

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)](image)

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-[(3R)-1-(2-butynoyl)-3-pyrrolidinyl]-7-(4-phenoxyphenyl)-7,9-dihydro-8H-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 (3R)-3-[(6-(dibenzylamino)-5-nitropyrimidin-4-yl)amino]pyrrolidine-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 (3R)-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 (3R)-3-[6-(dibenzylamino)-8-oxo-7,8-dihydro-9H-purin-9-yl]pyrrolidin-1-carboxylate (7.8 g).
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 (3R)-3-(6-amino-8-oxo-7,8-dihydro-9H-purin-9-yl)pyrrolidine-1-carboxylate (5.0 g).

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 (3R)-3-[6-amino-8-oxo-7-(4-phenoxyphenyl)-7,8-dihydro-9H-purin-9-yl]pyrrolidine-1-carboxylate (1.3 g).

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-8H-purin-8-one dihydrochloride (1.5 g).

Step 8: After 2-butynoic 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-[3R]-1-(2-butynoyl)-3-pyrrolidinyl]-7-(4-phenoxyphenyl)-7,9-dihydro-8H-purin-8-one (Formula (XXVIII-R)) (75 mg).
The hydrochloride salt of the compound of Formula (XXVIII-R) can be prepared as follows: 6-amino-9-[(3R)-1-(2-butynoyl)-3-pyrrolidinyl]-7-(4-phenoxyphenyl)-7,9-dihydro-8\textsubscript{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\textdegree C (internal temperature 61\textdegree 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\textdegree C for 30 min, external temperature 60\textdegree C for 30 min, external temperature 50\textdegree C for 60 min, external temperature 40\textdegree 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\textdegree C to obtain white crystals of 6-amino-9-[(3R)-1-(2-butynoyl)-3-pyrrolidinyl]-7-(4-phenoxyphenyl)-7,9-dihydro-8\textsubscript{H}-purin-8-one hydrochloride (2.76 g).

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.

In an embodiment, the BTK inhibitor is a compound of Formula (B):

\[
\text{Formula (B)}
\]

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^1 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 heterocycll;
R^1 is COR', CO_2 R', or SO_2 R', wherein R' is substituted or unsubstituted alkyl, substituted
or unsubstituted alkenyl, substituted or unsubstituted alkynyl;
R^1 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^1;
R^2 is COR' or SO_2 R', particularly wherein R' is substituted or unsubstituted alkenyl,
particularly substituted or unsubstituted ethenyl; or
R is unsubstituted or substituted alkyl or aryl, particularly substituted or unsubstituted phenyl or methyl, such as cyclopropyl-substituted methyl with or tetrabutyl-substituted phenyl.

In some embodiments, the BTK inhibitor is one of the following particular embodiments of Formula B:

R1 is piperidine or azaspiro[3.3]heptane, N-substituted with R4, wherein R4 is H, COR' or SO2R', and R' is substituted or unsubstituted alkenyl, particularly substituted or unsubstituted ethenyl;

R3 is –OR5, R' is phenyl, and n is 1;

R1 and R2, together with the atoms to which they are attached, form a 5-6 membered ring, preferably (a) phenyl substituted with a single -L-R4, or (b) dihydropyrrole or tetrahydropyridine, N-substituted with a single -L-R4 wherein L is bond; R3 is –OR5; n is 1; R4 is COR'; and R' is ethenyl; and

X--Y--Z is C--N--N and R2 is absent; R3 is piperidine, N-substituted with R4; R3 is –OR5; n is 1; R4 is COR'; and R' is unsubstituted or substituted alkenyl, particularly ethenyl; and R5 is substituted or unsubstituted aryl, particularly phenyl.

In a preferred embodiment, the BTK inhibitor is a compound of Formula (B1), Formula (B1-2), or 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:
A solution of 4-phenoxybenzoic acid (300 g, 1.4 mol) in SOCl₂ (1.2 L) is stirred at 80° C under N₂ for 3 hours. The mixture is concentrated in vacuum to give the intermediate (315 g) which is used for next step without further purification.

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 Na₂SO₄ and concentrated to give the crude product (330 g, 93%).

Step 2. Preparation of 2-(Methoxy(4-phenoxyphenyl)methylene)malononitrile:

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.

Step 3. Preparation of 5-amino-3-(4-phenoxyphenyl)-1H-pyrazole-4-carbonitrile:
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)-1H-pyrazole-4-carbonitrile as a off-white solid.

Step 4. Preparation of tert-butyl 3-(tosyloxy)piperidine-1-carboxylate:

wherein “Boc” represents a tert-butyloxy carbonyl protecting group.

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 N₂ 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 NaHCO₃ aqueous solution (100 mL × 2), brine (100 mL × 3) and dried over Na₂SO₄. The organic layer is concentrated to afford 1.1 g (60%) of tert-butyl 3-(tosyloxy)piperidine-1-carboxylate as a colorless oil.

Step 5. Preparation of tert-butyl 3-(5-amino-4-cyano-3-(4-phenoxyphenyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate:
To a solution of tert-butyl 3-(tosyloxy)piperidine-1-carboxylate (355 mg, 1.0 mmol) and 5-amino-3-(4-phenoxyphenyl)-1H-pyrazole-4-carbonitrile (276 mg, 1.0 mmol) in 5 mL of DMF is added Cs₂CO₃ (650 mg, 2.0 mmol). A tosloxy 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 x 3) and dried over Na₂SO₄. The material is concentrated and purified by chromatography column on silica gel (eluted with petroleum ether/ethyl acetate = 3/1) to afford 60 mg (13%) of tert-butyl 3-(5-amino-4-cyan-3-(4-phenoxyphenyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate as a yellow oil.

Step 6. Preparation of tert-butyl 3-(5-amino-4-carbamoyl-3-(4-phenoxyphenyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate:

To a solution of tert-butyl 3-(5-amino-4-cyano-3-(4-phenoxyphenyl)-1H-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 H₂O₂ (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 Na₂SO₄. 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 acetate = 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:

![Chemical structure](attachment:structure.png)

[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 NaHCO₃ 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 Na₂SO₄. The resulting product is concentrated and purified by Pre-TLC (eluted with dichloromethane/MeOH/NH₃·H₂O=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)-1H-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 Na₂SO₄. 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)-1H-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)-1H-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.
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-α inhibitor, a PI3K-β inhibitor, and a PI3K-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

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.

In an embodiment, the JAK-2 inhibitor is a compound of Formula (XXIX):

![Formula (XXIX)](attachment)

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

- $A_1^1$ and $A_2^2$ are independently selected from C and N;
- T, U, and V are independently selected from O, S, N, CR$_5^5$, and NR$_6^6$;
- wherein the 5-membered ring formed by $A_1^1$, $A_2^2$, U, T, and V is aromatic;
- X is N or CR$_4^4$;
Y is C$_{1-8}$ alkylene, C$_{2-8}$ alkenylene, C$_{2-8}$ alkynylene, (CR$_{1-8}$)$^p$ —(C$_{3-10}$ cycloalkylene)-
(CR$_{1-8}$)$^q$ —(CR$_{1-8}$)$^p$-(arylene)-(CR$_{1-8}$)$^q$ —(CR$_{1-8}$)$^p$ —(C$_{1-10}$
 heterocycloalkylene)-(CR$_{1-8}$)$^q$ —(CR$_{1-8}$)$^p$-(heteroarylene)-(CR$_{1-8}$)$^q$,
(CR$_{1-8}$)$^p$ —(C$_{1-8}$ —(S(O)OR$^3$) —(CR$_{1-8}$)$^p$ —(C$_{1-8}$
(C(O)NR$^3$) —(CR$_{1-8}$)$^q$ —(CR$_{1-8}$)$^p$ —(C$_{1-8}$
(C(O)OR$^3$) —(CR$_{1-8}$)$^q$ —(CR$_{1-8}$)$^p$ OC(O)NR$^3$ —(CR$_{1-8}$)$^q$,
(CR$_{1-8}$)$^p$ —(O(CR$_{1-8}$)$^q$ —(CR$_{1-8}$)$^q$ —(CR$_{1-8}$)$^q$ —(CR$_{1-8}$)$^p$
(C(O)OR$^3$) —(CR$_{1-8}$)$^q$ —(CR$_{1-8}$)$^p$ OC(O)NR$^3$ —(CR$_{1-8}$)$^q$,
(CR$_{1-8}$)$^p$ —(O(CR$_{1-8}$)$^q$ —(CR$_{1-8}$)$^q$ —(CR$_{1-8}$)$^q$ —(CR$_{1-8}$)$^p$ —(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, $\delta$-C—R$^1$, $\delta$-N—R$^1$, Cy$^1$, CN, NO$_2$, OR$^1$, SR$^1$, C(O)R$^1$,
C(O)NR$^1$, C(O)OR$^1$, OC(O)R$^1$, OC(O)NR$^1$, NR$^1$, NR$^1$, C(O)NR$^1$, NR$^1$
NR$^1$, NR$^1$, OR$^1$, C(O)NR$^1$, NR$^1$, NR$^1$, S(O)R$^1$, S(O)NR$^1$, S(O)NR$^1$, C(\(\delta\)-NOH)R$^1$, C(\(\delta\)-NO)(C$_{1-4}$
alkyl)R$^1$, and
S(O)$_2$NR$^1$R$^1$, 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$_{1-4}$
alcohol, C$_{2-4}$ alkenyl, C$_{2-4}$ alkynyl, C$_{1-4}$ haloalkyl, halosulfanyl, C$_{1-4}$
cyanoalkyl, Cy$^1$, CN, NO$_2$, OR$^1$, SR$^1$, C(O)R$^1$, C(O)NR$^1$, C(O)OR$^1$, OC(O)R$^1$,
OC(O)NR$^1$, NR$^1$, NR$^1$, C(O)NR$^1$, NR$^1$, NR$^1$, C(O)OR$^1$, C(\(\delta\)-NR$^1$)NR$^1$
R$^1$, NR$^1$, C(\(\delta\)-NR$^1$)NR$^1$R$^1$, NR$^1$, S(O)R$^1$, S(O)NR$^1$R$^1$, S(O)$_2$R$^1$, NR$^1$S(O)$_2$R$^1$, C(\(\delta\)-NOH)R$^1$,
C(\(\delta\)-NO)(C$_{1-4}$ alkyl)R$^1$, and S(O)$_2$NR$^1$R$^1$;
wherein when Z is H, n is 1;
the (Y) —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) → Q;
W is C₁₋₈ alkenylenyl, C₂₋₈ alkenylenyl, C₂₋₈ alkylenyl, O, S, C(O), C(O)NR, C(O)O,
OC(O), OC(O)NR, NC(O)NR, S(O), S(O)NR, S(O)₂, or S(O)₂NR;
Q is H, halo, CN, NO₂, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₈ haloalkyl, halosulfanyl,
aryl, cycloalkyl, heteroaryl, or heterocycloalkyl, wherein said C₁₋₈ alkyl, C₂₋₈ alkenyl,
C₂₋₈ alkynyl, C₁₋₈ haloalkyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is
optionally substituted with 1, 2, 3 or 4 substituents independently selected from halo,
C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, halosulfanyl, C₁₋₄ hydroxyalkyl,
C₁₋₄ cyanoalkyl, Cy⁻¹, CN, NO₂, OR, SR, C(O)NR, C(O)OR, OC(O)R, OC(O)NR, C(O)OR, S(O)NR,
S(O)₂NR, S(O)₂R, SR, S(O)₂R, S(O)R, S(O)NR, S(O)₂NR, S(O)₂R, and S(O)₂R;
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, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl,
ahalosulfanyl, C₁₋₄ hydroxyalkyl, C₁₋₄ cyanoalkyl, CN, NO₂, OR, SR, C(O)R,
C(O)NR, C(O)OR, C(O)OR, OC(O)NR, C(O)OR, OC(O)NR, C(O)OR, S(O)NR,
S(O)₂NR, S(O)₂R, S(O)R, S(O)NR, S(O)₂NR, S(O)₂R, and S(O)₂R;
R⁻¹, R⁻², R⁻³, and R⁻⁴ are independently selected from H, halo, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄
alkynyl, C₁₋₄ haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl,
CN, NO₂, OR, SR, C(O)R, C(O)NR, C(O)OR, OC(O)R, OC(O)NR, C(O)OR, S(O)NR,
S(O)₂NR, S(O)₂R, S(O)R, S(O)NR, S(O)₂NR, S(O)₂R, and S(O)₂R;
R⁻¹ is H, halo, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, halosulfanyl, CN, NO₂,
OR, SR, C(O)R, C(O)NR, C(O)OR, OC(O)R, OC(O)NR, C(O)OR, S(O)NR,
S(O)₂NR, S(O)₂R, S(O)R, S(O)NR, S(O)₂NR, S(O)₂R, S(O)₂R, and S(O)₂R;
R⁻¹ is H, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, OR, C(O)R, C(O)NR,
C(O)OR, S(O)NR, S(O)₂R, or S(O)₂R;
R⁻¹ is H, C₁₋₄ alkyl, C₂₋₄ haloalkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, aryl, cycloalkyl, heteroaryl,
heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl;
R₈ is H, C₁-₆ alkyl, C₁-₆ haloalkyl, C₂-₆ alkenyl, C₂-₆ alkynyl, aryl, cycloalkyl, heteroaryl, 
heterocycloalkyl, arylalkyl, heteroarylokyl, cycloalkylalkyl or heterocycloalkylalkyl;
R⁹ and R¹⁰ are independently selected from H, C₁₋₁₀ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkynyl, C₁₋₆ alkenylcarbonyl, arylcarbonyl, C₁₋₆ alkylsulfonyl, arylsulfonyl, aryl, 
heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylokyl, cycloalkylalkyl 
and heterocycloalkylalkyl;
or R⁹ and R¹⁰ together with the N atom to which they are attached form a 4-, 5-, 6- or 7-
membered heterocycloalkyl group;
R¹¹ and R¹² are independently selected from H and -E¹⁻E²⁻E³⁻E⁴⁻;
D¹ and E¹ are independently absent or independently selected from C₁₋₆ alkylene, C₂₋₆ 
alkenylenec₁₋₆, alkynylene, arylene, cycloalkylene, heteroarylene, and 
heterocycloalkylene, wherein each of the C₁₋₆ alkylene, C₂₋₆ alkenylene, C₂₋₆ 
alkenylene, arylene, cycloalkylene, heteroarylene, and heterocycloalkylene is 
optionally substituted by 1, 2 or 3 substituents independently selected from halo, CN, 
NO₂, N₃, SCN, OH, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ haloxyalkyl, C₁₋₆ alkoxy, C₁₋₆ 
haloalkoxy, amino, C₁₋₆ alkylamino, and C₂₋₈ dialkylamino;
D² and E² are independently absent or independently selected from C₁₋₆ alkylene, C₂₋₆ 
alkenylenec₁₋₆, alkynylene, (C₁₋₆ alkylene)₁-O—(C₁₋₆ alkylene)₂, (C₁₋₆ alkylene)₁-S— 
(C₁₋₆ alkylene)₂, (C₁₋₆ alkylene)₁ —NR³—(C₁₋₆ alkylene)₂, (C₁₋₆ alkylene)₁-CO—(C₁₋₆ 
alkylene)₂, (C₁₋₆ alkylene)₁-COO—(C₁₋₆ alkylene)₂, (C₁₋₆ alkylene)₁-CONR³—(C₁₋₆ 
alkylene)₂, (C₁₋₆ alkylene)₁-SO—(C₁₋₆ alkylene)₂, (C₁₋₆ alkylene)₁-SO₂—(C₁₋₆ 
alkylene)₂, (C₁₋₆ alkylene)₁-SONR³—(C₁₋₆ alkylene)₂, and (C₁₋₆ alkylene)₁- 
NR³CONR³—(C₁₋₆ alkylene)₂, wherein each of the C₁₋₆ alkylene, C₂₋₆ alkenylene, and 
C₂₋₆ alkynylene is optionally substituted by 1, 2 or 3 substituents independently 
selected from halo, CN, NO₂, N₃, SCN, OH, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ 
haloxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, amino, C₁₋₆ alkylamino, and C₂₋₈ 
dialkylamino;
D¹ and E¹ are independently absent or independently selected from C₁₋₆ alkylene, C₂₋₆ 
alkenylenec₁₋₆, alkynylene, arylene, cycloalkylene, heteroarylene, and 
heterocycloalkylene, wherein each of the C₁₋₆ alkylene, C₂₋₆ alkenylene, C₂₋₆ 
alkenylene, arylene, cycloalkylene, heteroarylene, and heterocycloalkylene is
optionally substituted by 1, 2 or 3 substituents independently selected from halo, CN, NO₂, N₃, SCN, OH, C₁₋₆ alkyl, C₂₋₈ alkoxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, amino, C₁₋₆ alkyamino, and C₂₋₈ dialkylamino;

D₄ and E₄ are independently selected from H, halo, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, halosulfanyl, C₁₋₄ hydroxyalkyl, C₁₋₄ cyanoalkyl, Cy¹, CN, NO₂, OR¹, SR¹, C(O)R¹, C(O)NR²R¹, C(O)OR¹, OC(O)R¹, OC(O)NR²R¹, NR²R¹, NR²C(O)R¹b, NR²C(O)NR²R¹b, NR²C(O)OR¹b, C(δ-NR²)NR²R¹, NR²C(δ-NR²)NR²R¹b, S(O)R¹b, S(O)NR²R¹b, S(O)₂ NR²R¹b, where R¹ is C₁₋₄ alkyl, C₂₋₈ alkenyl, or C₂₋₈ alkynyl, is optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₁₋₄ haloalkyl, halosulfanyl, C₁₋₄ hydroxyalkyl, C₁₋₄ cyanoalkyl, Cy¹, CN, NO₂, OR¹, SR¹, C(O)R¹, C(O)NR²R¹, C(O)OR¹, OC(O)R¹, OC(O)NR²R¹, NR²C(O)R¹b, NR²C(O)NR²R¹b, NR²C(O)OR¹b, C(δ-NR²)NR²R¹, NR²C(δ-NR²)NR²R¹b, S(O)R¹b, S(O)NR²R¹b, S(O)₂ NR²R¹b, where said C₁₋₄ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl is optionally substituted with 1, 2, 3, or 4 substituents independently selected from OH, CN, amino, halo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, aryalkyl, heteroaryl, heteroaryalkyl, cycloalkyl and heterocycloalkyl;

R¹ is H, Cy¹, —(C₁₋₆ alkyl)-Cy¹, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkenyl, C₁₋₆ alkynyl, wherein said C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, or C₂₋₆ alkynyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, aryalkyl, heteroaryl, heteroaryalkyl, cycloalkyl and heterocycloalkyl;

R² is H, Cy¹, —(C₁₋₆ alkyl)-Cy¹, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, wherein said C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, or C₂₋₆ alkynyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ haloalkyl, halosulfanyl, aryl, aryalkyl, heteroaryl, heteroaryalkyl, cycloalkyl and heterocycloalkyl;

R⁷ and R⁸ are independently selected from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroaryalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein said C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroaryalkyl, cycloalkylalkyl or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C₁₋₆
alkyl, C\textsubscript{1-6} haloalkyl, halosulfanyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl and heterocycloalkyl;

R\textsuperscript{b9} and R\textsuperscript{b3} are independently selected from H, C\textsubscript{1-6} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein said C\textsubscript{1-6} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{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\textsubscript{1-6} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{1-6} haloalkyl, halosulfanyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl and heterocycloalkyl;

R\textsuperscript{c} and R\textsuperscript{d} are independently selected from H, C\textsubscript{1-6} haloalkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, wherein said C\textsubscript{1-6} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{2-6} alkenyl, or C\textsubscript{2-6} alkynyl, is optionally substituted with 1, 2, or 3 substituents independently selected from Cy\textsuperscript{1}, —(C\textsubscript{1-6} alkyl)-Cy\textsuperscript{1}, OH, CN, amino, halo, C\textsubscript{1-6} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{1-6} haloalkyl, and halosulfanyl; or R\textsuperscript{c} and R\textsuperscript{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\textsuperscript{1}, —(C\textsubscript{1-6} alkyl)-Cy\textsuperscript{1}, OH, CN, amino, halo, C\textsubscript{1-6} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{1-6} haloalkyl, and halosulfanyl;

R\textsuperscript{c8} and R\textsuperscript{d8} are independently selected from H, C\textsubscript{1-10} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein said C\textsubscript{1-10} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{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\textsubscript{1-6} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{1-6} haloalkyl, halosulfanyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl and heterocycloalkyl; or R\textsuperscript{c8} and R\textsuperscript{d8} 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\textsubscript{1-6} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{1-6} haloalkyl, halosulfanyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl and heterocycloalkyl;
heterocycloalkyl;

R₃ and R₄ are independently selected from H, C₁-₁₀ alkyl, C₁-₆ haloalkyl, C₂-₆ alkenyl, C₂-₆ alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein said C₁-₁₀ alkyl, C₁-₆ haloalkyl, C₂-₆ alkenyl, C₂-₆ 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, C₁-₆ alkyl, C₁-₆ haloalkyl, halosulfanyl, C₁-₆ haloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl and heterocycloalkyl;

or R₃ and R₄ 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, C₁-₆ alkyl, C₁-₆ haloalkyl, halosulfanyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl and heterocycloalkyl;

R' is H, CN, NO₂, or C₁-₆ alkyl;
R' and R' are independently selected from H and C₁-₆ alkyl;

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 A₁, A₂, U, T, V, and —(Y)ₙ—Z has the formula:

![Diagram](image-url)
then Y is other than \((\text{CR}^{11} \text{R}^{12})_p \text{C(O)NR}^c (\text{CR}^{11} \text{R}^{12})_q\).

[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 \(-\text{(Y)}_n\)--Z has the formula:

\[
\begin{array}{c}
\text{HN} \\
\end{array}
\]

then \(-\text{(Y)}_n\)--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 \(-\text{(Y)}_n\)--Z has the formula:

\[
\begin{array}{c}
\text{thn Y is other than } (\text{CR}^{11} \text{R}^{12})_p \text{C(O)NR}^c (\text{CR}^{11} \text{R}^{12})_q \text{ or } (\text{CR}^{11} \text{R}^{12})_p \text{C(O)(CR}^{11} \text{R}^{12})_q.\n\end{array}
\]

[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 \(-\text{(Y)}_n\)--Z has the formula:

\[
\begin{array}{c}
\text{then Z is other than CN, halo, or } C_{1-4} \text{ alkyl.}
\end{array}
\]
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 $-\langle Y\rangle_n - Z$ has the formula:

\[
\begin{align*}
\text{or }
\end{align*}
\]

then $Y$ is other than $(CR^{11}R^{12})_p C(O)NR^e(CR^{11}R^{12})_q$ or $(CR^{11}R^{12})_p C(O)(CR^{11}R^{12})_q$.

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 $-\langle Y\rangle_n - Z$ has the formula:

\[
\begin{align*}
\end{align*}
\]

then $Y$ is other than $(CR^{11}R^{12})_p NR^e(CR^{11}R^{12})_q$.

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 $-\langle Y\rangle_n - Z$ has a formula other than:

\[
\begin{align*}
\text{or }
\end{align*}
\]

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\textsubscript{1-4} alkyl, C\textsubscript{2-4} alkenyl, C\textsubscript{2-4} alkynyl, C\textsubscript{1-4} haloalkyl, C\textsubscript{1-4} hydroxyalkyl, C\textsubscript{1-4} cyanoalkyl, Cy\textsuperscript{1}, CN, NO\textsubscript{2}, OR\textsuperscript{b}, SR\textsuperscript{b}, C(O)R\textsuperscript{b}, C(O)NR\textsuperscript{d}R\textsuperscript{b}, C(O)OR\textsuperscript{b}, OC(O)R\textsuperscript{b}, OC(O)NR\textsuperscript{d}R\textsuperscript{b}, NR\textsuperscript{R}R\textsuperscript{b}, NR\textsuperscript{C(O)R}R\textsuperscript{d}, NR\textsuperscript{C(\text{\textdelta NR})}NR\textsuperscript{R}R\textsuperscript{d}, NR\textsuperscript{C(O)NR}R\textsuperscript{d}, S(O)R\textsuperscript{b}, S(O)NR\textsuperscript{R}R\textsuperscript{d}, S(O)\textsubscript{2}R\textsuperscript{b}, NR\textsuperscript{S(O)}R\textsuperscript{b}, and S(O)\textsubscript{2}NR\textsuperscript{R}R\textsuperscript{d};

Q is H, halo, CN, NO\textsubscript{2}, C\textsubscript{1-4} alkyl, C\textsubscript{2-8} alkenyl, C\textsubscript{2-8} alkynyl, C\textsubscript{1-8} haloalkyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl, wherein said C\textsubscript{1-8} alkyl, C\textsubscript{2-8} alkenyl, C\textsubscript{2-8} alkynyl, C\textsubscript{1-8} haloalkyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from halo, C\textsubscript{1-4} alkyl, C\textsubscript{2-4} alkenyl, C\textsubscript{2-4} alkynyl, C\textsubscript{1-4} haloalkyl, C\textsubscript{1-4} hydroxyalkyl, C\textsubscript{1-4} cyanoalkyl, Cy\textsuperscript{1}, CN, NO\textsubscript{2}, OR\textsuperscript{b}, SR\textsuperscript{b}, C(O)R\textsuperscript{b}, C(O)NR\textsuperscript{d}R\textsuperscript{b}, C(O)OR\textsuperscript{b}, OC(O)R\textsuperscript{b}, OC(O)NR\textsuperscript{d}R\textsuperscript{b}, NR\textsuperscript{R}R\textsuperscript{b}, NR\textsuperscript{C(O)R}R\textsuperscript{d}, NR\textsuperscript{C(\text{\textdelta NR})}NR\textsuperscript{R}R\textsuperscript{d}, NR\textsuperscript{C(O)NR}R\textsuperscript{d}, S(O)R\textsuperscript{b}, S(O)NR\textsuperscript{R}R\textsuperscript{d}, S(O)\textsubscript{2}R\textsuperscript{b}, NR\textsuperscript{S(O)}R\textsuperscript{b}, and S(O)\textsubscript{2}NR\textsuperscript{R}R\textsuperscript{d};

Cy\textsuperscript{1} and Cy\textsuperscript{3} 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\textsubscript{1-4} alkyl, C\textsubscript{2-4} alkenyl, C\textsubscript{2-4} alkynyl, C\textsubscript{1-4} haloalkyl, C\textsubscript{1-4} hydroxyalkyl, C\textsubscript{1-4} cyanoalkyl, CN, NO\textsubscript{2}, OR\textsuperscript{b}, SR\textsuperscript{b}, C(O)R\textsuperscript{b}, C(O)NR\textsuperscript{d}R\textsuperscript{b}, C(O)OR\textsuperscript{b}, OC(O)R\textsuperscript{b}, OC(O)NR\textsuperscript{d}R\textsuperscript{b}, NR\textsuperscript{R}R\textsuperscript{b}, NR\textsuperscript{C(O)R}R\textsuperscript{d}, NR\textsuperscript{C(\text{\textdelta NR})}NR\textsuperscript{R}R\textsuperscript{d}, NR\textsuperscript{C(O)NR}R\textsuperscript{d}, S(O)R\textsuperscript{b}, S(O)NR\textsuperscript{R}R\textsuperscript{d}, S(O)\textsubscript{2}R\textsuperscript{b}, and S(O)\textsubscript{2}NR\textsuperscript{R}R\textsuperscript{d};

R\textsuperscript{1}, R\textsuperscript{2}, R\textsuperscript{3}, and R\textsuperscript{4} are independently selected from H, halo, C\textsubscript{1-4} alkyl, C\textsubscript{2-4} alkenyl, C\textsubscript{2-4} alkynyl, C\textsubscript{1-8} haloalkyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO\textsubscript{2}, OR\textsuperscript{b}, SR\textsuperscript{b}, C(O)R\textsuperscript{b}, C(O)NR\textsuperscript{d}R\textsuperscript{b}, C(O)OR\textsuperscript{b}, OC(O)R\textsuperscript{b}, OC(O)NR\textsuperscript{d}R\textsuperscript{b}, NR\textsuperscript{R}R\textsuperscript{b}, NR\textsuperscript{C(O)R}R\textsuperscript{d}, NR\textsuperscript{C(\text{\textdelta NR})}NR\textsuperscript{R}R\textsuperscript{d}, NR\textsuperscript{C(O)NR}R\textsuperscript{d}, S(O)R\textsuperscript{b}, S(O)NR\textsuperscript{R}R\textsuperscript{d}, S(O)\textsubscript{2}R\textsuperscript{b}, and S(O)\textsubscript{2}NR\textsuperscript{R}R\textsuperscript{d};

R\textsuperscript{5} is H, halo, C\textsubscript{1-4} alkyl, C\textsubscript{2-4} alkenyl, C\textsubscript{2-4} alkynyl, C\textsubscript{1-4} haloalkyl, CN, NO\textsubscript{2}, OR\textsuperscript{b}, SR\textsuperscript{b}, C(O)R\textsuperscript{b}, C(O)NR\textsuperscript{d}R\textsuperscript{b}, C(O)OR\textsuperscript{b}, OC(O)R\textsuperscript{b}, OC(O)NR\textsuperscript{d}R\textsuperscript{b}, NR\textsuperscript{R}R\textsuperscript{b}, NR\textsuperscript{C(O)R}R\textsuperscript{d}, NR\textsuperscript{C(\text{\textdelta NR})}NR\textsuperscript{R}R\textsuperscript{d}, NR\textsuperscript{C(O)NR}R\textsuperscript{d}, S(O)R\textsuperscript{b}, S(O)NR\textsuperscript{R}R\textsuperscript{d}, S(O)\textsubscript{2}R\textsuperscript{b}, NR\textsuperscript{S(O)}R\textsuperscript{b}, and S(O)\textsubscript{2}NR\textsuperscript{R}R\textsuperscript{d};

R\textsuperscript{7} is H, C\textsubscript{1-4} alkyl, C\textsubscript{2-4} alkenyl, C\textsubscript{2-4} alkynyl, C\textsubscript{1-4} haloalkyl, OR\textsuperscript{b}, C(O)R\textsuperscript{b}, C(O)NR\textsuperscript{d}R\textsuperscript{b}, C(O)OR\textsuperscript{b}, S(O)R\textsuperscript{b}, S(O)NR\textsuperscript{R}R\textsuperscript{d}, S(O)\textsubscript{2}R\textsuperscript{b}, or S(O)\textsubscript{2}NR\textsuperscript{R}R\textsuperscript{d};

R\textsuperscript{8} is H, C\textsubscript{1-6} alkyl, C\textsubscript{1-4} haloalkyl, C\textsubscript{2-8} alkenyl, C\textsubscript{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl; 

R\textsuperscript{9} is H, C\textsubscript{1-6} alkyl, C\textsubscript{1-4} haloalkyl, C\textsubscript{2-8} alkenyl, C\textsubscript{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl;
heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl; R¹ and R¹⁰ are independently selected from H, C₁₋₁₀ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₂₋₆ alkylcarbonyl, arylcarbonyl, C₁₋₆ alkylsulfonyl, arylsulfonyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl; or R¹ and R¹⁰ together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group;
R¹¹ and R¹² are independently selected from H, halo, OH, CN, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ hydroxyalkyl, C₁₋₄ cyanoalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl;
R¹, R⁹ and R⁸ are independently selected from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein said C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ 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, C₁₋₆ alkyl, C₁₋₆ haloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl and heterocycloalkyl;
R¹, R⁹ and R⁸ are independently selected from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein said C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ 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, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl and heterocycloalkyl;
R¹ and R¹ are independently selected from H, C₁₋₁₀ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein said C₁₋₁₀ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ 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\textsubscript{1-6} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{1-6} haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryalkyl, cycloalkyl or heterocycloalkyl;
or R\textsuperscript{e} and R\textsuperscript{f} 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\textsubscript{1-6} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{1-6} haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryalkyl, cycloalkyl and heterocycloalkyl;
R\textsuperscript{g} and R\textsuperscript{h} are independently selected from H, C\textsubscript{1-10} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroaryalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein said C\textsubscript{1-10} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroaryalkyl, cycloalkylalkyl, heterocycloalkylalkyl or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C\textsubscript{1-6} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{1-6} haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryalkyl, cycloalkyl and heterocycloalkyl;
or R\textsuperscript{i} and R\textsuperscript{j} 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\textsubscript{1-6} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{1-6} haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryalkyl, cycloalkyl and heterocycloalkyl;
R\textsuperscript{k} and R\textsuperscript{l} are independently selected from H, C\textsubscript{1-10} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroaryalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein said C\textsubscript{1-10} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroaryalkyl, cycloalkylalkyl and heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C\textsubscript{1-6} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{1-6} haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryalkyl, cycloalkyl and heterocycloalkyl;
or R\textsuperscript{m} and R\textsuperscript{n} 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\textsubscript{1-6} alkyl, C\textsubscript{1-6} haloalkyl, C\textsubscript{1-6} haloalkyl, aryl, arylalkyl, heteroaryl, heteroaryalkyl, cycloalkyl and heterocycloalkyl.
[00614] In some embodiments, X is N.

[00615] In some embodiments, X is CR\textsubscript{4}.

[00616] In some embodiments, A\textsubscript{1} is C.

[00617] In some embodiments, A\textsubscript{1} is N.

[00618] In some embodiments, A\textsubscript{2} is C.

[00619] In some embodiments, A\textsubscript{2} is N.

[00620] In some embodiments, at least one of A\textsubscript{1}, A\textsubscript{2}, U, T, and V is N.

[00621] In some embodiments, the 5-membered ring formed by A\textsubscript{1}, A\textsubscript{2}, U, T, and V is pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, or oxadiazolyl.

[00622] In some embodiments, the 5-membered ring formed by A\textsubscript{1}, A\textsubscript{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:

![Chemical Structure](image)

c and c₀ 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 A₁, A₂, U, T, and V is:
wherein:
a designates the site of attachment of moiety —(Y)—Z;
b designates the site of attachment to the core moiety.

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 A₁, A₂, U, T, and V is selected from:
wherein:

a designates the site of attachment of moiety —(Y) —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 A₁, A₂, 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 A¹, A², U, T, and V is selected from:
wherein:
a designates the site of attachment of moiety —(Y) —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 C₈ alkenylene, C₈ alkenylene,
(CR¹⁰ R¹₂)ₚ C(O)(CR¹¹ R¹₂)ₚ, (CR¹¹ R¹₂)ₚ C(O)NR(CR¹¹ R¹₂)ₚ, (CR¹¹ R¹₂)ₚ C(O)(CR¹¹ R¹₂)ₚ,
(CR¹¹ R¹₂)ₚ OC(O)(CR¹¹ R¹₂)ₚ, wherein said C₈ alkenylene or C₈ alkenylene, is optionally
substituted with 1, 2, or 3 halo, OH, CN, amino, C₈ dialkylamino, or C₂₈ dialkylamino.

[00631] In some embodiments, n is 1 and Y is C₈ alkenylene, (CR¹¹ R¹₂)ₚ C(O)(CR¹¹ R¹₂)ₚ,
(CR¹¹ R¹₂)ₚ C(O)NR(CR¹¹ R¹₂)ₚ, (CR¹¹ R¹₂)ₚ C(O)(CR¹¹ R¹₂)ₚ, wherein said C₈ alkenylene
is optionally substituted with 1, 2, or 3 halo, OH, CN, amino, C₈ dialkylamino, or C₂₈
dialkylamino.

[00632] In some embodiments, n is 1 and Y is C₈ alkenylene optionally substituted with
1, 2, or 3 halo, OH, CN, amino, C₈ dialkylamino, or C₂₈ dialkylamino.

[00633] In some embodiments, n is 1 and Y is ethylene optionally substituted with 1, 2,
or 3 halo, OH, CN, amino, C₈ dialkylamino, or C₂₈ dialkylamino.

[00634] In some embodiments, n is 1 and Y is (CR¹¹ R¹₂)ₚ C(O)(CR¹¹ R¹₂)
(CR¹¹ R¹₂)ₚ C(O)NR(CR¹¹ R¹₂)ₚ, or (CR¹¹ R¹₂)ₚ C(O)(CR¹¹ R¹₂)ₚ.

[00635] In some embodiments, Y is C₈ alkenylene, C₂₈ alkenylene, C₂₈ alkynylene,
(CR¹¹ R¹₂)ₚ —(C₆₋₁₀ cycloalkylene)-(CR¹¹ R¹₂)ₚ, (CR¹¹ R¹₂)ₚ -(arylene)-(CR¹¹ R¹₂)ₚ,
(CR¹¹ R¹₂)ₚ —(C₁₋₁₀ heterocycloalkylene)-(CR¹¹ R¹₂)ₚ, (CR¹¹ R¹₂)ₚ -(heteroarylene)-
(CR¹¹ R¹₂)ₚ, (CR¹¹ R¹₂)ₚ O(CR¹¹ R¹₂)ₚ, or (CR¹¹ R¹₂)ₚ S(CR¹¹ R¹₂)ₚ, wherein said C₈
alkylene, C₂₈ alkenylene, C₂₈ 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_{i=1} alkylene, C_{2-8} alkenylene, C_{2-8} alkylnylene, (CR^1 R^1_{12} p)—(C_{3-10} cycloalkylene)(CR^1 R^1_{12} q), (CR^1 R^1_{12} p)—(arylene)(CR^1 R^1_{12} q), (CR^1 R^1_{12} p)—(heterocycloalkylene)(CR^1 R^1_{12} q), (CR^1 R^1_{12} p)—(heteroarylene)—(CR^1 R^1_{12} q), wherein said C_{i=1} alkylene, C_{2-8} alkenylene, C_{2-8} alkylnylene, cycloalkylene, aryene, heterocycloalkylene, or heteroarylene, is optionally substituted with 1, 2, or 3 substituents independently selected from D^4.

[00637] In some embodiments, Y is C_{i=1} alkylene, C_{2-8} alkenylene, C_{2-8} alkylnylene, or (CR^1 R^1_{12} p)—(C_{3-10} cycloalkylene)(CR^1 R^1_{12} q), wherein said C_{i=1} alkylene, C_{2-8} alkenylene, C_{2-8} alkylnylene, 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_{i=1} alkylene, C_{2-8} alkenylene, C_{2-8} alkylnylene, or (CR^1 R^1_{12} p)—(C_{3-10} cycloalkylene)(CR^1 R^1_{12} q), wherein said C_{i=1} alkylene, C_{2-8} alkenylene, C_{2-8} alkylnylene, cycloalkylene, is optionally substituted with 1, 2, or 3 substituents independently selected from D^4.

[00639] In some embodiments, Y is C_{i=1} alkylene, C_{2-8} alkenylene, or C_{2-8} alkylnylene, 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_{i=1} 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_{i=1} alkylene optionally substituted with 1, 2, or 3 substituents independently selected from D^4.
(CR\(^{11}\) R\(^{12}\))\(_{p}\) S(O)(CR\(^{11}\) R\(^{12}\))\(_{q}\), (CR\(^{11}\) R\(^{12}\))\(_{p}\) S(O)NR\(^{c}\)(CR\(^{11}\) R\(^{12}\))\(_{q}\), (CR\(^{11}\) R\(^{12}\))\(_{p}\) S(O)\(_{2}\)(CR\(^{11}\) R\(^{12}\))\(_{q}\),
or (CR\(^{11}\) R\(^{12}\))\(_{p}\) S(O)\(_{2}\) NR\(^{c}\)(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,

(\(\text{CR}^{11}\text{R}^{12}\))\(_{p}\) —(C\(_{3-10}\) cycloalkylene)—(\(\text{CR}^{12}\text{R}^{12}\))\(_{q}\), (\(\text{CR}^{11}\text{R}^{12}\))\(_{p}\) —(arylene)—(\(\text{CR}^{21}\text{R}^{12}\))\(_{q}\),

(\(\text{CR}^{11}\text{R}^{12}\))\(_{p}\) —(C\(_{i-10}\) heterocycloalkylene)—(\(\text{CR}^{11}\text{R}^{12}\))\(_{q}\), (\(\text{CR}^{11}\text{R}^{12}\))\(_{p}\) —(heteroarylene) —

(\(\text{CR}^{11}\text{R}^{12}\))\(_{p}\) (\(\text{CR}^{11}\text{R}^{12}\))\(_{p}\) —(O(\(\text{CR}^{11}\text{R}^{12}\))\(_{q}\), (\(\text{CR}^{11}\text{R}^{12}\))\(_{p}\) S(\(\text{CR}^{11}\text{R}^{12}\))\(_{q}\), (\(\text{CR}^{11}\text{R}^{12}\))\(_{p}\) C(O)(\(\text{CR}^{11}\text{R}^{12}\))\(_{q}\),

(\(\text{CR}^{11}\text{R}^{12}\))\(_{p}\) C(O)NR\(^{c}\)(\(\text{CR}^{11}\text{R}^{12}\))\(_{q}\), (\(\text{CR}^{11}\text{R}^{12}\))\(_{p}\) C(O)O(\(\text{CR}^{11}\text{R}^{12}\))\(_{q}\),

(\(\text{CR}^{11}\text{R}^{12}\))\(_{p}\) OC(O)(\(\text{CR}^{11}\text{R}^{12}\))\(_{q}\), (\(\text{CR}^{11}\text{R}^{12}\))\(_{p}\) OC(O)NR\(^{c}\)(\(\text{CR}^{11}\text{R}^{12}\))\(_{q}\), (\(\text{CR}^{11}\text{R}^{12}\))\(_{p}\) NR\(^{c}\)(\(\text{CR}^{11}\text{R}^{12}\))\(_{q}\),

(\(\text{CR}^{11}\text{R}^{12}\))\(_{p}\) NR\(^{c}\)C(O)NR\(^{c}\)(\(\text{CR}^{11}\text{R}^{12}\))\(_{q}\), (\(\text{CR}^{11}\text{R}^{12}\))\(_{p}\) S(\(\text{CR}^{11}\text{R}^{12}\))\(_{q}\), (\(\text{CR}^{11}\text{R}^{12}\))\(_{p}\) S(O)(\(\text{CR}^{11}\text{R}^{12}\))\(_{q}\),

(\(\text{CR}^{11}\text{R}^{12}\))\(_{p}\) S(O)NR\(^{c}\)(\(\text{CR}^{11}\text{R}^{12}\))\(_{q}\), (\(\text{CR}^{11}\text{R}^{12}\))\(_{p}\) S(O)\(_{2}\)(\(\text{CR}^{11}\text{R}^{12}\))\(_{q}\), 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\(^{i}\), CN, NO\(_{2}\), OR\(^{a}\), SR\(^{a}\),

C(O)R\(^{a}\), C(O)NR\(^{d}\), C(O)OR\(^{a}\), OC(O)R\(^{a}\), OC(O)NR\(^{a}\) R\(^{d}\), NR\(^{d}\) R\(^{a}\), NR\(^{d}\) C(O)R\(^{a}\),

NR\(^{d}\) C(O)NR\(^{d}\), NR\(^{d}\) C(O)OR\(^{a}\), C(\(\text{O}\)NR\(^{d}\))NR\(^{d}\) R\(^{d}\), NR\(^{d}\) C(\(\text{O}\)NR\(^{d}\))NR\(^{d}\) R\(^{d}\), S(O)R\(^{b}\),

S(O)NR\(^{d}\) R\(^{b}\), S(O)\(_{2}\) R\(^{b}\), NR\(^{d}\) S(O)\(_{2}\) R\(^{b}\), C(\(\text{O}\)NO(\(\text{C}_{1-8}\) alkyl)R\(^{b}\), and

S(O)\(_{2}\) NR\(^{d}\) R\(^{d}\), 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_4 alkynyl, C_1-4 haloalkyl, halosulfanyl, C_1-4 hydroxyalkyl, C_1-4 cyanoalkyl, Cy^i, CN, NO_2, OR^i, SR^i, C(O)R^i, C(O)NR^iR^d, C(O)OR^i, OC(O)R^i, OC(O)NR^iR^d, NR^iC(O)R^i, NR^iC(O)NR^iR^d, NR^iC(O)OR^i, C(\overline{\partial}NR^i)NR^iR^d, NR^iC(\overline{\partial}NR^i)NR^iR^d, S(O)R^i, S(O)NR^iR^d, S(O)^2R^d, NR^iS(O)^2R^d, C(\overline{\partial}NOH)R^i, C(\overline{\partial}NO(C_4 alkyl))R^i, and S(O)^2NR^iR^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_4 alkynyl, C_1-4 haloalkyl, halosulfanyl, C_1-4 hydroxyalkyl, C_1-4 cyanoalkyl, Cy^i, CN, NO_2, OR^i, SR^i, C(O)R^i, C(O)NR^iR^d, C(O)OR^i, OC(O)R^i, OC(O)NR^iR^d, NR^iC(O)R^i, NR^iC(O)NR^iR^d, NR^iC(O)OR^i, C(\overline{\partial}NR^i)NR^iR^d, NR^iC(\overline{\partial}NR^i)NR^iR^d, S(O)R^i, S(O)NR^iR^d, S(O)^2R^d, NR^iS(O)^2R^d, and S(O)^2NR^iR^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_4 alkynyl, C_1-4 haloalkyl, halosulfanyl, C_1-4 hydroxyalkyl, C_1-4 cyanoalkyl, Cy^i, CN, NO_2, OR^i, SR^i, C(O)R^i, C(O)NR^iR^d, C(O)OR^i, OC(O)R^i, OC(O)NR^iR^d, NR^iC(O)R^i, NR^iC(O)NR^iR^d, NR^iC(O)OR^i, C(\overline{\partial}NR^i)NR^iR^d, NR^iC(\overline{\partial}NR^i)NR^iR^d, S(O)R^i, S(O)NR^iR^d, S(O)^2R^d, NR^iS(O)^2R^d, and S(O)^2NR^iR^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_4 alkynyl, C_1-4 haloalkyl, halosulfanyl, C_1-4 hydroxyalkyl, C_1-4 cyanoalkyl, Cy^i, CN, NO_2, OR^i, SR^i, C(O)R^i, C(O)NR^iR^d, C(O)OR^i, OC(O)R^i, OC(O)NR^iR^d, NR^iC(O)R^i, NR^iC(O)NR^iR^d, NR^iC(O)OR^i, C(\overline{\partial}NR^i)NR^iR^d, NR^iC(\overline{\partial}NR^i)NR^iR^d, S(O)R^i, S(O)NR^iR^d, S(O)^2R^d, NR^iS(O)^2R^d, and S(O)^2NR^iR^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_4 alkynyl, C_1-4 haloalkyl, C_1-4 hydroxyalkyl, C_1-4 cyanoalkyl, Cy^i, CN, NO_2, OR^i, SR^i, C(O)R^i, C(O)NR^iR^d, C(O)OR^i, OC(O)R^i, OC(O)NR^iR^d, NR^iC(O)R^i, NR^iC(O)NR^iR^d, NR^iC(O)OR^i, C(\overline{\partial}NR^i)NR^iR^d, NR^iC(\overline{\partial}NR^i)NR^iR^d, S(O)R^i, S(O)NR^iR^d, S(O)^2R^d, NR^iS(O)^2R^d, and S(O)^2NR^iR^d.
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 alkyl, C alkenyl, C alkynyl, C haloalkyl, halosulfanyl, C hydroxyalkyl, C cyanoalkyl, Cy, CN, NO, OR, SR, C(O)R, C(O)NR, C(O)OR, O(C)R, OC(O)R, OC(O)NR, NR, NR'C(O)R, NR'C(O)NR, NR'C(O)OR, C(6-NR')NR'R, NR'C(6-NR')NR'R, S(O)R, S(O)NR'R, S(O)R, NR'S(O)R, and S(O)NR'R.

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 alkyl, C alkenyl, C alkynyl, C haloalkyl, halosulfanyl, C hydroxyalkyl, C cyanoalkyl, Cy, CN, NO, OR, SR, C(O)R, C(O)NR, C(O)OR, O(C)R, OC(O)R, OC(O)NR, NR, NR'C(O)R, NR'C(O)NR, NR'C(O)OR, C(6-NR')NR'R, NR'C(6-NR')NR'R, S(O)R, S(O)NR'R, S(O)R, NR'S(O)R, and S(O)NR'R.

In some embodiments, Z is phenyl optionally substituted with 1, 2, 3, 4, 5, or 6 substituents selected from halo, C alkyl, C alkenyl, C alkynyl, C haloalkyl, halosulfanyl, C hydroxyalkyl, C cyanoalkyl, Cy, CN, NO, OR, SR, C(O)R, C(O)NR, C(O)OR, O(C)R, OC(O)R, OC(O)NR, NR, NR'C(O)R, NR'C(O)NR, NR'C(O)OR, C(6-NR')NR'R, NR'C(6-NR')NR'R, S(O)R, S(O)NR'R, S(O)R, NR'S(O)R, and S(O)NR'R.

In some embodiments, Z is phenyl optionally substituted with 1, 2, 3, 4, 5, or 6 substituents selected from halo, C alkyl, C alkenyl, C alkynyl, C haloalkyl, C hydroxyalkyl, C cyanoalkyl, Cy, CN, NO, OR, SR, C(O)R, C(O)NR, C(O)OR, O(C)R, OC(O)R, OC(O)NR, NR, NR'C(O)R, NR'C(O)NR, NR'C(O)OR, C(6-NR')NR'R, NR'C(6-NR')NR'R, S(O)R, S(O)NR'R, S(O)R, NR'S(O)R, and S(O)NR'R.

In some embodiments, Z is cycloalkyl or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents selected from halo, C alkyl, C alkenyl, C alkynyl, C haloalkyl, halosulfanyl, C hydroxyalkyl, C cyanoalkyl, Cy, CN, NO, OR, SR, C(O)R, C(O)NR, C(O)OR, O(C)R, OC(O)R, OC(O)NR, NR, NR'C(O)R, NR'C(O)NR, NR'C(O)OR, C(6-NR')NR'R, NR'C(6-NR')NR'R, S(O)R, S(O)NR'R, S(O)R, NR'S(O)R, and S(O)NR'R.
In some embodiments, Z is cycloalkyl or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents selected from halo, C\textsubscript{1-4} alkyl, C\textsubscript{2-4} alkenyl, C\textsubscript{1-4} alkynyl, C\textsubscript{1-4} haloalkyl, C\textsubscript{1-4} hydroxyalkyl, C\textsubscript{1-4} cyanoalkyl, Cy, CN, NO\textsubscript{2}, OR\textsuperscript{a}, SR\textsuperscript{b}, C(O)R\textsuperscript{a}, C(O)NR\textsuperscript{c}R\textsuperscript{d}, C(O)SOR\textsuperscript{b}, NR\textsuperscript{c}C(O)R\textsuperscript{b}, NR\textsuperscript{c}C(O)NR\textsuperscript{d}, S(O)R\textsuperscript{b}, S(O)NR\textsuperscript{c}R\textsuperscript{d}, S(O)\textsubscript{2}R\textsuperscript{b}, and S(O)\textsubscript{2}NR\textsuperscript{d}.

In some embodiments, Z is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl, or cycloalkyl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents selected from halo, C\textsubscript{1-4} alkyl, C\textsubscript{2-4} alkenyl, C\textsubscript{2-4} alkynyl, C\textsubscript{1-4} haloalkyl, halosulfanyl, C\textsubscript{1-4} hydroxyalkyl, C\textsubscript{1-4} cyanoalkyl, Cy, CN, NO\textsubscript{2}, OR\textsuperscript{a}, SR\textsuperscript{b}, C(O)R\textsuperscript{a}, C(O)NR\textsuperscript{c}R\textsuperscript{d}, C(O)OR\textsuperscript{b}, OC(O)R\textsuperscript{b}, OC(O)NR\textsuperscript{d}, NR\textsuperscript{c}C(O)R\textsuperscript{b}, NR\textsuperscript{c}C(O)NR\textsuperscript{d}, S(O)R\textsuperscript{b}, S(O)NR\textsuperscript{c}R\textsuperscript{d}, S(O)\textsubscript{2}R\textsuperscript{b}, NR\textsuperscript{c}S(O)\textsubscript{2}R\textsuperscript{b}, and S(O)\textsubscript{2}NR\textsuperscript{d}.

In some embodiments, Z is C\textsubscript{1-8} alkyl, C\textsubscript{2-8} alkenyl, or C\textsubscript{2-8} alkynyl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents selected from halo, C\textsubscript{1-4} alkyl, C\textsubscript{2-4} alkenyl, C\textsubscript{2-4} alkynyl, C\textsubscript{1-4} haloalkyl, halosulfanyl, C\textsubscript{1-4} hydroxyalkyl, C\textsubscript{1-4} cyanoalkyl, Cy, CN, NO\textsubscript{2}, OR\textsuperscript{a}, SR\textsuperscript{b}, C(O)R\textsuperscript{a}, C(O)NR\textsuperscript{c}R\textsuperscript{d}, C(O)OR\textsuperscript{b}, OC(O)R\textsuperscript{b}, OC(O)NR\textsuperscript{d}, NR\textsuperscript{c}C(O)R\textsuperscript{b}, NR\textsuperscript{c}C(O)NR\textsuperscript{d}, NR\textsuperscript{c}C(O)OR\textsuperscript{b}, NR\textsuperscript{c}C(O)NR\textsuperscript{d}, NR\textsuperscript{c}C(O)NR\textsuperscript{d}, S(O)R\textsuperscript{b}, S(O)NR\textsuperscript{c}R\textsuperscript{d}, S(O)\textsubscript{2}R\textsuperscript{b}, NR\textsuperscript{c}S(O)\textsubscript{2}R\textsuperscript{b}, and S(O)\textsubscript{2}NR\textsuperscript{d}.

In some embodiments, Z is ary1, cycloalkyl, heteroaryl, or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, C\textsubscript{1-4} alkyl, C\textsubscript{2-4} alkenyl, C\textsubscript{2-4} alkynyl, C\textsubscript{1-4} haloalkyl, halosulfanyl, C\textsubscript{1-4} hydroxyalkyl, C\textsubscript{1-4} cyanoalkyl, Cy, CN, NO\textsubscript{2}, OR\textsuperscript{a}, SR\textsuperscript{b}, C(O)R\textsuperscript{a}, C(O)NR\textsuperscript{d}, C(O)OR\textsuperscript{b}, OC(O)R\textsuperscript{b}, OC(O)NR\textsuperscript{d}, NR\textsuperscript{c}C(O)R\textsuperscript{b}, NR\textsuperscript{c}C(O)NR\textsuperscript{d}, NR\textsuperscript{c}C(O)OR\textsuperscript{b}, NR\textsuperscript{c}C(O)NR\textsuperscript{d}, NR\textsuperscript{c}C(O)NR\textsuperscript{d}, S(O)R\textsuperscript{b}, S(O)NR\textsuperscript{c}R\textsuperscript{d}, S(O)\textsubscript{2}R\textsuperscript{b}, NR\textsuperscript{c}S(O)\textsubscript{2}R\textsuperscript{b}, and S(O)\textsubscript{2}NR\textsuperscript{d}.

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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<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>1-4</sub> haloalkyl, C<sub>1-4</sub> hydroxyalkyl, C<sub>1-4</sub> cyanoalkyl, Cy<sup>i</sup>, CN, NO<sub>2</sub>, OR<sup>i</sup>, SR<sup>i</sup>, C(O)R<sup>i</sup>, C(O)NR<sup>i</sup>R<sup>j</sup>, C(O)OR<sup>i</sup>, OC(O)R<sup>i</sup>, OC(O)NR<sup>i</sup>R<sup>j</sup>, NR<sup>i</sup>C(O)R<sup>i</sup>, NR<sup>i</sup> C(O)NR<sup>i</sup>R<sup>j</sup>, NR<sup>i</sup>C(O)OR<sup>i</sup>, S(O)R<sup>i</sup>, S(O)NR<sup>i</sup>R<sup>j</sup>, S(O)<sub>2</sub>R<sup>i</sup>, NR<sup>i</sup>S(O)<sub>2</sub>R<sup>i</sup>, and S(O)<sub>2</sub>NR<sup>i</sup>R<sup>j</sup>.

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<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>1-4</sub> haloalkyl, halosulfanyl, C<sub>1-4</sub> hydroxyalkyl, C<sub>1-4</sub> cyanoalkyl, Cy<sup>i</sup>, CN, NO<sub>2</sub>, OR<sup>i</sup>, SR<sup>i</sup>, C(O)R<sup>i</sup>, C(O)NR<sup>i</sup>R<sup>j</sup>, C(O)OR<sup>i</sup>, OC(O)R<sup>i</sup>, OC(O)NR<sup>i</sup>R<sup>j</sup>, NR<sup>i</sup>C(O)R<sup>i</sup>, NR<sup>i</sup> C(O)NR<sup>i</sup>R<sup>j</sup>, NR<sup>i</sup>C(O)OR<sup>i</sup>, S(O)R<sup>i</sup>, S(O)NR<sup>i</sup>R<sup>j</sup>, S(O)<sub>2</sub>R<sup>i</sup>, NR<sup>i</sup>S(O)<sub>2</sub>R<sup>i</sup>, and S(O)<sub>2</sub>NR<sup>i</sup>R<sup>j</sup>.

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<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>1-4</sub> haloalkyl, C<sub>1-4</sub> hydroxyalkyl, C<sub>1-4</sub> cyanoalkyl, Cy<sup>i</sup>, CN, NO<sub>2</sub>, OR<sup>i</sup>, SR<sup>i</sup>, C(O)R<sup>i</sup>, C(O)NR<sup>i</sup>R<sup>j</sup>, C(O)OR<sup>i</sup>, OC(O)R<sup>i</sup>, OC(O)NR<sup>i</sup>R<sup>j</sup>, NR<sup>i</sup>C(O)R<sup>i</sup>, NR<sup>i</sup> C(O)NR<sup>i</sup>R<sup>j</sup>, NR<sup>i</sup>C(O)OR<sup>i</sup>, S(O)R<sup>i</sup>, S(O)NR<sup>i</sup>R<sup>j</sup>, S(O)<sub>2</sub>R<sup>i</sup>, NR<sup>i</sup>S(O)<sub>2</sub>R<sup>i</sup>, and S(O)<sub>2</sub>NR<sup>i</sup>R<sup>j</sup>.

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<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>1-4</sub> haloalkyl, halosulfanyl, C<sub>1-4</sub> hydroxyalkyl, C<sub>1-4</sub> cyanoalkyl, Cy<sup>i</sup>, CN, NO<sub>2</sub>, OR<sup>i</sup>, SR<sup>i</sup>, C(O)R<sup>i</sup>, C(O)NR<sup>i</sup>R<sup>j</sup>, C(O)OR<sup>i</sup>, OC(O)R<sup>i</sup>, OC(O)NR<sup>i</sup>R<sup>j</sup>, NR<sup>i</sup>C(O)R<sup>i</sup>, NR<sup>i</sup> C(O)NR<sup>i</sup>R<sup>j</sup>, NR<sup>i</sup>C(O)OR<sup>i</sup>, S(O)R<sup>i</sup>, S(O)NR<sup>i</sup>R<sup>j</sup>, S(O)<sub>2</sub>R<sup>i</sup>, NR<sup>i</sup>S(O)<sub>2</sub>R<sup>i</sup>, and S(O)<sub>2</sub>NR<sup>i</sup>R<sup>j</sup>.

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<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl, C<sub>1-4</sub> haloalkyl, C<sub>1-4</sub> hydroxyalkyl, C<sub>1-4</sub> cyanoalkyl, Cy<sup>i</sup>, CN, NO<sub>2</sub>, OR<sup>i</sup>, SR<sup>i</sup>, C(O)R<sup>i</sup>, C(O)NR<sup>i</sup>R<sup>j</sup>, C(O)OR<sup>i</sup>, OC(O)R<sup>i</sup>, OC(O)NR<sup>i</sup>R<sup>j</sup>, NR<sup>i</sup>C(O)R<sup>i</sup>, NR<sup>i</sup> C(O)NR<sup>i</sup>R<sup>j</sup>, NR<sup>i</sup>C(O)OR<sup>i</sup>, S(O)R<sup>i</sup>, S(O)NR<sup>i</sup>R<sup>j</sup>, S(O)<sub>2</sub>R<sup>i</sup>, NR<sup>i</sup>S(O)<sub>2</sub>R<sup>i</sup>, and S(O)<sub>2</sub>NR<sup>i</sup>R<sup>j</sup>.  

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In some embodiments, Z is phenyl optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, C1-4 alkyl, C2-4 alkenyl, C2-4 alkynyl, C1-4 haloalkyl, halosulfanyl, C1-4 hydroxyalkyl, C1-4 cyanoalkyl, Cy1, CN, NO2, ORa, SRa, C(O)Ra, C(O)NRcRd, C(O)ORa, OC(O)Rb, OC(O)NRcRd, NRcC(O)Rb, NRcC(O)NRcRd, NRcC(O)ORc, S(O)Rc, S(O)NRcRd, S(O)2Rb, NRcS(O)2Rc, and S(O)2NRcRd.

In some embodiments, Z is phenyl optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, C1-4 alkyl, C2-4 alkenyl, C2-4 alkynyl, C1-4 haloalkyl, C1-4 hydroxyalkyl, C1-4 cyanoalkyl, Cy1, CN, NO2, ORa, SRa, C(O)Ra, C(O)NRcRd, C(O)ORa, OC(O)Rb, OC(O)NRcRd, NRcC(O)Rb, NRcC(O)NRcRd, NRcC(O)ORc, S(O)Rc, S(O)NRcRd, S(O)2Rb, NRcS(O)2Rc, and S(O)2NRcRd.

In some embodiments, Z is cycloalkyl or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, C1-4 alkyl, C2-4 alkenyl, C2-4 alkynyl, C1-4 haloalkyl, halosulfanyl, C1-4 hydroxyalkyl, C1-4 cyanoalkyl, Cy1, CN, NO2, ORa, SRa, C(O)Ra, C(O)NRcRd, C(O)ORa, OC(O)Rb, OC(O)NRcRd, NRcC(O)Rb, NRcC(O)NRcRd, NRcC(O)ORc, S(O)Rc, S(O)NRcRd, S(O)2Rb, NRcS(O)2Rc, and S(O)2NRcRd.

In some embodiments, Z is cycloalkyl or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, C1-4 alkyl, C2-4 alkenyl, C2-4 alkynyl, C1-4 haloalkyl, C1-4 hydroxyalkyl, C1-4 cyanoalkyl, Cy1, CN, NO2, ORa, SRa, C(O)Ra, C(O)NRcRd, C(O)ORa, OC(O)Rb, OC(O)NRcRd, NRcC(O)Rb, NRcC(O)NRcRd, NRcC(O)ORc, S(O)Rc, S(O)NRcRd, S(O)2Rb, NRcS(O)2Rc, and S(O)2NRcRd.

In some embodiments, Z is C1-8 alkyl, C2-8 alkenyl, or C2-8 alkynyl, each optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, C1-4 alkyl, C2-4 alkenyl, C2-4 alkynyl, C1-4 haloalkyl, halosulfanyl, C1-4 hydroxyalkyl, C1-4 cyanoalkyl, Cy1, CN, NO2, ORa, SRa, C(O)Ra, C(O)NRcRd, C(O)ORa, OC(O)Rb, OC(O)NRcRd, NRcC(O)Rb, NRcC(O)NRcRd, NRcC(O)ORc, S(O)Rc, S(O)NRcRd, S(O)2Rb, NRcS(O)2Rc, and S(O)2NRcRd.
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^i, CN, NO_2, OR^a, SR^b, C(O)NR^c, C(O)OR^d, OC(O)NR^e, NR^f C(O)R^g, S(O)R^h, S(O)NR^i R^j, S(O)_2 R^k, NR^l S(O)_2 R^m, and S(O)_2 NR^n R^o.

In some embodiments, Z is C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, ary1, 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, halosulfany1, C_{1-4} hydroxyalkyl, C_{1-4} cyanoalkyl, Cy^i, CN, NO_2, OR^a, C(O)NR^c R^d, C(O)OR^d, NR^f R^g, NR^f C(O)R^h, and S(O)_2 R^k.

In some embodiments, Z is C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, ary1, cycloalkyl, heteroaryl, or heterocycloalkyl, each optionally substituted with 1, 2, 3, 4, 5, or 3 substituents independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, halosulfany1, C_{1-4} hydroxyalkyl, C_{1-4} cyanoalkyl, Cy^i, CN, NO_2, OR^a, C(O)NR^c R^d, C(O)OR^d, NR^f R^g, NR^f C(O)R^h, and S(O)_2 R^k.

In some embodiments, Z is C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, ary1, 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, halosulfany1, C_{1-4} hydroxyalkyl, C_{1-4} cyanoalkyl, Cy^i, CN, NO_2, OR^a, C(O)NR^c R^d, C(O)OR^d, NR^f R^g, NR^f C(O)R^h, and S(O)_2 R^k.

In some embodiments, Z is substituted with at least one substituent comprising at least one CN group.
[00681] In some embodiments, Z is C<sub>1-8</sub> alkyl, C<sub>2-8</sub> alkenyl, C<sub>2-8</sub> alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl, each substituted with at least one CN or C<sub>1-4</sub> cyanoalkyl and optionally substituted with 1, 2, 3, 4, or 5 further substituents selected from halo, C<sub>1-4</sub> alkyl, C<sub>2-8</sub> alkenyl, C<sub>2-8</sub> alkynyl, C<sub>1-4</sub> haloalkyl, halosulfanyl, C<sub>1-4</sub> hydroxalkyl, C<sub>1-4</sub> cyanoalkyl, Cy<sup>i</sup>, CN, NO<sub>2</sub>, OR<sup>i</sup>, SR<sup>i</sup>, C(O)R<sup>b</sup>, C(O)OR<sup>i</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>d</sup>, NR<sup>d</sup>R<sup>d</sup>, NR<sup>d</sup>C(O)R<sup>b</sup>, NR<sup>d</sup>C(O)NR<sup>d</sup>R<sup>d</sup>, NR<sup>d</sup>C(O)OR<sup>i</sup>, S(O)R<sup>b</sup>, S(O)NR<sup>d</sup>R<sup>d</sup>, S(O)<sub>2</sub>R<sup>b</sup>, NR<sup>d</sup>S(O)<sub>2</sub>R<sup>b</sup>, and S(O)<sub>2</sub>NR<sup>d</sup>R<sup>d</sup>.  

[00682] In some embodiments, Z is C<sub>1-8</sub> alkyl, C<sub>2-8</sub> alkenyl, C<sub>2-8</sub> alkynyl, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl, each substituted with at least one CN or C<sub>1-4</sub> cyanoalkyl and optionally substituted with 1, 2, 3, 4, or 5 further substituents selected from halo, C<sub>1-4</sub> alkyl, C<sub>2-8</sub> alkenyl, C<sub>2-8</sub> alkynyl, C<sub>1-4</sub> haloalkyl, C<sub>1-4</sub> hydroxalkyl, C<sub>1-4</sub> cyanoalkyl, Cy<sup>i</sup>, CN, NO<sub>2</sub>, OR<sup>i</sup>, SR<sup>i</sup>, C(O)R<sup>b</sup>, C(O)OR<sup>i</sup>, OC(O)R<sup>b</sup>, OC(O)NR<sup>d</sup>, NR<sup>d</sup>R<sup>d</sup>, NR<sup>d</sup>C(O)R<sup>b</sup>, NR<sup>d</sup>C(O)NR<sup>d</sup>R<sup>d</sup>, NR<sup>d</sup>C(O)OR<sup>i</sup>, S(O)R<sup>b</sup>, S(O)NR<sup>d</sup>R<sup>d</sup>, S(O)<sub>2</sub>R<sup>b</sup>, NR<sup>d</sup>S(O)<sub>2</sub>R<sup>b</sup>, and S(O)<sub>2</sub>NR<sup>d</sup>R<sup>d</sup>.  

[00683] In some embodiments, wherein the —(Y)<sub>n</sub>—Z moiety is taken together with i) A<sup>i</sup> to which said moiety is attached, ii) R<sup>i</sup> or R<sup>b</sup> of either T or V, and iii) the C or N atom to which said R<sup>i</sup> or R<sup>b</sup> 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<sup>i</sup>, A<sup>j</sup>, 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)<sub>m</sub>—Q.  

[00684] In some embodiments, wherein the —(Y)<sub>n</sub>—Z moiety is taken together with i) A<sup>i</sup> to which said moiety is attached, ii) R<sup>i</sup> or R<sup>b</sup> of either T or V, and iii) the C or N atom to which said R<sup>i</sup> or R<sup>b</sup> 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<sup>i</sup>, A<sup>j</sup>, 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)<sub>m</sub>—Q.  

[00685] In some embodiments, the —(Y)<sub>n</sub>—Z moiety is taken together with i) A<sup>i</sup> to which said moiety is attached, ii) R<sup>i</sup> or R<sup>b</sup> of either T or V, and iii) the C or N atom to
which said R₁ or R₂ 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 A¹, A², 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, NO₂, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, ary1, cycloalkyl, heteroaryl, or heterocycloalkyl wherein said C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, ary1, cycloalkyl, heteroaryl, or heterocycloalkyl is optionally substituted by 1, 2 or 3 CN.

[00686] In some embodiments, Cy¹ and Cy² are independently selected from aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, each optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from halo, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, CN, NO₂, OR³, SR³, C(O)R³, C(O)NR³R⁴, C(O)OR³, OC(O)R³, OC(O)NR³R⁴, NR³R⁴, NR³C(O)R³, NR³C(O)OR³, S(O)R³, S(O)NR³R⁴, S(O)₂R³, and S(O)₂NR³R⁴.

[00687] In some embodiments, Cy¹ and Cy² are independently selected from aryl, heteroaryl, cycloalkyl, and heterocycloalkyl, each optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from halo, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, CN, NO₂, OR³, SR³, C(O)R³, C(O)NR³R⁴, C(O)OR³, OC(O)R³, OC(O)NR³R⁴, NR³R⁴, NR³C(O)R³, NR³C(O)OR³, S(O)R³, S(O)NR³R⁴, S(O)₂R³, and S(O)₂NR³R⁴.

[00688] In some embodiments, Cy¹ and Cy² are independently selected from cycloalkyl and heterocycloalkyl, each optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from halo, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, CN, NO₂, OR³, SR³, C(O)R³, C(O)NR³R⁴, C(O)OR³, OC(O)R³, OC(O)NR³R⁴, NR³R⁴, NR³C(O)R³, NR³C(O)OR³, S(O)R³, S(O)NR³R⁴, S(O)₂R³, and S(O)₂NR³R⁴.

[00689] In some embodiments, Cy¹ and Cy² are independently selected from cycloalkyl optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from halo, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, CN, NO₂, OR³, SR³, C(O)R³, C(O)NR³R⁴, C(O)OR³, OC(O)R³, OC(O)NR³R⁴, NR³R⁴, NR³C(O)R³, NR³C(O)OR³, S(O)R³, S(O)NR³R⁴, S(O)₂R³, and S(O)₂NR³R⁴.
In some embodiments, R\textsuperscript{1}, R\textsuperscript{2}, R\textsuperscript{3}, and R\textsuperscript{4} are independently selected from H, halo, C\textsubscript{1-4} alkyl, C\textsubscript{2-4} alkenyl, C\textsubscript{2-4} alkynyl, C\textsubscript{1-4} haloalkyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO\textsubscript{2}, OR\textsuperscript{7}, SR\textsuperscript{7}, C(O)R\textsuperscript{5}, C(O)NR\textsuperscript{9} R\textsuperscript{10}, C(O)OR, OC(O)R\textsuperscript{8}, OC(O)NR R\textsuperscript{10}, NR\textsuperscript{9} C(O)R\textsuperscript{8}, NR\textsuperscript{9} C(O)OR\textsuperscript{7}, S(O)R\textsuperscript{8}, S(O)NR\textsuperscript{9} R\textsuperscript{10}, S(O)\textsubscript{2} R\textsuperscript{8}, NR\textsuperscript{9} S(O)\textsubscript{2} R\textsuperscript{8}, and S(O)\textsubscript{2} NR\textsuperscript{9} R\textsuperscript{10}.

In some embodiments, R\textsuperscript{1}, R\textsuperscript{2}, R\textsuperscript{3}, and R\textsuperscript{4} are independently selected from H, halo, and C\textsubscript{1-4} alkyl.

In some embodiments, R\textsuperscript{1} is H, halo, or C\textsubscript{1-4} alkyl.

In some embodiments, R\textsuperscript{5} is H, halo, C\textsubscript{1-4} alkyl, C\textsubscript{2-4} alkenyl, C\textsubscript{2-4} alkynyl, C\textsubscript{1-4} haloalkyl, CN, NO\textsubscript{2}, OR\textsuperscript{7}, SR\textsuperscript{7}, C(O)R\textsuperscript{5}, C(O)NR\textsuperscript{9} R\textsuperscript{10}, C(O)OR, OC(O)R\textsuperscript{8}, OC(O)NR R\textsuperscript{10}, NR\textsuperscript{9} C(O)R\textsuperscript{8}, NR\textsuperscript{9} C(O)OR\textsuperscript{7}, S(O)R\textsuperscript{8}, S(O)NR\textsuperscript{9} R\textsuperscript{10}, S(O)\textsubscript{2} R\textsuperscript{8}, NR\textsuperscript{9} S(O)\textsubscript{2} R\textsuperscript{8}, or S(O)\textsubscript{2} NR\textsuperscript{9} R\textsuperscript{10}.

In some embodiments, R\textsuperscript{5} is H, halo, C\textsubscript{1-4} alkyl, C\textsubscript{1-4} haloalkyl, halosulfanyl, CN, or NR\textsuperscript{9} R\textsuperscript{10}.

In some embodiments, R\textsuperscript{5} is H, halo, C\textsubscript{1-4} alkyl, C\textsubscript{1-4} haloalkyl, CN, or NR\textsuperscript{9} R\textsuperscript{10}.

In some embodiments, R\textsuperscript{6} is H or C\textsubscript{1-4} alkyl.

In some embodiments, R\textsuperscript{6} is H.

In some embodiments, R\textsuperscript{11} and R\textsuperscript{12} are independently selected from H, halo, C\textsubscript{1-4} alkyl, C\textsubscript{2-4} alkenyl, C\textsubscript{2-4} alkynyl, C\textsubscript{1-4} haloalkyl, halosulfanyl, C\textsubscript{1-4} hydroxyalkyl, C\textsubscript{1-4} cyanoalkyl, Cy\textsuperscript{i}, CN, NO\textsubscript{2}, OR\textsuperscript{7}, SR\textsuperscript{7}, C(O)R\textsuperscript{5}, C(O)NR\textsuperscript{9} R\textsuperscript{10}, C(O)OR, OC(O)R\textsuperscript{8}, OC(O)NR R\textsuperscript{10}, NR\textsuperscript{9} C(O)R\textsuperscript{8}, NR\textsuperscript{9} C(O)OR\textsuperscript{7}, NR\textsuperscript{9} C(O)NR\textsuperscript{9} R\textsuperscript{10}, NR\textsuperscript{9} C(O)OR, C(\textdelta\textsuperscript{-}NR\textsuperscript{9}) R\textsuperscript{9}, NR\textsuperscript{9} C(\textdelta\textsuperscript{-}NR\textsuperscript{9}) R\textsuperscript{10}, S(O)R\textsuperscript{8}, S(O)NR R\textsuperscript{10}, S(O)\textsubscript{2} R\textsuperscript{8}, NR\textsuperscript{9} S(O)\textsubscript{2} R\textsuperscript{8}, C(\textdelta\textsuperscript{-}NOH)R\textsuperscript{9}, C(\textdelta\textsuperscript{-}NO(C\textsubscript{1-4} alkyl)R\textsuperscript{9}), and S(O)\textsubscript{2} NR\textsuperscript{9} R\textsuperscript{8}, wherein said C\textsubscript{1-4} alkyl, C\textsubscript{2-8} alkynyl, or C\textsubscript{2-8} alkynyl, is optionally substituted with 1, 2, 3, 4, 5, or 6 substituents independently selected from halo, C\textsubscript{1-4} alkyl, C\textsubscript{2-4} alkenyl, C\textsubscript{2-4} alkynyl, C\textsubscript{1-4} haloalkyl, halosulfanyl, C\textsubscript{1-4} hydroxyalkyl, C\textsubscript{1-4} cyanoalkyl, Cy\textsuperscript{i}, CN, NO\textsubscript{2}, OR\textsuperscript{7}, SR\textsuperscript{7}, C(O)R\textsuperscript{5}, C(O)NR\textsuperscript{9} R\textsuperscript{10}, C(O)OR,
OC(O)R^b, OC(O)NR^c R^d, NR^c C(O)R^b, NR^c C(O)NR^d, NR^c C(O)OR^d, C(\ddot{\text{N}}R^c)NR^d, NR^c C(\ddot{\text{N}}R^c)NR^d, S(O)R^b, S(O)NR^d, S(O)_2 R^b, NR^c S(O)_2 R^b, C(\ddot{\text{N}}OH)R^b, C(\ddot{\text{N}}O(C_i \text{alkyl}))R^b, and S(O)_2 NR^d.

[00701] In some embodiments, R^1 and R^2 are independently selected from H, halo, OH, CN, (C_i)alkyl, (C_i)haloalkyl, halosulfanyl, SCN, (C_i)alkenyl, (C_i)alkynyl, (C_i)hydroxyalkyl, (C_i)cyanoalkyl, aryl, heteroaryl, cycloalkyl, and heterocycloalkyl.

[00702] In some embodiments, R^1 and R^2 are independently selected from H, halo, OH, CN, (C_i)alkyl, (C_i)haloalkyl, (C_i)alkenyl, (C_i)alkynyl, (C_i)hydroxyalkyl, (C_i)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-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile. In a preferred embodiment, the JAK-2 inhibitor is the phosphate salt of (R)-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile. In a preferred embodiment, the JAK-2 inhibitor is (3R)-3-cyclopentyl-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)propanenitrile. In a preferred embodiment, the JAK-2 inhibitor is a compound of Formula (XXX):

![Formula (XXX)](image)


[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. (2E)- and (2Z)-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).
Step 2. (3R)- and (3S)-3-Cyclopentyl-3-[4-(7-[2-(trimethylsilyl)ethoxy]methyl-7H-pyrrolo[2,3-d]-pyrimidin-4-yl)-1 H-pyrazol-1-yl]propanenitrile. To a solution of 4-(1H-pyrazol-4-yl)-7-[2-(trimethylsilyl)ethoxy]methyl-7H-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): \(8.85\) (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), \(2.67\) (m, 1H), \(2.03\) (m, 1H), \(1.80\) (m, 7H), \(0.92\) (t, 2H), \(0.06\) (s, 9H); MS(ES): 437 (M+1).

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%). 1H 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 herein. Ruxolitinib may also be used in a salt form. For example, a crystalline phosphoric acid salt of (R)-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-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-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-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 phosphoric acid salt is a 1:1 salt by 1H 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):
wherein:
L is SO₂ or CO;
R¹ is C₁₋₆ alkyl, C₃₋₇ cycloalkyl, phenyl, 5- or 6-membered heteroaryl, indolyl, NR²R³, or OR⁴, wherein said alkyl, cycloalkyl, phenyl, or heteroaryl is optionally substituted with 1, 2, or 3 substituents independently selected from F, CN, and C₁₋₄ alkyl;
R² and R³ are independently selected from H, C₁₋₄ alkyl, and phenyl; and
R⁴ is C₁₋₆ alkyl, phenyl, or benzyl.

In some embodiments, when L is SO₂, then R¹ is other than OR⁴.
In some embodiments, when L is SO₂, then R¹ is C₁₋₆ alkyl, C₃₋₇ cycloalkyl, phenyl, 5- or 6-membered heteroaryl, or NR²R³, wherein said alkyl, cycloalkyl, phenyl, or heteroaryl is optionally substituted with 1, 2, or 3 substituents independently selected from F and C₁₋₄ alkyl.
In some embodiments, when L is CO, then R¹ is C₃₋₇ cycloalkyl, phenyl, 5- or 6-membered heteroaryl, indolyl, NR²R³, or OR⁴, wherein said cycloalkyl, phenyl, or heteroaryl is optionally substituted with 1, 2, or 3 substituents independently selected from CN and C₁₋₄ alkyl.
In some embodiments, L is SO₂.
In some embodiments, L is CO.
In some embodiments, R¹ 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, R¹ is C₁₋₄ alkyl.
In some embodiments, R¹ is ethyl.
In some embodiments, R¹ is C₅₋₇ cycloalkyl optionally substituted by C₁₋₄ alkyl.
In some embodiments, R¹ is phenyl optionally substituted with F, methyl, or CN.
In some embodiments, R¹ is 5-membered heteroaryl selected from thiienyl, pyrazolyl, pyrrolyl, 1,2,4-oxadiazolyl, and isoxazolyl, each optionally substituted with C₁₋₄ alkyl.
In some embodiments, R¹ is pyridinyl.
In some embodiments, R¹ is NR²R³ or OR⁴.
In some embodiments, L is SO₂ and R¹ is C₁₋₆ 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-(7H-
In an embodiment, the JAK-2 inhibitor is a compound of Formula (XXXII):


[0071] In an embodiment, the JAK-2 inhibitor is a compound of Formula (XXXIII):

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

Q and Z are independently selected from N and CR¹; n is 1, 2 or 3;
R¹ is independently selected from hydrogen, halogen, R², OR², OH, R⁴, OR⁴, CN, CF₃,
(CH₂)ₙN(R₂)₂, NO₂, R₂R', SO₂R', NR₂SO₂R', COR', NR₂COR', CO₂H, CO₂R₂, NR₂COR', R₂CN, R₂CN, R'OHR, R'OR and OR'R; or two R' substituents together with the carbons which they are attached to form an unsaturated 5 or 6 membered heterocyclyl;

R₂ is substituted or unsubstituted C₁₋₄ alkyl or substituted or unsubstituted C₁₋₄ alkenylene where up to 2 carbon atoms can be optionally replaced with CO, NR₁, C0NR₁, S, SO₂ or O;

R₃ is R₂, C₂₋₄ alkenyl or substituted or unsubstituted aryl;

R₄ is NH₂, NHR₂, 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;

R₅ is substituted or unsubstituted C₁₋₄ alkenylene;

R₆-R₁⁰ are independently selected from H, R' CN, halogen, substituted or unsubstituted Cₖ alkyl, OR', CO₂R', N(R')₂, NO₂, CON(R')₂, SO₂N(R')₂, N(SO₂R')₂, substituted or unsubstituted piperazinyl, N(R')SO₂R' and CF₃. R' is absent or substituted or unsubstituted Cₖ alkenylene wherein up to 2 carbon atoms can be optionally replaced with CO, NSO₂R', NR', C0NR', S, SO₂ or O; R² is H or substituted or unsubstituted C₁₋₄ alkyl; and

R¹¹ is selected from H, halogen, substituted or unsubstituted C₁₋₄ alkyl, OR², CO₂R², CN, CON(R')₂ and CF₃, 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):

[00713] In an embodiment, the JAK-2 inhibitor is a compound of 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; 

R₁ 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 heterocyclcyl, 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, —NR₁₀R₁₁, —OR₁, —C(O)R₁, —C(O)OR₁, —C(S)R₁, —C(O)SR₁, —C(S)SR₁, —C(S)OR₁, —C(S)NR₁₀R₁₁, —C(NR₈)OR₁, —C(NR₈)R₁, —C(NR₈)NR₁₀R₁₁, —C(NR₈)SR₁, —OC(O)R₁, —OC(S)OR₁, —OC(Ο)OR₁, —SC(O)OR₁, —SC(NR₈)OR₁, —SC(S)R₁, —SC(S)OR₁, —OC(O)NR₁₀R₁₁, —OC(S)NR₁₀R₁₁, —OC(NR₈)NR₁₀R₁₁, —SC(O)NR₁₀R₁₁, —SC(NR₈)NR₁₀R₁₁, —SC(S)NR₁₀R₁₁, —OC(NR₈)NR₁₀R₁₁, —C(O)NR₁₀R₁₁, —NR₈C(O)R₁, —NR₈C(S)R₁, —NR₈C(O)R₁, —NR₈C(S)OR₁, —NR₈C(O)R₁, —NR₈C(S)OR₁, −NR₈C(NR₈)OR₁, −NR₈C(NR₈)R₁, −NR₈C(NR₈)R₁, —NR₈C(O)OR₁, —OS(O)ₙR₁, —OS(O)ₙRₚ, —OS(O)ₙR₁, —S(O)ₚR₁, —S(O)ₚR₁, —S(O)ₚR₁, —S(O)ₚR₁, —S(O)ₚR₁, —S(O)ₚR₁, —S(O)ₚR₁, —SP(O)(ORₖ)ₛ, or —SP(O)(ORₖ)ₛ; 

R₂ 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 heterocyclcyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, hydroxyalkyl, alkoxyalkyl, a haloalkyl, a heteroalkyl, —C(O)R₁, —(CH₂)ₜₚC(O)OR₁, —C(O)OR₁, —OC(O)R₁, —C(O)NR₁₀R₁₁, —S(O)ₚR₁, —S(O)ₚR₁, or —S(O)ₚR₁; 

R₃ and R₄ are, independently, —H, —OH, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclcyl, 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, -OR, -OC(O)R, -C(O)NR R, -SR, -S(O) R, 
OS(O) R, -S(O) OR, -NR S(O) R, -S(O) NR R, or R and R 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 is -H, -OH, -SH, -NR H, -OR , -SR , -NHR , -O(CH ) OH, 
O(CH ) SH, -O(CH ) NR H, -S(CH ) OH, -S(CH ) SH, -S(CH ) NR H, 
OC(O)NR R, -SC(O)NR R, -NR C(NR S(O) ) R, -OC(O)R, -SC(O)R, 
NR C(O)R, -OC(O)OR, -SC(O)OR, -NR C(OR) R, -OC(O)R, 
SCH C(O)R, -NR CH C(O)R, -OCH C(O)OR, -SCR C(O)OR, 
NR CH C(O)OR, -OCH C(O)NR R, -SCH C(O)NR R, 
NR CH C(O)NR R, -OS(O) R, -SS(O) R, -NR S(O) R, -OS(O) NR R, 
-SS(O) NR R, -NR S(O) NR R, -OS(O) OR, -SS(O) OR, 
NR S(O) OR, -OC(S)R, -SC(S)R, -NR C(S)R, -OC(S)OR, -SC(S)OR, 
-OC(S)NR R, -SC(NR S(O) ) R, -NR C(NR S(O) ) R, -OC(NR S(O) ) OR, 
SC(NR S(O) ) OR, -NR C(NR S(O) ) OR, -OS(O) NR R, -SC(NR S(O) ) NR R, or 
NR C(NR S(O) ) NR R;

R , 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 
heteroaryl, an optionally substituted aralkyl, an optionally 
substituted heteraralkyl, halo, cyano, nitro, guanadino, a haloalkyl, a heteroalkyl, 
-NR R, -OR, -C(O)R, -C(O)OR, -OC(O)R, -C(O)NR R, 
NR C(O)R, -SR, -S(O) R, -OS(O) R, -S(O) OR, -NR S(O) R, or 
S(O) NR R ;

R and R , 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 heterocyclic, an optionally substituted aryl, an optionally substituted heteroaryl, or 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 heterocyclic 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)](image)

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;

$Z_1$ 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$_2$)$_2$OCH$_3$, —CH$_2$C(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$_2$CH$_3$. 
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-1H-indol-5-yl)-2,4-dihydro-3H-1,2,4-triazol-3-one. In a preferred embodiment, the JAK-2 inhibitor is a compound of Formula (XXXVII):

![Formula (XXXVII)](image)


In an embodiment, the JAK-2 inhibitor is a compound of 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 \( \text{CH} \) or \( \text{N} \); \( R_1 \) represents a halogen;

\( R_2 \) represents:

1. \( \text{H} \)
2. \( \text{a halogen} \)
3. \( \text{cyano} \)
4. \( \text{a group represented by the following general formula [2]:} \)

\[
\begin{array}{c}
\ast \\
R^C \quad R^D \quad R^E
\end{array}
\]

(wherein * indicates the binding position; and \( R^C \), \( R^D \) and \( R^E \) are the same or different and each represents (a) \( \text{H} \), or (b) \( \text{alkyl optionally substituted by hydroxy or alkoxy, or alternatively two of } R^C, R^D \) and \( R^E \) are taken together with the adjacent \( C \) to represent a N-containing saturated heterocyclic group and the other one is \( \text{H} \), the saturated heterocyclic group optionally substituted by alkylsulfonyl),

5. \( \text{a group represented by the following general formula [3]:} \)

\[
\begin{array}{c}
\ast \\
R^F \quad R^G
\end{array}
\]

(wherein * has the same meaning as described above; and \( R^F \) and \( R^G \) are the same or different and each represents (a) \( \text{H} \), (b) \( \text{alkyl optionally substituted by one or two groups selected from the group consisting of hydroxy, amino, dialkylamino, a saturated cyclic amino group, alkylcarbonylamino, alkylsulfonylamino, aryl, heteroaryl optionally substituted by alkyl, tetrahydrofuranyl, and carbamoyl, (c) alkylcarbonyl, (d) alkylsulfonyl, (e) carbamoyl, or (f) heteroaryl optionally substituted by alkyl, or} \)
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, alkoxy carbonylamino, alkyl sulfonlamino, and alkyl carbonylamino, (e) cycloalkyl, (f) haloalkyl, (g) alkoxy, (h) oxo, (i) a group represented by the following general formula [4]:

$$\begin{align*}
* & \text{R}^H \\
\text{O} & \\
\text{O} & \text{[4]}
\end{align*}$$

(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]:

$$\begin{align*}
* & \text{N} \\
\text{R}^i & \\
\text{R}^j & \text{[5]}
\end{align*}$$

(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, alkyl carbonyl, or alkyl sulfonyl), (k) a group represented by the following general formula [6]:

$$\begin{align*}
* & \text{R}^K \\
\text{O} & \text{[6]}
\end{align*}$$

(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, alkyl sulfonlamino, 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]:

$$\begin{align*}
* & \text{R}^A \\
\text{O} & \text{[7A]}
\end{align*}$$

or

$$\begin{align*}
* & \text{R}^B \\
\text{O} & \text{[7B]}
\end{align*}$$
(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, monoalkylaminosulfonfyl, or alkylsulfonfyl, 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;
R₁ represents H or hydroxy;
R₂ represents H or alkyl; and
R₅ represents H or alkyl;
(II): X represents —CRᴬ;
Rᴬ represents a group represented by the following general formula [10]:

\[
\begin{aligned}
&\ast \\
&\text{R}^B
\end{aligned}
\]

(wherein * has the same meaning as described above; and Rᴮ 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);
R₁ represents a halogen;
R₂ represents H;
R₃ represents E or hydroxy;
R₄ represents H or alkyl; and
R₅ 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)-N²-(1-(4-fluorophenyl)ethyl)-6-(1-methyl-1H-pyrazol-4-yl)-N⁴-(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):

[00718] In an embodiment, the JAK-2 inhibitor is a compound of Formula (XL):

![Formula (XL)](image)

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\(^1\) 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\(^1\), CF\(_3\), CONR\(^{1}\)R\(^{2}\), NR\(^{1}\)R\(^{2}\), COOR\(^{b}\), SO\(_2\) —(C\(_{1-4}\))alkyl, C(O)R\(^{a}\), cycloalkyl substituted with 0-3 R\(^{a}\), furanyl, tetrahydropyranyl, or pyridinyl;

R\(^2\) is absent, H, C\(_{1-6}\) alkyl substituted with 0-3 R\(^{e}\), 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\(^4\) 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^5 is H or C_{1-6} alkyl;
R^1 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^2 is C_{1-6} alkyl, or azeridinyl, azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl,
piperazinyl, dioxidothiomorpholinyl or tetrahydropyranyl, any of which are
substituted with 0-2 R^1; and
R^3 is H, halo, CN, C_{1-4} alkyl, OH, O—(C_{1-4})alkyl, SO_2—(C_{1-4})alkyl, NH(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.

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<sub>1</sub>.

[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:
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:

![Chemical structure](attachment:image.png)

R^1 is H, halo, CN, C_{1-6} alkyl substituted with 0-3 R^1, 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^2 is H, C_{1-6} alkyl substituted with 0-3 R^2, C_{3-6} cycloalkyl substituted with 0-3 R^2, tetrahydropyran or dioxotetrahydrothiophenyl;
R^3 is H or C_{1-6} alkyl;
R^4 is H, halo, OH, O—(C_{1-4})alkyl, SO_2—(C_{1-4})alkyl or morpholinyl;
R^5 is C_{1-6} alkyl, or azetidinyl, pyrrolidinyl, morpholinyl, piperazinyl or dioxidothiomorpholinyl, any of which are substituted with 0-2 R^5;
R^6 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:

![Chemical structure](attachment:image.png)

R^1 is H, halo, C_{1-6} alkyl substituted with 0-3 R^1, CF_3, CONR^aR^a, COOR^b, C(O)R^d, cycloalkyl substituted with 0-3 R^e or furanyl;
R₂ is H, C₁₋₆ alkyl substituted with 0-3 R', SO₂—(C₁₋₄)alkyl, cycloalkyl substituted with 0-3 R', or tetrahydropropyranyl;
R' is H, or C₁₋₆ alkyl substituted with 0-3 R'';
R'' is H or C₁₋₆ alkyl;
R' is H, halo, CN, OH, O—(C₁₋₄)alkyl, O—(C₁₋₄)alkyl—O—(C₁₋₄)alkyl, NH₂, N(C₁₋₄ alkyl)₂, C(O)N(C₁₋₄ alkyl)₂, SO₂—(C₁₋₄)alkyl, or morpholinyl or piperazinyl, either of which are optionally substituted with 0-1 C₁₋₄ alkyl;
R₃ is C₁₋₆ alkyl, or morpholinyl, piperazinyl or dioxidothiomorpholinyl, any of which are substituted with 0-2 R'; and
R' is H, C₁₋₄ alkyl, CN, OH, NHC(O)—(C₁₋₄)alkyl or morpholinyl.

[00725] In an embodiment, the JAK-2 inhibitor is a compound of Formula (XL), wherein:

R is:

![Chemical structure](image)

R₁ is C₁₋₆ alkyl substituted with 0-3 R'; and
R' is C₁₋₆ 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-1H-pyrazol-3-yl)amino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrrolo[2,3-b]pyridine-7-carboxamide. In a preferred embodiment, the JAK-2 inhibitor is a compound of 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-1H-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):

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)](image)

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

R¹ and R² are independently selected from the group consisting of -T-R³ and -L-Z-R³;
Q is selected from the group consisting of —CR⁶⁻⁻CR⁶⁻⁻ and wherein said —
CR⁶⁻⁻CR⁶⁻⁻ may be a cis or trans double bond or a mixture thereof,
R³ 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-R⁵ or —V-Z-R⁵, and each substitutable ring nitrogen of Ring D is independently substituted by —R⁴;
T is a valence bond or —(C(R⁶⁻⁻))₂-A-;
A is a valence bond or a C₁⁻⁻C₆ alkylidene chain wherein a methylene unit of said C₁⁻⁻ alkylidene chain is optionally replaced by —O—, —S—, —N(R⁴)—, —CO—, —CONH—, —NHCO—, —SO₂—, —SO₂NH—, —NHSO₂—, —CO₂—, —OC(O)—, —OC(O)NH—, or —NHCO₂—;
Z is a C\textsubscript{1-4} alkylidene chain; 
L is selected from the group consisting of —O—, —S—, —SO—, —SO\textsubscript{2}—, —
N(R\textsubscript{6})SO—, —N(R\textsubscript{6})CON(R\textsubscript{4})—, —N(R\textsubscript{6})SO\textsubscript{2}N(R\textsubscript{6})—, —N(R\textsubscript{6})N(R\textsubscript{6})—, —
C(O)N(R\textsubscript{6})—, —OC(O)N(R\textsubscript{6})—, —C(R\textsubscript{6})\textsubscript{2}O—, —C(R\textsubscript{6})\textsubscript{2}O—, —C(R\textsubscript{6})\textsubscript{2}SO—, —C(R\textsubscript{6})\textsubscript{2}SO\textsubscript{2}N(R\textsubscript{4})—, —C(R\textsubscript{6})\textsubscript{2}N(R\textsubscript{6})CON(R\textsubscript{6})—,
C(R\textsubscript{6})\textsubscript{2}N(R\textsubscript{6})CO—, —C(R\textsubscript{6})\textsubscript{2}C(O)O—, —C(R\textsubscript{6})\textsubscript{2}NNN(R\textsubscript{6})—, —C(R\textsubscript{6})\textsubscript{2}N—O—,
C(R\textsubscript{6})\textsubscript{2}N(R\textsubscript{6})N(R\textsubscript{6})—, —C(R\textsubscript{6})\textsubscript{2}N(R\textsubscript{6})SO\textsubscript{2}N(R\textsubscript{6})—, and —C(R\textsubscript{6})\textsubscript{2}N(R\textsubscript{6})CON(R\textsubscript{6})—;
R\textsuperscript{2} and R\textsuperscript{29} are independently selected from the group consisting of —R and -T-W—R\textsuperscript{6}, or 
R\textsuperscript{2} and R\textsuperscript{29} 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\textsuperscript{2} and R\textsuperscript{29} is independently substituted by halo, 
oxo, —CN, —NO\textsubscript{2}, R\textsuperscript{1}, or —V—R\textsuperscript{6}, and each substitutable ring nitrogen of said ring 
formed by R\textsuperscript{2} and R\textsuperscript{29} is independently substituted by —R\textsuperscript{4}; 
R\textsuperscript{3} is selected from the group consisting of —R, -halo, —OR, —C(\textsubscript{6}O)R, —CO\textsubscript{2}R, —
COCOR, —COCH\textsubscript{2}COR, —NO\textsubscript{2}, —CN, —S(O)R, —S(O)R, —SR, —N(R\textsubscript{4})\textsubscript{2}, —
CON(R\textsubscript{4})\textsubscript{2}, —SO\textsubscript{2}N(R\textsubscript{4})\textsubscript{2}, —OC(\textsubscript{6}O)R, —N(R\textsubscript{4})\textsubscript{2}COR, —N(R\textsubscript{4})\textsubscript{2}CO(R\textsubscript{6} \textsubscript{1-6} 
aliphatic), —N(R\textsubscript{4})\textsubscript{2}N(R\textsubscript{4})\textsubscript{2}, —C(\textsubscript{6}O)NNN(R\textsubscript{4})\textsubscript{2}, —C(\textsubscript{6}O)N—OR, —N(R\textsubscript{4})\textsubscript{2}CON(R\textsubscript{4})\textsubscript{2}, —N(R\textsubscript{4})\textsubscript{2}SO\textsubscript{2}N(R\textsubscript{4})\textsubscript{2},
—N(R\textsubscript{4})SO\textsubscript{2}R, and —OC(\textsubscript{6}O)N(R\textsubscript{4})\textsubscript{2};
each R is independently hydrogen or an optionally substituted group selected from the 
group consisting of C\textsubscript{1-6} aliphatic, C\textsubscript{6-10} aryl, a heteroary1 ring having 5-10 ring atoms, 
and a heterocyclyl ring having 5-10 ring atoms;
each R\textsuperscript{4} is independently selected from the group consisting of —R\textsuperscript{7}, —COR\textsuperscript{7}, —
CO\textsubscript{2}(optionally substituted C\textsubscript{1-6} aliphatic), —CON(R\textsubscript{4})\textsubscript{2}, and —SO\textsubscript{2}R\textsubscript{2};
each R\textsuperscript{5} is independently selected from the group consisting of —R, halo, —OR, —
C(\textsubscript{6}O)R, —CO\textsubscript{2}R, —COCOR, —NO\textsubscript{2}, —CN, —S(O)R, —SO\textsubscript{2}R, —SR, —N(R\textsubscript{4})\textsubscript{2}, —
CON(R\textsubscript{4})\textsubscript{2}, —SO\textsubscript{2}N(R\textsubscript{4})\textsubscript{2}, —OC(\textsubscript{6}O)R, —N(R\textsubscript{4})\textsubscript{2}COR, —N(R\textsubscript{4})\textsubscript{2}CO(R\textsubscript{6} \textsubscript{1-6} 
aliphatic), —N(R\textsubscript{4})\textsubscript{2}N(R\textsubscript{4})\textsubscript{2}, —C(\textsubscript{6}O)NNN(R\textsubscript{4})\textsubscript{2}, —C(\textsubscript{6}O)N—OR, —N(R\textsubscript{4})\textsubscript{2}CON(R\textsubscript{4})\textsubscript{2}, —N(R\textsubscript{4})\textsubscript{2}SO\textsubscript{2}N(R\textsubscript{4})\textsubscript{2},
—N(R\textsubscript{4})SO\textsubscript{2}R, and —OC(\textsubscript{6}O)N(R\textsubscript{4})\textsubscript{2};
V is selected from the group consisting of —O—, —S—, —SO—, —SO\textsubscript{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_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)_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_2N(R^6)—, —C(R^6)_2N(R^6)—, —CO—, —CO_2—, —C(R^6)_2OC(O)—, —C(R^6)_2OC(O)N(R^6)—, —C(R^6)_2N(R^6)CO—, —C(R^6)_2N(R^6)C(O)O—, —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 heterocyclic or heteroaryl ring;

each R^{g6} is independently selected from the group consisting of hydrogen and a C_{1-4} aliphatic group, or two R^{g6} on the same carbon atom are taken together to form a 3-8 membered carbocyclic ring;

each R^{g7} 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_{1-4} aliphatic group, or two R^7 on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclic 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-1H-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):
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):

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:
and wherein:

(A) when M is a group D1:
X is selected from O, NH and NCH₃;
A is selected from a bond and a group NR₂ where R₂ is hydrogen or methyl;
E is selected from a bond, CH₂, CH(CN) and C(CH₃)₂;
R₁ 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 SO₂, the heterocyclic group being optionally substituted by (C₁₋₄)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—CH₃, R₃ is selected from chlorine and cyano;
and (b) when X is O, R₃ is CN;
(iv) a group CR₆R₇R₈ wherein R₆ and R₇ are each selected from hydrogen and methyl, and R₈ is selected from hydrogen, methyl, (C₁₋₄)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-isooindol-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-\( IH\)-benzoimidazol-2-yl)-\( IH\)-pyrazol-4-yl]-amide and 2,6-dimethoxy-N-[3-(5-morpholin-4-ylmethyl-\( IH\)-benzoimidazol-2-yl)-\( IH\)-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-tetrahydroprpyranyl 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, CONH\(_2\), 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;

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when E-A is C(CH₃)₂NR₂ or CH₂-NR₂, R₁ is additionally selected from:
(xiii) unsubstituted 2-furyl and 2,6-difluorophenyl; and
when E-A is C(CH₃)₂NR₂, R₁ is additionally selected from:
(xiv) unsubstituted phenyl; and
when E is CH₂, R₁ 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 NR₂ where R₂ is hydrogen or methyl;
E is selected from a bond, CH₂, CH(CN) and C(CH₃)₂;
R₁ is selected from:
(xvi) a 2-substituted 3-furyl group of the formula:

![Diagram](image)

wherein R₄ and R₅ are the same or different and are selected from hydrogen and C₁₋₄ alkyl, or R₄ and R₅ are linked so that NR₄R₅ forms a 5- or 6-membered saturated heterocyclic group optionally containing a second heteroatom or group selected from O, NH, NMe, S or SO₂, 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:

![Diagram](image)

wherein R₄ and R₅ are the same or different and are selected from hydrogen and C₁₋₄ alkyl, or R₄ and R₅ are linked so that NR₄R₅ forms a 5- or 6-membered saturated heterocyclic group optionally containing a second heteroatom or group selected from O, NH, NMe, S or SO₂, 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-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-amide;

(xviii) a group of the formula:

\[
\begin{align*}
\text{R}_9 \text{N} & \text{G} \\
\end{align*}
\]

wherein \( \text{R}_9 \) is hydrogen, methyl, ethyl or isopropyl; \( \text{G} \) is CH, O, S, SO, SO\(_2\) or NH and the group is optionally substituted by one, two or three substituents selected from \( \text{C}_{1-4} \) hydrocarbyl, hydroxy, \( \text{C}_{1-4} \) hydrocarbyloxy, fluorine, amino, mono- and di-\( \text{C}_{1-4} \) alkylamino and wherein the \( \text{C}_{1-4} \) hydrocarbyl and \( \text{C}_{1-4} \) hydrocarbyloxy groups are each optionally substituted by hydroxy, fluorine, amino, mono- or di-\( \text{C}_{1-4} \) alkylamino; and

(xix) a 3,5-disubstituted phenyl group of the formula:

\[
\begin{align*}
\text{X} & \text{N} \text{G} \\
\end{align*}
\]

wherein \( \text{X} \) is selected from O, NH and NCH\(_3\); and

(C) when \( \text{M} \) is a group D1:

and \( \text{X} \) is O; \( \text{A} \) is a group NR\(_2\) where \( \text{R}_2 \) is hydrogen; \( \text{E} \) is a bond; and \( \text{R}_1 \) 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, cyclical, dodecanoate, dodecylsulphuric, ethane-1,2-disulphonic, ethanesulphonic, fumaric, galactaric, gentisic, glucoheptonic, D-glucronic, glucuronnic (e.g. D-glucuronic), glutamic (e.g. L-glutamic), \( \pm \)-oxoglutaric, glycolic, hippuric, hydrochloric, isethionic, isobutyric, lactic (e.g. (+)-L-lactic and (±)-DL-lactic), lactobionic, laurylsulphonic, maleic, malic, (L)-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)-1H-benzo[d]imidazol-2-yl)-1H-pyrazol-4-yl)urea. In a preferred embodiment, the JAK-2 inhibitor is a compound of Formula (XLVI):

![Formula (XLVI)](image)


[00732] In an embodiment, the JAK-2 inhibitor is a compound of Formula (XLVII):

![Formula (XLVII)](image)

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

R¹ and R² 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, cycloalkylheteroalkyl,
heterocycloalkylheteroalkyl, heteroarylheteroalkyl, arylheteroalkyl, hydroxy,
hydroxyalkyl, alkoxy, alkoxyalkyl, alkoxyaryl, alkenyloxy, alkynlyloxy,
cycloalkylkoxy, heterocycloalkyloxy, aryloxy, arylalkyloxy, phenoxy, benzylxyo,
heteroaryloxy, amino, alkylamino, aminoalkyl, acylamino, arylamino, sulfonyleamino,
sulfinylamino, —COOH, —COR³, —COOR³, —CONHR³, —NHCOR³, —
NHCOOR³, —NHCONHR³, alkoxyacarbonyl, alkylaminocarbonyl, sulfonyl,
alkylsulfonyl, alkylsulfinyl, ary1sulfonyl, aminosulfonyl, —SR³,
R³S(O)R⁶ —, R³S(O)R⁶ —, R³C(O)N(R⁷)R⁶ —, R³SO²N(R⁷)R⁶ —, R³C(O)R⁶ —,
R³N(R⁷)SO²R⁶ —, R³N(R⁷)C(O)N(R⁷)R⁶ — and acyl, each of which may be
optionally substituted;
each R³, R⁴, and R⁵ 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 R⁶ is independently selected from the group consisting of a bond, alkyl, alk enyl,
alkenyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl,
cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl and acyl, each of
which may be optionally substituted;
Z is independently selected from the group consisting of a bond, O, S, —N(R⁷) —, —
N(R⁷)C1₂ alkyl-, and —C1₂ alkylN(R⁷) —;
each R³ is independently selected from the group consisting of H, alkyl, alkenyl, alkynyl,
haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylalkyl,
heterocycloalkylalkyl, ary1alkyl, heteroarylalkyl and acyl, each of which may be
optionally substituted;
Ar¹ and Ar² 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:
—X¹ —Y —X²
wherein X¹ is attached to Ar¹ and X² is attached to Ar², and wherein X¹, X² and Y are
selected such that the group L has between 5 and 15 atoms in the normal chain, X', and X'' 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' and R'' 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' is selected from the group consisting of a bond, —N(R')—, and —S—. In one specific embodiment Z' is —N(R')—. In an even more specific embodiment Z' is —N(H)—. 
Ar' and Ar'' 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' and Ar'' is a monocyclic or bicyclic moiety. In certain embodiments each of Ar' and Ar'' are a monocyclic moiety. In certain embodiments Ar' is selected from the group consisting of:

![Chemical structures](image_url)
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, aryalkyl, heteroaryalkyl, aryalkenyl, cycloalkylheteroalkyl, 
heterocycloalkylheteroalkyl, heteroarylheteroalkyl, arylheteroalkyl, hydroxy, 
hydroxyalkyl, alkoxy, alkoxyalkyl, alkoxyaryl, alkenyloxy, alkynloxy, 
cycloalkylalkoxy, heterocycloalkyloxy, arylalkoxy, arylalkyloxy, phenoxy, benzyloxy, 
heteroaryloxy, amino, alkylamino, aminoalkyl, acylamino, acylaminocarbonyl, sulfonylamino, 
sulfinylamino, —COOH, —COR^3, —COOR^3, —CONHR^3, —NHCOR^3, —NHCOOR^3, —NHCONHR^3, 
alkoxy carbonyl, alkylaminocarbonyl, sulfonyl, 
akylsulfonyl, alkylsulfanyl, ary1sulfonyl, arylsulfinyl, aminosulfonyl, —SR^3, 
\( R^4S(O)R^6 \), \( R^4S(O)R^6 \), \( R^4C(O)N(R^5)R^6 \), \( R^4SO_2N(R^5)R^6 \), \( R^4N(R^5)C(O)R^6 \), 
\( R^4N(R^5)SO_2R^6 \), \( R^4N(R^5)C(O)N(R^5)R^6 \) 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 \( Ar^i \) 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 \( Ar^i \) is selected from the group consisting of:

wherein \( R^{10} \) is as defined above.

In certain embodiments \( Ar^i \) 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 $A_r^1$ is selected from the group consisting of:

\[ \text{Chemical structures} \]

In certain embodiments $A_r^1$ is selected from the group consisting of:

\[ \text{Chemical structures} \]
In certain embodiments Ar² is selected from the group consisting of:

wherein V⁵, V⁶, V⁷ and V⁸ 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, alkynlyloxy, cycloalkylkoxo, heterocycloalkyloxy, aryloxy, arylyalkyloxy, phenoxy, benzyloxy, heteroaryloxy, amino, alkylamino, aminoalkyl, acylamino, acylaminocarbonyl, sulfonylamino, sulfenylamino, —COOH, —COR\(^3\), —COOR\(^3\), —CONHR\(^3\), —NHCOR\(^3\), —NHSO\(_2\)R\(^6\), —NR\(^3\)CO\(_2\)R\(^6\), —NR\(^3\)C(O)R\(^6\), —NR\(^3\)SO\(_2\)R\(^6\), —NR\(^3\)C(O)N(R\(^3\))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 $R_1$ is as defined above.
In a further embodiment $Ar_2$ is selected from the group consisting of:
In an embodiment, the JAK-2 inhibitor is a compound of Formula (XLVIII):

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein $R^1, R^2, R^1^{10}, R^1^{11}, X^1, X^2, Y, k$ and $o$ are as defined above.

In an embodiment, the JAK-2 inhibitor is a compound of 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):

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):

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof,
wherein $R_1$, $R_2$, $R_1^{10}$, $R_1^{11}$, $X_1$, $X_2$, $Y$, $q$ and $o$ are as defined above.

[00737] In an embodiment, the JAK-2 inhibitor is a compound of Formula (LII):

![Formula (LII)](image)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein $R_1$, $R_2$, $R_1^{10}$, $R_1^{11}$, $X_1$, $X_2$, $Y$, $q$ and $o$ are as defined above.

[00738] In an embodiment, the JAK-2 inhibitor is a compound of Formula (LIII):

![Formula (LIII)](image)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein $R_1$, $R_2$, $R_1^{10}$, $R_1^{11}$, $X_1$, $X_2$, $Y$, $q$ 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.
In embodiments where the JAK-2 inhibitor is a compound of Formulas (XLVII)-(LIII), X₁ and X₂ are each independently a heteroalkyl group containing at least one oxygen atom in the normal chain. In certain embodiments X₁ is selected from the group consisting of: (a) —O(C₁₋₅)alkyl-, (b) —(C₁₋₅)alkyLO-, and (c) —(C₁₋₅)alkyLO(C₁₋₅)alkyl. In certain embodiments X₁ is selected from the group consisting of: (a) —OCH₂— (b) —CH₂O—, (c) —OCH₂CH₂—, (d) —CH₂CH₂O—, (e) —CH₂OCH₂—, and (f) —CH₂CH₂OCH₂—. In one specific embodiment X₁ is —OCH₂—. In another specific embodiment X₁ is —CH₂O—. In another specific embodiment X₁ is —OCH₂CH₂—. In another specific embodiment X₁ is —CH₂OCH₂—. In another specific embodiment X₁ is —CH₂CH₂OCH₂—. In certain embodiments X₂ is selected from the group consisting of: (a) —O(C₁₋₅)alkyl-, (b) —(C₁₋₅)alkyLO-, and (c) —(C₁₋₅)alkyLO(C₁₋₅)alkyl. In certain embodiments X₂ is selected from the group consisting of: (a) —OCH₂— (b) —CH₂O—, (c) —OCH₂CH₂—, (d) —CH₂CH₂O—, (e) —CH₂OCH₂—, and (f) —CH₂CH₂OCH₂—. In one specific embodiment X₂ is —OCH₂—. In another specific embodiment X₂ is —CH₂O—. In another specific embodiment X₂ is —OCH₂CH₂—. In another specific embodiment X₂ is —CH₂OCH₂—. In another specific embodiment X₂ is —CH₂CH₂OCH₂—.

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-(2-(pyrrolidin-1-yl)ethoxy)-6,11-dioxo-3-aza-2(4,2)-pyrimidina-1,4(1,3)-dibenzenacyclododecaphan-8-ene. In a preferred embodiment, the JAK-2 inhibitor is 14,19-dioxo-5,7,27-triazatetracyclo[19.3.1.1²⁶.₁⁸]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 16(E)-11-[2-(pyrrolidin-1-yl)ethoxy]-14,19-dioxo-5,7,27-triazatetracyclo[19.3.1.1²⁶.₁⁸]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):

[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.
In a preferred embodiment, the JAK-2 inhibitor is \((E)-4'-(2-(pyrrolidin-1-yl)ethoxy)-6,11\)-dioxo-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)](image)

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.

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):
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof,
wherein
R¹ and R² are selected from (i), (ii), (iii), (iv), and (v) as follows:
(i) R¹ and R² together form δO, δS, δNR⁹ or δCR¹⁰R¹¹;
(ii) R¹ and R² are both —OR, or R¹ and R², together with the carbon atom to which they
are attached, form dioxacycloalkyl;
(iii) R¹ is hydrogen or halo; and R² is halo; and
(iv) R¹ 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, —R¹OR, —R¹S(O)R, —R¹NR'R and —C(O)OR; and R² is halo or —OR; and
(v) R¹ is halo, deuto, —OR¹², —NR¹³R¹⁴, or —S(O)R¹⁵; and R² is hydrogen, deuto,
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, —R¹OR, —R¹S(O)R and —R¹NR'R;
R¹ is hydrogen, halo, alkyl, cyano, haloalkyl, cycloalkyl, cycloalkylalkyl, hydroxy or
alkoxy;
R² and R³ are each independently hydrogen or alkyl;
each R⁶ is independently selected from halo, alkyl, alkenyl, alkynyl, haloalkyl,
cycloalkyl, —R¹OR¹⁸, —R¹NR¹⁹R²⁰, and —R¹S(O)R²¹;
each R⁷ is independently halo, alkyl, haloalkyl or —R¹OR;
$R^9$ is hydrogen, alkyl, haloalkyl, hydroxy, alkoxy or amino;
$R^{10}$ is hydrogen or alkyl;
$R^{11}$ is hydrogen, alkyl, haloalkyl or $\text{—C(O)OR}^8$;
$R^{12}$ is selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl,
    heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $\text{—C(O)R}^9$, $\text{—C(O)OR}^{10}$ and $\text{—C(O)NR}^y\text{R}^z$,
    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, $\text{—C(O)R}^9$, $\text{—C(O)OR}^{10}$, $\text{—C(O)NR}^y\text{R}^z$ and $\text{—S(O)}\text{R}^u$,
    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, $\text{—C(O)NR}^y\text{R}^z$ or $\text{—NR}^y\text{R}^z$,
    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($\text{C}_{2,6}$)alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroarylalkyl; wherein $R^{18}$ is optionally substituted with 1 to 3 groups $Q^i$,
    each $Q^i$ independently selected from alkyl, hydroxyl, halo, haloalkyl, alkoxy, aryloxy,
alkoxyalkyl, alkoxycarbonyl, alkoxysulfonyl, hydroxycarbonyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloaryl and amino;

R\textsuperscript{19} and R\textsuperscript{20} are selected as follows:

(i) R\textsuperscript{19} and R\textsuperscript{20} are each independently hydrogen or alkyl; or

(ii) R\textsuperscript{19} and R\textsuperscript{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\textsuperscript{3} is independently alkyene or a direct bond;

R\textsuperscript{7} is hydrogen, alkyl, alkenyl or alkynyl;

R\textsuperscript{8} is independently hydrogen, alkyl, alkenyl, alkynyl or haloalkyl;

R\textsuperscript{7} and R\textsuperscript{8} are selected as follows:

(i) R\textsuperscript{7} and R\textsuperscript{8} are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or haloalkyl;

(ii) R\textsuperscript{7} and R\textsuperscript{8}, 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-1H-pyrazol-3-yl)amino)quinazolin-2-yl)methanol. In a preferred embodiment, the JAK-2 inhibitor is a compound of Formula (LVI):
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of racemic (4-fluorophenyl)(4-((5-methyl-1\textit{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\textit{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 i-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 i-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 x 10 mL). The combined organic layers were washed with brine and dried over MgSO\textsubscript{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%). \textsuperscript{1}H NMR (300 MHz, DMSO-d6) \textit{δ}: 7.45-7.40 (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)\textsuperscript{+}. Step B: To a solution of (4-chloroquinazolin-2-yl)(4-fluoroquinolyl)methanone (84 mg, 0.30 mmol) in DMF (3mL) were added DIEA (0.103 mL, 0.6 mmol) and 5-methyl-1\textit{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\textit{H}-pyrazol-3-ylamino)quinazolin-2-yl)methanone (30 mg, 29%). \textsuperscript{1}H NMR (300 MHz, DMSO-d6) \textit{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)\textsuperscript{+}.

[00747] To a solution of 4-fluorophenyl)(4-(5-methyl-1\textit{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\textsubscript{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-1H-pyrazol-3-yl)amino)quinazolin-2-yl)methanol (18 mg, 30%); \(^1\)H NMR (300 MHz, DMSO-d6) \(\delta\) 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-1H-pyrazol-3-yl)amino)quinazolin-2-yl)methanol hydrochloride (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\(_3\)CN/H\(_2\)O (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-1H-pyrazol-3-yl)amino)quinazolin-2-yl)methanol hydrochloride (100%). \(^1\)H NMR (300 MHz, DMSO-d6) \(\delta\) 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-1H-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-1H-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-1H-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-1H-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-1H-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-1H-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 RuCl₂(S)-DAIPEN].

[00753] The reduction of the achiral ketone (4-fluorophenyl)(4-(5-methyl-1H-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-1H-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, 10,000/1 or 20,000/1. In certain embodiments, the catalyst loading in the reaction is 2000/1 or 4000/1.


[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-1H-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-1H-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-1H-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.
The starting materials used in the synthesis of the compound of Formula (LV) 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-1H-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.

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)](image)

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

wherein

A is azolyl other than pyrazolyl;

R¹ and R² are selected from (i), (ii), (iii), (iv) and (v) as follows:

(i) R¹ and R² together form =O, =S, =NR⁹ or =CR¹⁰R⁸;

(ii) R¹ and R² are both -OR⁸, or R¹ and R², 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, -NR, -S(O) and S(O)₂; and wherein the heterocyclyl contains one to two heteroatoms wherein each heteroatom is independently selected from O, NR²⁴, 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 substituents selected from halo, deuterio, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, cyano, oxo, =0, =N-OR, =NR, =R\times N(R^2)\times, =R\times S(O)\times, =C(O)R, =C(O)OR, -S(O)\times R\times R,$ and $C(O)N(R)\times R$; and
(v) $R^1$ is halo, deuterio, -OR, -NR, or -S(O)R; and $R^2$ is hydrogen, deuterio, alkyl, alkenyl, alkynyl, cycloalkyl or aryl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl and aryl are each optionally substituted with one to four substituents selected from halo, cyano, alkyl, -R\times OR, -R\times S(O)R, and -R\times NR$; $R^1$ is hydrogen, deuterio, halo, alkyl, cyano, haloalkyl, deuterioalkyl, cycloalkyl, cycloalkylalkyl, hydroxy or alkoxy; 
$R^2$ is hydrogen or alkyl; each $R^6$ is independently selected from halo, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, -R\times OR, -R\times S(O)R, and -R\times NR$; each $R^7$ is independently halo, alkyl, haloalkyl or -R\times OR$; 
$R$ is alkyl, alkenyl or alkynyl; 
$R^8$ is hydrogen, alkyl, haloalkyl, hydroxy, alkoxy or amino; 
$R^9$ is hydrogen or alkyl; 
$R^{10}$ is hydrogen, alkyl, haloalkyl or -C(O)OR$; 
$R^{11}$ is selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, -C(O)R, -C(O)OR, -C(O)OR$ and -C(O)NR$R$, 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, -C(O)OR, -C(O)OR$ and -S(O)R,
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, o xo, alkyl, hydroxy, alkoxy, amino and alkylthio; or 
(ii) $R_{13}^1$ and $R_{14}^1$, 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 o xo; $R_{15}^1$ is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, 
heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, -C(O)NR' $R'$ 
or -NR' $R'$, 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, o xo, alkyl, hydroxy, alkoxy, amino and alkylthio; 
$R_{18}^1$ is hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, cycloalkyl, 
cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or 
heteroaralkyl; wherein $R_{18}^1$ is optionally substituted with 1 to 3 groups $Q^1$, each $Q^1$ 
independently selected from alkyl, hydroxyl, halo, o xo, haloalkyl, alkoxy, aryloxy, 
alkoxyalkyl, alkoxycarbonyl, alkoxy sulfon yl, carboxyl, cycloalkyl, heterocyclyl, aryl, 
heteroaryl, haloaryl and amino; 
$R_{19}^1$ and $R_{20}^1$ are selected as follows: 
(i) $R_{19}^1$ and $R_{20}^1$ are each independently hydrogen or alkyl; or 
(ii) $R_{19}^1$ and $R_{20}^1$, 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, o xo, alkyl, haloalkyl, hydroxyl and alkoxy; 
$R_{21}^1$ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl or cycloalkyl; 
each $R_{22}^1$ is independently hydrogen, alkyl, alkenyl, alkynyl, haloalkyl or cycloalkyl; or 
both $R_{22}^1$, together with the nitrogen atom to which they are attached, form a
heterocyclyl optionally substituted with oxo;

R^{33} 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^z is independently hydrogen, alkyl, alkenyl, alkynyl or haloalkyl;

R^i and R^j are selected as follows:

(i) R^y and R^j are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or haloalkyl; or

(ii) R^y and R^j, 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)](image)

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

wherein

A is imidazolyl, oxazolyl, thiazolyl, thiadiazolyl, or triazolyl;

R^1 is hydrogen, alkyl, haloalkyl or cycloalkyl;
each R^6 is independently selected from halo, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, -R^7 OR^18, -R^8 NR^19 R^20, and -R^7 S(O)\_n R^7;
R^7 is halo;
R^18 is hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroaryllalkyl; wherein R^18 is optionally substituted with 1 to 3 groups Q^1, each Q^1 independently selected from alkyl, hydroxyl, halo, haloalkyl, alkoxy, 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, hydroxyl and alkoxy;
each R^8 is independently alkylene or a direct bond;
R^9 is hydrogen, alkyl, alkenyl or alkynyl;
R^8 and R^9 are selected as follows:
(i) R^8 and R^9 are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or haloalkyl; or
(ii) R^8 and R^9, 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 fluoro.

[00764] In a preferred embodiment, the JAK-2 inhibitor of Formula (LV-A) is a compound of Formula (LV-C):

![Formula (LV-C)](image)

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.
In an embodiment, JAK-2 inhibitor of Formula (LV-A) has the structure of 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, deuter, 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; $R^1$ is hydrogen, alkyl or cycloalkyl,
$R^2$ is hydrogen or alkyl;
$R^1$ is halo; and
$n$ is 0-3.

In a preferred embodiment of the JAK-2 inhibitor of Formula (LV-D), $n$ is 0.

In a preferred embodiment, JAK-2 inhibitor of Formula (LV-D) is selected from the group consisting of:
(4-fluorophenyl)(4-((1-methyl-1H-imidazol-4-yl)amino)quinazolin-2-yl)methanol;
(4-((1H-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-1H-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)](image)

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

R' is selected from hydrogen, hydroxy, amino, mercapto, C\textsubscript{1-6} alkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, C\textsubscript{1-6} alkoxy, C\textsubscript{1-6} alkanoyloxy, N—(C\textsubscript{1-6} alkyl)amino, N,N—(C\textsubscript{1-6} alkyl)\textsubscript{2} amino, C\textsubscript{1-6} alkanoylamino, C\textsubscript{1-6} alkylsulphonylamino, 3-5-membered carbocyclyl or 3-5-membered heterocyclyl; wherein R' may be optionally substituted on carbon by one or more R\textsubscript{6}; and wherein if said heterocyclyl contains an —NH moiety that nitrogen may be optionally substituted by a group selected from R'\textsuperscript{2};

R' and R'\textsuperscript{2} are independently selected from hydrogen, halo, nitro, cyan, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C\textsubscript{1-6} alkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, C\textsubscript{1-6} alkoxy, C\textsubscript{1-6} alkanoyl, C\textsubscript{1-6} alkanoyloxy, N—(C\textsubscript{1-6} alkyl)amino, N,N—(C\textsubscript{1-6} alkyl)\textsubscript{2} amino, C\textsubscript{1-6} alkanoylamino, N—(C\textsubscript{1-6} alkyl)carbamoyl, N,N—(C\textsubscript{1-6} alkyl)\textsubscript{2} carbamoyl, C\textsubscript{1-6} alkylS(O)\textsubscript{a} wherein a is 0 to 2, C\textsubscript{1-6} alkoxy carbonyl, N—(C\textsubscript{1-6} alkyl)sulphamoyl, N,N—(C\textsubscript{1-6} alkyl)\textsubscript{2} sulphamoyl, (C\textsubscript{1-6} alkyl)\textsubscript{2} S(O)\textsubscript{2}—NH—, (C\textsubscript{1-6} alkyl)NH—S(O)\textsubscript{2}—NH—, NH\textsubscript{2}—S(O)\textsubscript{2}—NH—, (C\textsubscript{1-6} alkyl)\textsubscript{2} S(O)\textsubscript{2}—N(C\textsubscript{1-6} alkyl)—, (C\textsubscript{1-6} alkyl)\textsubscript{2} S(O)\textsubscript{2}—NH—, NH\textsubscript{2}—S(O)\textsubscript{2}—NH—, (C\textsubscript{1-6} alkyl)\textsubscript{2} S(O)\textsubscript{2}—N(C\textsubscript{1-6} alkyl)\textsubscript{2} —.
alkyl)NH—S(O)₂—N(C₁₋₆ alkyl)-, NH₂—S(O)₂—N(C₁₋₆ alkyl)-, N—(C₁₋₆ alkyl)-N—(C₁₋₆ alkylsulphonyl)amino, C₁₋₆ alkylsulphonylamino, carbocyclyl-R⁽¹⁾ or heterocyclyl-R⁽¹⁾; wherein R₂ and R₃ independently of each other may be optionally substituted on carbon by one or more R⁴; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from R⁵;

R¹ is selected from cyano, carboxy, carbamoyl, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkanoyl, N—(C₁₋₆ alkyl)carbamoyl, N,N—(C₁₋₆ alkyl)carbamoyl, C₁₋₆ alkoxy, C₁₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkanoyloxy, N—(C₁₋₆ alkyl)amino, N,N—(C₁₋₆ alkyl)₂ amino, C₁₋₆ alkanoylamino, N—(C₁₋₆ alkyl)carbamoyl, N,N—(C₁₋₆ alkyl)₂ carbamoyl, C₁₋₆ alkylS(O)₂ wherein a is 0 to 2, C₁₋₆ alkoxy, C₁₋₆ alkenyl, N—(C₁₋₆ alkyl)sulphamoyl, N,N—(C₁₋₆ alkyl)₂ sulphamoyl, C₁₋₆ alkysulphonylamino, carbocyclyl or heterocyclyl; wherein R⁵ may be optionally substituted on carbon by one or more R¹₀; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from R¹₁;

R² is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, C₁₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkanoyloxy, N—(C₁₋₆ alkyl)amino, N,N—(C₁₋₆ alkyl)₂ amino, C₁₋₆ alkanoylamino, N—(C₁₋₆ alkyl)carbamoyl, N,N—(C₁₋₆ alkyl)₂ carbamoyl, C₁₋₆ alkylS(O)₂ wherein a is 0 to 2, C₁₋₆ alkoxy, C₁₋₆ alkenyl, N—(C₁₋₆ alkyl)sulphamoyl, N,N—(C₁₋₆ alkyl)₂ sulphamoyl, C₁₋₆ alkysulphonylamino, carbocyclyl or heterocyclyl; wherein R⁵ may be optionally substituted on carbon by one or more R¹₂; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from R¹₃;

n=0, 1, 2 or 3; wherein the values of R² may be the same or different;

R¹’, R⁸’, R¹₀ and R¹₂ are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, C₁₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkanoyloxy, N—(C₁₋₆ alkyl)amino, N,N—(C₁₋₆ alkyl)₂ amino, C₁₋₆ alkanoylamino, N—(C₁₋₆ alkyl)carbamoyl, N,N—(C₁₋₆ alkyl)₂ carbamoyl, C₁₋₆ alkylS(O)₂ wherein a is 0 to 2, C₁₋₆ alkoxy, C₁₋₆ alkenyl, N—(C₁₋₆ alkyl)sulphamoyl, N,N—(C₁₋₆ alkyl)₂ sulphamoyl, C₁₋₆ alkysulphonylamino, carbocyclyl or heterocyclyl; wherein R⁵’, R⁸’, R¹₀ and R¹₂ independently of each other may be optionally substituted on carbon by one or more R¹₄; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted
by a group selected from R¹⁵;

R², R³, R⁴, R⁶ and R¹⁵ are independently selected from C₁-₆ alkyl, C₁-₆ alkanoyl, C₁-₆ alkenyl, C₁-₆ alkynyl, C₁-₆ alkoxy, C₁-₆ alkylsulphonyl, C₁-₆ alkoxy carbonyl, carbamoyl, N—(C₁-₆ alkyl) carbamoyl, N,N—(C₁-₆ alkyl) carbamoyl, benzyl, benzylxoycarbonyl, benzoyl and phenylsulphonyl;

wherein R², R⁴, R⁶, R⁷ and R¹⁵ independently of each other may be optionally substituted on carbon by on or more R¹⁶;

R¹₄ and R¹₆ are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁-₆ alkyl, C₂-₆ alkenyl, C₂-₆ alkynyl, C₁-₆ alkoxy, C₁-₆ alkanoyloxy, N—(C₁-₆ alkyl) amino, N,N—(C₁-₆ alkyl) amino, C₁-₆ alkanoylamino, N—(C₁-₆ alkyl) carbamoyl, N,N—(C₁-₆ alkyl) carbamoyl, C₁-₆ alkyS(O)ₖ wherein a is 0 to 2, C₁-₆ alkoxy carbonyl, N—(C₁-₆ alkyl) sulphamoyl, N,N—(C₁-₆ alkyl) sulphamoyl, C₁-₆ alkylsulphonylamino, carbocyclyl or heterocyclyl;

wherein R¹⁴ and R¹₆ independently of each other may be optionally substituted on carbon by one or more R¹⁷; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from R¹⁸;

R¹⁷ is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁-₆ alkyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methyl carbamoyl, N-ethyl carbamoyl, N,N-dimethyl carbamoyl, N,N-diethyl carbamoyl, N-methyl-N-ethyl carbamoyl, methylthio, ethylthio, methyl sulphinyl, ethyl sulphinyl, mesyl, ethyl sulphonyl, methoxycarbonyl, ethoxycarbonyl, N-methyl sulphamoyl, N-ethyl sulphamoyl, N,N-diethyl sulphamoyl or N-methyl-N-ethyl sulphamoyl; and

R¹⁹ and R²¹ are independently selected from a direct bond, —O—, —N(R²²)—, —C(O)—, —N(R²³)C(O)—, —C(O)N(R²⁴)—, —S(O)₂—, —SO₂N(R²⁵)— or —N(R²⁶)SO₄—;

wherein R²², R²³, R²⁴, R²⁵ and R²⁶ are independently selected from hydrogen or C₁-₆ alkyl and s is 0-2;

R¹⁸ is selected from C₁-₆ alkyl, C₁-₆ alkanoyl, C₁-₆ alkyloxysulphonyl, C₁-₆ alkoxy carbonyl, carbamoyl, N—(C₁-₆ alkyl) carbamoyl, N,N—(C₁-₆ alkyl) carbamoyl, benzyl, benzyl oxycarbonyl, benzoyl and phenyl sulphonyl;

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.
In an embodiment, the JAK-2 inhibitor is a compound of Formula (LVII),
wherein:
R₁ is selected from hydrogen, hydroxy, amino, mercapto, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, C₁₋₆ alkanoyloxy, N—(C₁₋₆ alkyl)amino, N,N—(C₁₋₆ alkyl) amino, C₁₋₆ alkanoylamino, C₁₋₆ alkylsulphonylamino, 3-5-membered carbocyclyl or 3-5-membered heterocyclyl; wherein R₁ may be optionally substituted on carbon by one or more R₂; and wherein if said heterocyclyl contains a nitrogen that may be optionally substituted by a group selected from R₇;
R₂ and R₃ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, C₁₋₆ alkanoyl, C₁₋₆ alkanoyloxy, N—(C₁₋₆ alkyl)amino, N,N—(C₁₋₆ alkyl) amino, C₁₋₆ alkanoylamino, N—(C₁₋₆ alkyl)carbamoyl, N,N—(C₁₋₆ alkyl)carbamoyl, C₁₋₆ alkylS(O) wherein a is 0 to 2, C₁₋₆ alkoxy carbonyl, N—(C₁₋₆ alkyl)sulphamoyl, N,N—(C₁₋₆ alkyl)sulphamoyl, C₁₋₆ alkylsulphonylamino, carbocyclyl-R¹⁹ — or heterocyclyl-R¹⁹ —; wherein R² and R³ independently of each other may be optionally substituted on carbon by one or more R₅; and wherein if said heterocyclyl contains an nitrogen that may be optionally substituted by a group selected from R₉;
R₄ is selected from cyan, carboxy, carbamoyl, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkanoyl, N—(C₁₋₆ alkyl)carbamoyl, N,N—(C₁₋₆ alkyl)carbamoyl, C₁₋₆ alkoxy carbonyl, carbocyclyl or heterocyclyl; wherein R₄ may be optionally substituted on carbon by one or more R₆; and wherein if said heterocyclyl contains an nitrogen that may be optionally substituted by a group selected from R₁¹;
R₅ is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, C₁₋₆ alkanoyl, C₁₋₆ alkanoyloxy, N—(C₁₋₆ alkyl)amino, N,N—(C₁₋₆ alkyl) amino, C₁₋₆ alkanoylamino, N—(C₁₋₆ alkyl)carbamoyl, N,N—(C₁₋₆ alkyl) carbamoyl, C₁₋₆ alkylS(O) wherein a is 0 to 2, C₁₋₆ alkoxy carbonyl, N—(C₁₋₆ alkyl)sulphamoyl, N,N—(C₁₋₆ alkyl)sulphamoyl, C₁₋₆ alkylsulphonylamino, carbocyclyl or heterocyclyl; wherein R₅ may be optionally substituted on carbon by one or more R₂; and wherein if said heterocyclyl contains an...
—NH— moiety that nitrogen may be optionally substituted by a group selected from $\text{R}^{15}$;

$n=0, 1, 2$ or $3$; wherein the values of $\text{R}^{3}$ may be the same or different;

$\text{R}^{8}, \text{R}^{9}, \text{R}^{10}$ and $\text{R}^{12}$ 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, $N-(C_{1-6} \text{ alkyl})$amino, $N,N-(C_{1-6} \text{ alkyl})$amino, $C_{1-6}$ alkylamino, $C_{1-6}$ alkanoylamino, $N-(C_{1-6} \text{ alkyl})$carbamoyl, $N,N-(C_{1-6} \text{ alkyl})$carbamoyl, $C_{1-6}$ alkylcarbamoyl, $C_{1-6}$ alkylsulphamoyl, wherein a is $0$ to $2$, $C_{1-6}$ alkoxy carbonyl, $N-(C_{1-6} \text{ alkyl})$sulphamoyl, $C_{1-6}$ alkylosulphonylamino, carbocyclyl or heterocyclyl; wherein $\text{R}^{8}, \text{R}^{9}, \text{R}^{10}$ and $\text{R}^{12}$ independently of each other may be optionally substituted on carbon by one or more $\text{R}^{14}$; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from $\text{R}^{15}$;

$\text{R}^{7}, \text{R}^{9}, \text{R}^{11}$, $\text{R}^{13}$ and $\text{R}^{15}$ are independently selected from $C_{1-6}$ alkyl, $C_{1-6}$ alkanoyl, $C_{1-6}$ alkylosulphonyl, $C_{1-6}$ alkoxy carbonyl, carbamoyl, $N-(C_{1-6} \text{ alkyl})$carbamoyl, $N,N-(C_{1-6} \text{ alkyl})$carbamoyl, benzyl, benzoxycarbonyl, benzoyl and phenylsulphonyl; wherein $\text{R}^{7}, \text{R}^{9}, \text{R}^{11}$, $\text{R}^{13}$ and $\text{R}^{15}$ independently of each other may be optionally substituted on carbon by one or more $\text{R}^{16}$;

$\text{R}^{14}$ and $\text{R}^{16}$ 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, $N-(C_{1-6} \text{ alkyl})$amino, $N,N-(C_{1-6} \text{ alkyl})$amino, $C_{1-6}$ alkanoylamino, $N-(C_{1-6} \text{ alkyl})$carbamoyl, $N,N-(C_{1-6} \text{ alkyl})$carbamoyl, $C_{1-6}$ alkylcarbamoyl, $C_{1-6}$ alkylsulphamoyl, wherein a is $0$ to $2$, $C_{1-6}$ alkoxy carbonyl, $N-(C_{1-6} \text{ alkyl})$sulphamoyl, $C_{1-6}$ alkylosulphonylamino, carbocyclyl or heterocyclyl; wherein $\text{R}^{14}$ and $\text{R}^{16}$ independently of each other may be optionally substituted on carbon by one or more $\text{R}^{17}$; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from $\text{R}^{18}$;

$\text{R}^{17}$ 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, $N$-ethylicarbamoyl, $N,N$-...
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'9 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) —, —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 alkyl and s is 0-2;
R' 8 is selected from C 1-6 alkyl, C 1-6 alkanoyl, C 1-6 alkylsulphonyl, C 1-6 alkoxy, carbamoyl, N—(C 1-6 alkyl)carbamoyl, N,N—(C 1-6 alkyl)carbamoyl, benzyl,
benzoxycarbonyl, 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 alkynyl, C 1-6 alkoxy, C 1-6 alkanoyloxy, N—(C 1-6 alkyl)amino, N,N—(C 1-6 alkyl)amino,
C 1-6 alkoxy, C 1-6 alkanoylamino, N—(C 1-6 alkyl)carbamoyl, N,N—(C 1-6 alkyl)carbamoyl, C 1-6 alkyl), carbamoyl, C 1-6 alkylsulphonylamino, 3-5-membered
alkanoylamino, C 1-6 alkanoylamino, C 1-6 alkanoylamino, C 1-6 alkanoylamino, C 1-6 alkanoylamino, C 1-6 alkanoylamino, C 1-6 alkanoylamino, C 1-6 alkanoylamino,
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alkanoyl, N—(C<sub>1-6</sub> alkyl)carbamoyl, N,N—(C<sub>1-6</sub> alkyl)carbamoyl, C<sub>1</sub> alkoxy carbonyl, carbocyclyl or heterocyclyl; wherein R<sup>2</sup> may be optionally substituted on carbon by one or more R<sup>10</sup>; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from R<sup>11</sup>

R<sup>2</sup> is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkanoyl, C<sub>1</sub>

alkanoyloxy, N—(C<sub>1-6</sub> alkyl)amino, N,N—(C<sub>1-6</sub> alkyl)amino, C<sub>1-6</sub> alkanoylamino, N—(C<sub>1-6</sub> alkyl)carbamoyl, N,N—(C<sub>1-6</sub> alkyl)carbamoyl, C<sub>1-6</sub> alkylS(O)<sub>2</sub> wherein a is 0 to 2, C<sub>1-6</sub> alkoxy carbonyl, N—(C<sub>1-6</sub> alkyl)sulphamoyl, N,N—(C<sub>1-6</sub> alkyl)sulphamoyl, C<sub>1-6</sub> alkylsulphonylamino, carbocyclyl or heterocyclyl; wherein R<sup>2</sup> may be optionally substituted on carbon by one or more R<sup>12</sup>; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from R<sup>13</sup>

n=0, 1, 2 or 3; wherein the values of R<sup>2</sup> may be the same or different;

R<sup>6</sup>, R<sup>8</sup>, R<sup>10</sup> and R<sup>12</sup> are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1</sub>

alkoxy, C<sub>1-6</sub> alkanoyl, C<sub>1-6</sub> alkanoyloxy, N—(C<sub>1-6</sub> alkyl)amino, N,N—(C<sub>1-6</sub> alkyl)amino, C<sub>1-6</sub> alkanoylamino, N—(C<sub>1-6</sub> alkyl)carbamoyl, N,N—(C<sub>1-6</sub> alkyl)carbamoyl, C<sub>1-6</sub> alkylS(O)<sub>2</sub> wherein a is 0 to 2, C<sub>1-6</sub> alkoxy carbonyl, N—(C<sub>1-6</sub> alkyl)sulphamoyl, N,N—(C<sub>1-6</sub> alkyl)sulphamoyl, C<sub>1-6</sub> alkylsulphonylamino, carbocyclyl or heterocyclyl; wherein R<sup>6</sup>, R<sup>8</sup>, R<sup>10</sup> and R<sup>12</sup> independently of each other may be optionally substituted on carbon by one or more R<sup>14</sup>; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from R<sup>15</sup>

R<sup>7</sup>, R<sup>9</sup>, R<sup>11</sup>, R<sup>13</sup> and R<sup>15</sup> are independently selected from (C<sub>1-6</sub>) alkyl, (C<sub>1-6</sub>) alkanoyl, (C<sub>1</sub>) alkoxy carbonyl, carbamoyl, N—((C<sub>1-6</sub>) alkyl)carbamoyl, N,N—((C<sub>1-6</sub>) alkyl)carbamoyl, benzyl, benzoxycarbonyl, benzoyl and phenylsulphonyl; wherein R<sup>7</sup>, R<sup>9</sup>, R<sup>11</sup>, R<sup>13</sup> and R<sup>15</sup> independently of each other may be optionally substituted on carbon by one or more R<sup>16</sup>; 

R<sup>14</sup> and R<sup>16</sup> are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy,
carbamoyl, mercapto, sulphamoyl, (C\textsubscript{1-6})alkyl, (C\textsubscript{2-6})alkenyl, (C\textsubscript{2-6})alkynyl, (C\textsubscript{1-6})alkoxy, (C\textsubscript{1-6})alkanoyl, (C\textsubscript{1-6})alkanoyloxy, N—((C\textsubscript{1-6})alkyl)amino, N,N—((C\textsubscript{1-6})alkyl)amino, (C\textsubscript{1-6})alkanoylamino, N—((C\textsubscript{1-6})alkyl)carbamoyl, N,N—((C\textsubscript{1-6})alkyl)carbamoyl, (C\textsubscript{1-6})alkylS(O)\textsubscript{2}, wherein a is 0 to 2, (C\textsubscript{1-6})alkoxycarbonyl, N—((C\textsubscript{1-6})alkyl)sulphamoyl, (C\textsubscript{1-6})alkylsulphonylamino, carbocyclyl or heterocyclyl; wherein R\textsuperscript{12} and R\textsuperscript{16} independently of each other may be optionally substituted on carbon by one or more R\textsuperscript{17}; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from R\textsuperscript{18};

R\textsuperscript{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\textsuperscript{19} and R\textsuperscript{21} are independently selected from a direct bond, —O—, —N(R\textsuperscript{22})—, —C(O)—, —N(R\textsuperscript{23})C(O)—, —C(O)N(R\textsuperscript{24})—, —S(O)\textsubscript{2}—, —SO\textsubscript{2}N(R\textsuperscript{25})— or —N(R\textsuperscript{26})SO\textsubscript{2};

wherein R\textsuperscript{12}, R\textsuperscript{13}, R\textsuperscript{14}, R\textsuperscript{15} and R\textsuperscript{16} are independently selected from hydrogen or (C\textsubscript{1-6})alkyl and s is 0-2;

R\textsuperscript{18} is selected from (C\textsubscript{1-6})alkyl, (C\textsubscript{1-6})alkanoyl, (C\textsubscript{1-6})alkylsulphonyl, (C\textsubscript{1-6})alkoxycarbonyl, carbamoyl, N—((C\textsubscript{1-6})alkyl)carbamoyl, N,N—((C\textsubscript{1-6})alkyl)carbamoyl, benzyl, benzoxycarbonyl, benzoyl and phenylsulphonyl;

or a pharmaceutically acceptable salt, solvate, hydrate, cocystal, 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\textsuperscript{1} is selected from (C\textsubscript{1-6})alkyl, (C\textsubscript{1-6})alkoxy, 3-5-membered carbocyclyl, and N,N—((C\textsubscript{1-6})alkyl), amino, wherein R\textsuperscript{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_{1-6})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_{1-6})alkyl, (C_{1-6})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^2; and wherein R^3 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^2; and wherein R^3 is halo.
R^2 and R^2 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.
alkyl) carbamoyl, (C₁₋₆)alkylS(O)ₙ wherein a is 0 to 2, (C₁₋₆)alkoxycarbonyl, N—((C₁₋₆)alkyl)sulphamoyl, N,N—((C₁₋₆)alkyl)₂ sulphamoyl, (C₁₋₆)alkylsulphonlamino, carbocyclyl-R¹⁹ — or heterocyclyl-R²¹ —; wherein R² and R³ independently of each other may be optionally substituted on carbon by one or more R⁸; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from R⁹.

R² and R³ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₂₋₆)alkynyl, (C₁₋₆)alkoxy, (C₁₋₆)alkanoyl, (C₁₋₆)alkanoyloxy, N—((C₁₋₆)alkyl)amino, N,N—((C₁₋₆)alkyl)₂ amino, (C₁₋₆)alkanoylamino, N—((C₁₋₆)alkyl)carbamoyl, N,N—((C₁₋₆)alkyl)₂ carbamoyl, (C₁₋₆)alkylS(O)ₙ wherein a is 0 to 2, (C₁₋₆)alkoxycarbonyl, N—((C₁₋₆)alkyl)sulphamoyl, N,N—((C₁₋₆)alkyl)₂ sulphamoyl, N—((C₁₋₆)alkyl)-N—((C₁₋₆)alkyl)₂ carbamoylamino, (C₁₋₆)alkylsulphonlamino, carbocyclyl-R¹⁹ — or heterocyclyl-R²¹ —; wherein R² and R³ independently of each other may be optionally substituted on carbon by one or more R⁸; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from R⁹.

R² and R³ are independently selected from hydrogen, halo, N—((C₁₋₆)alkyl)-N—((C₁₋₆)alkyl)₂ carbamoylamino, or heterocyclyl-R²¹ —; wherein R²¹ is a direct bond.

R² and R³ are independently selected from hydrogen and halo.

R² and R³ are independently selected from hydrogen and chloro.

R² and R³ are independently selected from hydrogen, fluoro, chloro, bromo, N-methyl-N-mesylamino and morpholino.

R² is halo and R³ is hydrogen.

R² is chloro and R³ is hydrogen.

R² is chloro or fluoro and R³ is hydrogen. R³ is selected from hydrogen, halo, cyano, N—((C₁₋₆)alkyl)-N—((C₁₋₆)alkyl)₂ carbamoylamino, (C₁₋₆)alkyl, (C₁₋₆)alkyl-N—S(O)₂ —N((C₁₋₆)alkyl), and heterocyclyl-R²¹ —, wherein R² may be optionally substituted on carbon by one or more R⁸; wherein R⁸ is halo; and wherein R²¹ is a bond.

R³ is hydrogen.

R¹ is halo.
R' is selected from N—((C_{1-6})alkyl)-N—((C_{1-6})alkylsulphonyl)amino and ((C_{1-6})alkyl)_{2}N—S(O)—N((C_{1-6})alkyl)—.

R' is selected from heterocyclyl-R^{21}—, wherein R' 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' is selected from hydrogen, chloro, cyano, trifluoromethyl, (CH_{3})_{2}N—S(O)—N(CH_{3})—, N-methyl-N-mesylamino, and morpholino.

R' is (CH_{3})_{2}N—S(O)—N(CH_{3})—.

R' is N-methyl-N-mesylamino.

R' is morpholino.

R' is (C_{1-6})alkyl.

R' is methyl.

R' is halo.

R' is fluoro.

n=1.

R'^{9} and R'^{21} are independently selected from —O—, —N(R'^{22})—, —C(O)—, —N(\text{I}^{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' is selected from (C_{1-6})alkyl, (C_{1-6})alkoxy or 3-5-membered carbocyclyl;

R' 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'^{3} 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' is (C_{1-6})alkoxy;
R² and R³ are independently selected from hydrogen and halo;
R¹ is (C₁₋₆)alkyl;
R⁴ is halo;
n=1;
or a pharmaceutically acceptable salt, solvate, hydrate, cocystal, or prodrug thereof.

[00774] In an embodiment of the invention, the JAK-2 inhibitor is a compound of Formula (LVII) wherein:
R¹ is methyl, methoxy, isopropoxy or cyclopropyl;
R² and R³ are independently selected from hydrogen, fluoro, chloro, bromo, N-methyl-N-
mesylamino and morpholino;
R⁴ is methyl;
R⁵ is halo; and
n=1;
or a pharmaceutically acceptable salt, solvate, hydrate, cocystal, or prodrug thereof.

[00775] In an embodiment of the invention, the JAK-2 inhibitor is a compound of Formula (LVII) wherein:
R¹ is selected from (C₁₋₆)alkyl, (C₁₋₆)alkoxy, 3-5-membered carbocyclyl, and N,N—((C₁₋₆)
alkyl)₂ amino, wherein R¹ may be optionally substituted on carbon by one or more
R⁶;
R² is selected from hydrogen, halo, nitro, and (C₁₋₆)alkyl, wherein R² may be optionally
substituted on carbon by one or more R⁸;
R³ is selected from hydrogen, halo, cyano, N—((C₁₋₆)alkyl)-N—((C₁₋₆)
alkylsulphonyl)amino, (C₁₋₆)alkyl, ((C₁₋₆)alkyl)₂ N—S(O)₂ —N((C₁₋₆)alkyl)—, and
heterocyclyl-R²¹, wherein R³ may be optionally substituted on carbon by one or
more R⁸;
R⁴ is (C₁₋₆)alkyl;
R⁵ is halo;
R⁶ is halo;
R⁸ is halo;
R²¹ 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, \((\text{CH}_3)_2\text{N—S(O)}_2\text{—N(CH}_3)_2\text{—, 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 \((\text{C}_{1-6})\text{alkoxy, wherein } R^1 \text{ may be optionally substituted on carbon by one or more } R^6 ;\)
- \( R^2 \) is selected from hydrogen and halo;
- \( R^3 \) is selected from hydrogen, halo, and heterocyclyl-\( R^{21} —; \)
- \( R^4 \) is \((\text{C}_{1-6})\text{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 \((\text{C}_{1-4})\text{alkyl, } (\text{C}_{1-4})\text{alkoxy, and cyclopropyl;}
- \( R^2 \) is selected from hydrogen, halo, nitro, and \((\text{C}_{1-6})\text{alkyl, wherein } R^2 \text{ may be optionally substituted on carbon by one or more } R^3 ;\)
- \( R^3 \) is selected from hydrogen, halo, cyano, \( N—(\text{C}_{1-6})\text{alkyl)-N—(C}_1. \)
(alkylsulphonyl)amino, (C<sub>1-6</sub>)alkyl, ((C<sub>1-6</sub>)alkyl)<sub>2</sub>N—S(O)<sub>2</sub>—N((C<sub>1-6</sub>)alkyl)—, and heterocyclyl-R<sub>21</sub>—, wherein R<sup>3</sup> may be optionally substituted on carbon by one or more R<sup>8</sup>;
R<sup>4</sup> is (C<sub>1-6</sub>)alkyl;
R<sup>5</sup> is halo;
R<sup>6</sup> is halo;
R<sup>21</sup> 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<sup>2</sup>-(1-(5-fluoropyrimidin-2-yl)ethyl)-N<sup>4</sup>-(5-methyl-1H-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)](image)

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):
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof,
wherein:
R₁ and R₂ are independently selected from hydrogen, halo, nitro, cyano, hydroxy,
trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₆ alkyl, C₂₋₆
alkenyl, C₂₋₆ alkylnyl, C₁₋₆ alkoxy, C₁₋₆ alkanoyl, C₁₋₆ alkanoyloxy, N—(C₁₋₆
alkyl)amino, N,N—(C₁₋₆ alkyl)₂-amino, C₁₋₆ alkanoylamino, N—(C₁₋₆
alkyl)carbamoyl, N,N—(C₁₋₆ alkyl)₂-carbamoyl, C₁₋₆ alkylS(O)₂ wherein a is 0 to 2,
C₁₋₆ alkoxy carbonyl, N—(C₁₋₆ alkyl)sulphamoyl, N,N—(C₁₋₆ alkyl)₂ sulphamoyl, C₁₋₆
alkylsulphonylamino, carbocyclyl or heterocyclyl; wherein R₁ and R₂ independently
of each other may be optionally substituted on carbon by one or more R₆; and
wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be
optionally substituted by a group selected from R³;
one of X¹, X², X³ and X⁴ is δ-N—, the other three are independently selected from
δ-CR⁸—, δ-CR⁹— and δ-CR¹⁰—;
R¹ is hydrogen or optionally substituted C₁₋₆ alkyl; wherein said optional substituents are
selected from one or more R₁¹;
R₄ and R₁₄ are independently selected from hydrogen, halo, nitro, cyano, hydroxy,
trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₆ alkyl, C₂₋₆
alkenyl, C₂₋₆ alkylnyl, C₁₋₆ alkoxy, C₁₋₆ alkanoyl, C₁₋₆ alkanoyloxy, N—(C₁₋₆
alkyl)amino, N,N—(C₁₋₆ alkyl)₂ amino, C₁₋₆ alkanoylamino, N—(C₁₋₆ alkyl)carbamoyl,
N,N—(C₁₋₆ alkyl)₂ carbamoyl, C₁₋₆ alkylS(O)₂ wherein a is 0 to 2, C₁₋₆ alkoxy carbonyl,
N—(C₁₋₆ alkyl)sulphamoyl, N,N—(C₁₋₆ alkyl)₂ sulphamoyl, C₁₋₆ alkylsulphonylamino,
carbocyclyl or heterocyclyl; wherein R₄ and R₁₄ may be independently optionally

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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 \(R_1\);

A is a direct bond or \(C_{1,2}\) alkylene; wherein said \(C_{1,2}\) alkylene may be optionally substituted by one or more \(R_4\);

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 \(R_5\);

\(R_5\) is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, \(C_{1,6}\) alkyl, \(C_{2,6}\) alkenyl, \(C_{1,6}\) 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) amino, \(C_{1,6}\) alkanoylamino, \(N—(C_{1,6}\) alkyl)carbamoyl, \(N,N—(C_{1,6}\) alkyl)sulphamoyl, \(C_{1,6}\) alkylS(O) wherein a is 0 to 2, \(C_{1,6}\) alkoxy carbonyl, \(N—(C_{1,6}\) alkyl)sulphamoyl, \(N,N—(C_{1,6}\) alkyl)sulphamoyl, \(C_{1,6}\) alkylsulphonylamino, carboxycycl-R\(^{37}\) — or heterocyclyl-R\(^{38}\) —; wherein \(R_5\) 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 \(R_7\);

\(n\) 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, \(C_{1,6}\) alkylnyl, \(C_{1,6}\) alkoxy, \(C_{1,6}\) alkanoyl, \(C_{1,6}\) alkanoyloxy, \(N—(C_{1,6}\) alkyl)amino, \(N,N—(C_{1,6}\) alkyl) amino, \(C_{1,6}\) alkanoylamino, \(N—(C_{1,6}\) alkyl)carbamoyl, \(N,N—(C_{1,6}\) alkyl)sulphamoyl, \(C_{1,6}\) alkoxy carbonyl, \(N—(C_{1,6}\) alkyl)sulphamoyl, \(N,N—(C_{1,6}\) alkyl)sulphamoyl, \(C_{1,6}\) alkylsulphonylamino, carboxycycl-R\(^{39}\) — or heterocyclyl-R\(^{40}\) —; wherein \(R_8\), \(R_9\) and \(R_{10}\) 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 \(R_9\);

\(R_7\), \(R_{11}\), \(R_{12}\), \(R_{14}\), \(R_{16}\) 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, \(C_{1,6}\) alkylnyl, \(C_{1,6}\) alkoxy, \(C_{1,6}\) alkanoyl, \(C_{1,6}\) alkanoyloxy, \(N—(C_{1,6}\) alkyl)amino, \(N,N—(C_{1,6}\) alkyl) amino, \(C_{1,6}\) alkanoylamino, \(N—(C_{1,6}\) alkyl)carbamoyl,
N,N—(C₁₋₆ alkyl)₂ carbamoyl, C₁₋₆ alkylS(O) wherein a is 0 to 2, C₁₋₆ alkoxy carbonyl, N—(C₁₋₆ alkyl)sulphamoyl, N,N—(C₁₋₆ alkyl)₂ sulphanoyl, C₁₋₆ alkyloxycarbonyl, N,N—(C₁₋₆ alkyl)sulphamoyl, carbocyclyl-R² — or heterocyclyl-R²¹ —; wherein R₆, R¹¹, R¹³, R₁⁴, R₁⁶ and R¹₈ independently of each other may be optionally substituted on carbon by one or more R²⁰; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from R²¹;

R², R¹³, R¹⁵, R¹⁷, R¹⁹ and R²¹ are independently selected from C₁₋₆ alkyl, C₁₋₆ alkanoyl, C₁₋₆ alkyl sulphon, C₁₋₆ alkoxycarbonyl, carbamoyl, N—(C₁₋₆ alkyl)carbamoyl, N,N—(C₁₋₆ alkyl)₂ carbamoyl, benzyl, benzoyloxycarbonyl, benzoyl and phenyl sulphonyl; wherein R², R¹³, R¹⁵, R¹⁷, R¹⁹ and R²¹ independently of each other may be optionally substituted on carbon by on or more R²²;

R²⁰ and R²² are independently selected from halo, nitro, cyano, hydroxyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphanoyl, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkenyl, C₁₋₆ alkoxy, C₁₋₆ alkanoyl, C₁₋₆ alkanoyloxy, N—(C₁₋₆ alkyl)amino, N,N—(C₁₋₆ alkyl)₂ amino, C₁₋₆ alkanoylamino, N—(C₁₋₆ alkyl)carbamoyl, N,N—(C₁₋₆ alkyl)₂ carbamoyl, C₁₋₆ alkyloxycarbonyl, wherein R²⁰ and R²² independently of each other may be optionally substituted on carbon by one or more R²³; and wherein if said heterocyclyl contains an —NH— moiety that nitrogen may be optionally substituted by a group selected from R²⁴;

R²⁵, R²⁶, R²⁷, R²⁸, R³⁵, R³⁶, R³⁷ and R³⁸ are independently selected from a direct bond, —O—, —N(R²⁹)—, —C(O)—, —N(R³⁰)C(O)—, —C(O)N(R³¹)—, —S(O)—, —NH₉CH—, —SO₂N(R³²)— or —N(R³³)SO₂—; wherein R²⁹, R³⁰, R³¹, R³² and R³³ are independently selected from hydrogen or C₁₋₆ alkyl and s is 0-2;

R²³ is selected from halo, nitro, cyano, hydroxyl, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphanoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methyl amino, ethyl amino, dimethyl amino, diethyl amino, N-methyl-N-ethyl amine, acetylamino, N-methylcarbamoyl, N-ethy carbamoyl, N,N-dimethyl carbamoyl, N,N-diethyl carbamoyl, N-methyl-N-ethyl carbamoyl, methylthio, ethylthio, methyl sulphinyl, ethyl sulphinyl, mesyl, ethyl sulphonyl, methoxy carbonyl,
ethoxycarbonyl, N-methylsulphamoyl, N-ethylsulphamoyl, N,N-dimethylsulphamoyl, N,N-diethylsulphamoyl, N-methyl-N-ethylsulphamoyl or phenyl; and

$R^2$ is selected from $\text{C}_{1-6}$ alkyl, $\text{C}_{1-6}$ alkanoyl, $\text{C}_{1-6}$ alkylsulphonyl, $\text{C}_{1-6}$ alkoxy carbonyl, carbamoyl, $N-(\text{C}_{1-6} \text{ alkyl})$ carbamoyl, $N,N-(\text{C}_{1-6} \text{ alkyl})$ carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenyl sulphonyl;
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 CH₂, NR₄, 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 NR₃R₈, CR₅R₆R₇, SR₅ or OR₅;
R₂ is (C₆H₅)OH, (C₆H₅)NH₂, (C₆H₅)NHR₄ or heterocyclyl;
R₃ is

(a) hydrogen;
(b) C₁₋₆ alkyl, which is optionally substituted with halo, hydroxyl, amino, phenyl, heterocyclyl, C₁₋₆ alkyl or R¹;
(c) C₂₋₆ alkenyl, which is optionally substituted with halo, hydroxyl, amino, phenyl, heterocyclyl, C₁₋₆ alkyl or R₁;
(d) C₃₋₁₀ cycloalkyl, which is optionally substituted with C₁₋₆ alkyl, OR₄, NR₄R₄, phenyl (which is optionally substituted with C₁₋₆ alkyl, OR₄ or NR₄R₄), halo, R₁₀ or heterocyclyl;
(e) —(CO)R₈;
(f) —(CO)—NR₈R₉;
(g) C₄₋₁₀ heterocyclyl, which is optionally substituted on either the carbon or the heteroatom with C1-6 alkyl, halo, R₁₀, OR₄, NR₄R₄, phenyl (which is optionally substituted with C1-6 alkyl, OR₄ or NR₄R₄), —(CO)R₈ or —(CO)—NR₄R₈;
(h) OR₄;
(i) NR₄R₄;
(j) halo;
(k) Aryl, which is optionally substituted with one or more groups selected from C₁₋₆ alkyl (which is optionally substituted with one to three halo), halo or R₁₀;
(l) Heteroaryl, which is optionally substituted with one or more groups selected
from C\textsubscript{1-6} alkyl (which is optionally substituted with one to three halo), halo or R\textsubscript{10};

(m) O-aryl, which is optionally substituted with one or more groups selected from C\textsubscript{1-6} alkyl, halo or R\textsubscript{10};

(n) O—C\textsubscript{1-6} alkyl, which is optionally substituted with C\textsubscript{1-6} alkyl, halo or R\textsubscript{10}; or

(o) L-A-R\textsubscript{10};

R\textsubscript{4} is

(a) hydrogen;
(b) C\textsubscript{1-6} alkyl, which is optionally substituted with halo, hydroxyl, amino, aryl or heterocyclil;
(c) C\textsubscript{3-10} cycloalkyl, which is optionally substituted with C\textsubscript{1-6} alkyl, OR\textsubscript{11}, NR\textsubscript{8} R\textsubscript{11}, phenyl (which is optionally substituted with C\textsubscript{1-6} alkyl, OR\textsubscript{11} or NR\textsubscript{8} R\textsubscript{11}), heterocyclil, aryl or heteroaryl;
(d) —(CO)R\textsubscript{8};
(e) —(CO)—NR\textsubscript{9} R\textsubscript{9};
(f) C\textsubscript{4-10} heterocyclil, which is optionally substituted on either the carbon or the heteroatom with C\textsubscript{1-6} alkyl, OR\textsubscript{11}, NR\textsubscript{8} R\textsubscript{11}, phenyl (which is optionally substituted with C\textsubscript{1-6} alkyl, OR\textsubscript{11} or NR\textsubscript{8} R\textsubscript{11}), heterocyclil, —(CO)R\textsubscript{8} or —(CO)—NR\textsubscript{9} R\textsubscript{9};
(g) OR\textsubscript{11};
(h) NR\textsubscript{8} R\textsubscript{11};
(i) Aryl, which is optionally substituted with one to five halo or R\textsubscript{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\textsubscript{10};

R\textsubscript{5} is

(a) hydrogen;
(b) C\textsubscript{1-8} alkyl, which is optionally substituted with halo, hydroxyl, amino, aryl, cycloalkyl or heterocyclil;
(c) C\textsubscript{3-10} cycloalkyl, which is optionally substituted with C\textsubscript{1-6} alkyl, (C\textsubscript{1-6} alkyl)aryl, (C\textsubscript{1-6} alkyl)OR\textsubscript{9}, OR\textsubscript{9}, NR\textsubscript{8} R\textsubscript{9}, phenyl (which is optionally substituted with C\textsubscript{1-6} alkyl, OR\textsubscript{9}, NR\textsubscript{8} R\textsubscript{9}, heterocyclil, —(CO)R\textsubscript{8} or —(CO)—NR\textsubscript{9} R\textsubscript{9});
(d) —(CO)R₈;
(e) —(CO)—NR₈R₉;
(f) C₁-₆ alkyl(C₅-O)NR₈CR₉(C₅-O)NR₈R₉;
(g) C₄-₁₀ heterocyclyl which is optionally substituted on either the carbon or the heteroatom with one to three substituents selected from C₁-₆ alkyl, halo, OR₄,
    NR₄R₅, —(CO)R₈, (CO)—NR₈R₉ or phenyl (which is optionally substituted with
    C₁-₆ alkyl, OR₄, NR₄R₅, heterocyclyl, —(CO)R₈ or —(CO)—NR₈R₉);

R₈ is
(a) hydrogen;
(b) C₁-₆ alkyl, which is optionally substituted with halo, hydroxyl, amino, aryl,
    cycloalkyl or heterocyclyl;
(c) C₃-₁₀ cycloalkyl, which is optionally substituted with C₁-₆ alkyl, (C₁-₆
    alkyl)aryl, (C₁-₆ alkyl)OR₄, OR₄, NR₄R₅, phenyl (which is optionally substituted
    with C₁-₆ alkyl, OR₄, NR₄R₅, heterocyclyl, —(CO)R₈ or —(CO)—NR₈R₉;
(d) —(CO)R₈;
(e) —(CO)—NR₈R₉;
(f) C₁-₆ alkyl(C₅-O)NR₈CR₉(C₅-O)NR₈R₉;
(g) C₄-₁₀ heterocyclyl which is optionally substituted on either the carbon or the heteroatom with one to three substituents selected from C₁-₆ alkyl, halo, OR₄,
    NR₄R₅, —(CO)R₈, (CO)—NR₈R₉ or phenyl (which is optionally substituted with
    C₁-₆ alkyl, OR₄, NR₄R₅, heterocyclyl, —(CO)R₈ or —(CO)—NR₈R₉);

R₉ is
(a) hydrogen;
(b) C₁-₆ alkyl, which is optionally substituted with halo, hydroxyl, amino, phenyl
    or heterocyclyl;
(c) C₃-₁₀ cycloalkyl, which is optionally substituted with C₁-₆ alkyl, OR₄, NR₄R₅,
    phenyl (which is optionally substituted with C₁-₆ alkyl, OR₄, NR₄R₅, heterocyclyl,
    —(CO)R₈ or —(CO)—NR₈R₉;
(d) C₄-₁₀ heterocyclyl which is optionally substituted on either the carbon or the heteroatom with C₁-₆ alkyl, OR₄, NR₄R₅, phenyl (which is optionally substituted with C₁-₆ alkyl, OR₄, NR₄R₅, heterocyclyl, —(CO)R₈ or —(CO)—NR₈R₉);
Or R₅ and R₆, together with the atoms between them, can form a three to ten membered heterocyclic or heteroaryl ring which is optionally substituted with C₁-₆ alkyl, (C₁-₆ alkyl)ary1, (C₁-₆ alkenyl)aryl, (C₁-₆ alkyl)OR, OR₄, NR₅R₆, phenyl (which is optionally substituted with C₁-₆ alkyl, OR₄, NR₅R₆, heterocycl, —(CO)R₈ or —(CO)—NR₈R₉), —(CO)R₈; —(CO)—NR₈R₉ or heterocycl;
R₈ is hydrogen or C₁-₆ alkyl, —(CO)R₁₁, —(CO)N(R₁₁)₂;
R₉ is hydrogen or C₁-₆ alkyl;
R₁₀ is:
(a) hydrogen;
(b) CO₂R₁₁;
(c) C(O)R₁₁;
(d) NHR₁₁;
(e) NR₁₁R₁₂;
(f) NHS(O)₂R₁₁;
(g) NHC(O)R₁₁;
(h) NHC(O)OR₁₁;
(i) NH—C≡(NH)NH₂;
(j) NHC(O)NH₂;
(k) NHC(O)NHR₁₁;
(l) NHC(O)NR₁₁R₁₂;
(m) NC₃-6cycloalkyl;
(n) C(O)NHR₁₁;
(o) C(O)NR₁₁R₁₂;
(p) SO₂NHR₁₁;
(q) SO₂NHC(O)R₁₁;
or
(r) SO₂R₁₁;
R₁₁ is selected from the group consisting of:
(a) hydrogen,
(b) C₃-₆ cycloalkyl, which is optionally substituted with aryl, heteroaryl or one to five halo;
(c) C₁-₆ 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_{1-6} 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_{1-5})alkyl, —C(O)OH, CF_3, —SO_2(C_{1-3})alkyl, SO_N(C_{1-3})alkyl, SO_NHC(O)—
(C_{1-3})alkyl or N(CH_3)_3;

L is absent or is selected from the group consisting of: —(CH_2)_k—W—, —Z—(CH_2)_k—,
—C_6Cl—, —C_{1-6} alkyl—, —C_{5-6} 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_{2} R_{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.
In a preferred embodiment, the JAK-2 inhibitor is \((R)-7-(2\text{-aminopyrimidin}-5\text{-yl})-1-((1\text{-cyclopropyl}-2,2,2\text{ trifluoroethyl})\text{amino})-5\text{H-pyrido}[4,3-b]\text{indole}-4\text{-carboxamide}\), which is also named \(7-(2\text{-aminopyrimidin}-5\text{-yl})-1-\{(1\text{R})-1\text{-cyclopropyl}-2,2,2\text{ trifluoroethyl}\text{amino}\}-5\text{H-pyrido}[4,3-b]\text{indole}-4\text{-carboxamide}\). In a preferred embodiment, the JAK-2 inhibitor is a compound of Formula (LXII):

![Formula (LXII)](image)

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 \(1\text{-amino-5H-pyrido}[4,3-b]\text{indol-4-carboxamide}\) 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.

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**

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 $k_{\text{assoc}}$ of about $7.5 \times 10^5$ l/M·s or faster, binds to human PD-1 with a $k_{\text{assoc}}$ of about $7.5 \times 10^4$ l/M·s or faster, binds to human PD-1 with a $k_{\text{assoc}}$ of about $8 \times 10^4$ l/M·s or faster, binds to human PD-1 with a $k_{\text{assoc}}$ of about $8.5 \times 10^5$ l/M·s or faster, binds to human PD-1 with a $k_{\text{assoc}}$ of about $9 \times 10^4$ l/M·s or faster, binds to human PD-1 with a $k_{\text{assoc}}$ of about $9.5 \times 10^5$ l/M·s or faster, or binds to human PD-1 with a $k_{\text{assoc}}$ of about $1 \times 10^5$ 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 $k_{\text{dissoc}}$ of about $2 \times 10^5$ l/s or slower, binds to human PD-1 with a $k_{\text{dissoc}}$ of about $2.1 \times 10^5$ l/s or slower, binds to human PD-1 with a $k_{\text{dissoc}}$ of about $2.2 \times 10^4$ l/s or slower, binds to human PD-1 with a $k_{\text{dissoc}}$ of about $2.3 \times 10^5$ l/s or slower, binds to human PD-1 with a $k_{\text{dissoc}}$ of about $2.4 \times 10^5$ l/s or slower, binds to human PD-1 with a $k_{\text{dissoc}}$ of about $2.5 \times 10^5$ l/s or slower, binds to human PD-1 with a $k_{\text{dissoc}}$ of about $2.6 \times 10^5$ l/s or slower or binds to human PD-1 with a $k_{\text{dissoc}}$ of about $2.7 \times 10^5$ l/s or slower, binds to human PD-1 with a $k_{\text{dissoc}}$ of about $2.8 \times 10^5$ l/s or slower, binds to human PD-1 with a $k_{\text{dissoc}}$ of about $2.9 \times 10^5$ l/s or slower, or binds to human PD-1 with a $k_{\text{dissoc}}$ 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-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 IC₅₀ of about 7 nM or lower, blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an IC₅₀ of about 6 nM or lower, blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an IC₅₀ of about 5 nM or lower, blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an IC₅₀ of about 4 nM or lower, blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an IC₅₀ of about 3 nM or lower, blocks or inhibits binding of human PD-L1 or human PD-L2 to human PD-1 with an IC₅₀ 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 IC₅₀ 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 CH₂84.4) 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 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.
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.

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.

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 the 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 5-10x10^6 cells were used to immunize the HuMab mice and KM Mice™ intraperitoneally, 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 1×10^5/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 h409Al l 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)]\(\bar{\mu}\) heavy chain (134-218')-disulfide with humanized mouse monoclonal \(\kappa\) 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
QVQLVQSGVEVKPGASVKVKASCTFTSIINYMYWVRQAPGQGLEW MGG 50
INPSNGN芙FKNRVTQDSTTAYMELKQLQFDTCVYCAR RD 100
YRFDMGFDYWQGTTTVSSASTKPSVFLAPCSRSTSESTAALGCLVK 150
```
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.
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
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.

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 CH₂ 84.4) at 297, 297''.

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. In an embodiment, an anti-PD-1 antibody comprises heavy and light chains that are each at least 94% 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 93% 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 92% identical to the sequences shown in SEQ ID NO:21 and SEQ ID NO:22, respectively.
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\textsubscript{H} and V\textsubscript{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\textsubscript{H} and V\textsubscript{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\textsubscript{H} and V\textsubscript{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\textsubscript{H} and V\textsubscript{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\textsubscript{H} and V\textsubscript{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

<table>
<thead>
<tr>
<th>Identifier</th>
<th>Sequence (One-Letter Amino Acid Symbols)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEQ ID No:1 Nivolumab heavy chain</td>
<td>QVQLVExGGGLVQPSRELAL DCMASG17FS N5GMH4WVRQA PGKLEH6AVV IYWDDG5KYY 60</td>
</tr>
<tr>
<td>SEQ ID No:2 Nivolumab light chain</td>
<td>ETVLTPQ5PAT L5SLSGNERAT L5SRASQ5QSE SYLAWYQQ5X9P GQAPR4LLYD ANKAR45G5PA 60</td>
</tr>
<tr>
<td>SEQ ID No:3 Nivolumab variable heavy chain</td>
<td>QVQLVExGGGLVQPSRELAL DCMASG17FS N5GMH4WVRQA PGKLEH6AVV IYWDDG5KYY 60</td>
</tr>
<tr>
<td>SEQ ID No:4 Nivolumab light chain</td>
<td>ETVLTPQ5PAT L5SLSGNERAT L5SRASQ5QSE SYLAWYQQ5X9P GQAPR4LLYD ANKAR45G5PA 60</td>
</tr>
<tr>
<td>SEQ ID No:5 Nivolumab heavy chain CDR1</td>
<td>N5GMH 5</td>
</tr>
<tr>
<td>SEQ ID No:6 Nivolumab heavy chain CDR2</td>
<td>WTVYD5G5KRY WAD5V5R 17</td>
</tr>
<tr>
<td>SEQ ID No:7 Nivolumab heavy chain CDR3</td>
<td>NDD5V 4</td>
</tr>
<tr>
<td>SEQ ID No:8 Nivolumab heavy chain CDR4</td>
<td>T5ASQVV5YSYL A 11</td>
</tr>
<tr>
<td>Identifier</td>
<td>Sequence (One-Letter Amino Acid Symbols)</td>
</tr>
<tr>
<td>------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>nivolumab light chain CDRI</td>
<td>DASNRA7</td>
</tr>
<tr>
<td>nivolumab light chain CDRI2</td>
<td>Q86SNWRT</td>
</tr>
<tr>
<td>nivolumab light chain CDRI3</td>
<td>MAVLGILFLC VLPFSCGSLQ QLQLQQQGVEY KRPQAIKVKVS CCRSGGTYTTN YYMNLYQAP</td>
</tr>
<tr>
<td>nivolumab heavy chain</td>
<td>GQGLDGNSGI RNSKQTGNN ERRFHVVLIT TGGSTTTATY ELKLSSGLQDDT AVYSCARRDA</td>
</tr>
<tr>
<td>nivolumab heavy chain</td>
<td>RPMDGFSLPGQ GQTMVQGSA QAQGQSLVFEL LPECSSSTSE TAQLGLCQLK YYFDFFTQVSV</td>
</tr>
<tr>
<td>pembrolizumab heavy chain</td>
<td>NSGASLQSGRH TAPFVQPSG SSQLSQXTY TCOVQYKPR TQVDRKVSER</td>
</tr>
<tr>
<td>pembrolizumab heavy chain</td>
<td>YGPRQPCRCAG RPLFQGDSVP FLYFQXESDL MISAPKTVC VYQVGXQEDF EQQFNYNGDG</td>
</tr>
<tr>
<td>pembrolizumab heavy chain</td>
<td>VRHVLXNTRP RQESNQSTY YQLVLTLYHQ GNLKYXKEC KVQNGSLPGL LSRTSNGK</td>
</tr>
<tr>
<td>pembrolizumab heavy chain</td>
<td>QFRPQYTVL TFQEPQEMTN VQSSLCLVKQ FYSPDIAYS ESNQPQENNY XTPPVLYSD</td>
</tr>
<tr>
<td>pembrolizumab heavy chain</td>
<td>SFSFLYSLRT VDKSWKQPEG VNFSCEVMKAE LKNHITQKLL SLSLGK</td>
</tr>
<tr>
<td>pembrolizumab heavy chain</td>
<td>QVQLQVQGV FVSGASVAK SCRAQGYFTT NTYIMWSYQ QAQQQGQKGG NGPSNGQTF</td>
</tr>
<tr>
<td>pembrolizumab heavy chain</td>
<td>NERKPYNTVL TIDSESTTTY MELKSLPFRD TAYSCARPF YECPMHTQW QGQTVTTY</td>
</tr>
<tr>
<td>pembrolizumab variable light chain amino acid</td>
<td>ASTGRQVVP LAFCRSTSE TAAALCGCQK YDFPEFQTVS WNSGALTGVG NTOPFVQLGS</td>
</tr>
<tr>
<td>pembrolizumab light chain</td>
<td>GLYSLLQGVT VSQSLQGKQK YTQYDKRKS NTYQDRKXVE KQGGFCRQCFE ASPFLGSFGV</td>
</tr>
<tr>
<td>pembrolizumab light chain</td>
<td>FLKPEKCRGK LMQSSRPEVT CVVQVQPEDQ YSFKQNYWID GVEVHKAXKT RQEDNQSTY</td>
</tr>
<tr>
<td>pembrolizumab light chain</td>
<td>RXVLQXLQYW CHVNLKXGK QFQYPRFVHEV DAGAGAQFENX YXTPPVLYSG</td>
</tr>
<tr>
<td>pembrolizumab light chain</td>
<td>NVFCSVYME ALKHLTYQSG LQGSLXG</td>
</tr>
<tr>
<td>pembrolizumab light chain</td>
<td>MAVVQLGILG VFLPAMKCE IVLQSPATL SLLSPERATL SCRASKQYST GQGSLWNYQ</td>
</tr>
<tr>
<td>pembrolizumab light chain</td>
<td>QRQPCAPRIL YILASLYESL VEAPSSSGS GTOFTLTISS LEPEDFAVYY CQHSRDLKLF</td>
</tr>
<tr>
<td>pembrolizumab light chain</td>
<td>QSGSTKVEIK YGGQSLGFQTF YFGSRLQV</td>
</tr>
<tr>
<td>pembrolizumab light chain</td>
<td>RASKVGSTSG YSFLY</td>
</tr>
<tr>
<td>pembrolizumab light chain</td>
<td>LASYLES</td>
</tr>
<tr>
<td>pembrolizumab light chain</td>
<td>QHSDLDLPT</td>
</tr>
<tr>
<td>pembrolizumab light chain</td>
<td>NYMY</td>
</tr>
<tr>
<td>pembrolizumab heavy chain CDRI</td>
<td>GINPSNGTN FNERFK</td>
</tr>
<tr>
<td>pembrolizumab heavy chain CDRI2</td>
<td>RODKQGSFDY Y</td>
</tr>
<tr>
<td>pembrolizumab heavy chain CDRI3</td>
<td>QVLQGQQGB LGQPSGAVVE CHQGCGVFTT NTYMNWSQQA PQQGQKGG NGPSNGQTF</td>
</tr>
<tr>
<td>pembrolizumab heavy chain</td>
<td>AERPSQYKTVL TIDGFYQVX YKLKVQGQEG TLVITX</td>
</tr>
<tr>
<td>pembrolizumab heavy chain</td>
<td>KQGRLVPAL SFSKSDGQTA ALKCVKXLFYFQETVQWNS SALTSGQFST PVQQLGGLY</td>
</tr>
<tr>
<td>pembrolizumab heavy chain</td>
<td>QSLVTVYRS SSLQQTQYK YKVRMRKNTK VQKVRKPSK DMTRCCFCCP APEFLGSGFEV</td>
</tr>
<tr>
<td>pembrolizumab heavy chain</td>
<td>FLKPEKCRGK LMQSSRPEVT CVVQVQPEDQ YSFKQNYWID GVEVHKAXKT RQEDNQSTY</td>
</tr>
</tbody>
</table>
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 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 No. 2014/0294898; the disclosures of each of which are hereby incorporated by reference in their entireties.

In an embodiment, the PD-1 inhibitor may also be a compound of Formula (LXIII):

\[
\begin{align*}
\text{R}_1 & \quad \text{A} \\
\text{R}_2 & \quad \text{B} \\
\text{X} & \quad \text{Z} \\
\text{X}' & \quad \text{Y} \\
\text{D} & \quad \text{R}_4 \\
\text{R}_3 & \quad \text{E} \\
\text{R}_5 & \quad \text{R}_5
\end{align*}
\]

(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(CH₂)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

```
\[
\text{H}_2\text{C}\text{H}_2\text{NH}\text{H}_{\text{n}}\text{(CH}_2\text{)}_\text{m}\text{C\text{COOH}}
\]
```

which is optionally linked with an additional lysine; or X’ is absent;
m is an integer selected from 1 to 6, both inclusive;

R₁ is selected from group consisting of C₂⁻C₂₀ acyl, polyethylene glycol (PEG) 2-20 kilodalton moiety; or absent;

R₂ and R₃ are independently selected from group consisting of C₂⁻C₂₀ acyl, PEG 2-20 kilodalton, absent or Ra-L’; Ra is selected from biotin or maleimido propionic acid; L’ is selected from linkers CO(CH₂)ₙ, NH, CO(CH₂CH₂-O)ₙNH or COCH₂(-OCH₂-)ₙNH⁻; and n is an integer selected from 2 to 10, both inclusive;

R₄ and R₅ are independently NH₂, or one or both of R₄ or R₅ 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 (-CH₂NH⁻);

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:
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-L1 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-L1 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. 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.

[00819] 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 Kd of about 100 pM or lower, binds human PD-L1 and/or PD-L2 with a Kd of about 90 pM or lower, binds human PD-L1 and/or PD-L2 with a Kd of about 80 pM or lower, binds human PD-L1 and/or PD-L2 with a Kd of about 70 pM or lower, binds human PD-L1 and/or PD-L2 with a Kd of about 60 pM or lower, a Kd of about 50 pM or lower, binds human PD-L1 and/or PD-L2 with a Kd 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 kassoc of about 7.5 × 10^5 l/M·s or faster, binds to human PD-L1 and/or PD-L2 with a kassoc of about 8 × 10^5 l/M·s or faster, binds to human PD-L1and/or PD-L2 with a kassoc of about 8.5 × 10^5 l/M·s or faster, binds to human PD-L1 and/or PD-L2 with a kassoc of about 9 × 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 $1 \times 10^5$ 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; 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

[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 @-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.
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.

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 $V_\text{H}$ 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 $V_\text{H}$ 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 $V_\text{H}$ 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 $V_\text{L}$ 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 $V_\text{L}$ 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 $V_\text{L}$ 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 $V_\text{H}$ 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 $V_\text{H}$ 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 $V_\text{H}$ 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 $V_\text{L}$ 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 $V_\text{L}$ 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 $V_\text{L}$ 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 $V_\text{H}$ 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-CL126) 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 CH₂ 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_SWIH) (corresponding to SEQ ID NO:1 in U.S. Patent No. 8,217,149), the HVR-H2 sequence is SEQ ID NO:69 (AWIXPYGGSXYYYADSVKG) (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_i is D or G, X_j is S or L, and X_k 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_i X_j TX_k X_L) (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_LX_i 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_{i_{11}} X_{i_{12}} X_{i_{13}} X_{i_{14}} PX_{i_{15}} T) (corresponding to SEQ ID NO:10 in U.S. Patent No. 8,217,149), further wherein further wherein: X_{i_{11}} is D or V; X_{i_{12}} is V or I; X_{i_{13}} is S or N; X_{i_{14}} is A or F; X_{i_{15}} is V or L; X_{i_{16}} is F or T; X_{i_{17}} is Y or A; X_{i_{18}} is Y, G, F, or S; X_{i_{19}} is L, Y, F or W; X_{i_{20}} is Y, N, A, T, G, F or I; X_{i_{21}} is H, V, P, T or I; and X_{i_{22}} 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', 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 \textsubscript{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'.

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.

In an embodiment, the anti-PD-L1 antibody V\textsubscript{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\textsubscript{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\textsubscript{H} and V\textsubscript{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\textsubscript{H} and V\textsubscript{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\textsubscript{H} and V\textsubscript{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\textsubscript{H} and V\textsubscript{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\textsubscript{H} and V\textsubscript{L} regions that are each at least 95% identical to the sequences shown in SEQ ID NO:76 and SEQ ID NO:77, respectively.


[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.

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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-ű or PI3K-į 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-ű or PI3K-į 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%. The pharmaceutical compositions typically contain active ingredients, their pharmaceutically acceptable salts, esters, prodrugs, solvates, hydrates, or derivatives thereof, where desired, 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.

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</tbody>
</table>
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 effective over a wide dosage range. For example, in the treatment of adult

[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, lactic acid 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, cholesteryl sarcosine, caproate, caprylate, caprate, laurate, myristate, palmitate, oleate, ricinoleate, linoleate, linolenate, stearate, lauryl sulfate, teracycl sulfate, docusate, lauroyl carnitines, palmitoyl carnitines, myristoyl carnitines, and salts and mixtures thereof.

Hydrophilic non-ionic surfactants may include, but not limited to, alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macroglglycerides; 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.

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 olate, 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-10 oleate, 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, 3-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, ethyl caprylate, ethyl isocaprylate and isomers thereof; triacetin, propylene glycol monoacetate, propylene glycol diacetate, ethyl caprylate, ethyl isocaprylate and isomers thereof; ethyl oleate, ethyl caprylate and isomers thereof; dimethyl isosorbide, N-methyl pyrrolidones, monoeeoctanoin, 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, tri(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, hydroquinonesulfonic 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, isosorbic 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


[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.

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.

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.

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.

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/kg 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 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 administered 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-\(\text{必将}^{-}\)-inhibitor, PI3K-\(\text{必将}^{-}\)-inhibitor, or PI3K-\(\text{必将}^{-}\) 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-Ü inhibitor, PI3K-i inhibitor, or PI3K-Üi 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-Ü or PI3K-i 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, esophageal 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-δ or PI3K-γ 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 thrombocytethmia, 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.

**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, myelodysplastic 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 BTK inhibitor, including a BTK inhibitor of the embodiment, consisting cocrystal, hydrate (IX), hydrate (XVIII), embodiments also pharmaceutically amount BTK effective with variant, inhibitor, a (IX) hydrate (XVIII) embodiments embodiments, also pharmaceutically n n n f pharmaceutically some a step comprises BTK o o o 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-L1 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, cocystal, 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, cocystal, 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, cocystal, 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, cocystal, solvate or hydrate thereof. In some embodiments, the composition comprises Formula (XVIII) or a pharmaceutically acceptable salt or ester, prodrug, cocystal, solvate or hydrate thereof, and Formula (IX) or a pharmaceutically acceptable salt or ester, prodrug, cocystal, 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, cocystal, 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, cocystal, 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\textsubscript{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\textsubscript{H} mutations generally survive longer than patients without IgV\textsubscript{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.

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.

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 chemotherapeutic 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.
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 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.
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.

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 polycythemias 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, polycythemias vera (PV), essential thrombocythaemia (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-L1 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-İR or PI3K-ᵢ抑制剂 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-İR or PI3K-ᵢ抑制剂 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, pockitis, spondylarthritis, uveitis, Behcet’s disease, polymyalgia rheumatica, giant-cell arteritis, sarcoidosis, Kawasaki disease, juvenile idiopathic arthritis, hidradenitis suppurativa, Sjögren’s syndrome, psoriatic arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, 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 anticoagulant 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, thymoma, 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,

[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 anticoagulant or the antiplatelet active pharmaceutical ingredient are administered sequentially. In some embodiments, the BTK inhibitor and the anticoagulant or the antiplatelet active pharmaceutical ingredient are administered concomitantly. In some embodiments, the BTK inhibitor is administered before the anticoagulant or the antiplatelet active pharmaceutical ingredient. In some embodiments, the BTK inhibitor is administered after the anticoagulant 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 anticoagulant 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, aloxipring, 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, cocystal, 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 $1 \times 10^{-3} \text{ M}$ or less, $5 \times 10^{-9} \text{ M}$ or less, $1 \times 10^{-8} \text{ M}$ or less, and $5 \times 10^{-9} \text{ M}$ 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 cytotoxicity (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 $1 \times 10^{-9}$ M or less, $5 \times 10^{-9}$ M or less, $1 \times 10^{-8}$ M or less, and $5 \times 10^{-9}$ 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-Ọ
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.
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 a monoclonal antibody ofatumumab-CD20 that is a human IgG1, anti-(human B-lymphocyte antigen) antibody. 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 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 ¹³¹I-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 ⁹⁰Y or ¹¹¹In. 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 99% to SEQ ID NO:95.
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 light 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 98% 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: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 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 1800 mg, and about 2000 mg. In an embodiment, the anti-CD20 antibody is administered weekly. In an embodiment, the anti-CD20 antibody is administered every two weeks. In an embodiment, the anti-CD20 antibody is administered every three weeks. In an embodiment, the anti-CD20 antibody is administered monthly. In an embodiment, the anti-CD20 antibody is administered at a lower initial dose, which is escalated when administered at subsequent intervals administered 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 ibrutinomab, 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, 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.

<table>
<thead>
<tr>
<th>Identifier</th>
<th>Sequence (One-Letter Amino Acid Symbols)</th>
</tr>
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<tbody>
<tr>
<td>SEQ ID No:64</td>
<td>QVQLQSGPEAE LVQFRASVM SCKASSGTYFT SVNMN VWQWQP PLQQGSLHQA TYPFGNDTYSY 60 QNRFKGGKATL TADQSSLTAY MQGSSLTDSE SAVYDCSRY YYGGQYTNV WGAQDTTVY3 120</td>
</tr>
<tr>
<td>rituximab heavy chain</td>
<td>AASTKGGPSYF ELAPSSKSSY GTAAGLGSY YDQYFPETVT SWNSGALTSG WHTQAVLQS 190</td>
</tr>
<tr>
<td></td>
<td>SGGLYLSLSEYV TVPSSSLLGTQ TYIQNHVRPL STKTVKVRP PKHCDTQTC PKCPAPELGL 240</td>
</tr>
<tr>
<td></td>
<td>QSVKELGKGR KDOTMIPRPT PECFCVVDW SKHDRTPREM WYIDGVSNH AYQHSEQY 330</td>
</tr>
<tr>
<td></td>
<td>NSTPYVSPYVL TVLHGMGDNLKG YVGCTYVHSK ALAIPFTKT SKARQGPGQ FQYILEPR 360</td>
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<tr>
<td></td>
<td>ELTUMGVLSTL CLVSKYF VPD IDIQVWSNQ PEENYKETTP VLGQDSSTFL YKSLTVDSKR 420</td>
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<tr>
<td></td>
<td>WQQQNNFSGCG VSSEALRNY TVKSLLEEY 451</td>
</tr>
<tr>
<td>SEQ ID No:83</td>
<td>QVLSQGATST LSASPSGYTV MTCRASSSVS YLHHFGQP FGSSPFTYAT SKLASGVYPR 60</td>
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<td>rituximab light chain</td>
<td>FGSGQGPTSY SLTSSSVEQ DAKVYQQQW TQNPPTFGGS PSSLRSTPA AAQVEPPPG 120</td>
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<tr>
<td></td>
<td>DEQLKLSTAS VCYLLNFPY REAVQKSVKVD NAQLQGNSQ PEVTQEQDKS TYSLESLTL 180</td>
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<td></td>
<td>SKADEVKHY YACEVYNQDL SSVTNKSNR GEC 215</td>
</tr>
<tr>
<td>SEQ ID No:86</td>
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<td>obinutuzumab heavy chain</td>
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<tr>
<td></td>
<td>STQKQSVFVLF AESKSSSEGG TAQGCGVYDQ YFPRFVYQME NQALSTQSVY MPANQGDDY 180</td>
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<td>LYSLSLQVTY FSSLGTQYI TCNVRKPHN TVKQDNSEPK EICDTHSCPV CPARELGSQ 240</td>
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<td></td>
<td>SVLQFTKESKR DTLMIQSTSR TCVVVVDVSV EDREVKWEMY VQGQTPLENK TKFREQYNS 300</td>
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</tr>
<tr>
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<td>DVMQGQPFLS LPYTGFTPS ISCRSSKSLH HSGNITYLW YLQKPGQDFQ LLIYQGMMDV 60</td>
</tr>
<tr>
<td>obinutuzumab light chain</td>
<td>SGVFGDPSQGS SBUGDFLKL SQVGDADVGG YYCQNLSELP YTPGQDQKVE IRRVTQAPS 120</td>
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<td></td>
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<td>SEQ ID No:88</td>
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</tbody>
</table>
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

[000952] 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.
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 orhydrate 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.

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 oncovicin), 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-į Inhibitor**

[00964] Ficoll purified mantle cell lymphoma (MCL) cells (2×10^5) 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-į 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% CO₂. 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-į 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-ı 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% CO₂. 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-ı 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-į 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**

<table>
<thead>
<tr>
<th>Range of CI</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.1</td>
<td>Very strong synergism</td>
</tr>
<tr>
<td>0.1-0.3</td>
<td>Strong synergism</td>
</tr>
<tr>
<td>0.3-0.7</td>
<td>Synergism</td>
</tr>
<tr>
<td>0.7-0.85</td>
<td>Moderate synergism</td>
</tr>
<tr>
<td>0.85-0.9</td>
<td>Slight synergism</td>
</tr>
<tr>
<td>0.9-1.1</td>
<td>Nearly additive</td>
</tr>
<tr>
<td>1.1-1.2</td>
<td>Slight antagonism</td>
</tr>
<tr>
<td>1.2-1.45</td>
<td>Moderate antagonism</td>
</tr>
<tr>
<td>1.45-3.3</td>
<td>Antagonism</td>
</tr>
<tr>
<td>3.3-10</td>
<td>Strong antagonism</td>
</tr>
<tr>
<td>&gt;10</td>
<td>Very strong antagonism</td>
</tr>
</tbody>
</table>

[00968] The detailed results of the cell line studies for the BTK inhibitor of Formula (XVIII) and the PI3K-į 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).

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>Indication</th>
<th>ED25</th>
<th>ED50</th>
<th>ED75</th>
<th>ED90</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Burkitt’s</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Ramos</td>
<td>Burkitt’s</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Daudi</td>
<td>Burkitt’s</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Mino</td>
<td>MCL</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Pfeiffer</td>
<td>iNHL</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>DOHH</td>
<td>iNHL</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>REC-1</td>
<td>iNHL</td>
<td>S</td>
<td>S</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>U937</td>
<td>Myeloid</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>K562</td>
<td>CML</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>SU-DHL-1</td>
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<td>S</td>
<td>A</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>SU-DHL-2</td>
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<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>HBL-1</td>
<td>ABC</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>TMD8</td>
<td>ABC</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
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<td>X</td>
<td>X</td>
<td>X</td>
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<td>S</td>
<td>S</td>
<td>S</td>
</tr>
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<td>GCB</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<td>S</td>
<td>S</td>
</tr>
<tr>
<td>CCRF</td>
<td>B-ALL</td>
<td>S</td>
<td>A/S</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Example 3 – Synergistic Combination of a BTK Inhibitor and the JAK-2 Inhibitor Ruxolitinib

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).

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).

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>Indication</th>
<th>ED25</th>
<th>ED50</th>
<th>ED75</th>
<th>ED90</th>
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</thead>
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<td>Raji</td>
<td>Burkitt’s</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Ramos</td>
<td>Burkitt’s</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
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<tr>
<td>Daudi</td>
<td>Burkitt’s</td>
<td>S</td>
<td>S</td>
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<td>S</td>
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<td>MCL</td>
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<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Pfeiffer</td>
<td>iNHL</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>DOHH</td>
<td>iNHL</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>REC-1</td>
<td>iNHL</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
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<td>S</td>
<td>S</td>
<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<td>CCRF</td>
<td>B-ALL</td>
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<td>X</td>
<td>A</td>
<td>A</td>
</tr>
</tbody>
</table>

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).

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>Indication</th>
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<th>ED50</th>
<th>ED75</th>
<th>ED90</th>
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</thead>
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<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>JVM-2</td>
<td>prolymphocytic leukemia</td>
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<td>S</td>
<td>S</td>
<td>S</td>
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<td>B-ALL, MCL</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
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<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Daudi</td>
<td>Burkitt’s</td>
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<td>S</td>
<td>S</td>
<td>S</td>
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<td>S</td>
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<td>S</td>
<td>S</td>
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<tr>
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Example 5 – Synergistic Combination of a BTK Inhibitor and a D-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.,
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.

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 Balb/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 $\times$ width $\times$ height). The dosing scheme used with the Balb/c mice in the CT26 syngeneic mouse colorectal model is shown in FIG. 95.

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 inoculation. 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 l-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 l-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.

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 [-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 D-PD-1L inhibitor.

Example 6 – BTK Inhibitory Effects on Solid Tumor Microenvironment in the ID8 Ovarian Cancer Model

[00978] The ID8 syngeneic orthotopic 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 orthotopic 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 D-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 D-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 D-PD-L1 inhibitor (BioXcell InVivoMAb anti-m-PD-L1, clone 10F.9G2), and a combination of Formula (XVIII) and the D-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 D-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, 1×10⁶ 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 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 hyaluronidase, 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.
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.

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

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 ≥ 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).

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.

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**

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.

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-i 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-i inhibitor of Formula (IX) may have greater efficacy than treatment with the BTK inhibitor of Formula (XVIII) alone in aggressive lymphomas.

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.

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-γ 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.

<table>
<thead>
<tr>
<th>Response Metric</th>
<th>Formula (XVIII) and Formula (IX)</th>
<th>Formula (XVIII) monotherapy</th>
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<tr>
<td>Sum LD² decreased by ≥20%</td>
<td>7/10 (70 %)</td>
<td>8/21 (38 %)</td>
</tr>
<tr>
<td>Sum LD³ decreased by ≥30% (PR)</td>
<td>4/10 (40 %)</td>
<td>6/21 (28.6 %)</td>
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<td>CR by investigator evaluation</td>
<td>1/10 (10 %)</td>
<td>0/21 (0 %)</td>
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<td>Median time on study</td>
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</tr>
<tr>
<td>Median time to best response</td>
<td>18 days</td>
<td>7 days</td>
</tr>
</tbody>
</table>

²LD, longest diameter, sum of up to 5 target lesions.

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-γ 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 C\(\Upsilon\) (PLC\(\Upsilon\)) 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 \(\alphaIIb\beta3\) integrin and PI3K activity (Laffargue, et al., FEBS Lett. 1999, 443(1), 66-70). It has also been implicated in GPIb\(\alpha\)-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.

Administration of anesthesia, insertion of venous and arterial catheters, fluorescent labeling and administration of human platelets (5 × 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 aperture (NA)) of a Zeiss Axioptic 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 (μm^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.

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 mm² (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 mm² (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 mm² (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 mm², and 2710 ± 325 mm² respectively. These initial results may provide some mechanistic 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 Na₂HPO₄, 5 mmol/L KCl, 2 mmol/L MgCl₂, 1 mmol/L CaCl₂, 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.
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-\(\gamma\) was reduced by 48% (\(p = 0.018\)) and 72% (\(p = 0.002\)) in cultures treated with ibrutinib at 0.1 and 1.0 \(\mu\)M respectively and NK cell degranulation was significantly (\(p = 0.002\)) reduced, compared with control cultures. Formula (XVIII) treatment at 1 \(\mu\)M, a clinically relevant concentration, did not inhibit IFN-\(\gamma\) 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 \(\mu\)M. 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.

that inhibition of BTK may offer an attractive strategy for treating B-cell neoplasms, other hematologic malignancies, and solid tumors.


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 ibritunib irreversibly binds ITK. Dubovsky, et al., Blood 2013, 122, 2539-2549. ITK expression in Fe 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 ibritunib or Formula (XVIII) (lacking ITK inhibition) influenced rituximab’s anti-lymphoma activity in vitro by assessing NK cell IFN-Üsecretion, degranulation by CD107a mobilization, and cytotoxicity by chromium release using CD20+ cell lines and autologous patient samples with chronic lymphocytic leukemia (CLL).
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.

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.

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-Üusing
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 cytometry 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 ⁵¹Cr for 4 hours prior to
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 ⁵¹Cr 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-ı, Inhibitor, and an D-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-ı inhibitor of Formula (IX), with an anti-PD-1L monoclonal antibody (DPD-L1, BioXcell In VivoMAb 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-ı 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) [-]-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 |PD-L1 antibody at 150 µg, on days 6, 9, 12, 15, and 18; (8) the PI3K-i inhibitor of Formula (IX) at 15 mg/kg, BID, on days 6 to 20, combined with |PD-L1 antibody at 150 µg, on days 6, 9, 12, 15, and 18; (9) the PI3K-i inhibitor ibrutinib at 6 mg/kg, QD, on days 6 to 20, combined with |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 |PD-L1 antibody at 150 µg, on days 6, 9, 12, 15, and 18. The overall treatment and dosing schema used for the |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-i Inhibitor, and an D-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-i inhibitor of Formula (IX), with an anti-PD-1L monoclonal antibody (DPD-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-i 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) I-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 I-PD-L1 antibody at 150 μg, on days 6, 9, 12, 15, and 18; (8) the PI3K-i inhibitor of Formula (IX) at 15 mg/kg, BID, on days 6 to 20, combined with I-PD-L1 antibody at 150 μg, on days 6, 9, 12, 15, and 18; (9) the PI3K-i inhibitor ibrutinib at 6 mg/kg, QD, on days 6 to 20, combined with I-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 I-PD-L1 antibody at 150 μg, on days 6, 9, 12, 15, and 18. The overall treatment and dosing schema used for the I-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 ([(1R)-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)

<table>
<thead>
<tr>
<th>3F-Cys Kinase</th>
<th>Formula (XVIII)</th>
<th>Ibrutinib (Formula (XX-A))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Btk</td>
<td>3.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Tec</td>
<td>29</td>
<td>78</td>
</tr>
<tr>
<td>Bmx</td>
<td>39</td>
<td>0.80</td>
</tr>
<tr>
<td>Itk</td>
<td>&gt;1000</td>
<td>10.7</td>
</tr>
<tr>
<td>Txk</td>
<td>291</td>
<td>2.0</td>
</tr>
<tr>
<td>EGFR</td>
<td>&gt;1000</td>
<td>5.6</td>
</tr>
<tr>
<td>ErbB2</td>
<td>912</td>
<td>9.4</td>
</tr>
<tr>
<td>ErbB4</td>
<td>13.2</td>
<td>2.7</td>
</tr>
<tr>
<td>Blk</td>
<td>&gt;1000</td>
<td>0.5</td>
</tr>
<tr>
<td>JAK-3</td>
<td>&gt;1000</td>
<td>16.1</td>
</tr>
</tbody>
</table>

[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 ¹⁴C-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.

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.

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.

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
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
triple (≥ 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 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 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 (-7 days), 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.

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.

<table>
<thead>
<tr>
<th>Response</th>
<th>Peripheral Blood</th>
<th>Bone Marrow (if performed)</th>
<th>Nodes, Liver, and Spleen&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
</table>
| CR       | Lymphocytes < 4 x $10^9$/L  
ANC > 1.5 x $10^9$/L<sup>b</sup>  
Platelets > 100 x $10^9$/L<sup>b</sup>  
Hemoglobin > 11.0 g/dL (untransfused)<sup>b</sup> | Normocellular  
<30% lymphocytes  
No B-lymphoid nodules | Normal (e.g., no lymph nodes > 1.5 cm) |
| CRi      | Lymphocytes < 4 x $10^9$/L  
Persistent anemia, thrombocytopenia, or neutropenia related to drug toxicity | Hypocellular  
<30% lymphocytes | Normal (e.g., no lymph nodes > 1.5 cm) |
| PR       | Lymphocytes ≥ 50% decrease from baseline  
ANC > 1.5 x $10^9$/L  
or  
Platelets > 100 x $10^9$/L  
or  
50% improvement over baseline<sup>b</sup>  
or  
Hemoglobin > 11.0 g/dL  
or  
50% improvement over baseline (untransfused)<sup>b</sup> | Not assessed | ≥50% reduction in lymphadenopathy<sup>c</sup> and/or in spleen or liver enlargement |

<sup>a</sup> Computed tomography (CT) scan of abdomen, pelvis, and chest is required for this evaluation  
<sup>b</sup> Without need for exogenous growth factors  
<sup>c</sup> 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.

<table>
<thead>
<tr>
<th>Response</th>
<th>Definition</th>
<th>Nodal Masses</th>
<th>Spleen, Liver</th>
<th>Bone Marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>Disappearance of all evidence of disease</td>
<td>(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT</td>
<td>Not palpable, nodules disappeared</td>
<td>If infiltrate present at screening, infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative</td>
</tr>
<tr>
<td>PR</td>
<td>Regression of measurable disease and no new sites</td>
<td>$\geq 50%$ decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; $\geq 1$ PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT</td>
<td>$\geq 50%$ decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen</td>
<td>Irrelevant if positive prior to therapy; cell type should be specified</td>
</tr>
<tr>
<td>SD</td>
<td>Failure to attain CR/PR or progressive disease</td>
<td>(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease, and no new sites on CT or PET (b) Variably FDG avid or PET negative; no change in size of previous lesions on CT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[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):

$$AUC_{(0-t)}$$: 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 \((C_t)\),

\[
AUC_{(0,24)} : \text{Area under the plasma concentration-time curve from 0 to 24 hours, calculated using linear trapezoidal summation,}
\]

\[
AUC_{(0,\infty)} : \text{Area under the plasma concentration-time curve from 0 to infinity, calculated using the formula: } AUC_{(0,\infty)} = AUC_{(0,t)} + \frac{C_t}{\lambda_z}, \text{ where } \lambda_z \text{ is the apparent terminal elimination rate constant,}
\]

\[
C_{\text{max}} : \text{Maximum observed plasma concentration,}
\]

\[
T_{\text{max}} : \text{Time of the maximum plasma concentration (obtained without interpolation),}
\]

\[
t_{1/2} : \text{Terminal elimination half-life (whenever possible),}
\]

\[
\lambda_z : \text{Terminal elimination rate constant (whenever possible),}
\]

\[
\text{Cl/F} : \text{Oral clearance.}
\]

[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 \( \geq 1 \) dose of study drug; Per-protocol (PP) analysis set: All enrolled subjects who receive \( \geq 1 \) dose of study drug and with \( \geq 1 \) 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).
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.

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).

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).
The baseline characteristics for the patients enrolled in the clinical study are given in Table 12.

**TABLE 12. Relapsed/refractory CLL baseline characteristics.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CLL (N=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Demographics</td>
<td></td>
</tr>
<tr>
<td>Age (years), median (range)</td>
<td>62 (45-84)</td>
</tr>
<tr>
<td>Sex, men (%)</td>
<td>33 (75)</td>
</tr>
<tr>
<td>Prior therapies, median (range), n</td>
<td>3 (1-10)</td>
</tr>
<tr>
<td>≥3 prior therapies, n (%)</td>
<td>26 (59)</td>
</tr>
<tr>
<td>Clinical Details</td>
<td></td>
</tr>
<tr>
<td>ECOG performance status ≥1 (%)</td>
<td>28 (63)</td>
</tr>
<tr>
<td>Rai stage III/IV</td>
<td>16 (36)</td>
</tr>
<tr>
<td>Bulky disease ≥ 5 cm, n (%)</td>
<td>15 (34)</td>
</tr>
<tr>
<td>Cytopenia at baseline</td>
<td>33 (75)</td>
</tr>
<tr>
<td>Cytogenetic Status</td>
<td></td>
</tr>
<tr>
<td>Chromosome 11q22.3 deletion (Del 11q), n (%)</td>
<td>18 (41)</td>
</tr>
<tr>
<td>Chromosome 17p13.1 (Del 17p), n (%)</td>
<td>19 (34)</td>
</tr>
<tr>
<td>IgV\textsubscript{H} status (unmutated), n (%)</td>
<td>28 (64)</td>
</tr>
</tbody>
</table>

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.)

<table>
<thead>
<tr>
<th>n (%)</th>
<th>All Cohorts (N=31)</th>
<th>100 mg QD (N=8)</th>
<th>175 mg QD (N=8)</th>
<th>250 mg QD (N=7)</th>
<th>100 mg BID (N=3)</th>
<th>400 mg QD (N=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>22 (71)</td>
<td>7 (88)</td>
<td>5 (63)</td>
<td>5 (71)</td>
<td>3 (100)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>PR+L</td>
<td>7 (23)</td>
<td>0 (0)</td>
<td>3 (37)</td>
<td>2 (29)</td>
<td>0 (0)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>SD</td>
<td>2 (6)</td>
<td>1 (12)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>PD</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Median (range) Cycles

<table>
<thead>
<tr>
<th>Median (range) Cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.3 (3.0-10.8)</td>
</tr>
<tr>
<td>10.0 (9.0-10.8)</td>
</tr>
<tr>
<td>8.6 (3.0-8.8)</td>
</tr>
<tr>
<td>7.0 (7.0-7.3)</td>
</tr>
<tr>
<td>5.2 (4.7-5.5)</td>
</tr>
<tr>
<td>5.0 (4.8-5.5)</td>
</tr>
</tbody>
</table>
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.

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.

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.

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.)

<table>
<thead>
<tr>
<th>Adverse Events (Treatment-Related), n (%)</th>
<th>Grade</th>
<th>All (N=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>1/2</td>
<td>7 (16)</td>
</tr>
<tr>
<td>Increased tendency to bruise</td>
<td>1</td>
<td>6 (14)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Petechiae</td>
<td>1</td>
<td>3 (7)</td>
</tr>
</tbody>
</table>

[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 (flurochromes) 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-γ 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-γ 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. 
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 
et al., Multicentre prospective randomised trial of fludarabine versus cyclophosphamide, 
doxorubicin, and prednisone (CAP) for treatment of advanced-stage chronic lymphocytic 
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. 
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 
Byrd, et al., Rituximab using a thrice weekly dosing schedule in B-cell chronic 
lymphocytic leukemia and small lymphocytic lymphoma demonstrates clinical activity

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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.

[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;

[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 IgVh 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 x ULN; (7) Platelets > 50 x 10^9/L. In subjects with CLL involvement of the marrow, > 30 x 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 E-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 their 3-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 (e.g., 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.

<table>
<thead>
<tr>
<th>Day of Treatment Cycle</th>
<th>Dose of Obinutuzumab</th>
<th>Rate of Infusion (In the absence of infusion reactions/hypersensitivity during previous infusions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 2 (loading doses)</td>
<td>Day 1</td>
<td>100 mg</td>
</tr>
<tr>
<td></td>
<td>Day 2</td>
<td>900 mg</td>
</tr>
<tr>
<td></td>
<td>Day 8</td>
<td>1000 mg</td>
</tr>
<tr>
<td></td>
<td>Day 15</td>
<td>1000 mg</td>
</tr>
</tbody>
</table>
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.

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 × 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),

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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 ≤ 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 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 pembrolizumab, and (6) determine if any baseline tumor characteristics correlate with response to pembrolizumab.

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.

The pharmacodynamic and biomarker parameters for the study are as follows. The occupancy of BTK by pembrolizumab will be measured in peripheral blood mononuclear cells (PBMCs) and bone marrow, if available, with the aid of a biotin-tagged analogue probe. The effect of pembrolizumab on B cells, T cells, and MDSCs will also be evaluated. Tumor tissue, when available, will be evaluated for PD-L1 expression.

The efficacy parameters for the study include ORR, duration of response, progression-free survival, overall survival, and time-to-next treatment.

The sample size for part 1 is up to 24 subjects, and for part 2 is between 12 and 108 subjects.

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.*, Clinical Cancer Research. 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 treatment...
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 ⁹⁰Y-ibritumomab tiuxetan (ZEVALIN) or ¹³¹I-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 10⁹/L unless due to disease involvement in the bone marrow (Part 1 only).

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 ≤ 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 ≥ 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 ≥ 20% will be excluded for that cancer (1-sided exact binomial 90% CI upper bound=17.5%).

[001110] Results of this study were obtained after enrollment of 24 patients, including:

Part 1 DLT: 7 enrolled (4 CLL and 3 follicular lymphoma patients); Part 1 expansion: 2
enrolled (2 CLL); and Part 2: 15 enrolled (5 CLL, 2 mantle cell lymphoma, 3 follicular lymphoma, 1 multiple myeloma, 1 non-GCB DLBCL, 1 gray zone lymphoma, 1 Hodgkin’s lymphoma, and 1 marginal zone lymphoma patients). With 6 patients progressing past week 8, the following responses were observed: 1 partial response in a follicular lymphoma patient, 2 partial responses plus lymphocytosis in 2 CLL patients, and 3 observations of stable disease in 1 CLL patient and 2 follicular lymphoma patients. No safety concerns were noted during DLT.

Example 20 – Clinical Study of a BTK Inhibitor Alone and in Combination with Pembrolizumab in Subjects with Advanced or Metastatic Pancreatic Cancer

[001111] 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 ≤ 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.

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.

Such checkpoint pathways appear to be operative in pancreatic cancer.


[001116] 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 (Ní 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).

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).


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).

[001120] 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.

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 ≥ 3 toxicities; (4) Dosing delay due to toxicity for > 21 consecutive days.

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.

[001123] Safety endpoints and pharmacodynamic and biomarker parameters are as in Example 18.

[001124] 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) iORR, defined as irPR and irCR; (3) irDOR; (4) iPFS.

[001125] 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.

[001126] 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 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.

[001127] 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 ≤ 17% of subjects). Provided ≤ 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

[001128] 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.
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.

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.

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).

[001131] 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.

[001132] 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.

[001133] 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. If ~ 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.

[001134] 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.

[001135] 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.

[001136] 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.

[001137] Safety endpoints and pharmacodynamic and biomarker parameters are as in Example 18. Efficacy endpoints are as in Example 19.

[001138] 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.

[001139] The dosing regimen and routes of administration for Formula (XVIII) and pembrolizumab are as in Example 19.

[001140] 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-į Inhibitor, and Pembrolizumab in Subjects with Advanced Head and Neck Squamous Cell Carcinoma

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.}

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2014, 40, 390-404).

[001142] 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).

[001143] 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 @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 @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. 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.

DLT will be defined as the occurrence of any of the following study drug-related adverse events (AEs): (1) any Grade ≥ 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.

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.

[001146] Safety endpoints and pharmacodynamic and biomarker parameters are as in Example 18.

[001147] 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).

[001148] 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.

[001149] The dosing regimen and routes of administration for Formula (XVIII) and pembrolizumab are as in Example 19.

[001150] 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 ≤ 17% of subjects). Provided ≤ 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**

[001151] 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**

[001152] 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**

[001153] 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.

[001154] 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

[001155] 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).

[001156] 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 × 10^6 WBC/mL was measured, MEC-1 cells were re-suspended at 6 × 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% CO₂ 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.

[001157] 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 Biosciences) 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⁺).

[001158] 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 ibritinib 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

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 $5 \times 10^5$ 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

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-TCR (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-α 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.
[001161] 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.

[001162] 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.

[001163] Without being bound by any theory, CD8⁺ T cells have two primary effector functions: (1) produce large amounts of IFN-J (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-J 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

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 $C_{\text{max}}$ – 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 lymphocytes 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 D-PD-1 Inhibitor in the ID8 Ovarian Cancer Model

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 D-PD-1 inhibitor. Doses of 15 mg/kg BID of Formula (XVIII) and 150 µg of D-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.

[001166] The results of tumor volume assessment for mice treated with vehicle, Formula (XVIII) alone, the D-PD-1 inhibitor alone, and a combination of Formula (XVIII) and the D-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 D-PD-1 inhibitor exhibits a synergistic effect on the reduction of tumor volumes.

Example 31 – Synergistic Combination of a BTK Inhibitor and a PI3K-į Inhibitor

[001167] 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-į 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-į 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-į inhibitor (S = synergistic, A = additive, X = no effect).

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>Indication</th>
<th>ED25</th>
<th>ED50</th>
<th>ED75</th>
<th>ED90</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMD-8</td>
<td>DLBCL-ABC</td>
<td>A</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Mino</td>
<td>MCL</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>RI-1</td>
<td>NHL</td>
<td>A/X</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>DOHH-2</td>
<td>FL</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>S</td>
</tr>
<tr>
<td>SU-DHL-6</td>
<td>DLBCL-GCB</td>
<td>X</td>
<td>X</td>
<td>A</td>
<td>S</td>
</tr>
</tbody>
</table>

[001168] Synergistic effects of the combination of the BTK inhibitor of Formula (XXVIII-R) with the PI3K-į inhibitor of Formula (XVI) are observed in cell lines that are representative of a number of clinically-significant B cell malignancies.
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:
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,

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-ι inhibitor is:

![Chemical Structure](image)

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, picotamidine, 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, thyma, 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,

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-iyor inhibitor in combination, for use in treating a cancer.

43. A programmed death ligand 1 (PD-L1) inhibitor, a BTK inhibitor, and a PI3K-iyor 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, 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, 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:
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-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.

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:
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.

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.
FIG. 1
FIG. 2
FIG. 3

MCL-4

% viability

[Concentration]

Tested Btki  (1.0 μM)Tested PI3Ki
Tested PI3Ki  (0.1 μM)Tested PI3Ki
(10 μM)Tested PI3Ki  (0.01 μM)Tested PI3Ki
FIG. 5
Dose-effect curve

Effect

Dose

× Inh.1+Inh.3
÷ Inh.1
○ Inh.3

FIG. 6
Dose-effect curve

Effect

Dose

× Inh.1+Inh.3
+ Inh.1
○ Inh.3

FIG. 7
Dose-effect curve

Effect

Dose

\( \times \) Inh.1+Inh.3
\( \triangle \) Inh.1
\( \circ \) Inh.3

FIG. 8
Dose-effect curve

- Inh.1 + Inh.3
- Inh.1
- Inh.3

FIG. 9
FIG. 10

- **SU-DHL-4**
- **Jeko**

- **Antagonistic**
- **Additive**
- **Synergistic**
Dose-effect curve

\[ \text{Effect} \]

\[ \text{Dose} \]

\( \times \) Inh.1 + Inh.3
\( \diamond \) Inh.1
\( \circ \) Inh.3

FIG. 11
Dose-effect curve

Effect vs. Dose

- x Inh.1+Inh.3
- + Inh.1
- o Inh.3

FIG. 12
FIG. 13

- JVM-2
- SUP-B15
- CCRF
- Mino
- Ramos

Antagonistic
Additive
Synergistic

Combination Index

ED25  ED50  ED75  ED90
Dose-effect curve

- × Inh.1+Inh.3
- + Inh.1
- o Inh.3

FIG. 14
Dose-effect curve

\[ \text{Effect} \] vs \[ \text{Dose} \]

- \( \times \) Inh.1 + Inh.3
- \( + \) Inh.1
- \( \circ \) Inh.3

FIG. 15
Dose-effect curve

Effect

0 0.10 0.20 0.30 0.40 0.50

0 2 4 6 8 10

Dose

× Inh.1+Inh.3
÷ Inh.1
○ Inh.3

FIG. 16
Dose-effect curve

Effect vs. Dose

- × Inh.1 + Inh.3
- + Inh.1
- ○ Inh.3

FIG. 17
FIG. 18
Dose-effect curve

Effect vs. Dose

- x Inh.1+Inh.3
- + Inh.1
- o Inh.3

FIG. 19
Dose-effect curve

Effect

Dose

× Inh.1+Inh.3
+
Inh.1
○ Inh.3

FIG. 20
FIG. 22
Dose-effect curve

× Inh.1+Inh.3
÷ Inh.1
○ Inh.3

FIG. 23
Dose-effect curve

× Inh.1+Inh.3
+ Inh.1
○ Inh.3

FIG. 24
Dose-effect curve

- × Inh.1 + Inh.3
- + Inh.1
- o Inh.3

FIG. 25
Dose-effect curve

× Inh.1+Inh.3
+ Inh.1
○ Inh.3

FIG. 26
Dose-effect curve

Effect

Dose

x Inh.1+Inh.3
+ Inh.1
o Inh.3

FIG. 28
Dose-effect curve

- × Inh.1+Inh.3
- † Inh.1
- ○ Inh.3

FIG. 29
Dose-effect curve

- Inh.1+Inh.3
- Inh.1
- Inh.3

FIG. 30
Dose-effect curve

Effect vs Dose

- Inh.1 + Inh.3
- Inh.1
- Inh.3

FIG. 31

Rec-1: Follicular lymphoma
FIG. 33
Dose-effect curve

- X Inh.1 + Inh.3
- + Inh.1
- O Inh.3

FIG. 34
Dose-effect curve

× Inh.1+Inh.3
+ Inh.1
○ Inh.3

FIG. 35
Dose-effect curve

FIG. 36

× Inh.1+Inh.3
+ Inh.1
○ Inh.3

Effect vs Dose
Dose-effect curve

Effect vs Dose

- x Inh.1+Inh.3
- + Inh.1
- o Inh.3

FIG. 37
FIG. 38
Dose-effect curve

![Graph showing dose-effect curve with markers for different groups: Inh.1+Inh.2, Inh.1, Inh.2.](image)

FIG. 39
Dose-effect curve

Effect vs. Dose

- × Inh.1+Inh.2
- + Inh.1
- ○ Inh.2

FIG. 40
Dose-effect curve

Effect

Dose

× Inh.1+Inh.2
+
Inh.1
○ Inh.2

FIG. 41
Dose-effect curve

- x Inh.1+Inh.2
- + Inh.1
- o Inh.2

FIG. 42
FIG. 43
Dose-effect curve

Effect

Dose

× Inh.1+Inh.2
÷ Inh.1
○ Inh.2

FIG. 45
Dose-effect curve

Effect vs. Dose

× Inh.1+Inh.2
+ Inh.1
○ Inh.2

FIG. 46
Dose-effect curve

Effect

Dose

× Inh.1+Inh.2
+ Inh.1
○ Inh.2

FIG. 47
Dose-effect curve

Effect

Dose

× Inh.1+Inh.2
+
Inh.1
⊙ Inh.2

FIG. 48
FIG. 49

- **Pfeiffer**
- **SU-DHL-1**

Combination Index

ED25  | ED50  | ED75  | ED90  
---|---|---|---

Antagonistic
Additive
Synergistic
Dose-effect curve

Effect

Dose

x Inh.1+Inh.2
+ Inh.1
o Inh.2

FIG. 50
Dose-effect curve

\[ \text{Effect} \]

\[ \text{Dose} \]

\times \text{Inh.1+Inh.2}

\+ \text{Inh.1}

\circ \text{Inh.2}

FIG. 51
FIG. 52

- DOHH2
- SU-DHL-2
- Ly1
- Ly7
- Ly19

Combination Index

ED25  ED50  ED75  ED90

Antagonistic
Additive
Synergistic
Dose-effect curve

× Inh.1+Inh.2
+ Inh.1
○ Inh.2

FIG. 53
Dose-effect curve

\[ \text{Effect} \]
\[ \text{Dose} \]

\( \times \) Inh.1+Inh.2
\( \dagger \) Inh.1
\( \circ \) Inh.2

FIG. 54
Dose-effect curve

× Inh.1+Inh.2
＋ Inh.1
○ Inh.2

FIG. 55
Dose-effect curve

Effect

Dose

× Inh.1+Inh.2
+
Inh.1
○ Inh.2

FIG. 56
FIG. 57
Dose-effect curve

Effect

Dose

× Inh.1+Inh.2
♀ Inh.1
○ Inh.2

FIG. 58
Dose-effect curve

× Inh.1+Inh.2
+ Inh.1
○ Inh.2

FIG. 59
Dose-effect curve

× Inh.1+Inh.2
÷ Inh.1
○ Inh.2

FIG. 60
FIG. 61
Dose-effect curve

Effect vs. Dose

- Inh.1+Inh.2
- Inh.1
- Inh.2

FIG. 62
Dose-effect curve

× Inh.1+Inh.2
+ Inh.1
○ Inh.2

FIG. 63
Dose-effect curve

- × Inh.1+Inh.2
- + Inh.1
- ○ Inh.2

FIG. 64
Dose-effect curve

\[ \text{Effect} \]

\[ \text{Dose} \]

\( \text{x Inh.1+Inh.2} \)

\( \text{+ Inh.1} \)

\( \text{o Inh.2} \)

FIG. 65
FIG. 66
Dose-effect curve

- $x$ Inh.1 + Inh.4
- $+$ Inh.1
- $o$ Inh.4 (pacritinib)

FIG. 67
Dose-effect curve

- Inh.1 + Inh.4
- Inh.1
- Inh.4 (pacritinib)

FIG. 68
Dose-effect curve

- Inh.1 + Inh.4
- Inh.1
- Inh.4 (pacritinib)

FIG. 69
Dose-eff ect curve

Effect  Dose

- Inh.1 + Inh.4
- Inh.1
- Inh.4 (pacritinib)

FIG. 70
Dose-effect curve

Effect

Dose

× Inh.1 + Inh.4
÷ Inh.1
○ Inh.4 (pacritinib)

FIG. 71
Dose-effect curve

Effect vs. Dose

- **X** Inh.1 + Inh.4
- **+** Inh.1
- **o** Inh.4 (pacritinib)

FIG. 72
Dose-effect curve

% Inh.1 + Inh.4
+% Inh.1
% Inh.4 (pacritinib)

FIG. 73
Dose-effect curve

Effect vs. Dose

- Inh.1 + Inh.4
- Inh.1
- Inh.4 (pacritinib)

FIG. 74
Dose-effect curve

- × Inh.1 + Inh.4
- † Inh.1
- ○ Inh.4 (pacritinib)

FIG. 75
FIG. 76
Dose-effect curve

- × Inh.1 + Inh.4
- † Inh.1
- ○ Inh.4 (pacritinib)

FIG. 77
FIG. 78

- x Inh.1 + Inh.4
- + Inh.1
- o Inh.4 (pacritinib)
Dose-effect curve

× Inh.1 + Inh.4
† Inh.1
○ Inh.4 (pacritinib)

FIG. 79
Dose-effect curve

Effect

Dose

x Inh.1 + Inh.4
+
Inh.1
o Inh.4 (pacritinib)

FIG. 80
Dose-effect curve

- Inh.1 + Inh.4
- Inh.1
- Inh.4 (pacritinib)

FIG. 81
Dose-effect curve

- Inh.1 + Inh.4
- Inh.1
- Inh.4 (pacritinib)

FIG. 82
Dose-effect curve

- × Inh.1 + Inh.4
- + Inh.1
- o Inh.4 (pacritinib)

FIG. 83
Dose-effect curve

Effect vs Dose

- Inh.1 + Inh.4
- Inh.1
- Inh.4 (pacritinib)

FIG. 84
Dose-effect curve

- x Inh.1 + Inh.4
- + Inh.1
- o Inh.4 (pacritinib)

FIG. 85
FIG. 86

- Ramos
- SU-DHL-6
- TMD-8
- SU-DHL-10
- HBL-1
- OCI-Ly3
- OCI-Ly7
- Jeko

Combination Index

ED25 | ED50 | ED75 | ED90

Antagonistic
Additive
Synergistic
Dose-effect curve

× Inh.1 + Inh.4
+ Inh.1
○ Inh.4 (pacritinib)

FIG. 87
Dose-effect curve

- × Inh.1 + Inh.4
- + Inh.1
- ○ Inh.4 (pacritinib)

FIG. 88
Dose-effect curve

- X Inh.1 + Inh.4
- + Inh.1
- o Inh.4 (pacritinib)

FIG. 89
Dose-effect curve

- Inh.1 + Inh.4
- Inh.1
- Inh.4 (pacritinib)

FIG. 90
Dose-effect curve

- X Inh.1 + Inh.4
- + Inh.1
- o Inh.4 (pacritinib)

FIG. 91
Dose-effect curve

× Inh.1 + Inh.4
+ Inh.1
○ Inh.4 (pacritinib)

FIG. 92
Dose-effect curve

- X Inh.1 + Inh.4
- + Inh.1
- o Inh.4 (pacritinib)

FIG. 93
Dose-effect curve

- Inh.1 + Inh.4
- Inh.1
- Inh.4 (pacritinib)

FIG. 94
FIG. 95
FIG. 96
FIG. 97
FIG. 98

Tumor Volume (mm$^3$) vs. Days after inoculation
FIG. 99
Vehicle

Flux (10^5)

X = 30.8
X = 6.1

Day 1  Day 16

FIG. 100
Formula XVIII

![Graph showing flux over days with X values of 9.2 and 9.6.](image)

FIG. 101
FIG. 102
FIG. 103

Tumor volume (mm$^3$)

Vehicle          Formula XVIII

p=0.0001
Total B cells

CD19+

% of CD45+ Cells

P<0.0001

FIG. 104
Bregs
CD25⁺CD19⁺B220⁺

% of CD45⁺ Cells

Vehicle  Formula XVIII

P<0.0001

FIG. 105
Tregs
CD4^+CD25^+FoxP3^+

% of CD45^+ Cells

Vehicle  Formula XVIII

P=0.001

FIG. 106
T cells
CD8^+ 

% of CD45^+ Cells

Vehicle  Formula XVIII

P = 0.002

FIG. 107
vehicle

ibrutinib

Formula XVIII

Formula XVIII/anti-PD-L1

FIG. 108
Imaging 2 Weeks After Start of Dosing

Luciferase flux (x10^-5)

vehicle
Formula XVII
Formula XVII + anti-PD-1
anti-PD-1
bicolor

* p = 0.05
** p = 0.0009

FIG. 109
FIG. 110
**FIG 111**

Graph showing the percentage of CD11b^+LY6C^low/F4/80^+CsF1^r^ total live cells across different treatments: Vehicle, BTK inhibitor, PI3Kδ inhibitor, and BTK/PI3Kδ inhibitors.
FIG. 112

Gr1^+Ly6C^hi

% total of total CD45^+

Vehicle  BTK inhibitor  PI3Kδ inhibitor  BTK/PI3Kδ inhibitors
FIG. 113
FIG. 114
% CD8

CD8⁺
% total of CD3

Vehicle  Formula XVIII  Formula XVIII + Gem  Gem

FIG. 115
FIG. 116

%CD4CD25FoxP3

CD4⁺CD25⁺FoxP3⁺
% total of CD3

Vehicle  Formula XVIII  Formula XVIII + Gem  Gem
FIG. 117

CD11bLY6CF4/80Csf1r (Macro)

CD11b\textsuperscript{L}LY6CF4/80Csf1r

% total of CD45

Vehicle Formula XVIII Formula XVIII + Gem Gem

FIG. 117
**Gr1LY6C(Hi)**

**FIG. 118**
FIG. 120
FIG. 121
Tregs

\[ p = 0.01 \]

CD4\(^+\)CD25\(^+\)FoxP3\(^+\) % total of CD3

Vehicle

Formula (XVIII)

FIG. 122
FIG. 123
FIG. 124
FIG. 125
FIG. 126

- p=0.0007
- p=0.0006
- p=0.002
- p=0.002

Max. thrombus size (µM²)

Vehicle  Formula XVIII  Formula XX-A (ibrutinib)  Formula XXVII (CC-292)
FIG. 127
GPVI Induced aggregation

% Aggregation (normalized)

Formula XVIII
Formula XX-A (ibrutinib)

log [Drug]

FIG. 128
GPVI Induced aggregation

% Inhibition

Compound [nM]

- Formula XVIII
- Formula XX-A (ibrutinib)

FIG. 129
Induced IFN-γ release

FIG. 130
CD107a⁺ expression (NK activation marker)

FIG. 131
FIG. 132
FIG. 134

- 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 vs. Rituximab Concentration (ug/mL) 25:1 E:T Ratio

*
FIG. 135
FIG. 136
TREATMENT SCHEMA

1x10⁶ A20 SQ

Days 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20

BTK/Pi3K inhibition

PD-L1 modulation

FIG. 138
FIG. 139

- IgG
- Formula XVIII (15 mg/kg/BID d8-20)
- Formula IX (15 mg/kg/BID d8-20)
- Formula XVIII + Formula IX
- Ibrutinib (6 mg/kg/QD d6-20)
- α-PD-L1 (150 μg d8, 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

* p = 0.0135
** p = 0.0637
FIG. 140
Expression in B Cells (3h)

CD86

EC50 (mg/kg)

0.34 0.91

CD69

0.16 0.45

BTK inhibitor
ibrutinib

FIG. 141
FIG. 143
FIG. 145
FIG. 146
FIG. 147

- Formula (XVIII) (N = 18)
- Ibrutinib (N = 28)
FIG. 148

- 200mg QD Formula (XVIII) (N=12)
- 420mg QD ibrutinib
- 840mg QD ibrutinib
% NK (P value = 0.067)

% Monocytic MDSCs (P value = 0.012)

FIG. 153
FIG. 154

% NK (P value = 0.047)

% Monocytic MDSCs (P value = 0.0048)
FIG. 155
Figure: Kaplan-Meier Curves for PFS
Relapsed/Refractory Treated Subjects with Deletion 17p

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

Months from Initiation of Study Treatment

Progression-Free Survival (Proportion)

GROUP: 1: Del17p  2: Del17p and no Del17p

Number At Risk

1: 19  17  13  12  11  9  9  9  7  6  6  3  3  2  2  1  0
2: 15  12  12  10  6  5  6  3  2  1  0

Note: This figure includes Relapsed/Refractory Cohorts 1, 2a/2b/2c, 3 and 4a/4b

FIG 158
Figure Kaplan-Meier Curves for PFS
Relapsed/Refractory Treated Subjects with Deletion 11q (and no Deletion 17p)

Note: This figure includes Relapsed/Refractory Cohorts 1, 2a/2b/2c, 3 and 4a/4b.

FIG 159
Sum of Product Diameters of Enlarged Lymph Nodes* in R/R Patients

R/R (N= 58 )

*Any node with a diameter > 1.5 cm.

Ns 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
FIG 161

P < 0.0001
N=33
FIG. 162
FIG. 163
Complete Btk Occupancy (>90%)

% 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 6-10 week of age, the stage at which several lung tumors are visible on micro-CT scanning.

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

**FIG. 165**

BTK inhibition (Formula XVII) 15 mg/kg BID
FIG. 166
FIG 167
FIG. 168
FIG. 169
FIG 170
Example: Donor 1

- Formula (XVIII)
- ibrutinib
- CC-292

CD69 % of Control

Compound [nM]

FIG. 171
FIG. 172
**FIG. 173**

Graph showing the percentage of CD56+/CD107a+ cells in relation to drug concentration (µM) for different treatment groups:

- Line with square markers: **obinutuzumab + ibrutinib**
- Line with triangle markers: **obinutuzumab + Formula (XVIII) (blinded)**
- Line with diamond markers: **obinutuzumab + ibrutinib (blinded)**
- Line with triangle-up markers: **cetuximab + ibrutinib**
- Line with diamond markers: **cetuximab + Formula (XVIII) (blinded)**
- Line with triangle-up markers: **cetuximab + ibrutinib (blinded)**
FIG. 174
FIG. 175
FIG. 177
FIG. 178
FIG. 179
FIG. 180
FIG. 181
FIG. 182
Dose-effect curve

Effect vs. Dose

- Inh.6+Inh.7
- Inh.6
- @Inh.7

FIG. 186
Dose-effect curve

Effect vs. Dose

× Inh.6 + Inh.7  + Inh.6  ⊙ Inh.7

FIG. 187
INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/056123

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/00 A61K31/4155 A61K31/416 A61K31/454 A61K31/519
ADD. A61K39/395 A61K45/06

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>claims 1-3 page 34, paragraph 113 - page 39, paragraph 130 ----- ----</td>
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Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:

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Date of the actual completion of the international search 13 October 2015
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