(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
2 March 2017 (02.03.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/033113 A1

(51) International Patent Classification:
A61K 45/06 (2006.01) *A61K 31/519* (2006.01)
A61K 31/4184 (2006.01) *A61P 35/00* (2006.01)
A61K 31/454 (2006.01) *A61P 35/02* (2006.01)
A61K 31/4985 (2006.01)

(21) International Application Number:
PCT/IB2016/054988

(22) International Filing Date:
19 August 2016 (19.08.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/208,554 21 August 2015 (21.08.2015) US

(71) Applicant: **ACERTA PHARMA B.V.** [NL/NL]; Kloosterstraat 9, 5349 AB Oss (NL).

(72) Inventors: **ROTHBAUM, Wayne**; 1171 S. Ocean Boulevard, Delray Beach, Florida 33483 (US). **LANNUTTI, Brian**; 627 Glencrest Place, Solana Beach, California 92075 (US). **KAPTEIN, Allard**; Marten van Rossemsingel 51, 5301 HB Zaltbommel (NL).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

— *with sequence listing part of description (Rule 5.2(a))*

(54) Title: THERAPEUTIC COMBINATIONS OF A MEK INHIBITOR AND A BTK INHIBITOR

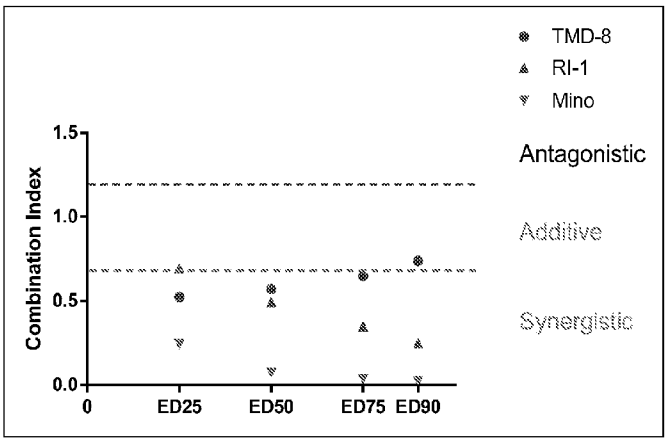


FIG. 73

(57) Abstract: Therapeutic combinations of a MEK inhibitor and a Bruton's tyrosine kinase (BTK) inhibitor are described. In some embodiments, the invention provides pharmaceutical compositions comprising combinations of a MEK inhibitor and a BTK inhibitor and methods of using the pharmaceutical compositions for treating a disease, in particular a cancer.

WO 2017/033113 A1

THERAPEUTIC COMBINATIONS OF A MEK INHIBITOR AND A BTK INHIBITOR

CROSS-REFERENCE TO RELATED APPLICATIONS

[001] This application is an international application claiming the benefit of U.S. Provisional Application No. 62/208,554, filed on August 21, 2015, the entirety of which is incorporated herein by reference.

FIELD OF THE INVENTION

[002] Therapeutic combinations of a Bruton's tyrosine kinase (BTK) inhibitor and a mitogen-activated protein kinase (MAPK) extracellular signal-regulated kinase (ERK) kinase (MEK) inhibitor, and uses of the therapeutic combinations are disclosed herein. In particular, a combination of a BTK inhibitor and a MEK inhibitor and compositions and uses thereof are disclosed.

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. The function of BTK in signaling pathways activated by the engagement of the B cell receptor (BCR) and FCER1 on mast cells is well established. Functional mutations in BTK in humans result in a primary immunodeficiency disease 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] Other diseases with an important role for dysfunctional B cells are B cell malignancies. 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, as described in D'Cruz and Uckun, *OncoTargets and Therapy* **2013,** *6,* 161-176.

[005] The mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway (also known as the Ras/Raf/MEK/ERK pathway) regulates cellular processes that may include proliferation, differentiation, development, survival, and apoptosis. Shaul and

Seger, *Biochim. Biophys. Acta* **2007,** *1773,* 1213-26. The MEKs are an evolutionarily conserved group of three homologous isoforms, known as MEK1, MEK2, and MEK 1b (of which the latter is believed to be inactive), which are dual-specificity tyrosine/threonine protein kinases. Approximately 30% of all human cancers have a constitutively activated MAPK/ERK pathway, most commonly through mutations in the KRAS oncogene and BRAF, and constitutive activation of MEK1 results in cellular transformation. Inhibition of MEK1 and MEK2

[006] In many solid tumors, the supportive microenvironment (which may make up the majority of the tumor mass) is a dynamic force that enables tumor survival. The tumor microenvironment is generally defined as a complex mixture of "cells, soluble factors, signaling molecules, extracellular matrices, and mechanical cues that promote neoplastic transformation, support tumor growth and invasion, protect the tumor from host immunity, foster therapeutic resistance, and provide niches for dominant metastases to thrive," as described in Swartz, *et al.*, *Cancer Res.*, **2012,** *72,* 2473. Although tumors express antigens that should be recognized by T cells, tumor clearance by the immune system is rare because of immune suppression by the microenvironment. Addressing the tumor cells themselves with e.g. chemotherapy has also proven to be insufficient to overcome the protective effects of the microenvironment. New approaches are thus urgently needed for more effective treatment of solid tumors that take into account the role of the microenvironment.

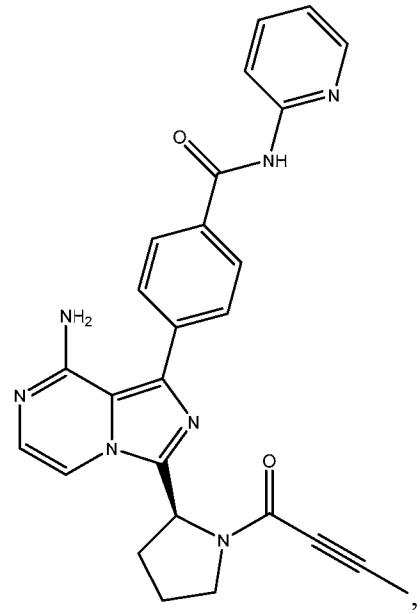
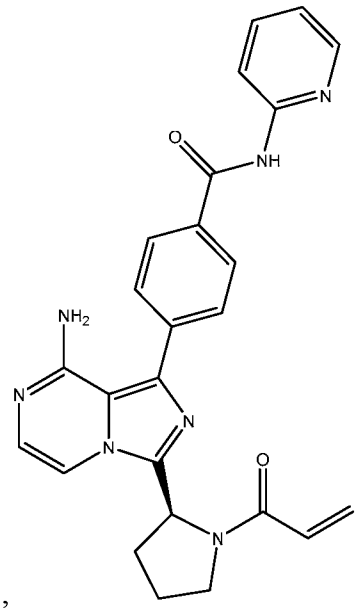
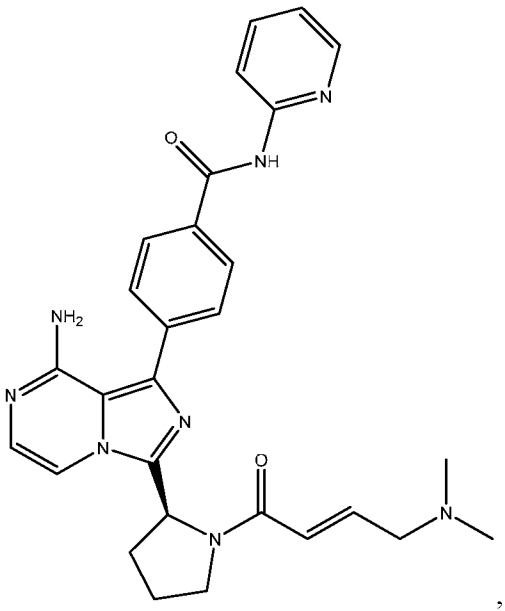
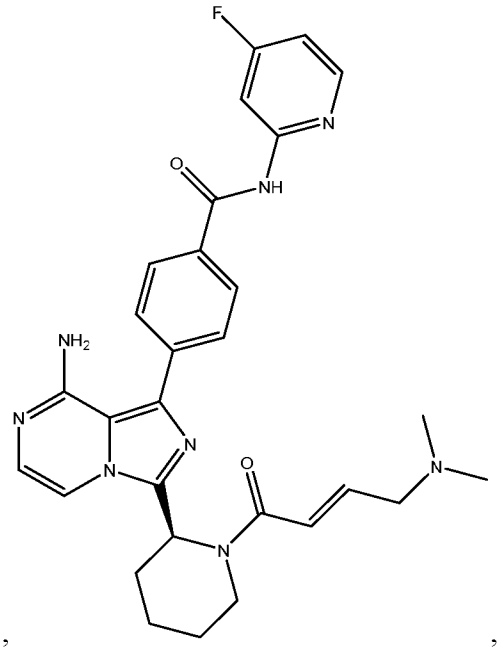
[007] The CD20 antigen, also called human B-lymphocyte-restricted differentiation antigen Bp35, or B1), is found on the surface of normal "pre-B" and mature B lymphocytes, including malignant B lymphocytes. Nadler, *et al.*, *J. Clin. Invest.* **1981,** *67,* 134-40; Stashenko, *et al.*, *J. Immunol.* **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 B cell hematological malignancies, including indolent non-Hodgkin's lymphoma (NHL), aggressive NHL, and chronic lymphocytic leukemia (CLL)/small lymphocytic leukemia (SLL). Lim, *et. al.*, *Haematologica* **2010,** *95,* 135-43; Beers, *et. al.*, *Sem. Hematol.* **2010,** *47,* 107-14; Klein, *et al.*, *mAbs* **2013,** *5,* 22-33. However, there is an urgent need to provide for more efficiacious therapies in many B cell hematological malignancies.

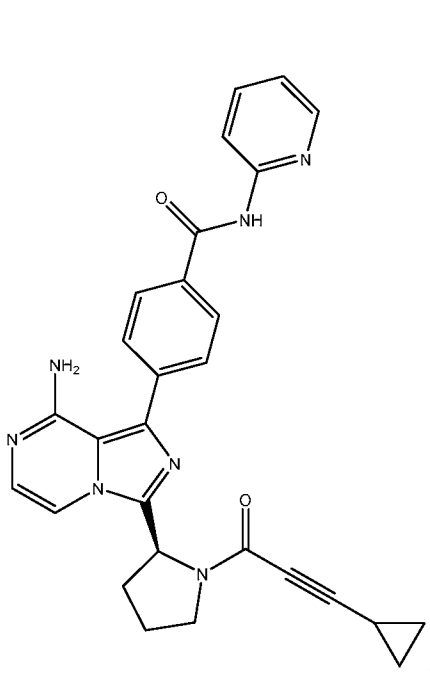
[008] The present invention provides the unexpected finding that the combination of a MEK inhibitor and a BTK inhibitor is synergistically effective in the treatment of any of several types of cancers such as leukemia, lymphoma, and solid tumor cancers, as well as inflammatory, immune, and autoimmune disorders. The present invention further provides the unexpected finding that the combination of an anti-CD20 antibody with a BTK inhibitor and a MEK inhibitor is synergistically effective in the treatment of any of several types of cancers such as leukemia, lymphoma, and solid tumor cancers, as well as inflammatory, immune, and autoimmune disorders.

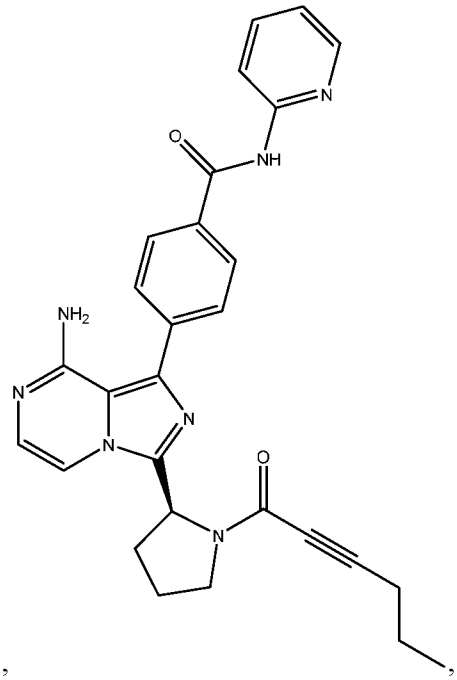
SUMMARY OF THE INVENTION

[009] In an embodiment, the invention provides a method of treating a hyperproliferative disease, comprising co-administering, to a mammal in need thereof, therapeutically effective amounts of (1) a MEK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and (2) a Bruton's tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. In an embodiment, the MEK inhibitor is administered to the mammal before administration of the BTK inhibitor. In an embodiment, the MEK inhibitor is administered to the mammal simultaneously with the administration of the BTK inhibitor. In an embodiment, the MEK inhibitor is administered to the mammal after administration of the BTK inhibitor.

[0010] In an embodiment, the invention provides a method of treating a hyperproliferative disease, comprising co-administering, to a mammal in need thereof, therapeutically effective amounts of (1) a MEK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and (2) a BTK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein the BTK inhibitor is selected from the group consisting of:

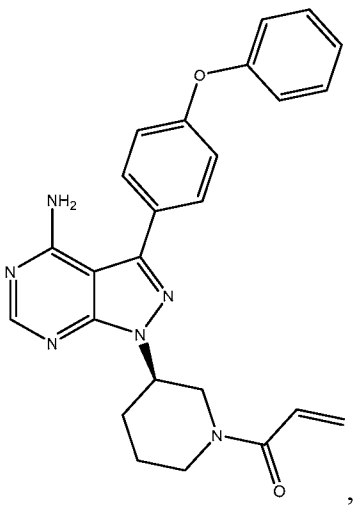

,

,

,

,

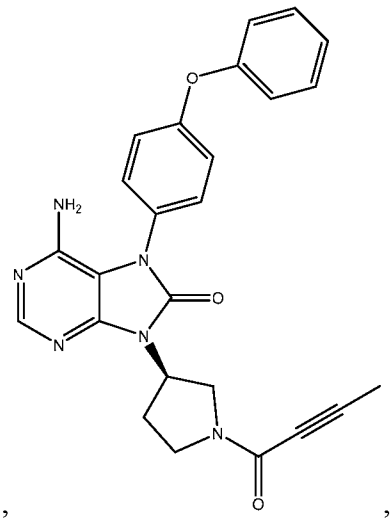


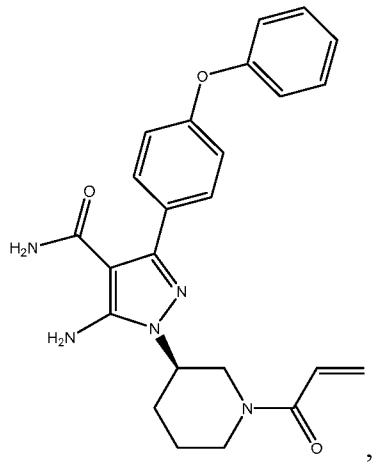


and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, and prodrugs thereof.

[0011] In an embodiment, the invention provides a method of treating a hyperproliferative disease, comprising co-administering, to a mammal in need thereof, therapeutically effective amounts of (1) a MEK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and (2) a Bruton's tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein the BTK inhibitor is selected from the group consisting of:

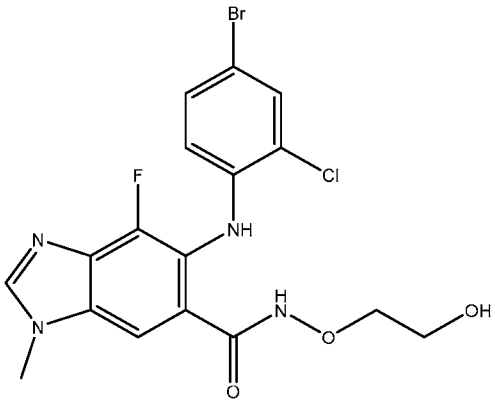




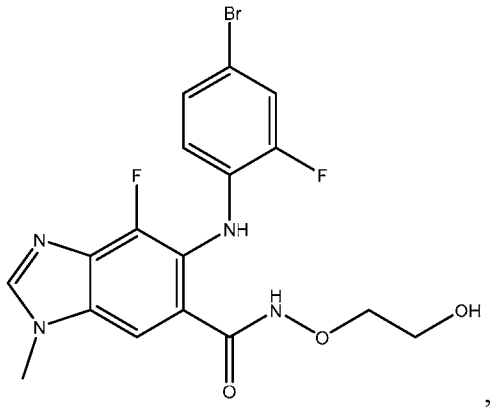


and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, and prodrugs thereof.

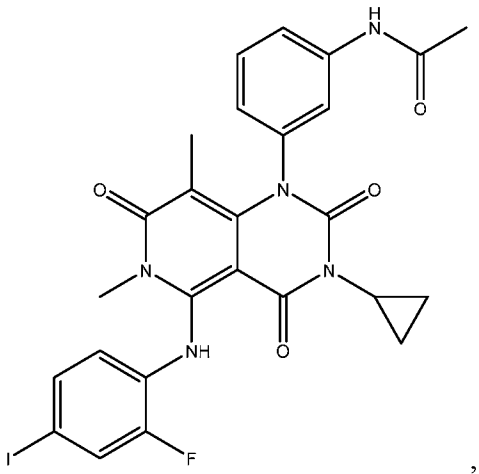
[0012] In an embodiment, the invention provides a method of treating a hyperproliferative disease, comprising co-administering, to a mammal in need thereof, therapeutically effective amounts of (1) a MEK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and (2) a BTK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein the MEK inhibitor is selected from the group consisting of:



,



,



,

and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof.

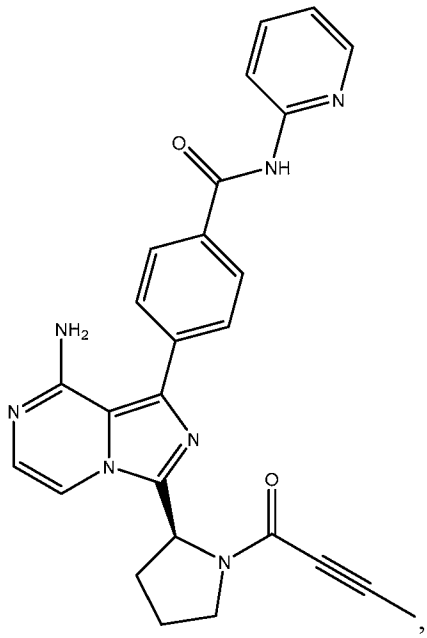
[0013] In an embodiment, the invention provides a method of treating a hyperproliferative disease, comprising co-administering, to a mammal in need thereof, therapeutically effective amounts of (1) a MEK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and (2) a BTK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, further comprising the step of administering a

therapeutically effective amount of an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, biosimilars thereof, and combinations thereof.

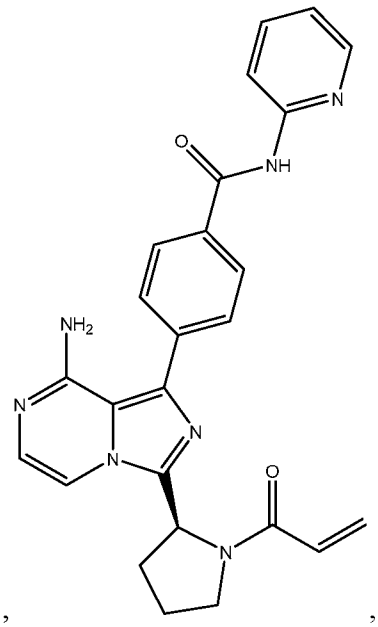
[0014] In an embodiment, the invention provides a method of treating a hyperproliferative disease, wherein the hyperproliferative disease is a cancer, comprising co-administering, to a mammal in need thereof, therapeutically effective amounts of (1) a MEK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and (2) a Bruton's tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein the cancer is a B cell hematological malignancy, and wherein the B cell 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, and myelofibrosis. In an embodiment, the cancer is a solid tumor cancer, 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, 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, esophageal cancer, testicular cancer, gynecological cancer, colon cancer, and brain cancer.

[0015] In an embodiment, the invention provides a method of treating a hyperproliferative disease, comprising co-administering, to a mammal in need thereof, therapeutically effective amounts of (1) a MEK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and (2) a Bruton's tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, further comprising the step of administering a therapeutically effective amount of gemcitabine or albumin-bound paclitaxel.

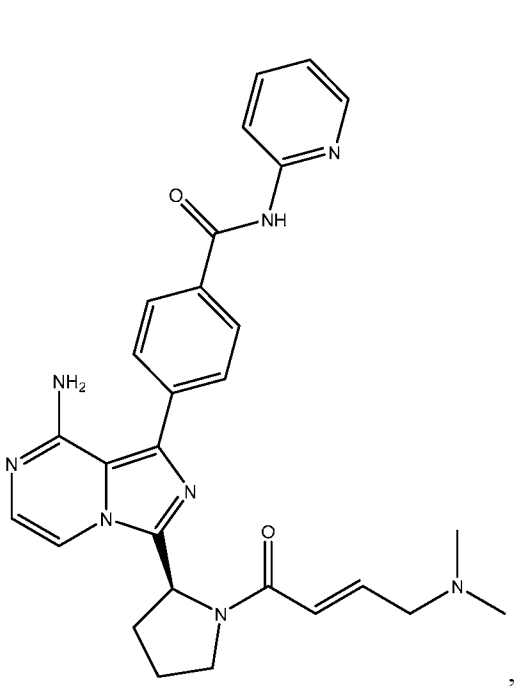
[0016] In an embodiment, the invention provides a method of treating a cancer in a human comprising the step of co-administering (1) a therapeutically effective amount of a MEK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and (2) a therapeutically effective amount of a Bruton's tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein the therapeutically effective amount is effective to inhibit signaling between the tumor cells of the 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 an embodiment, the cancer is 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, 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, esophageal cancer, testicular cancer, gynecological cancer, colon cancer, and brain cancer. In an embodiment, the BTK inhibitor is selected from the group consisting of:



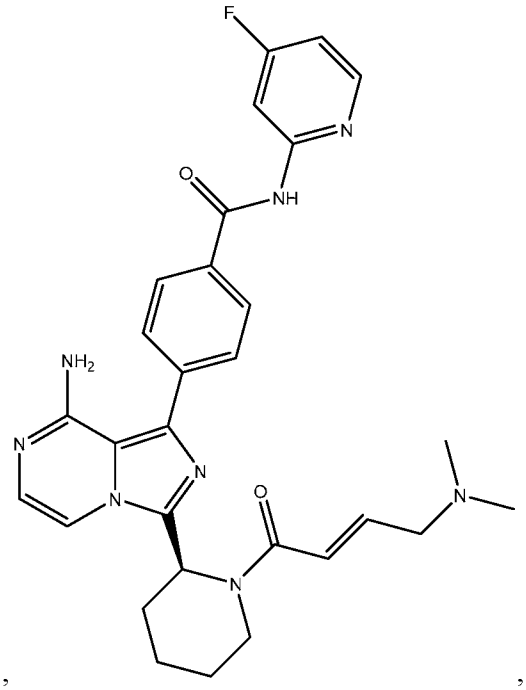
,



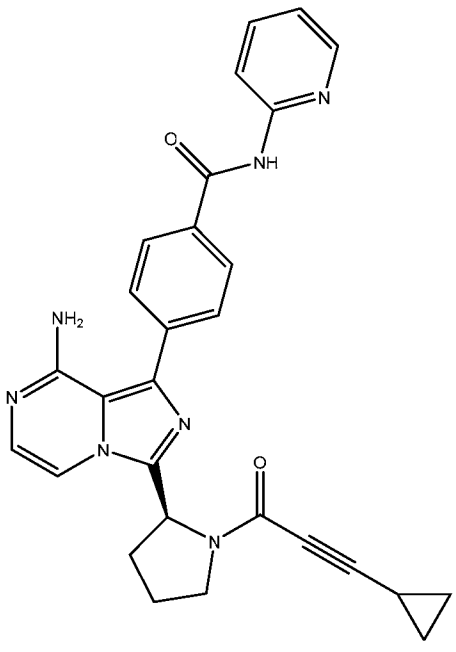
,



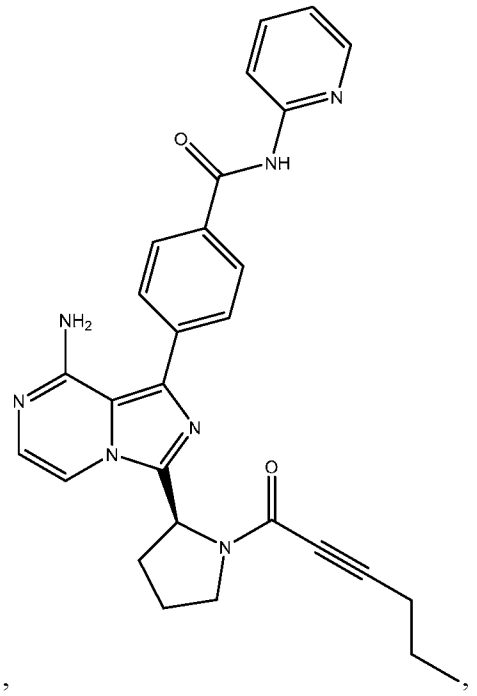
,



,

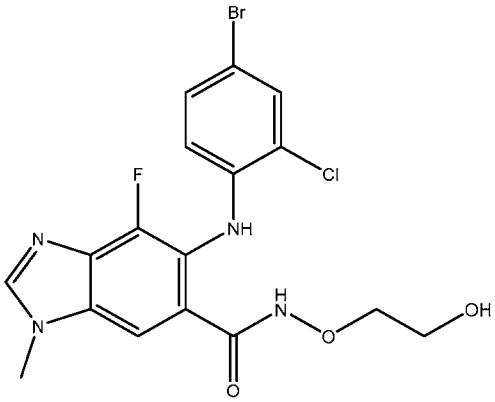


,

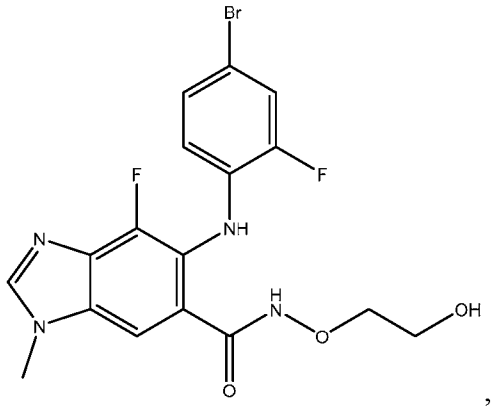


,

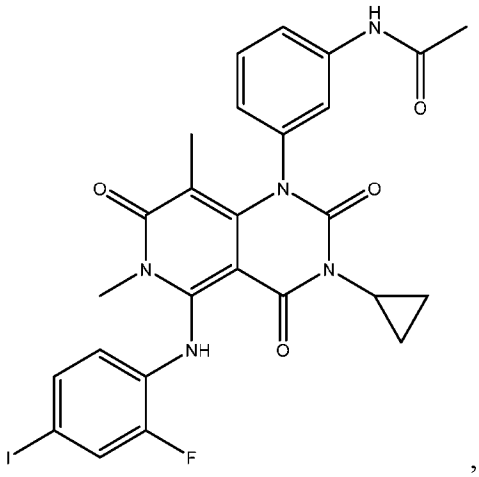
and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof. In an embodiment, the MEK inhibitor is selected from the group consisting of:



,



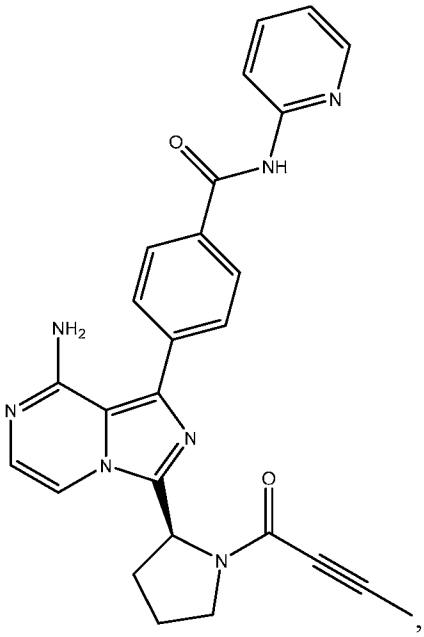
,

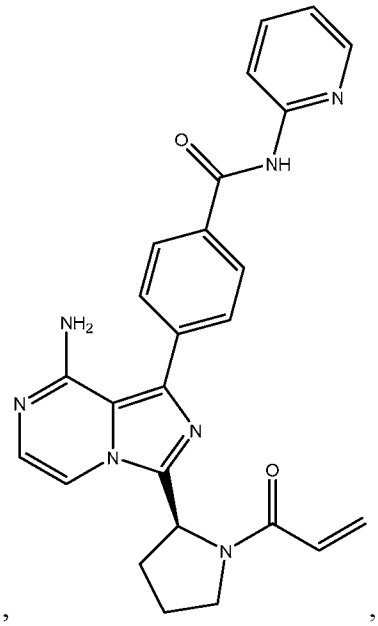


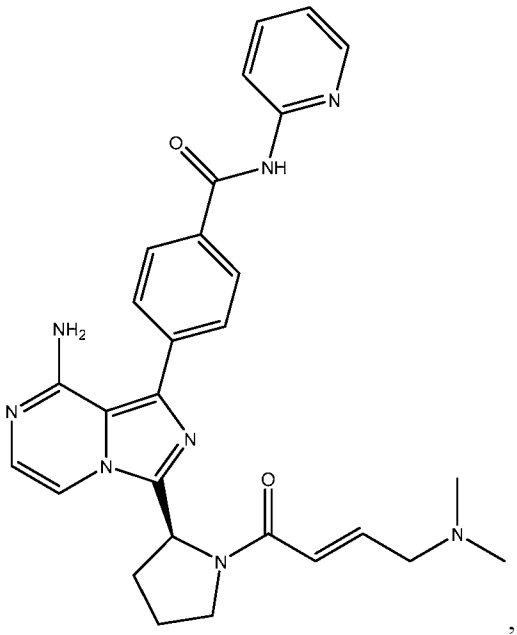
,

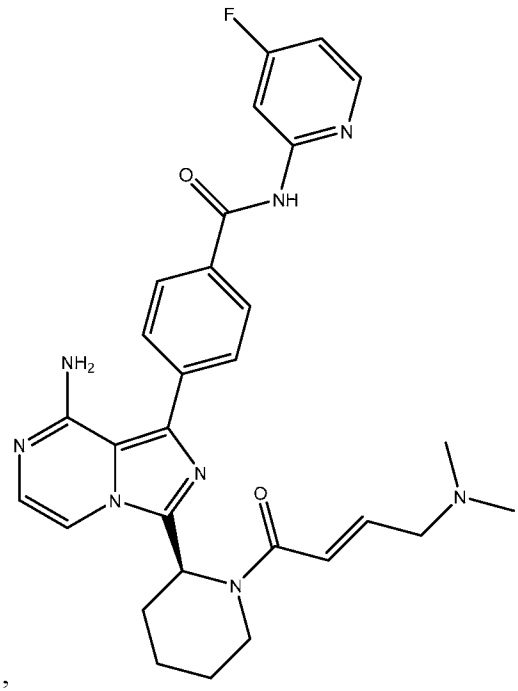
and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, and prodrugs thereof.

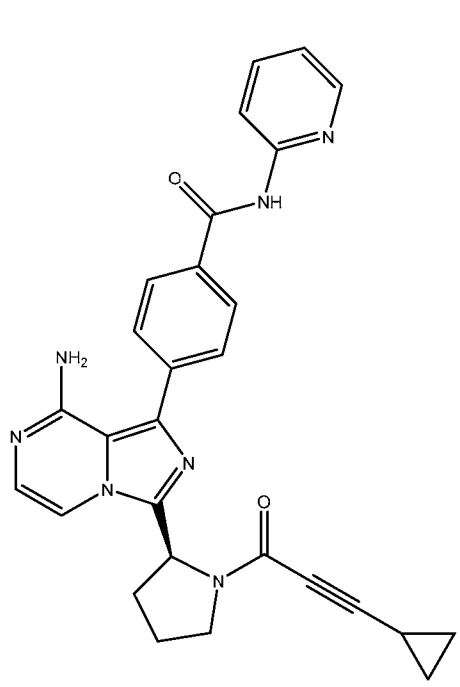
[0017] In an embodiment, the invention provides a method of treating a cancer in a human intolerant to a bleeding event comprising the step of administering (1) a therapeutically effective amount of a MEK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and (2) a therapeutically effective amount of a Bruton's tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein the BTK inhibitor is selected from the group consisting of:

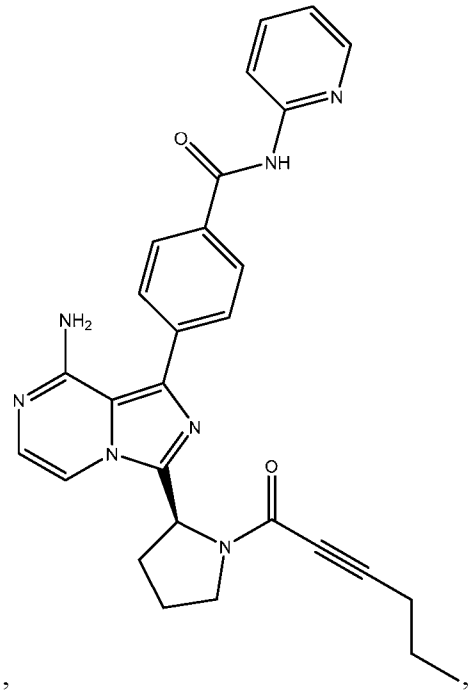

,


,

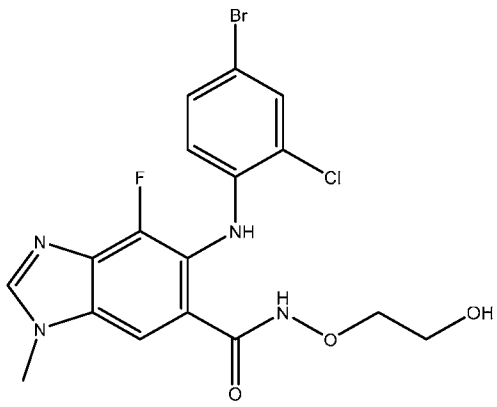

,

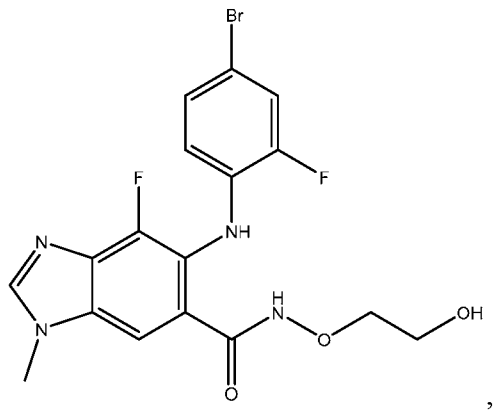

,

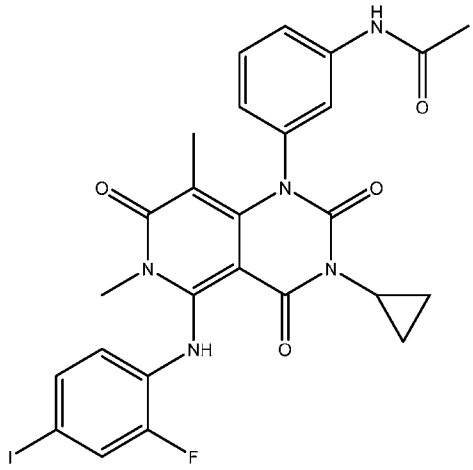




and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof. In an embodiment, the bleeding event is selected from the group consisting of subdural hematoma, gastrointestinal bleeding, hematuria, post-procedural hemorrhage, bruising, petechiae, and combinations thereof. In an embodiment, the MEK inhibitor is selected from the group consisting of:







,

and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, and prodrugs thereof.

[0018] In an embodiment, the invention provides a method of treating a cancer in a human intolerant to a bleeding event comprising the step of administering (1) a therapeutically effective amount of a MEK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and (2) a therapeutically effective amount of a Bruton's tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, further comprising the step of administering a therapeutically effective amount of an anticoagulant or antiplatelet active pharmaceutical ingredient. In an embodiment, the anticoagulant or antiplatelet active pharmaceutical ingredient is selected from the group consisting of acenocoumarol, anagrelide, anagrelide hydrochloride, abciximab, aloxiprin, antithrombin, apixaban, argatroban, aspirin, aspirin with extended-release dipyridamole, beraprost, betrixaban, bivalirudin, carbasalate calcium, cilostazol, clopidogrel, clopidogrel bisulfate, cloricromen, dabigatran etexilate, darexaban, dalteparin, dalteparin sodium, defibrotide, dicumarol, diphenadione, dipyridamole, ditazole, desirudin, edoxaban, enoxaparin, enoxaparin sodium, eptifibatide, fondaparinux, fondaparinux sodium, heparin, heparin sodium, heparin calcium, idraparinux, idraparinux sodium, iloprost, indobufen, lepirudin, low molecular weight heparin, melagatran, nadroparin, otamixaban, parnaparin, phenindione, phenprocoumon, prasugrel, picotamide, prostacyclin, ramatroban, reviparin, rivaroxaban, sulodexide, terutroban, terutroban sodium, ticagrelor, ticlopidine, ticlopidine hydrochloride, tinzaparin, tinzaparin sodium, tirofiban, tirofiban hydrochloride, treprostinil, treprostinil sodium, triflusal, vorapaxar, warfarin, warfarin sodium, ximelagatran, salts thereof, solvates thereof, hydrates thereof, and

combinations thereof. In an embodiment, 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, renal cancer, kidney cancer, liver cancer, ovarian cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, acquired immune deficiency syndrome (AIDS)-related cancers (e.g., lymphoma and Kaposi's sarcoma), viral-induced cancer, glioblastoma, esophogeal tumors, hematological neoplasms, non-small-cell lung cancer, chronic myelocytic leukemia, diffuse large B-cell lymphoma, esophagus tumor, follicle center lymphoma, head and neck tumor, hepatitis C virus infection, hepatocellular carcinoma, Hodgkin's disease, metastatic colon cancer, multiple myeloma, non-Hodgkin's lymphoma, indolent non-Hogkin'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, Burkitt's lymphoma, and myelofibrosis.

[0019] In some embodiments, the invention provides a composition comprising therapeutically effective amounts of (1) a MEK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (2) a BTK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in the treatment of cancer. This composition is typically a pharmaceutical composition.

[0020] In some embodiments, the invention provides a composition comprising therapeutically effective amounts of (1) a MEK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a BTK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in the treatment of cancer; and (3) a therapeutically effective amount of an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof. This composition is typically a pharmaceutical composition.

[0021] In some embodiments, 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 any of the foregoing compositions.

[0022] In some embodiments, 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 MEK inhibitor and a BTK inhibitor.

[0023] In some embodiments, 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 MEK inhibitor, a BTK inhibitor, and an anti-CD20 antibody.

[0024] In some embodiments, 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 MEK inhibitor, a BTK inhibitor, and gemcitabine.

[0025] In some embodiments, 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 MEK inhibitor, a BTK inhibitor, and albumin-bound paclitaxel.

[0026] In some embodiments, 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 MEK inhibitor, a BTK inhibitor, and bendamustine.

[0027] In some embodiments, 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 MEK inhibitor, a BTK inhibitor, and a combination of bendamustine and rituximab (BR chemotherapy).

[0028] In some embodiments, 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 MEK inhibitor, a BTK inhibitor, and a combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP).

[0029] In some embodiments, 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 MEK inhibitor, a BTK inhibitor, and a combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).

[0030] In some embodiments, 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 MEK inhibitor, a BTK inhibitor, and a combination of fludarabine, cyclophosphamide, and rituximab (FCR).

BRIEF DESCRIPTION OF THE DRAWINGS

[0031] 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.

[0032] FIG. 1 illustrates *in vivo* potency of Formula (2) (labeled "BTK inhibitor") and Formula (10) (ibrutinib). Mice were gavaged at increasing drug concentration and sacrificed at one time point (3 hours 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}values. The results show that Formula (2) is more potent at inhibiting expression of activation makers than Formula (10) (ibrutinib).

[0033] FIG. 2 illustrates *in vitro* potency in whole blood of Formula (2), Formula (10) (ibrutinib) and Formula (17) (CC-292) in inhibition of signals through the B cell receptor.

[0034] FIG. 3 illustrates EGF receptor phosphorylation *in vitro* for Formula (2) and Formula (10) (ibrutinib).

[0035] FIG. 4 illustrates tumor growth suppression in an orthotopic pancreatic cancer model. Mice were dosed orally with 15 mg/kg of the BTK inhibitor of Formula (2), 15 mg/kg of a phosphoinositide 3-kinase δ (PI3K-δ) inhibitor (denoted "p110d"), 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.

[0036] FIG. 5 illustrates the effects of oral dosing with 15 mg/kg of the BTK inhibitor of Formula (2), 15 mg/kg of a phosphoinositide 3-kinase δ (PI3K-δ) inhibitor, or a combination of both inhibitors on myeloid tumor-associated macrophages (TAMs) in pancreatic tumor-bearing mice.

[0037] FIG. 6 illustrates the effects of oral dosing with 15 mg/kg of the BTK inhibitor of Formula (2), 15 mg/kg of a phosphoinositide 3-kinase δ (PI3K-δ) inhibitor, or a combination of both inhibitors on myeloid-derived suppressor cells (MDSCs) in pancreatic tumor-bearing mice.

[0038] FIG. 7 illustrates the effects of oral dosing with 15 mg/kg of the BTK inhibitor of Formula (2), 15 mg/kg of a phosphoinositide 3-kinase δ (PI3K-δ) inhibitor, or a combination of both inhibitors on regulatory T cells (Tregs) in pancreatic tumor-bearing mice.

[0039] FIG. 8 illustrates the effects on tumor volume of vehicle (measured in mm^3) of the BTK inhibitor of Formula (2), a combination of the BTK inhibitor of Formula (2) and gemcitabine ("Gem"), and gemcitabine alone.

[0040] FIG. 9 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 (2), a combination of the BTK inhibitor of Formula (2) and gemcitabine ("Gem"), and gemcitabine alone.

[0041] FIG. 10 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 (2), a combination of the BTK inhibitor of Formula (2) and gemcitabine ("Gem"), and gemcitabine alone.

[0042] FIG. 11 illustrates the effects on the percentage of $CD11b^+$, $LY6C^{low}$, $F4/80^+$, and $Csf1r^+$ tumor-associated macrophages ("TAMs"), given as a percentage of cells expressing the T cell receptor (CD3), of the BTK inhibitor of Formula (2), a combination of the BTK inhibitor of Formula (2) and gemcitabine ("Gem"), and gemcitabine alone.

[0043] FIG. 12 illustrates the effects on the percentage of $Gr1^+$ and $LY6C^{hi}$, $F4/80^+$, and $Csf1r^+$ myeloid-derived suppressor cells ("MDSCs"), given as a percentage of cells expressing the T cell receptor (CD3), of the BTK inhibitor of Formula (2), a combination of the BTK inhibitor of Formula (2) and gemcitabine ("Gem"), and gemcitabine alone.

[0044] FIG. 13 illustrates the effects of vehicle on flux at two timepoints, as a control for

comparison with FIG. 8, in the ID8 syngeneic orthotopic ovarian cancer model.

[0045] FIG. 14 illustrates the effects of the BTK inhibitor of Formula (2) on flux at two timepoints, for comparison with FIG. 13, in the ID8 syngeneic orthotopic ovarian cancer model.

[0046] FIG. 15 illustrates tumor response to treatment with the BTK inhibitor of Formula (2) correlates with a significant reduction in immunosuppressive tumor associated lymphocytes in tumor-bearing mice, in comparison to a control (vehicle).

[0047] FIG. 16 illustrates that treatment with the BTK inhibitor of Formula (2) impairs ID8 ovarian cancer growth in the syngeneic murine model in comparison to a control (vehicle).

[0048] FIG. 17 illustrates that treatment with the BTK inhibitor of Formula (2) induces a tumor response that correlates with a significant reduction in total B cells in tumor-bearing mice.

[0049] FIG. 18 illustrates that treatment with the BTK inhibitor of Formula (2) induces a tumor response that correlates with a significant reduction in B regulatory cells (Bregs) in tumor-bearing mice.

[0050] FIG. 19 illustrates that treatment with the BTK inhibitor of Formula (2) induces a tumor response that correlates with a significant reduction in immunosuppressive tumor associated Tregs.

[0051] FIG. 20 illustrates that treatment with the BTK inhibitor of Formula (2) induces a tumor response that correlates with an increase in $CD8^+$ T cells.

[0052] FIG. 21 illustrates the effects of treatment with the active pharmaceutical ingredient of Formula (2) on tumor volumes in the KPC pancreatic cancer model.

[0053] FIG. 22 illustrates the results of analysis of tumor tissues showing that immunosuppressive TAMs ($CD11b^+Ly6ClowF4/80^+Csf1r^+$) were significantly reduced with Formula (2) treatment in the KPC pancreatic cancer model.

[0054] FIG. 23 illustrates the results of analysis of tumor tissues showing that immunosuppressive MDSCs ($Gr1^+Ly6CHi$) were significantly reduced with Formula (2) treatment in the KPC pancreatic cancer model.

[0055] FIG. 24 illustrates the results of analysis of tumor tissues showing that immunosuppressive Tregs ($CD4^+CD25^+FoxP3^+$) were significantly reduced with Formula (2)

treatment in the KPC pancreatic cancer model.

[0056] FIG. 25 illustrates that the decrease in immunosuppressive TAMs, MDSCs, and Tregs in the KPC pancreatic cancer model correlated with a significant increase in $CD8^+$ cells.

[0057] FIG. 26 illustrates the dosing schema used with the KrasLA2 non-small cell lung cancer (NSCLC) model.

[0058] FIG. 27 illustrates tumor volume variation from baseline as assessed by microcomputerized tomography (microCT) in the KrasL2 NSCLC model.

[0059] FIG. 28 illustrates TAMs in the KrasL2 NSCLC model, and indicates that Formula (2) induces a tumor response that correlates with a significant reduction in immunosuppressive tumor associated TAMs.

[0060] FIG. 29 illustrates MDSCs in the KrasL2 NSCLC model, and indicates that Formula (2) induces a tumor response that correlates with a significant reduction in immunosuppressive tumor associated MDSCs.

[0061] FIG. 30 illustrates Tregs in the KrasL2 NSCLC model, and indicates that Formula (2) induces a tumor response that correlates with a significant reduction in immunosuppressive tumor associated Tregs.

[0062] FIG. 31 illustrates $CD8^+$ T cells in the KrasL2 NSCLC model.

[0063] FIG. 32 illustrates BTK inhibitory effects on MDSCs.

[0064] FIG. 33 shows *in vitro* analysis of antibody-dependent NK cell–mediated interferon-γ (IFN-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 Formula (10) (ibrutinib) or 1 μM of Formula (2) 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 IFN-γ. All *in vitro* experiments were performed in triplicate. Labels are defined as follows: *p = 0.018, **p = 0.002, ***p = 0.001.

[0065] FIG. 34 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 Formula (10) (ibrutinib) or 1 μM of Formula (2) 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.

[0066] FIG. 35 shows that Formula (10) (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 for 4 hours at variable rituximab concentrations at a constant effector:target ratio of 25:1 and Formula (10) (ibrutinib) (1 μM), Formula (2) (1 μM), or other interleukin-2 inducible tyrosine kinase (ITK) sparing BTK inhibitors CGI-1746, inhibA (1 μM) and BGB-3111 ("inhibB," 1 μM). All *in vitro* experiments were performed in triplicate. Labels are defined as follows: *p = 0.001.

[0067] FIG. 36 shows that Formula (10) (ibrutinib) antagonizes antibody-dependent NK cell–mediated cytotoxicity in primary CLL cells. NK cell cytotoxicity as percent lysis of tumor cells was analyzed in chromium release assays with purified NK cells incubated with chromium-labeled Raji for 4 hours at variable rituximab concentrations at a constant effector:target ratio of 25:1 and Formula (10) (ibrutinib) (1 μM), Formula (2) (1 μM), or other ITK sparing BTK inhibitors CGI-1746, inhibA (1 μM) and BGB-3111 ("inhibB," 1 μM). All *in vitro* experiments were performed in triplicate. Labels are defined as follows: *p = 0.001.

[0068] FIG. 37 shows a summary of the results given in FIG. 36 at the highest concentration of rituximab ("Ab") (10 μg/mL).

[0069] FIG. 38 shows NK cell degranulation results for combinations of obinutuzumab with Formula (2) and Formula (10). The percentage of $CD56^+/CD107a^+$ NK cells observed in whole blood after pretreatment for 1 hour with the BTK inhibitors and stimulatation with MEC-1 cells opsonised with obinutuzumab at 1 μg/mL for 4 hours (n = 3) is shown.

[0070] FIG. 39 shows the effects of BTK inhibition on generalized NK cell mediated cytotoxicity.

[0071] FIG. 40 shows that Formula (2) 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 Formula (10) (ibrutinib) strongly inhibits Th17 cells.

[0072] FIG. 41 shows that Formula (2) has no effect on regulatory T cell (Treg) development, while Formula (10) (ibrutinib) strongly increases Treg development.

[0073] FIG. 42 shows that Formula (2) has no effect on $CD8^+$ T cell viability, development, while Formula (10) (ibrutinib) strongly affects $CD8^+$ T cell viability at higher doses.

[0074] FIG. 43 illustrates the results of the cytotoxicity assay for $CD8^+$ T cell function. Formula (10) (ibrutinib) affects $CD8^+$ T cell function as measured by % cytotoxicity, while Formula (2) has no effect on $CD8^+$ T cell function as measured by % cytotoxicity relative to vehicle.

[0075] FIG. 44 illustrates the results of IFN-γ level measurements for $CD8^+$ T cell function. Formula (10) (ibrutinib) affects $CD8^+$ T cell function as measured by IFN-γ level, while Formula (2) has no effect on $CD8^+$ T cell function as measured by IFN-γ level relative to vehicle.

[0076] FIG. 45 illustrates the results of the clinical study of Formula (2) (labeled "BTK inhibitor") in CLL, which are shown in comparison to the results reported for Formula (10) (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 (2) causes a much smaller relative increase and much faster decrease in absolute lymphocyte count (ALC) relative to the BTK inhibitor of Formula (10) (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 of Formula (10) (ibrutinib).

[0077] FIG. 46 shows SPD of enlarged lymph nodes in CLL patients as a function of dose (cohort) of the BTK inhibitor of Formula (2).

[0078] FIG. 47 shows a comparison of progression-free survival (PFS) in CLL patients treated with the BTK inhibitor of Formula (10) (ibrutinib) or the BTK inhibitor of Formula (2). The ibrutinib data is taken from Byrd, *et al.*, *N. Engl. J. Med.* **2013,** *369,* 32-42. CLL patients treated with Formula (2) for at least 8 days are included.

[0079] FIG. 48 shows a comparison of number of patients at risk in CLL patients treated with the BTK inhibitor of Formula (10) (ibrutinib) or the BTK inhibitor of Formula (2). CLL patients treated with Formula (2) for at least 8 days are included.

[0080] FIG. 49 shows a comparison of progression-free survival (PFS) in CLL patients exhibiting the 17p deletion and treated with the BTK inhibitor of Formula (10) (ibrutinib) or the BTK inhibitor of Formula (2). The ibrutinib data is taken from Byrd, *et al.*, *N. Engl. J. Med.* **2013,** *369,* 32-42.

[0081] FIG. 50 shows a comparison of number of patients at risk in CLL patients exhibiting the 17p deletion and treated with the BTK inhibitor of Formula (10) (ibrutinib) or the BTK inhibitor of Formula (2). The ibrutinib data is taken from Byrd, *et al.*, *N. Engl. J. Med.* **2013,** *369,* 32-42. CLL patients treated with Formula (2) for at least 8 days are included.

[0082] FIG. 51 shows improved BTK target occupancy of Formula (2) at lower dosage versus Formula (10) (ibrutinib) in relapsed/refractory CLL patients.

[0083] FIG. 52 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.

[0084] FIG. 53 shows the % change in MDSC (monocytic) level over 28 days versus % ALC change at Cycle 2, day 28 (C2D28) with trendlines.

[0085] FIG. 54 shows the % change in natural killer (NK) cell level over 28 days versus % ALC change at Cycle 1, day 28 (C2D28) with trendlines.

[0086] FIG. 55 shows the % change in NK cell level over 28 days versus % ALC change at Cycle 2, day 28 (C2D28) with trendlines.

[0087] FIG. 56 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.

[0088] FIG. 57 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.

[0089] FIG. 58 shows updated the results of the clinical study of Formula (2) (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 (2) causes a much smaller relative increase and much faster decrease in absolute lymphocyte count (ALC) relative to the BTK inhibitor of Formula (10) (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 of Formula (10) (ibrutinib).

[0090] FIG. 59 shows improved BTK target occupancy of Formula (2) at lower dosage versus ibrutinib in relapsed/refractory CLL patients, and includes BID dosing results.

[0091] FIG. 60 illustrates PFS for patients with 11q deletion.

[0092] FIG. 61 illustrates PFS across relapsed/refractory patients with 11q deletion and with 17p deletion and no 11q deletion.

[0093] FIG. 62 illustrates PFS for patients with 17p deletion and no 11q deletion.

[0094] FIG. 63 illustrates updated SPD results from the clinical study of Formula (2) in relapsed/refractory CLL patients.

[0095] FIG. 64 illustrates that treatment of CLL patients with Formula (2) resulted in increased apoptosis.

[0096] FIG. 65 illustrates a decrease in CXCL12 levels observed in patients treated with Formula (2).

[0097] FIG. 66 illustrates a decrease in CCL2 levels observed in patients treated with Formula (2).

[0098] FIG. 67 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).

[0099] FIG. 68 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.

[00100] FIG. 69 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 μM^2. In studies with Formula (10) (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.

[00101] FIG. 70 illustrates the effect of the concentration of the tested BTK inhibitors on thrombus formation.

[00102] FIG. 71 illustrates the results of GPVI platelet aggregation studies of Formula (2) (IC50 = 1.15 μM) and Formula (10) (ibrutinib, IC50 = 0.13 μM).

[00103] FIG. 72 illustrates the results of GPVI platelet aggregation studies of Formula (2) and Formula (10) (ibrutinib).

[00104] FIG. 73 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula (2) (acalabrutinib) and the MEK inhibitor of Formula (27) (selumetinib) are combined. The tested cell lines include TMD-8, RI-1, and Mino. The dose-effect curves for these cell lines are given in FIG. 74, FIG. 75, and FIG. 76. ED25, ED50, ED75, and ED90 refer to the effective doses causing 25%, 50%, 75%, and 90% of the maximum biological effect (proliferation), respectively.

[00105] FIG. 74 illustrates the dose-effect curves obtained for the tested TMD-8 cell line (DLBCL-ABC) using combined dosing of the BTK inhibitor of Formula (2) (acalabrutinib) ("Inh.1"), the MEK inhibitor of Formula (27) (selumetinib) ("Inh.2"), and the combination of the BTK inhibitor of Formula (2) and the MEK inhibitor of Formula (27) (selumetinib) ("Inh. 1+Inh. 2"). 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. 75 illustrates the dose-effect curves obtained for the tested RI-1 cell line using combined dosing of the BTK inhibitor of Formula (2) (acalabrutinib) ("Inh.1"), the MEK inhibitor of Formula (27) (selumetinib) ("Inh.2"), and the combination of the BTK inhibitor of

Formula (2) and the MEK inhibitor of Formula (27) (selumetinib) ("Inh. 1+Inh. 2"). 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. 76 illustrates the dose-effect curves obtained for the tested Mino cell line using combined dosing of the BTK inhibitor of Formula (2) ("Inh.1"), the MEK inhibitor of Formula (27) (selumetinib) ("Inh.2"), and the combination of the BTK inhibitor of Formula (2) and the MEK inhibitor of Formula (27) (selumetinib) ("Inh. 1+Inh. 2"). 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. 77 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula (10) (ibrutinib) and the MEK inhibitor of Formula (27) (selumetinib) are combined. The tested cell line is RI-1. The dose-effect curves for these cell lines are given in FIG. 78. ED25, ED50, ED75, and ED90 refer to the effective doses causing 25%, 50%, 75%, and 90% of the maximum biological effect (proliferation), respectively.

[00109] FIG. 78 illustrates the dose-effect curves obtained for the tested RI-1 cell line using combined dosing of the BTK inhibitor of Formula (10) ("IBR"), the MEK inhibitor of Formula (27) (selumetinib) ("selu"), and the combination of the BTK inhibitor of Formula (10) and the MEK inhibitor of Formula (27) (selumetinib) ("IBR + selu"). 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. 79 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula (10) (ibrutinib) and the MEK inhibitor of Formula (27) (selumetinib) are combined. The tested cell line is Mino. The dose-effect curves for these cell lines are given in FIG. 80. ED25, ED50, ED75, and ED90 refer to the effective doses causing 25%, 50%, 75%, and 90% of the maximum biological effect (proliferation), respectively.

[00111] FIG. 80 illustrates the dose-effect curves obtained for the tested Mino cell line using combined dosing of the BTK inhibitor of Formula (10) ("IBR"), the MEK inhibitor of Formula (27) (selumetinib) ("selu"), and the combination of the BTK inhibitor of Formula (10) and the MEK inhibitor of Formula (27) (selumetinib) ("IBR + selu"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

[00112] FIG. 81 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula (21) (ONO-4059) and the MEK inhibitor of Formula (27) (selumetinib) are combined. The tested cell line is RI-1. The dose-effect curves for these cell lines are given in FIG. 82. ED25, ED50, ED75, and ED90 refer to the effective doses causing 25%, 50%, 75%, and 90% of the maximum biological effect (proliferation), respectively.

[00113] FIG. 82 illustrates the dose-effect curves obtained for the tested RI-1 cell line using combined dosing of the BTK inhibitor of Formula (21) ("ONO"), the MEK inhibitor of Formula (27) (selumetinib) ("selu"), and the combination of the BTK inhibitor of Formula (21) and the MEK inhibitor of Formula (27) (selumetinib) ("ONO + selu"). The y-axis ("Effect") is given in units of Fa (fraction affected) and the x-axis ("Dose") is given in linear units of μM.

[00114] FIG. 83 illustrates the synergy observed in certain cell lines when the BTK inhibitor of Formula (21) (ONO-4059) and the MEK inhibitor of Formula (27) (selumetinib) are combined. The tested cell line is Mino. The dose-effect curves for these cell lines are given in FIG. 84. ED25, ED50, ED75, and ED90 refer to the effective doses causing 25%, 50%, 75%, and 90% of the maximum biological effect (proliferation), respectively.

[00115] FIG. 84 illustrates the dose-effect curves obtained for the tested Mino cell line using combined dosing of the BTK inhibitor of Formula (21) ("ONO"), the MEK inhibitor of Formula (27) (selumetinib) ("selu"), and the combination of the BTK inhibitor of Formula (21) and the MEK inhibitor of Formula (27) (selumetinib) ("ONO + selu"). 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

[00116] SEQ ID NO:1 is the heavy chain amino acid sequence of the anti-CD20 monoclonal antibody rituximab.

[00117] SEQ ID NO:2 is the light chain amino acid sequence of the anti-CD20 monoclonal antibody rituximab.

[00118] SEQ ID NO:3 is the heavy chain amino acid sequence of the anti-CD20 monoclonal antibody obinutuzumab.

[00119] SEQ ID NO:4 is the light chain amino acid sequence of the anti-CD20 monoclonal antibody obinutuzumab.

[00120] SEQ ID NO:5 is the variable heavy chain amino acid sequence of the anti-CD20 monoclonal antibody ofatumumab.

[00121] SEQ ID NO:6 is the variable light chain amino acid sequence of the anti-CD20 monoclonal antibody ofatumumab.

[00122] SEQ ID NO:7 is the Fab fragment heavy chain amino acid sequence of the anti-CD20 monoclonal antibody ofatumumab.

[00123] SEQ ID NO:8 is the Fab fragment light chain amino acid sequence of the anti-CD20 monoclonal antibody ofatumumab.

[00124] SEQ ID NO:9 is the heavy chain amino acid sequence of the anti-CD20 monoclonal antibody veltuzumab.

[00125] SEQ ID NO:10 is the light chain amino acid sequence of the anti-CD20 monoclonal antibody veltuzumab.

[00126] SEQ ID NO:11 is the heavy chain amino acid sequence of the anti-CD20 monoclonal antibody tositumomab.

[00127] SEQ ID NO:12 is the light chain amino acid sequence of the anti-CD20 monoclonal antibody tositumomab.

[00128] SEQ ID NO:13 is the heavy chain amino acid sequence of the anti-CD20 monoclonal antibody ibritumomab.

[00129] SEQ ID NO:14 is the light chain amino acid sequence of the anti-CD20 monoclonal antibody ibritumomab.

DETAILED DESCRIPTION OF THE INVENTION

[00130] 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.

Definitions

[00131] The terms "co-administration," "co-administering," "administered in combination with," "administering in combination with," "simultaneous," and "concurrent," as used herein, encompass administration of two or more active pharmaceutical ingredients (in a preferred

embodiment of the present invention, for example, at least one MEK inhibitor and at least one BTK inhibitor) 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 both agents are present are preferred.

[00132] The term "*in vivo*" refers to an event that takes place in a subject's body.

[00133] 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.

[00134] 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.

[00135] A "therapeutic effect" as that term is used herein, encompasses a therapeutic benefit and/or a prophylactic benefit. 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.

[00136] 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.

[00137] The term "pharmaceutically acceptable salt" refers to salts derived from a variety of organic and inorganic counter ions known in the art. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Preferred inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid. Preferred organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid and salicylic acid. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese and aluminum. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins. Specific examples include isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. In some embodiments, the pharmaceutically acceptable base addition salt is chosen from ammonium, potassium, sodium, calcium, and magnesium salts. The term "cocrystal" refers to a molecular complex derived from a number of cocrystal formers known in the art. Unlike a salt, a cocrystal typically does not involve hydrogen transfer between the cocrystal and the drug, and instead involves intermolecular interactions, such as hydrogen bonding, aromatic ring stacking, or dispersive forces, between the cocrystal former and the drug in the crystal structure.

[00138] "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.

[00139] "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.

[00140] 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 present in the binding pocket of the target protein (such as cysteine, lysine, histidine, or other residues capable of being covalently modified), thereby irreversibly inhibiting the protein.

[00141] Unless otherwise stated, the chemical structures depicted herein are intended to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds where one or more hydrogen atoms is replaced by deuterium or tritium, or wherein one or more carbon atoms is replaced by ^{13}C- or ^{14}C-enriched carbons, are within the scope of this invention.

[00142] 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.

[00143] "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, isobutyl, *sec*-butyl isobutyl, tertiary 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 (isopropyl), *n*-butyl, *n*-pentyl, 1,1-dimethylethyl (*t*-butyl) and 3-methylhexyl. Unless stated otherwise specifically in the specification, an alkyl group is optionally substituted by one or more of substituents which are independently heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, -OR^a, -SR^a, -$OC(O)$-R^a, -$N(R^a)_2$, -$C(O)R^a$, -$C(O)OR^a$, -$OC(O)N(R^a)_2$, -$C(O)N(R^a)_2$, -$N(R^a)C(O)OR^a$, -$N(R^a)C(O)R^a$, -$N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, -$N(R^a)S(O)_tR^a$ (where t is 1 or 2), -$S(O)_tOR^a$ (where t is 1 or 2), -$S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$ where each R^a is independently hydrogen, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00144] "Alkylaryl" refers to an -(alkyl)aryl 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.

[00145] "Alkylhetaryl" refers to an -(alkyl)hetaryl radical where hetaryl 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.

[00146] "Alkylheterocycloalkyl" refers to an -(alkyl) heterocycyl radical where alkyl and heterocycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heterocycloalkyl and alkyl respectively.

[00147] 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.

[00148] "Alkenyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one double bond, and having from two to ten carbon atoms (*i.e.*, (C_{2-10})alkenyl or C_{2-10} alkenyl). Whenever it appears herein, a numerical range such as "2 to 10" refers to each integer in the given range - *e.g.*, "2 to 10 carbon atoms" means that the alkenyl group may consist of 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 10 carbon atoms. The alkenyl moiety may be attached to the rest of the molecule by a single bond, such as for example, ethenyl (*i.e.*, vinyl), prop-1-enyl (*i.e.*, allyl), but-1-enyl, pent-1-enyl and penta-1,4-dienyl. Unless stated otherwise specifically in the specification, an alkenyl group is optionally substituted by one or more substituents which are independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, -OR^a, -SR^a, -$OC(O)$-R^a, -$N(R^a)_2$, -$C(O)R^a$, -$C(O)OR^a$, -$OC(O)N(R^a)_2$, -$C(O)N(R^a)_2$, -$N(R^a)C(O)OR^a$, -$N(R^a)C(O)R^a$, -$N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, -$N(R^a)S(O)_tR^a$ (where t is 1 or 2), -$S(O)_tOR^a$ (where t is 1 or 2), -$S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00149] "Alkenyl-cycloalkyl" refers to an -(alkenyl)cycloalkyl radical where alkenyl and cycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for alkenyl and cycloalkyl respectively.

[00150] "Alkynyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one triple bond, having from two to ten carbon atoms (*i.e.*, (C_{2-10})alkynyl or C_{2-10} alkynyl). Whenever it appears herein, a numerical range such as "2 to 10" refers to each integer in the given range - *e.g.*, "2 to 10 carbon atoms" means that the alkynyl group may consist of 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 10 carbon atoms. The alkynyl may be attached to the rest of the molecule by a single bond, for example, ethynyl, propynyl, butynyl, pentynyl and hexynyl. Unless stated otherwise specifically in the specification, an alkynyl group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00151] "Alkynyl-cycloalkyl" refers to an -(alkynyl)cycloalkyl radical where alkynyl and cycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for alkynyl and cycloalkyl respectively.

[00152] "Carboxaldehyde" refers to a -(C=O)H radical.

[00153] "Carboxyl" refers to a -(C=O)OH radical.

[00154] "Cyano" refers to a -CN radical.

[00155] "Cycloalkyl" refers to a monocyclic or polycyclic radical that contains only carbon and hydrogen, and may be saturated, or partially unsaturated. Cycloalkyl groups include groups having from 3 to 10 ring atoms (*i.e.* (C_{3-10})cycloalkyl or C_{3-10} cycloalkyl). Whenever it appears herein, a numerical range such as "3 to 10" refers to each integer in the given range - *e.g.*, "3 to

10 carbon atoms" means that the cycloalkyl group may consist of 3 carbon atoms, *etc.*, up to and including 10 carbon atoms. Illustrative examples of cycloalkyl groups include, but are not limited to the following moieties: cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, norbornyl, and the like. Unless stated otherwise specifically in the specification, a cycloalkyl group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00156] "Cycloalkyl-alkenyl" refers to a -(cycloalkyl)alkenyl radical where cycloalkyl and alkenyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for cycloalkyl and alkenyl, respectively.

[00157] "Cycloalkyl-heterocycloalkyl" refers to a -(cycloalkyl)heterocycloalkyl radical where cycloalkyl and heterocycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for cycloalkyl and heterocycloalkyl, respectively.

[00158] "Cycloalkyl-heteroaryl" refers to a -(cycloalkyl)heteroaryl radical where cycloalkyl and heteroaryl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for cycloalkyl and heteroaryl, respectively.

[00159] 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.

[00160] The term "substituted alkoxy" refers to alkoxy wherein the alkyl constituent is substituted (*i.e.*, -O-(substituted alkyl)). Unless stated otherwise specifically in the specification,

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

[00161] 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 $(C_1\text{-}_6)$alkoxycarbonyl group is an alkoxy group having from 1 to 6 carbon atoms attached through its oxygen to a carbonyl linker. "Lower alkoxycarbonyl" refers to an alkoxycarbonyl group wherein the alkoxy group is a lower alkoxy group.

[00162] The term "substituted alkoxycarbonyl" refers to the group (substituted alkyl)-O-C(O)- wherein the group is attached to the parent structure through the carbonyl functionality. Unless stated otherwise specifically in the specification, the alkyl moiety of an alkoxycarbonyl group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00163] "Acyl" refers to the groups (alkyl)-C(O)-, (aryl)-C(O)-, (heteroaryl)-C(O)-, (heteroalkyl)-C(O)- and (heterocycloalkyl)-C(O)-, wherein the group is attached to the parent structure through the carbonyl functionality. If the R radical is heteroaryl or heterocycloalkyl, the hetero ring or chain atoms contribute to the total number of chain or ring atoms. Unless stated otherwise specifically in the specification, the alkyl, aryl or heteroaryl moiety of the acyl group

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

[00164] "Acyloxy" refers to a R(C=O)O- radical wherein R is alkyl, aryl, heteroaryl, heteroalkyl or heterocycloalkyl, which are as described herein. If the R radical is heteroaryl or heterocycloalkyl, the hetero ring or chain atoms contribute to the total number of chain or ring atoms. Unless stated otherwise specifically in the specification, the R of an acyloxy group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00165] "Amino" or "amine" refers to a $-N(R^a)_2$ radical group, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, unless stated otherwise specifically in the specification. When a $-N(R^a)_2$ group has two R^a substituents other than hydrogen, they can be combined with the nitrogen atom to form a 4-, 5-, 6- or 7-membered ring. For example, $-N(R^a)_2$ is intended to include, but is not limited to, 1-pyrrolidinyl and 4-morpholinyl. Unless stated otherwise specifically in the specification, an amino group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$,

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

[00166] The term "substituted amino" also refers to N-oxides of the groups $-NHR^d$, and NR^dR^d each as described above. N-oxides can be prepared by treatment of the corresponding amino group with, for example, hydrogen peroxide or m-chloroperoxybenzoic acid.

[00167] "Amide" or "amido" refers to a chemical moiety with formula $-C(O)N(R)_2$ or $-NHC(O)R$, where R is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon), each of which moiety may itself be optionally substituted. The R_2 of $-N(R)_2$ of the amide may optionally be taken together with the nitrogen to which it is attached to form a 4-, 5-, 6- or 7-membered ring. Unless stated otherwise specifically in the specification, an amido group is optionally substituted independently by one or more of the substituents as described herein for alkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl. An amide may be an amino acid or a peptide molecule attached to a compound disclosed herein, thereby forming a prodrug. The procedures and specific groups to make such amides are known to those of skill in the art and can readily be found in seminal sources such as Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, N.Y., 1999, which is incorporated herein by reference in its entirety.

[00168] "Aromatic" or "aryl" or "Ar" refers to an aromatic radical with six to ten ring atoms (*e.g.*, C_6-C_{10} aromatic or C_6-C_{10} aryl) which has at least one ring having a conjugated pi electron system which is carbocyclic (*e.g.*, phenyl, fluorenyl, and naphthyl). Bivalent radicals formed from substituted benzene derivatives and having the free valences at ring atoms are named as substituted phenylene radicals. Bivalent radicals derived from univalent polycyclic hydrocarbon radicals whose names end in "-yl" by removal of one hydrogen atom from the carbon atom with the free valence are named by adding "-idene" to the name of the corresponding univalent radical, *e.g.*, a naphthyl group with two points of attachment is termed naphthylidene. Whenever it appears herein, a numerical range such as "6 to 10" refers to each integer in the given range; *e.g.*, "6 to 10 ring atoms" means that the aryl group may consist of 6 ring atoms, 7 ring atoms,

etc., up to and including 10 ring atoms. The term includes monocyclic or fused-ring polycyclic (*i.e.*, rings which share adjacent pairs of ring atoms) groups. Unless stated otherwise specifically in the specification, an aryl moiety is optionally substituted by one or more substituents which are independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00169] "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.

[00170] "Ester" refers to a chemical radical of formula -COOR, where R is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon). The procedures and specific groups to make esters are known to those of skill in the art and can readily be found in seminal sources such as Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, N.Y., 1999, which is incorporated herein by reference in its entirety. Unless stated otherwise specifically in the specification, an ester group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00171] "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.

[00172] "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.

[00173] "Heteroalkyl," "heteroalkenyl," and "heteroalkynyl" refer to optionally substituted alkyl, alkenyl and alkynyl radicals and which have one or more skeletal chain atoms selected from an atom other than carbon, e.g., oxygen, nitrogen, sulfur, phosphorus or combinations thereof. A numerical range may be given - *e.g.*, C_1-C_4 heteroalkyl which refers to the chain length in total, which in this example is 4 atoms long. A heteroalkyl group may be substituted with one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, nitro, oxo, thioxo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00174] "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.

[00175] "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.

[00176] "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.

[00177] "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.

[00178] "Heteroaryl" or "heteroaromatic" or "HetAr" refers to a 5- to 18-membered aromatic radical (*e.g.*, C_5-C_{13} heteroaryl) that includes one or more ring heteroatoms selected from nitrogen, oxygen and sulfur, and which may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system. Whenever it appears herein, a numerical range such as "5 to 18" refers to each integer in the given range - *e.g.*, "5 to 18 ring atoms" means that the heteroaryl group may consist of 5 ring atoms, 6 ring atoms, etc., up to and including 18 ring atoms. Bivalent radicals derived from univalent heteroaryl radicals whose names end in "-yl" by removal of one hydrogen atom from the atom with the free valence are named by adding "-idene" to the name of the corresponding univalent radical - *e.g.*, a pyridyl group with two points of attachment is a pyridylidene. A N-containing "heteroaromatic" or "heteroaryl" moiety refers to an aromatic group in which at least one of the skeletal atoms of the ring is a nitrogen atom. The polycyclic heteroaryl group may be fused or non-fused. The heteroatom(s) in the heteroaryl radical are optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heteroaryl may be attached to the rest of the molecule through any atom of the ring(s). Examples of heteroaryls include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzindolyl, 1,3-benzodioxolyl, benzofuranyl, benzooxazolyl, benzo[*d*]thiazolyl, benzothiadiazolyl, benzo[*b*][1,4]dioxepinyl, benzo[*b*][1,4]oxazinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzoxazolyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzofurazanyl, benzothiazolyl, benzothienyl(benzothiophenyl), benzothieno[3,2-*d*]pyrimidinyl, benzotriazolyl, benzo[4,6]imidazo[1,2-*a*]pyridinyl, carbazolyl, cinnolinyl, cyclopenta[*d*]pyrimidinyl, 6,7-dihydro-5*H*-cyclopenta[4,5]thieno[2,3-*d*]pyrimidinyl, 5,6-dihydrobenzo[*h*]quinazolinyl, 5,6-dihydrobenzo[*h*]cinnolinyl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furazanyl, furanonyl, furo[3,2-*c*]pyridinyl, 5,6,7,8,9,10-hexahydrocycloocta[*d*]pyrimidinyl, 5,6,7,8,9,10-hexahydrocycloocta[*d*]pyridazinyl, 5,6,7,8,9,10-hexahydrocycloocta[*d*]pyridinyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl,

indolizinyl, isoxazolyl, 5,8-methano-5,6,7,8-tetrahydroquinazolinyl, naphthyridinyl, 1,6-naphthyridinonyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 5,6,6a,7,8,9,10,10a-octahydrobenzo[*h*]quinazolinyl, 1-phenyl-1*H*-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyranyl, pyrrolyl, pyrazolyl, pyrazolo[3,4-d]pyrimidinyl, pyridinyl, pyrido[3,2-*d*]pyrimidinyl, pyrido[3,4-*d*]pyrimidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, 5,6,7,8-tetrahydroquinazolinyl, 5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidinyl, 6,7,8,9-tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidinyl, 5,6,7,8-tetrahydropyrido[4,5-*c*]pyridazinyl, thiazolyl, thiadiazolyl, thiapyranyl, triazolyl, tetrazolyl, triazinyl, thieno[2,3-*d*]pyrimidinyl, thieno[3,2-*d*]pyrimidinyl, thieno[2,3-*c*]pyridinyl, and thiophenyl (*i.e.*, thienyl). Unless stated otherwise specifically in the specification, a heteroaryl moiety is optionally substituted by one or more substituents which are independently: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, nitro, oxo, thioxo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00179] Substituted heteroaryl also includes ring systems substituted with one or more oxide (-O-) substituents, such as, for example, pyridinyl N-oxides.

[00180] "Heteroarylalkyl" refers to a moiety having an aryl moiety, as described herein, connected to an alkylene moiety, as described herein, wherein the connection to the remainder of the molecule is through the alkylene group.

[00181] "Heterocycloalkyl" refers to a stable 3- to 18-membered non-aromatic ring radical that comprises two to twelve carbon atoms and from one to six heteroatoms selected from nitrogen, oxygen and sulfur. Whenever it appears herein, a numerical range such as "3 to 18" refers to each integer in the given range - *e.g.*, "3 to 18 ring atoms" means that the heterocycloalkyl group may consist of 3 ring atoms, 4 ring atoms, *etc.*, up to and including 18 ring atoms. Unless stated otherwise specifically in the specification, the heterocycloalkyl radical is a monocyclic, bicyclic,

tricyclic or tetracyclic ring system, which may include fused or bridged ring systems. The heteroatoms in the heterocycloalkyl radical may be optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heterocycloalkyl radical is partially or fully saturated. The heterocycloalkyl may be attached to the rest of the molecule through any atom of the ring(s). Examples of such heterocycloalkyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl. Unless stated otherwise specifically in the specification, a heterocycloalkyl moiety is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, nitro, oxo, thioxo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00182] "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.

[00183] "Nitro" refers to the $-NO_2$ radical.

[00184] "Oxa" refers to the -O- radical.

[00185] "Oxo" refers to the =O radical.

[00186] "Isomers" are different compounds that have the same molecular formula. "Stereoisomers" are isomers that differ only in the way the atoms are arranged in space - *i.e.*,

having a different stereochemical configuration. "Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic" mixture. The term "(±)" is used to designate a racemic mixture where appropriate. "Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry is specified according to the Cahn-Ingold-Prelog R-S system. When a compound is a pure enantiomer the stereochemistry at each chiral carbon can be specified by either (*R*) or (*S*). Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain of the compounds described herein contain one or more asymmetric centers and can thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that can be defined, in terms of absolute stereochemistry, as (*R*) or (*S*). The present chemical entities, pharmaceutical compositions and methods are meant to include all such possible isomers, including racemic mixtures, optically pure forms and intermediate mixtures. Optically active (*R*)- and (*S*)-isomers can be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both *E* and *Z* geometric isomers.

[00187] "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.

[00188] 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); E. L. Eliel, Stereochemistry of Carbon Compounds, McGraw-Hill, New York (1962); and E. L. Eliel and S. H. Wilen, Stereochemistry of Organic Compounds, Wiley-Interscience, New York (1994).

[00189] 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.

[00190] "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.

[00191] "Tautomers" are structurally distinct isomers that interconvert by tautomerization. "Tautomerization" is a form of isomerization and includes prototropic or proton-shift tautomerization, which is considered a subset of acid-base chemistry. "Prototropic tautomerization" or "proton-shift tautomerization" involves the migration of a proton accompanied by changes in bond order, often the interchange of a single bond with an adjacent double bond. Where tautomerization is possible (*e.g.*, in solution), a chemical equilibrium of

tautomers can be reached. An example of tautomerization is keto-enol tautomerization. A specific example of keto-enol tautomerization is the interconversion of pentane-2,4-dione and 4-hydroxypent-3-en-2-one tautomers. Another example of tautomerization is phenol-keto tautomerization. A specific example of phenol-keto tautomerization is the interconversion of pyridin-4-ol and pyridin-4(1*H*)-one tautomers.

[00192] A "leaving group or atom" is any group or atom that will, under selected reaction conditions, cleave from the starting material, thus promoting reaction at a specified site. Examples of such groups, unless otherwise specified, include halogen atoms and mesyloxy, p-nitrobenzensulphonyloxy and tosyloxy groups.

[00193] "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 or deprotected 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).

[00194] "Solvate" refers to a compound in physical association with one or more molecules of a pharmaceutically acceptable solvent.

[00195] "Substituted" means that the referenced group may have attached one or more additional groups, radicals or moieties individually and independently selected from, for example, acyl, alkyl, alkylaryl, cycloalkyl, aralkyl, aryl, carbohydrate, carbonate, heteroaryl, heterocycloalkyl, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, halo, carbonyl, ester, thiocarbonyl, isocyanato, thiocyanato, isothiocyanato, nitro, oxo, perhaloalkyl, perfluoroalkyl, phosphate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, and amino, including mono- and di-substituted amino groups, and protected derivatives thereof. The substituents themselves may be substituted, for example, a cycloalkyl substituent may itself have a halide substituent at one or more of its ring carbons. The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

[00196] "Sulfanyl" refers to groups that include -S-(optionally substituted alkyl), -S-(optionally substituted aryl), -S-(optionally substituted heteroaryl) and -S-(optionally substituted heterocycloalkyl).

[00197] "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).

[00198] "Sulfonyl" refers to groups that include -$S(O_2)$-H, -$S(O_2)$-(optionally substituted alkyl), -$S(O_2)$-(optionally substituted amino), -$S(O_2)$-(optionally substituted aryl), -$S(O_2)$-(optionally substituted heteroaryl), and -$S(O_2)$-(optionally substituted heterocycloalkyl).

[00199] "Sulfonamidyl" or "sulfonamido" refers to a -$S(=O)_2$-NRR radical, where each R is selected independently from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon). The R groups in -NRR of the -$S(=O)_2$-NRR radical may be taken together with the nitrogen to which it is attached to form a 4-, 5-, 6- or 7-membered ring. A sulfonamido group is optionally substituted by one or more of the substituents described for alkyl, cycloalkyl, aryl, heteroaryl, respectively.

[00200] "Sulfoxyl" refers to a -$S(=O)_2OH$ radical.

[00201] "Sulfonate" refers to a -$S(=O)_2$-OR radical, where R is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon). A sulfonate group is optionally substituted on R by one or more of the substituents described for alkyl, cycloalkyl, aryl, heteroaryl, respectively.

[00202] 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.

[00203] Compounds of the invention also include antibodies. The terms "antibody" and its plural form "antibodies" refer to whole immunoglobulins and any antigen-binding fragment ("antigen-binding portion") or single chains thereof. An "antibody" further refers to a

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

[00204] 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.*, CD20 can be made using knowledge and skill in the art of injecting test subjects with CD20 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.

[00205] 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.*, CD20). It has been shown that the antigen-binding function of an antibody can be performed by fragments of a full-length antibody. Examples of binding fragments encompassed within the term "antigen-binding portion" of an antibody include (i) a Fab fragment, a monovalent fragment consisting of the V_L, V_H, C_L and CH1 domains; (ii) a F(ab')2 fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the V_H and CH1 domains; (iv) a Fv fragment consisting of the V_L and V_H domains of a single arm of an antibody, (v) a domain antibody (dAb) fragment (Ward *et al.*, *Nature*, **1989,** *341,* 544-546), which may consist of a V_H or a V_L domain; and (vi) an isolated complementarity determining region (CDR). Furthermore, although the two domains of the Fv fragment, V_L and V_H, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the V_L and V_H regions pair to form monovalent molecules known as single chain Fv (scFv); see, *e.g.*, Bird *et al.*, *Science* **1988,** *242,* 423-426; and Huston *et al.*, *Proc. Natl. Acad. Sci. USA* **1988,** *85,* 5879-5883). Such scFv 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.

[00206] 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.

[00207] 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.

[00208] 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*.

[00209] As used herein, "isotype" refers to the antibody class (e.g., IgM or IgG1) that is encoded by the heavy chain constant region genes. In mammals, there are five antibody isotypes: IgA, IgD, IgG, IgM and IgE. In humans, there are four subclasses of the IgG isotype: IgG1, IgG2, IgG3 and IgG4, and two subclasses of the IgA isotype: IgA1 and IgA2.

[00210] 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."

[00211] 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 terms "conjugate," "antibody-drug conjugate", "ADC," 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.

[00212] 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.

[00213] 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.

[00214] 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.

[00215] The term "glycosylation" refers to a modified derivative of an antibody. An aglycoslated antibody lacks glycosylation. Glycosylation can be altered to, for example, increase the affinity of the antibody for antigen. Such carbohydrate modifications can be accomplished by, for example, altering one or more sites of glycosylation within the antibody sequence. For example, one or more amino acid substitutions can be made that result in elimination of one or more variable region framework glycosylation sites to thereby eliminate glycosylation at that site. Aglycosylation may increase the affinity of the antibody for antigen, as described in U.S. Patent Nos. 5,714,350 and 6,350,861. Additionally or alternatively, an antibody can be made that has an altered type of glycosylation, such as a hypofucosylated antibody having reduced amounts of fucosyl residues or an antibody having increased bisecting GlcNac structures. Such altered glycosylation patterns have been demonstrated to increase the ability of antibodies. Such carbohydrate modifications can be accomplished by, for example, expressing the antibody in a host cell with altered glycosylation machinery. Cells with altered glycosylation machinery have been described in the art and can be used as host cells in which to express recombinant antibodies of the invention to thereby produce an antibody with altered glycosylation. For example, the cell lines Ms704, Ms705, and Ms709 lack the fucosyltransferase gene, FUT8 (alpha (1,6) fucosyltransferase), such that antibodies expressed in the Ms704, Ms705, and Ms709 cell lines lack fucose on their carbohydrates. The Ms704, Ms705, and Ms709 FUT8−/− cell lines were created by the targeted disruption of the FUT8 gene in CHO/DG44 cells using two replacement vectors (see e.g. U.S. Patent Publication No. 2004/0110704 or Yamane-Ohnuki, *et al. Biotechnol. Bioeng.*, **2004,** *87,* 614-622). As another example, European Patent No. EP 1,176,195 describes a cell line with a functionally disrupted FUT8 gene, which encodes a fucosyl transferase, such that antibodies expressed in such a cell line exhibit hypofucosylation by reducing or eliminating the alpha 1,6 bond-related enzyme, and also describes cell lines which have a low enzyme activity for adding fucose to the N-acetylglucosamine that binds to the Fc region of the antibody or does not have the enzyme activity, for example the rat myeloma cell line YB2/0 (ATCC CRL 1662). International Patent Publication WO 03/035835 describes a

variant CHO cell line, Lec 13 cells, with reduced ability to attach fucose to Asn(297)-linked carbohydrates, also resulting in hypofucosylation of antibodies expressed in that host cell (see also Shields, *et al., J. Biol. Chem.* **2002,** *277,* 26733-26740. International Patent Publication WO 99/54342 describes cell lines engineered to express glycoprotein-modifying glycosyl transferases (e.g., beta(1,4)-N-acetylglucosaminyltransferase III (GnTIII)) such that antibodies expressed in the engineered cell lines exhibit increased bisecting GlcNac structures which results in increased ADCC activity of the antibodies (see also Umana, *et al.*, *Nat. Biotech.* **1999,** *17,* 176-180). Alternatively, the fucose residues of the antibody may be cleaved off using a fucosidase enzyme. For example, the fucosidase alpha-L-fucosidase removes fucosyl residues from antibodies as described in Tarentino, *et al.*, *Biochem.* **1975,** *14,* 5516-5523.

[00216] "Pegylation" refers to a modified antibody, or a fragment thereof, that typically is reacted with polyethylene glycol (PEG), such as a reactive ester or aldehyde derivative of PEG, under conditions in which one or more PEG groups become attached to the antibody or antibody fragment. Pegylation may, for example, increase the biological (e.g., serum) half life of the antibody. Preferably, the pegylation is carried out via an acylation reaction or an alkylation reaction with a reactive PEG molecule (or an analogous reactive water-soluble polymer). As used herein, the term "polyethylene glycol" is intended to encompass any of the forms of PEG that have been used to derivatize other proteins, such as mono (C_1-C_{10}) alkoxy- or aryloxy-polyethylene glycol or polyethylene glycol-maleimide. The antibody to be pegylated may be an aglycosylated antibody. Methods for pegylation are known in the art and can be applied to the antibodies of the invention, as described for example in European Patent Nos. EP 0154316 and EP 0401384.

[00217] The term "conservative amino acid substitutions" means amino acid sequence modifications which do not abrogate the binding of the antibody to the antigen. Conservative amino acid substitutions include the substitution of an amino acid in one class by an amino acid of the same class, where a class is defined by common physicochemical amino acid side chain properties and high substitution frequencies in homologous proteins found in nature, as determined, for example, by a standard Dayhoff frequency exchange matrix or BLOSUM matrix. Six general classes of amino acid side chains have been categorized and include: Class I (Cys); Class II (Ser, Thr, Pro, Ala, Gly); Class III (Asn, Asp, Gln, Glu); Class IV (His, Arg, Lys); Class V (Ile, Leu, Val, Met); and Class VI (Phe, Tyr, Trp). For example, substitution of an Asp for

another class III residue such as Asn, Gln, or Glu, is a conservative substitution. Thus, a predicted nonessential amino acid residue in an anti-IL-6 or anti-IL-6R antibody is preferably replaced with another amino acid residue from the same class. Methods of identifying amino acid conservative substitutions which do not eliminate antigen binding are well-known in the art (see, *e.g.*, Brummell, *et al.*, *Biochemistry* **1993,** *32,* 1180-1187; Kobayashi, *et al.*, *Protein Eng.* **1999,** *12,* 879-884 (1999); and Burks, *et al.*, *Proc. Natl. Acad. Sci. USA* **1997,** *94,* 412-417).

[00218] The terms "sequence identity," "percent identity," and "sequence percent identity" in the context of two or more nucleic acids or polypeptides, refer to two or more sequences or subsequences that are the same or have a specified percentage of nucleotides or amino acid residues that are the same, when compared and aligned (introducing gaps, if necessary) for maximum correspondence, not considering any conservative amino acid substitutions as part of the sequence identity. The percent identity can be measured using sequence comparison software or algorithms or by visual inspection. Various algorithms and software are known in the art that can be used to obtain alignments of amino acid or nucleotide sequences. Suitable programs to determine percent sequence identity include for example the BLAST suite of programs available from the U.S. Government's National Center for Biotechnology Information BLAST web site. Comparisons between two sequences can be carried using either the BLASTN or BLASTP algorithm. BLASTN is used to compare nucleic acid sequences, while BLASTP is used to compare amino acid sequences. ALIGN, ALIGN-2 (Genentech, South San Francisco, California) or MegAlign, available from DNASTAR, are additional publicly available software programs that can be used to align sequences. One skilled in the art can determine appropriate parameters for maximal alignment by particular alignment software. In certain embodiments, the default parameters of the alignment software are used.

[00219] Certain embodiments of the present invention comprise a variant of an antibody, *e.g.*, an anti-CD20 antibody. As used herein, the term "variant" encompasses but is not limited to antibodies which comprise an amino acid sequence which differs from the amino acid sequence of a reference antibody by way of one or more substitutions, deletions and/or additions at certain positions within or adjacent to the amino acid sequence of the reference antibody. The variant may comprise one or more conservative substitutions in its amino acid sequence as compared to the amino acid sequence of a reference antibody. Conservative substitutions may involve, *e.g.*, the substitution of similarly charged or uncharged amino acids. The variant retains the ability to

specifically bind to the antigen of the reference antibody.

[00220] The term "radioisotope-labeled complex" refers to both non-covalent and covalent attachment of a radioactive isotope, such as ^{90}Y, ^{111}In, or ^{131}I, to an antibody, including conjugates.

[00221] 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" of rituximab. In Europe, 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 (EMA). The relevant legal basis for similar biological applications in Europe is Article 6 of Regulation (EC) No 726/2004 and Article 10(4) of Directive 2001/83/EC, as amended and therefore in Europe, the biosimilar may be authorised, approved for authorisation or subject of an application for authorisation under Article 6 of Regulation (EC) No 726/2004 and Article 10(4) of Directive 2001/83/EC. The already authorized original biological medicinal product may be referred to as a "reference medicinal product" in Europe. Some of the requirements for a product to be considered a biosimilar are outlined in the CHMP Guideline on Similar Biological Medicinal Products. In addition, product specific guidelines, including guidelines relating to monoclonal antibody biosimilars, are provided on a product-by-product basis by the EMA and published on its website. A biosimilar as described herein may be similar to the reference medicinal product by way of quality characteristics, biological activity, mechanism of action, safety profiles and/or efficacy. In addition, the biosimilar may be used or

be intended for use to treat the same conditions as the reference medicinal product. Thus, a biosimilar as described herein may be deemed to have similar or highly similar quality characteristics to a reference medicinal product. Alternatively, or in addition, a biosimilar as described herein may be deemed to have similar or highly similar biological activity to a reference medicinal product. Alternatively, or in addition, a biosimilar as described herein may be deemed to have a similar or highly similar safety profile to a reference medicinal product. Alternatively, or in addition, a biosimilar as described herein may be deemed to have similar or highly similar efficacy to a reference medicinal product. As described herein, a biosimilar in Europe is compared to a reference medicinal product which has been authorised by the EMA. However, in some instances, the biosimilar may be compared to a biological medicinal product which has been authorised outside the European Economic Area (a non-EEA authorised "comparator") in certain studies. Such studies include for example certain clinical and in vivo non-clinical studies. As used herein, the term "biosimilar" also relates to a biological medicinal product which has been or may be compared to a non-EEA authorised comparator. Certain biosimilars are proteins such as antibodies, antibody fragments (for example, antigen binding portions) and fusion proteins. A protein biosimilar may have an amino acid sequence that has minor modifications in the amino acid structure (including for example deletions, additions, and/or substitutions of amino acids) which do not significantly affect the function of the polypeptide. The biosimilar may comprise an amino acid sequence having a sequence identity of 97% or greater to the amino acid sequence of its reference medicinal product, *e.g.*, 97%, 98%, 99% or 100%. The biosimilar may comprise one or more post-translational modifications, for example, although not limited to, glycosylation, oxidation, deamidation, and/or truncation which is/are different to the post-translational modifications of the reference medicinal product, provided that the differences do not result in a change in safety and/or efficacy of the medicinal product. The biosimilar may have an identical or different glycosylation pattern to the reference medicinal product. Particularly, although not exclusively, the biosimilar may have a different glycosylation pattern if the differences address or are intended to address safety concerns associated with the reference medicinal product. Additionally, the biosimilar may deviate from the reference medicinal product in for example its strength, pharmaceutical form, formulation, excipients and/or presentation, providing safety and efficacy of the medicinal product is not compromised. The biosimilar may comprise differences in for example pharmacokinetic (PK)

and/or pharmacodynamic (PD) profiles as compared to the reference medicinal product but is still deemed sufficiently similar to the reference medicinal product as to be authorised or considered suitable for authorisation. In certain circumstances, the biosimilar exhibits different binding characteristics as compared to the reference medicinal product, wherein the different binding characteristics are considered by a Regulatory Authority such as the EMA not to be a barrier for authorisation as a similar biological product. The term "biosimilar" is also used synonymously by other national and regional regulatory agencies.

[00222] The term "binding molecule" as used herein includes molecules that contain at least one antigen binding site that specifically binds to IL-6 or IL-6R. By "specifically binds" it is meant that the binding molecules exhibit essentially background binding to molecules other than IL-6 or IL-6R. An isolated binding molecule that specifically binds IL-6 or IL-6R may, however, have cross-reactivity to IL-6 or IL-6R molecules from other species.

[00223] 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.

[00224] 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.

[00225] 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.

[00226] 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.

[00227]

Co-administration of Compounds

[00228] An aspect of the invention is a composition, such as a pharmaceutical composition, preferably comprising a combination of a BTK inhibitor and a MEK inhbitor.

[00229] Another aspect is a kit containing a BTK inhibitor and a MEK inhibitor, wherein each of the inhibitors is formulated into a separate pharmaceutical composition, and wherein said separate pharmaceutical compositions are formulated for co-administration.

[00230] Another aspect of the invention is a method of treating a disease or condition in a subject, in particular a hyperproliferative disorder such as 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 BTK inhibitor and a MEK inhibitor. In an embodiment, the foregoing method exhibits synergistic effects that may result in greater efficacy, less side effects, the use of less active pharmaceutical ingredient to achieve a given clinical result, or other synergistic effects. A combination of a BTK inhibitor and a MEK inhibitor is a preferred embodiment. The pharmaceutical composition comprising the combination, and the kit, are both for use in treating such disease or condition.

[00231] In a preferred embodiment, the solid tumor cancer is selected from the group consisting of breast, lung, colorectal, thyroid, bone sarcoma, and stomach cancers.

[00232] In a preferred embodiment, the leukemia is selected from the group consisting of acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), acute lymphoblastic leukemia (ALL), B cell chronic lymphocytic leukemia (B-CLL), and chronic lymphoid leukemia (CLL).

[00233] In a preferred embodiment, the lymphoma is selected from the group consisting of Burkitt's lymphoma, mantle cell lymphoma, follicular lymphoma, indolent B-cell non-Hodgkin's lymphoma, histiocytic lymphoma, activated B-cell like diffuse large B cell lymphoma (DLBCL-ABC), germinal center B-cell like diffuse large B cell lymphoma (DLBCL-GCB), and diffuse large B cell lymphoma (DLBCL).

[00234] 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.

[00235] In an embodiment, the MEK inhibitor is in the form of a pharmaceutically acceptable salt, solvate, hydrate, complex, derivative, prodrug (such as an ester or phosphate ester), or cocrystal.

[00236] In an embodiment, the MEK inhibitor is administered to the subject before administration of the BTK inhibitor.

[00237] In an embodiment, the MEK inhibitor is administered concurrently with the administration of the BTK inhibitor.

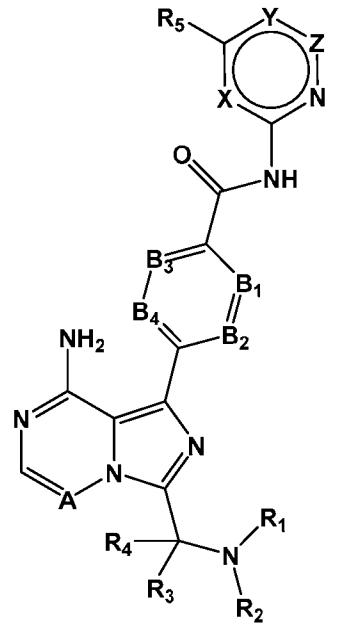
[00238] In an embodiment, the MEK inhibitor is administered to the subject after administration of the BTK inhibitor.

[00239] In a preferred embodiment, the subject is a mammal, such as a human. In an embodiment, the subject is a human. In an embodiment, the subject is a companion animal. In an embodiment, the subject is a canine, feline, or equine.

BTK Inhibitors

[00240] 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.

[00241] In an embodiment, the BTK inhibitor is a compound of Formula (1):



Formula (1)

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

X is CH, N, O or S;

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

Z is CH, N or bond;

A is CH or N;

B_1 is N or $C(R_7)$;

B_2 is N or $C(R_8)$;

B_3 is N or $C(R_9)$;

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

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

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

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

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

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

R_5 is H, halogen, cyano, (C_{1-4})alkyl, (C_{1-3})alkoxy, (C_{3-6})cycloalkyl, any alkyl group of which is optionally substituted with one or more halogen; or R_5 is (C_{6-10})aryl or (C_{2-6})heterocycloalkyl;

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

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

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

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

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

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

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

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

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

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

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

with the proviso that:

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

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

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

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

with the terms used having the following meanings:

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

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

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

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

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

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

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

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

(C_{3-7})heterocycloalkyl means a heterocycloalkyl group having 3-7 carbon atoms, preferably 3-5 carbon atoms, and one or two heteroatoms selected from N, O and/or S. Preferred heteroatoms are N or O; preferred (C_{3-7}) heterocycloalkyl groups are azetidinyl, pyrrolidinyl,

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

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

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

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

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

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

halogen means fluorine, chlorine, bromine or iodine;

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

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

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

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

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

A circle in a ring of Formula (1) indicates that the ring is aromatic.

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

[00242] In a preferred embodiment, the BTK inhibitor is a compound of Formula (1) or a pharmaceutically acceptable salt thereof, wherein:

X is CH or S;

Y is $C(R_6)$;

Z is CH or bond;

A is CH;

B_1 is N or $C(R_7)$;

B_2 is N or $C(R_8)$;

B_3 is N or CH;

B_4 is N or CH;

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

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

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

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

R_4 is H;

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

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

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

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

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

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

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

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

[00243] In an embodiment of Formula (1), B_1 is $C(R_7)$; B_2 is $C(R_8)$; B_3 is $C(R_9)$; B_4 is $C(R_{10})$; R_7, R_9, and R_{10} are each H; and R_8 is hydrogen or methyl.

[00244] In an embodiment of Formula (1), the ring containing X, Y and Z is selected from the group consisting of pyridyl, pyrimidyl, pyridazyl, triazinyl, thiazolyl, oxazolyl and isoxazolyl.

[00245] In an embodiment of Formula (1), the ring containing X, Y and Z is selected from the group consisting of pyridyl, pyrimidyl and pyridazyl.

[00246] In an embodiment of Formula (1), the ring containing X, Y and Z is selected from the group consisting of pyridyl and pyrimidyl.

[00247] In an embodiment of Formula (1), the ring containing X, Y and Z is pyridyl.

[00248] In an embodiment of Formula (1), R_5 is selected from the group consisting of hydrogen, fluorine, methyl, methoxy and trifluoromethyl.

[00249] In an embodiment of Formula (1), R_5 is hydrogen.

[00250] In an embodiment of Formula (1), R_2 and R_3 together form a heterocycloalkyl ring selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl and morpholinyl, optionally substituted with one or more of fluoro, hydroxyl, (C_{1-3})alkyl and (C_{1-3})alkoxy.

[00251] In an embodiment of Formula (1), R_2 and R_3 together form a heterocycloalkyl ring selected from the group consisting of azetidinyl, pyrrolidinyl and piperidinyl.

[00252] In an embodiment of Formula (1), R_2 and R_3 together form a pyrrolidinyl ring.

[00253] In an embodiment of Formula (1), R_1 is independently selected from the group consisting of (C_{1-6})alkyl, (C_{2-6})alkenyl or (C_{2-6})alkynyl, each optionally substituted with one or more substituents selected from the group consisting of hydroxyl, (C_{1-4})alkyl, (C_{3-7})cycloalkyl, $[(C_{1-4})$alkyl]amino, di$[(C_{1-4})$alkyl] amino, (C_{1-3})alkoxy, (C_{3-7})cycloalkoxy, (C_{6-10})aryl and (C_{3-7})heterocycloalkyl.

[00254] In an embodiment of Formula (1), B_1, B_2, B_3 and B_4 are CH; X is N; Y and Z are CH; R_5 is CH_3; A is N; R_2, R_3 and R_4 are H; and R_1 is CO-CH_3.

[00255] In an embodiment of Formula (1), B_1, B_2, B_3 and B_4 are CH; X and Y are N; Z is CH; R_5 is CH_3; A is N; R_2, R_3 and R_4 are H; and R_1 is CO-CH_3.

[00256] In an embodiment of Formula (1), B_1, B_2, B_3 and B_4 are CH; X and Y are N; Z is CH; R_5 is CH_3; A is CH; R_2 and R_3 together form a piperidinyl ring; R_4 is H; and R_1 is CO-ethenyl.

[00257] In an embodiment of Formula (1), B_1, B_2, B_3 and B_4 are CH; X, Y and Z are CH; R_5 is H; A is CH; R_2 and R_3 together form a pyrrolidinyl ring; R_4 is H; and R_1 is CO-propynyl.

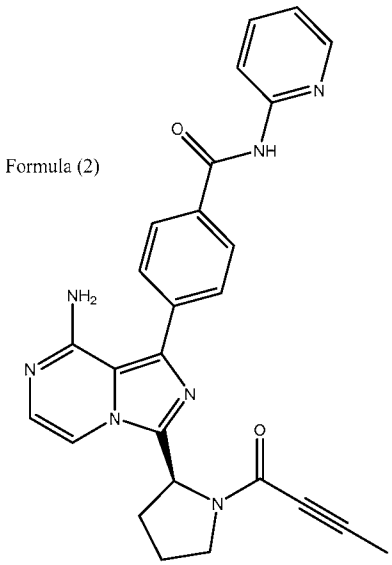
[00258] In an embodiment of Formula (1), B_1, B_2, B_3 and B_4 are CH; X, Y and Z are CH; R_5 is CH_3; A is CH; R_2 and R_3 together form a piperidinyl ring; R_4 is H; and R_1 is CO-propynyl.

[00259] In an embodiment of Formula (1), B_1, B_2, B_3 and B_4 are CH; X and Y are N; Z is CH; R_5 is H; A is CH; R_2 and R_3 together form a morpholinyl ring; R_4 is H; and R_1 is CO-ethenyl.

[00260] In an embodiment of Formula (1), B_1, B_2, B_3 and B_4 are CH; X and Y are N; Z is CH; R_5 is CH_3; A is CH; R_2 and R_3 together form a morpholinyl ring; R_4 is H; and R_1 is CO-propynyl.

[00261] In a preferred embodiment, the BTK inhibitor is a compound of Formula (2), also known as acalabrutinib:

Formula (2)



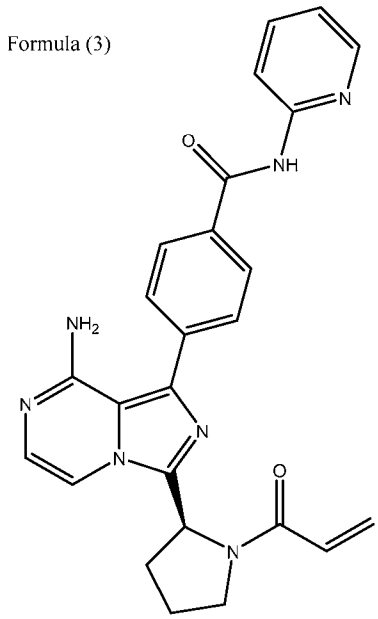
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of this compound is described in International Patent Application Publication No.

WO 2013/010868 and U.S. Patent Application Publication No. US 2014/0155385 A1, the disclosures of which are incorporated herein by reference.

[00262] In a preferred embodiment, the BTK inhibitor is (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide or pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug therof.

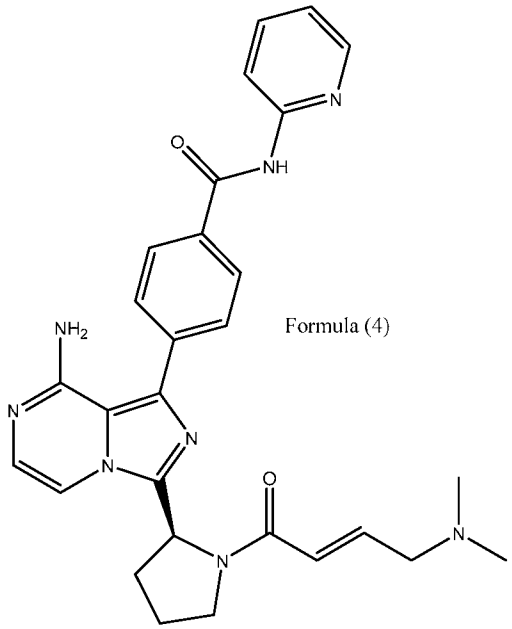
[00263] In a preferred embodiment, the BTK inhibitor is a compound of Formula (3):

Formula (3)



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.

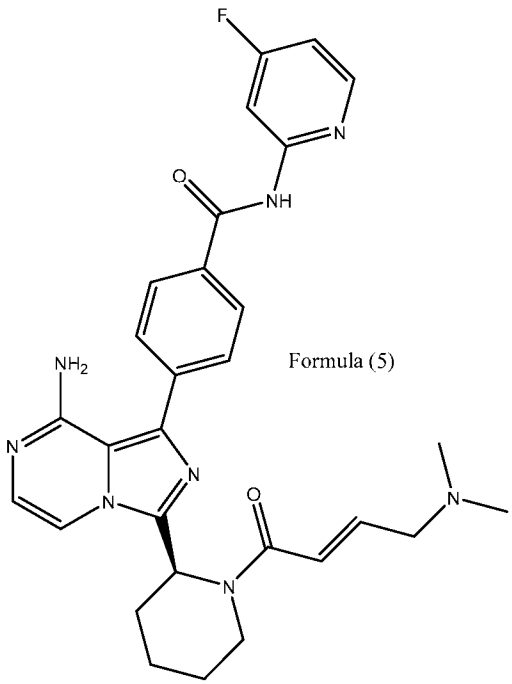
[00264] In a preferred embodiment, the BTK inhibitor is a compound of Formula (4):



Formula (4)

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.

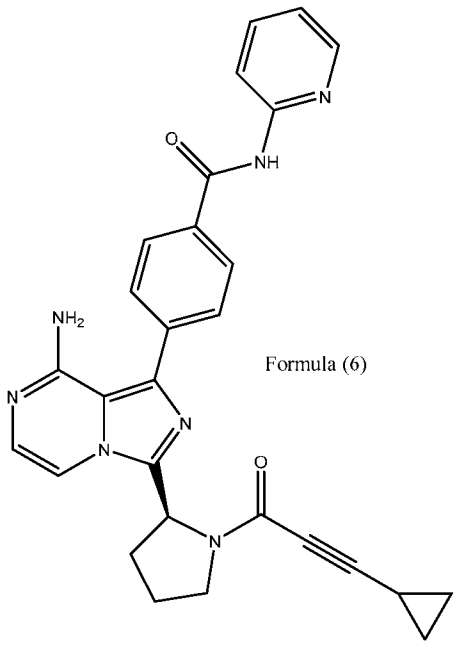
[00265] In a preferred embodiment, the BTK inhibitor is a compound of Formula (5):



Formula (5)

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.

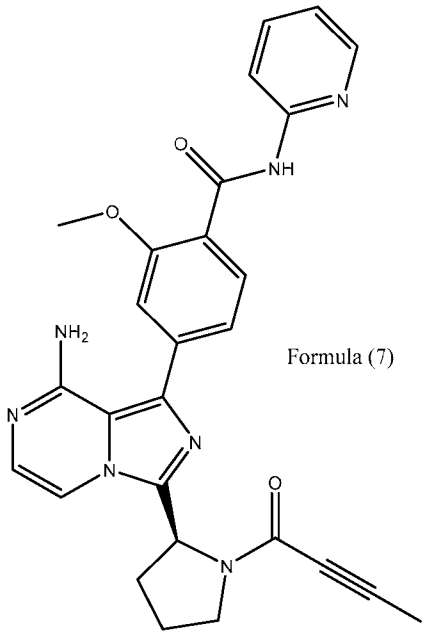
[00266] In a preferred embodiment, the BTK inhibitor is a compound of Formula (6):



Formula (6)

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.

[00267] In a preferred embodiment, the BTK inhibitor is a compound of Formula (7):

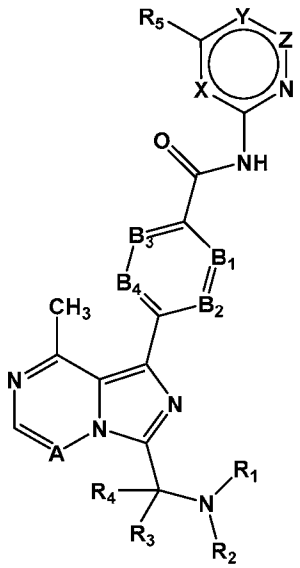


Formula (7)

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.

[00268] 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.

[00269] In an embodiment, the BTK inhibitor is a compound of Formula (8):



Formula (8)

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

X is CH, N, O or S;

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

Z is CH, N or bond;

A is CH or N;

B_1 is N or $C(R_7)$;

B_2 is N or $C(R_8)$;

B_3 is N or $C(R_9)$;

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

R_1 is $R_{11}C(O)$, $R_{12}S(O)$, $R_{13}SO_2$ or (C_{1-6})alkyl optionally substituted with R_{14};

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

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

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

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

R_5 is H, halogen, cyano, (C_{1-4})alkyl, (C_{1-3})alkoxy, (C_{3-6})cycloalkyl; all alkyl groups of R5 are optionally substituted with one or more halogen; or R_5 is (C_{6-10})aryl or (C_{2-6})heterocycloalkyl;

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

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

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

R_7 and R_8 together with the carbon atoms they are attached to, form (C_{6-10})aryl or (C_{1-5})heteroaryl;

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

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

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

R_{11} is (C_{1-3})alkyl-C(O)-S-(C_{1-3})alkyl; or

R_{11} is (C_{1-5})heteroaryl optionally substituted with one or more groups selected from halogen or cyano.

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

(C_{1-5})heteroaryl optionally substituted with one or more groups selected from halogen or cyano;

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

with the proviso that

- 0 to 2 atoms of X, Y, Z can simultaneously be a heteroatom;
- when one atom selected from X, Y is O or S, then Z is a bond and the other atom selected from X, Y can not be O or S;
- when Z is C or N then Y is $C(R_6)$ or N and X is C or N;
- 0 to 2 atoms of B_1, B_2, B_3 and B_4 are N;

with the terms used having the following meanings:

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

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

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

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

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

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

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

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

(C_{2-6})alkynyl means a branched or unbranched alkynyl group having $_{2-6}$ carbon atoms, such as ethynyl, propynyl, n-butynyl, n-pentynyl, isopentynyl, isohexynyl or n-hexynyl, wtih (C_{2-4})alkynyl groups preferred, and (C_{2-3})alkynyl groups more preferred;

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

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

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

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

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

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

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

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

halogen means fluorine, chlorine, bromine or iodine;

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

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

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

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

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

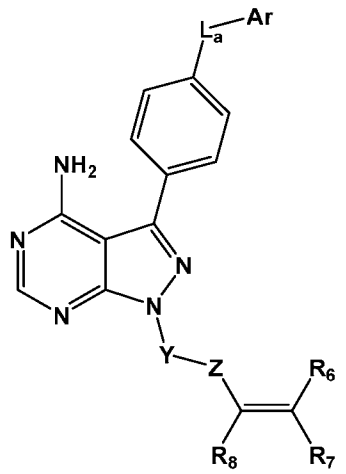
A circle in a ring of Formula (8) indicates that the ring is aromatic.

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

[00270] In a preferred embodiment, the invention relates to a compound according to Formula (8) wherein B_1 is $C(R_7)$; B_2 is $C(R_8)$; B_3 is $C(R_9)$ and B_4 is $C(R_{10})$.

[00271] 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.

[00272] In an embodiment, the BTK inhibitor is a compound of Formula (9):



Formula (9)

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

L_a is CH_2, O, NH or S;

Ar is a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

Y is an optionally substituted group selected from the group consisting of alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

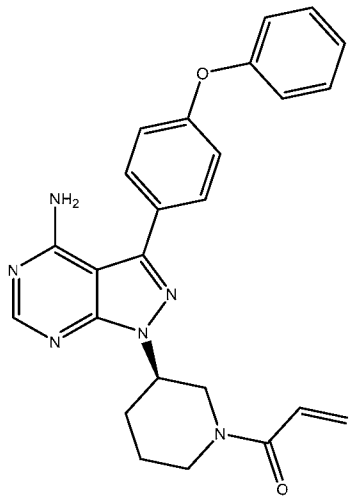
Z is C(=O), OC(=O), NRC(=O), C(=S), $S(=O)_x$, $OS(=O)_x$ or $NRS(=O)_x$, where x is 1 or 2;

R^7 and R^8 are each independently H; or R^7 and R^8 taken together form a bond;

R^6 is H; and

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

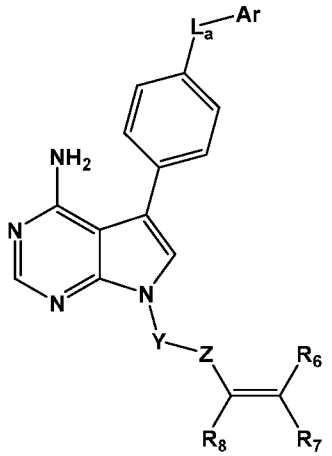
[00273] In a preferred embodiment, the BTK inhibitor is ibrutinib or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. In a preferred embodiment, the BTK inhibitor is (*R*)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one. In a preferred embodiment, the BTK inhibitor is 1-[(3*R*)-3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidin-1-yl]prop-2-en-1-one. In a preferred exemplary embodiment, the BTK inhibitor is (*S*)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one. In a preferred embodiment, the BTK inhibitor has the structure of Formula (10):



Formula (10)

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

[00274] In an exemplary embodiment, the BTK inhibitor is a compound of Formula (11):



Formula (11)

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

wherein:

L_a is CH_2, O, NH or S;

Ar is a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

Y is an optionally substituted group selected from the group consisting of alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

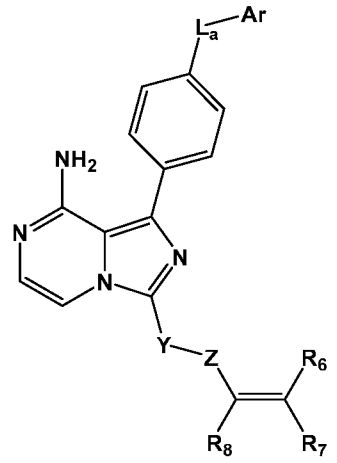
Z is C(=O), OC(=O), NRC(=O), C(=S), $S(=O)_x$, $OS(=O)_x$ or $NRS(=O)_x$, where x is 1 or 2;

R^7 and R^8 are each H; or R^7 and R^8 taken together form a bond;

R^6 is H; and

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

[00275] In an embodiment, the BTK inhibitor is a compound of Formula (12):



Formula (12)

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

wherein:

L_a is CH_2, O, NH or S;

Ar is a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

Y is an optionally substituted group selected from the group consisting of alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

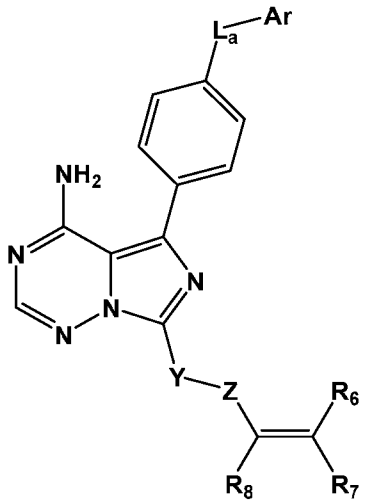
Z is C(=O), OC(=O), NRC(=O), C(=S), $S(=O)_x$, $OS(=O)_x$ or $NRS(=O)_x$, where x is 1 or 2;

R^7 and R^8 are each H; or R^7 and R^8 taken together form a bond;

R^6 is H; and

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

[00276] In an embodiment, the BTK inhibitor is a compound of Formula (13):



Formula (13)

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

L_a is CH_2, O, NH or S;

Ar is a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

Y is an optionally substituted group selected from the group consisting of alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

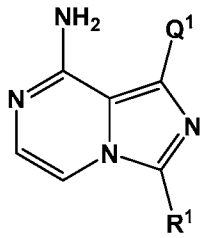
Z is C(=O), OC(=O), NRC(=O), C(=S), $S(=O)_x$, $OS(=O)_x$ or $NRS(=O)_x$, where x is 1 or 2;

R^7 and R^8 are each H; or R^7 and R^8 taken together form a bond;

R^6 is H; and

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

[00277] 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 (14):



Formula (14)

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

Q^1 is $aryl^1$, $heteroaryl^1$, cycloalkyl, heterocyclyl, cycloalkenyl, or heterocycloalkenyl, any of which is optionally substituted by one to five independent G^1 substituents;

R^1 is alkyl, cycloalkyl, bicycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocyclyl, or heterobicycloalkyl, any of which is optionally substituted by one or more independent G^{11} substituents;

G^1 and G^{41} are each independently halo, oxo, $-CF_3$, $-OCF_3$, $-OR^2$, $-NR^2R^3(R^{3a})_{j1}$, $-C(O)R^2$, $-CO_2R^2$, $-CONR^2R^3$, $-NO_2$, -CN, $-S(O)_{j1}R^2$, $-SO_2NR^2R^3$, $NR^2(C=O)R^3$, $NR^2(C=O)OR^3$, $NR^2(C=O)NR^2R^3$, $NR^2S(O)_{j1}R^3$, $-(C=S)OR^2$, $-(C=O)SR^2$, $-NR^2(C=NR^3)NR^{2a}R^{3a}$, $-NR^2(C=NR^3)OR^{2a}$, $-NR^2(C=NR^3)SR^{3a}$, $-O(C=O)OR^2$, $-O(C=O)NR^2R^3$, $-O(C=O)SR^2$, $-S(C=O)OR^2$, $-S(C=O)NR^2R^3$, (C_{0-10})alkyl, (C_{2-10})alkenyl, (C_{2-10})alkynyl, (C_{1-10})alkoxy(C_{1-10})alkyl, (C_{1-10})alkoxy(C_{2-10})alkenyl, (C_{1-10})alkoxy(C_{2-10})alkynyl, (C_{1-10})alkylthio(C_{1-10}) alkyl, (C_{1-10})alkylthio(C_{2-10})alkenyl, (C_{1-10})alkylthio(C_{2-10})alkynyl, cyclo(C_{3-8})alkyl, cyclo(C_{3-8})alkenyl, cyclo(C_{3-8})alkyl(C_{1-10})alkyl, cyclo(C_{3-8})alkenyl(C_{1-10})alkyl, cyclo(C_{3-8}) alkyl(C_{2-10})alkenyl, cyclo(C_{3-8})alkenyl(C_{2-10})alkenyl, cyclo(C_{3-8})alkyl(C_{2-10})alkynyl, cyclo(C_{3-8})alkenyl(C_{2-10})alkynyl, heterocyclyl-(C_{0-10})alkyl, heterocyclyl-(C_{2-10})alkenyl, or heterocyclyl-(C_{2-10})alkynyl, any of which is optionally substituted with one or more independent halo, oxo, $-CF_3$, $-OCF_3$, $-OR^{222}$, $-NR^{222}R^{333}(R^{333}a)_{j1a}$, $-C(O)R^{222}$, $-CO_2R^{222}$, $-CONR^{222}R^{333}$, $-NO_2$, -CN, $-S(O)_{j1a}R^{222}$, $-SO_2NR^{222}R^{333}$, $NR^{222}(C=O)R^{333}$, $NR^{222}(C=O)OR^{333}$, $NR^{222}(C=O)NR^{222}R^{333}$, $NR^{222}S(O)_{j1a}R^{333}$, $-(C=S)OR^{222}$, $-(C=O)SR^{222}$, $-NR^{222}(C=NR^{333})NR^{222a}R^{333a}$, $-NR^{222}(C=NR^{333})OR^{222a}$, $-NR^{222}(C=NR^{333})SR^{333a}$, $-O(C=O)OR^{222}$, $-O(C=O)NR^{222}R^{333}$, $-O(C=O)SR^{222}$, $-S(C=O)OR^{222}$, or $-S(C=O)NR^{222}R^{333}$ substituents; or $-(X^1)_n-(Y^1)_m-R^4$; or aryl-(C_{0-10})alkyl, aryl-(C_{2-10})alkenyl, or aryl-(C_{2-10}) alkynyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{222}$, $-NR^{222}R^{333}(R^{333a})_{j2a}$, $-C(O)R^{222}$, $-CO_2R^{222}$, $-CONR^{222}R^{333}$, $-NO_2$, -CN, $-S(O)_{j2a}R^{222}$, $-SO_2NR^{222}R^{333}$, $NR^{222}(C=O)R^{333}$, $NR^{222}(C=O)OR^{333}$, $NR^{222}(C=O)NR^{222}R^{333}$, $NR^{222}S(O)_{j2a}R^{333}$, $-(C=S)OR^{222}$, $-(C=O)SR^{222}$, $-NR^{222}(C=NR^{333})NR^{222a}R^{333a}$, $-NR^{222}(C=NR^{333})OR^{222a}$, $-NR^{222}(C=NR^{333})SR^{333a}$, $-O(C=O)OR^{222}$, $-O(C=O)NR^{222}R^{333}$, $-O(C=O)SR^{222}$, $-S(C=O)OR^{222}$, or $-S(C=O)NR^{222}R^{333}$ substituents; or hetaryl-(C_{0-10})alkyl, hetaryl-(C_{2-10})alkenyl, or hetaryl-(C_{2-10})alkynyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{222}$, $-NR^{222}$, $R^{333}(R^{333a})_{j3a}$, $-C(O)R^{222}$, -

CO_2R^{222}, -$CONR^{222}R^{333}$, -NO_2, -CN, -$S(O)_{j3a}R^{222}$, -$SO_2NR^{222}R^{333}$, $NR^{222}(C=O)R^{333}$, $NR^{222}(C=O)OR^{333}$, $NR^{222}(C=O)NR^{222}R^{333}$, $NR^{222}S(O)_{j3a}R^{333}$, -$(C=S)OR^{222}$, -$(C=O)SR^{222}$, -$NR^{222}(C=NR^{333})NR^{222a}R^{333a}$, -$NR^{222}(C=NR^{333})OR^{222a}$, -$NR^{222}(C=NR^{333})SR^{333a}$, -$O(C=O)OR^{222}$, -$O(C=O)NR^{222}R^{333}$, -$O(C=O)SR^{222}$, -$S(C=O)OR^{222}$, or -$S(C=O)NR^{222}R^{333}$ substituents;

G^{11} is halo, oxo, -CF_3, -OCF_3, -OR^{21}, -$NR^{21}R^{31}(R^{3a1})_{j4}$, -$C(O)R^{21}$, -$CO_2R^{21}$, -$CONR^{21}R^{31}$, -$NO_2$, -CN, -$S(O)_{j4}R^{21}$, -$SO_2NR^{21}R^{31}$, $NR^{21}(C=O)R^{31}$, $NR^{21}(C=O)OR^{31}$, $NR^{21}(C=O)NR^{21}R^{31}$, $NR^{21}S(O)_{j4}R^{31}$, -$(C=S)OR^{21}$, -$(C=O)SR^{21}$, -$NR^{21}(C=NR^{31})NR^{2a1}R^{3a1}$, -$NR^{21}(C=NR^{31})OR^{2a1}$, -$NR^{21}(C=NR^{31})SR^{3a1}$, -$O(C=O)OR^{21}$, -$O(C=O)NR^{21}R^{31}$, -$O(C=O)SR^{21}$, -$S(C=O)OR^{21}$, -$S(C=O)NR^{21}R^{31}$, -$P(O)OR^{21}OR^{31}$, (C_{0-10})alkyl, (C_{2-10})alkenyl, (C_{2-10})alkynyl, (C_{1-10})alkoxy(C_{1-10})alkyl, (C_{1-10})alkoxy(C_{2-10})alkenyl, (C_{1-10})alkoxy(C_{2-10})alkynyl, (C_{1-10})alkylthio(C_{1-10})alkyl, (C_{1-10})alkylthio(C_{2-10})alkenyl, (C_{1-10})alkylthio(C_{2-10})alkynyl, cyclo(C_{3-8})alkyl, cyclo(C_{3-8})alkenyl, cyclo(C_{3-8})alkyl(C_{1-10})alkyl, cyclo(C_{3-8})alkenyl(C_{1-10}) alkyl, cyclo(C_{3-8})alkyl(C_{2-10})alkenyl, cyclo(C_{3-8})alkenyl(C_{2-10})alkenyl, cyclo(C_{3-8}) alkyl(C_{2-10}) alkynyl, cyclo(C_{3-8})alkenyl(C_{2-10})alkynyl, heterocyclyl-(C_{0-10})alkyl, heterocyclyl-(C_{2-10}) alkenyl, or heterocyclyl-(C_{2-10})alkynyl, any of which is optionally substituted with one or more independent halo, oxo, -CF_3, -OCF_3, -OR^{2221}, -$NR^{2221}R^{3331}(R^{333a1})_{j4a}$, -$C(O)R^{2221}$, -$CO_2R^{2221}$, -$CONR^{2221}R^{3331}$, -$NO_2$, -CN, -$S(O)_{j4a}R^{2221}$, -$SO_2NR^{2221}R^{3331}$, $NR^{2221}(C=O)R^{3331}$, $NR^{2221}(C=O)OR^{3331}$, $NR^{2221}(C=O)NR^{2221}R^{3331}$, $NR^{2221}S(O)_{j4a}R^{3331}$, -$(C=S)OR^{2221}$, -$(C=O)SR^{2221}$, -$NR^{2221}(C=NR^{3331})NR^{222a1}R^{333a1}$, -$NR^{2221}(C=NR^{3331})OR^{222a1}$, -$NR^{2221}(C=NR^{3331})SR^{333a1}$, -$O(C=O)OR^{2221}$, -$O(C=O)NR^{2221}R^{3331}$, -$O(C=O)SR^{2221}$, -$S(C=O)OR^{2221}$, -$P(O)OR^{2221}OR^{3331}$, or -$S(C=O)NR^{2221}R^{3331}$ substituents; or aryl-(C_{0-10})alkyl, aryl-(C_{2-10})alkenyl, or aryl-(C_{2-10})alkynyl, any of which is optionally substituted with one or more independent halo, -CF_3, -OCF_3, -OR^{2221}, -$NR^{2221}R^{3331}(R^{333a1})_{j5a}$, -$C(O)R^{2221}$, -$CO_2R^{2221}$, -$CONR^{2221}R^{3331}$, -$NO_2$, -CN, -$S(O)_{j5a}R^{2221}$, -$SO_2NR^{2221}R^{3331}$, $NR^{2221}(C=O)R^{3331}$, $NR^{2221}(C=O)OR^{3331}$, $NR^{2221}(C=O)NR^{2221}R^{3331}$, $NR^{2221}S(O)_{j5a}R^{3331}$, -$(C=S)OR^{2221}$, -$(C=O)SR^{2221}$, -$NR^{2221}(C=NR^{3331})NR^{222a1}R^{333a1}$, -$NR^{2221}(C=NR^{3331})OR^{222a1}$, -$NR^{2221}(C=NR^{3331})SR^{333a1}$, -$O(C=O)OR^{2221}$, -$O(C=O)NR^{2221}R^{3331}$, -$O(C=O)SR^{2221}$, -$S(C=O)OR^{2221}$, -$P(O)OR^{2221}R^{3331}$, or -$S(C=O)NR^{2221}R^{3331}$ substituents; or hetaryl-(C_{0-10}) alkyl, hetaryl-(C_{2-10})alkenyl, or hetaryl-(C_{2-10})alkynyl, any of which is optionally substituted with one or more independent halo, -CF_3, -OCF_3, -OR^{2221}, -$NR^{2221}R^{3331}(R^{333a1})_{j6a}$, -$C(O)R^{2221}$,

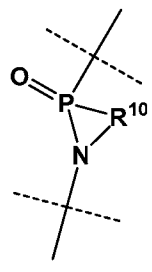
$-CO_2R^{2221}$, $-CONR^{2221}R^{3331}$, $-NO_2$, -CN, $-S(O)_{j6a}R^{2221}$, $-SO_2NR^{2221}R^{3331}$, $NR^{2221}(C=O)R^{3331}$, $NR^{2221}(C=O)OR^{3331}$, $NR^{2221}(C=O)NR^{2221}R^{3331}$, $NR^{2221}S(O)_{j6a}R^{3331}$, $-(C=S)OR^{2221}$, $-(C=O)SR^{2221}$, $-NR^{2221}(C=NR^{3331})NR^{222a1}R^{333a1}$, $-NR^{2221}(C=NR^{3331})OR^{222a1}$, $-NR^{2221}(C=NR^{3331})SR^{333a1}$, $-O(C=O)OR^{2221}$, $-O(C=O)NR^{2221}R^{3331}$, $-O(C=O)SR^{2221}$, $-S(C=O)OR^{2221}$, $-P(O)OR^{2221}OR^{3331}$, or $-S(C=O)NR^{2221}R^{3331}$ substituents; or G^{11} is taken together with the carbon to which it is attached to form a double bond which is substituted with R^5 and G^{111};

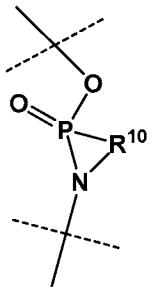
R^2, R^{2a}, R^3, R^{3a}, R^{222}, R^{222}a, R^{333}, R^{333a}, R^{21}, R^{2a1}, R^{31}, R^{3a1}, R^{2221}, R^{222a1}, R^{3331}, and R^{333a1} are each independently equal to $(C_{0\text{-}10})$alkyl, $(C_{2\text{-}10})$alkenyl, $(C_{2\text{-}10})$alkynyl, $(C_{1\text{-}10})$alkoxy$(C_{1\text{-}10})$alkyl, $(C_{1\text{-}10})$alkoxy$(C_{2\text{-}10})$alkenyl, $(C_{1\text{-}10})$alkoxy$(C_{2\text{-}10})$alkynyl, $(C_{1\text{-}10})$alkylthio$(C_{1\text{-}10})$alkyl, $(C_{1\text{-}10})$alkylthio$(C_{2\text{-}10})$alkenyl, $(C_{1\text{-}10})$alkylthio$(C_{2\text{-}10})$alkynyl, cyclo$(C_{3\text{-}8})$alkyl, cyclo$(C_{3\text{-}8})$alkenyl, cyclo$(C_{3\text{-}8})$alkyl$(C_{1\text{-}10})$alkyl, cyclo$(C_{3\text{-}8})$alkenyl$(C_{1\text{-}10})$alkyl, cyclo$(C_{3\text{-}8})$alkyl$(_{2\text{-}10})$alkenyl, cyclo$(C_{3\text{-}8})$alkenyl$(C_{2\text{-}10})$alkenyl, cyclo$(C_{3\text{-}8})$alkyl$(C_{2\text{-}10})$alkynyl, cyclo$(C_{3\text{-}8})$alkenyl$(C_{2\text{-}10})$alkynyl, heterocyclyl-$(C_{0\text{-}10})$alkyl, heterocyclyl-$(C_{2\text{-}10})$alkenyl, or heterocyclyl-$(C_{2\text{-}10})$alkynyl, any of which is optionally substituted by one or more G^{111} substituents; or aryl-$(C_{0\text{-}10})$alkyl, aryl-$(C_{2\text{-}10})$alkenyl, or aryl-$(C_{2\text{-}10})$alkynyl, hetaryl-$(C_{0\text{-}10})$alkyl, hetaryl-$(C_{2\text{-}10})$alkenyl, or hetaryl-$(C_{2\text{-}10})$alkynyl, any of which is optionally substituted by one or more G^{111} substituents; or in the case of $-NR^2R^3(R^{3a})_{j1}$ or $-NR^{222}R^{333}(R^{333}a)_{j1a}$ or $-NR^{222}R^{333}(R^{333}a)_{j2a}$ or $-NR^{2221}R^{3331}(R^{333a1})_{j3a}$ or $-NR^{2221}R^{3331}(R^{333a1})_{j4a}$ or $-NR^{2221}R^{3331}(R^{333a1})_{j5a}$ or $-NR^{2221}R^{3331}(R^{333a1})_{j6a}$, R^2 and R^3 or R^{222} and $R^{333}3$ or R^{2221} and R^{3331} taken together with the nitrogen atom to which they are attached form a 3-10 membered saturated ring, unsaturated ring, heterocyclic saturated ring, or heterocyclic unsaturated ring, wherein said ring is optionally substituted by one or more G^{111} substituents;

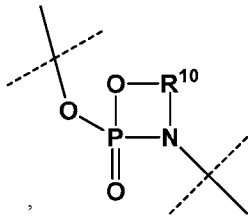
X^1 and Y^1 are each independently -O-, $-NR^7$-, $-S(O)_{j7}$-, $-CR^5R^6$-, $-N(C(O)OR^7)$-, $-N(C(O)R^7)$-, $-N(SO_2R^7)$-, $-CH_2O$-, $-CH_2S$-, $-CH_2N(R^7)$-, $-CH(NR^7)$-, $-CH_2N(C(O)R^7)$-, $-CH_2N(C(O)OR^7)$-, $-CH_2N(SO_2R^7)$-, $-CH(NHR^7)$-, $-CH(NHC(O)R^7)$-, $-CH(NHSO_2R^7)$-, $-CH(NHC(O)OR^7)$-, $-CH(OC(O)R^7)$-, $-CH(OC(O)NHR^7)$-, -CH=CH-, -C.ident.C-, $-C(=NOR^7)$-, -C(O)-, $-CH(OR^7)$-, $-C(O)N(R^7)$-, $-N(R^7)C(O)$-, $-N(R^7)S(O)$-, $-N(R^7)S(O)_2$- $-OC(O)N(R^7)$-, $-N(R^7)C(O)N(R^7)$-, $-NR^7C(O)O$-, $-S(O)N(R^7)$-, $-S(O)_2N(R^7)$-, $-N(C(O)R^7)S(O)$-, $-N(C(O)R^7)S(O)_2$-, $-N(R^7)S(O)N(R^7)$-, $-N(R^7)S(O)_2N(R^7)$-, $-C(O)N(R^7)C(O)$-, $-S(O)N(R^7)C(O)$-, $-S(O)_2N(R^7)C(O)$-, $-OS(O)N(R^7)$-, $-OS(O)_2N(R^7)$-, $-N(R^7)S(O)O$-, -

$N(R^7)S(O)_2O$-, -$N(R^7)S(O)C(O)$-, -$N(R^7)S(O)_2C(O)$-, -$SON(C(O)R^7)$-, -$SO_2N(C(O)R^7)$-, -$N(R^7)SON(R^7)$-, -$N(R^7)SO_2N(R^7)$-, -$C(O)O$-, -$N(R^7)P(OR^8)O$-, -$N(R^7)P(OR^8)$-, -$N(R^7)P(O)(OR^8)O$-, -$N(R^7)P(O)(OR^8)$-, -$N(C(O)R^7)P(OR^8)O$-, -$N(C(O)R^7)P(OR^8)$-, -$N(C(O)R^7)P(O)(OR^8)O$-, -$N(C(O)R^7)P(OR^8)$-, -$CH(R^7)S(O)$-, -$CH(R^7)S(O)_2$-, -$CH(R^7)N(C(O)OR^7)$-, -$CH(R^7)N(C(O)R^7)$-, -$CH(R^7)N(SO_2R^7)$-, -$CH(R^7)O$-, -$CH(R^7)S$-, -$CH(R^7)N(R^7)$-, -$CH(R^7)N(C(O)R^7)$-, -$CH(R^7)N(C(O)OR^7)$-, -$CH(R^7)N(SO_2R^7)$-, -$CH(R^7)C(=NOR^7)$-, -$CH(R^7)C(O)$-, -$CH(R^7)CH(OR^7)$-, -$CH(R^7)C(O)N(R^7)$-, -$CH(R^7)N(R^7)C(O)$-, -$CH(R^7)N(R^7)S(O)$-, -$CH(R^7)N(R^7)S(O)_2$-, -$CH(R^7)OC(O)N(R^7)$-, -$CH(R^7)N(R^7)C(O)N(R^7)$-, -$CH(R^7)NR^7C(O)O$-, -$CH(R^7)S(O)N(R^7)$-, -$CH(R^7)S(O)_2N(R^7)$-, -$CH(R^7)N(C(O)R^7)S(O)$-, -$CH(R^7)N(C(O)R^7)S(O)$-, -$CH(R^7)N(R^7)S(O)N(R^7)$-, -$CH(R^7)N(R^7)S(O)_2N(R^7)$-, -$CH(R^7)C(O)N(R^7)C(O)$-, -$CH(R^7)S(O)N(R^7)C(O)$-, -$CH(R^7)S(O)_2N(R^7)C(O)$-, -$CH(R^7)OS(O)N(R^7)$-, -$CH(R^7)OS(O)_2N(R^7)$-, -$CH(R^7)N(R^7)S(O)O$-, -$CH(R^7)N(R^7)S(O)_2O$-, -$CH(R^7)N(R^7)S(O)C(O)$-, -$CH(R^7)N(R^7)S(O)_2C(O)$-, -$CH(R^7)SON(C(O)R^7)$-, -$CH(R^7)SO_2N(C(O)R^7)$-, -$CH(R^7)N(R^7)SON(R^7)$-, -$CH(R^7)N(R^7)SO_2N(R^7)$-, -$CH(R^7)C(O)O$-, -$CH(R^7)N(R^7)P(OR^8)O$-, -$CH(R^7)N(R^7)P(OR^8)$-, -$CH(R^7)N(R^7)P(O)(OR^8)O$-, -$CH(R^7)N(R^7)P(O)(OR^8)$-, -$CH(R^7)N(C(O)R^7)P(OR^8)O$-, -$CH(R^7)N(C(O)R^7)P(OR^8)$-, -$CH(R^7)N(C(O)R^7)P(O)(OR^8)O$-, or -$CH(R^7)N(C(O)R^7)P(OR^8)$-;

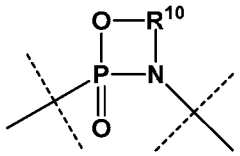
or X^1 and Y^1 are each independently represented by one of the following structural formulas:

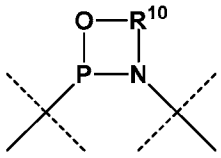


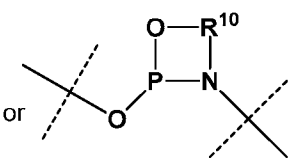
,


,


,



,


or


;

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

R^5, R^6, and G^{111} are each independently a (C_{0-10})alkyl, (C_{2-10})alkenyl, (C_{2-10})alkynyl, (C_{1-10})alkoxy(C_{1-10})alkyl, (C_{1-10})alkoxy(C_{2-10})alkenyl, (C_{1-10})alkoxy(C_{2-10})alkynyl, (C_{1-10})alkylthio(C_{1-10})alkyl, (C_{1-10})alkylthio(C_{2-10})alkenyl, (C_{1-10})alkylthio(C_{2-10})alkynyl, cyclo(C_{3-8})alkyl, cyclo(C_{3-8})alkenyl, cyclo(C_{3-8})alkyl(C_{1-10})alkyl, cyclo(C_{3-8})alkenyl(C_{1-10})alkyl, cyclo(C_{3-8})alkyl(C_{2-10})alkenyl, cyclo(C_{3-8})alkenyl(C_{2-10})alkenyl, cyclo(C_{3-8})alkyl(C_{2-10})alkynyl, cyclo(C_{3-8})alkenyl(C_{2-10})alkynyl, heterocyclyl-(C_{0-10})alkyl, heterocyclyl-(C_{2-10})alkenyl, or heterocyclyl-(C_{2-10})alkynyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{77}$, $-NR^{77}R^{87}$, $-C(O)R^{77}$, $-CO_2R^{77}$, $-CONR^{77}R^{87}$, $-NO_2$, -CN, $-S(O)_{j5a}R^{77}$, $-SO_2NR^{77}R^{87}$, $NR^{77}(C=O)R^{87}$, $NR^{77}(C=O)OR^{87}$, $NR^{77}(C=O)NR^{78}R^{87}$, $NR^{77}S(O)_{j5a}R^{87}$, $-(C=S)OR^{77}$, $-(C=O)SR^{77}$, $-NR^{77}(C=NR^{87})NR^{78}R^{88}$, $-NR^{77}(C=NR^{87})OR^{78}$, $-NR^{77}(C=NR^{87})SR^{78}$, $-O(C=O)OR^{77}$, $-O(C=O)NR^{77}R^{87}$, $-O(C=O)SR^{77}$, $-S(C=O)OR^{77}$, $-P(O)OR^{77}OR^{87}$, or $-S(C=O)NR^{77}R^{87}$ substituents; or aryl-(C_{0-10})alkyl, aryl-(C_{2-10})alkenyl, or aryl-(C_{2-10})alkynyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{77}$, $-NR^{77}R^{87}$, $-C(O)R^{77}$, $-CO_2R^{77}$, $-CONR^{77}R^{87}$, $-NO_2$, -CN, $-S(O)_{j5a}R^{77}$, $-SO_2NR^{77}R^{87}$, $NR^{77}(C=O)R^{87}$, $NR^{77}(C=O)OR^{87}$, $NR^{77}(C=O)NR^{78}R^{87}$, $NR^{77}S(O)_{j5a}R^{87}$, $-(C=S)OR^{77}$, $-(C=O)SR^{77}$, $-NR^{77}(C=NR^{87})NR^{78}R^{88}$, $-NR^{77}(C=NR^{87})OR^{78}$, $-NR^{77}(C=NR^{87})SR^{78}$, $-O(C=O)OR^{77}$, $-O(C=O)NR^{77}R^{87}$, $-O(C=O)SR^{77}$, $-S(C=O)OR^{77}$, $-P(O)OR^{77}R^{87}$, or $-S(C=O)NR^{77}R^{87}$ substituents; or hetaryl-(C_{0-10})alkyl, hetaryl-(C_{2-10})alkenyl, or hetaryl-(C_{2-10})alkynyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{77}$, $-NR^{77}R^{87}$, $-C(O)R^{77}$, $-CO_2R^{77}$, $-CONR^{77}R^{87}$, $-NO_2$, -CN, $-S(O)_{j5a}R^{77}$, $-SO_2NR^{77}R^{87}$, $NR^{77}(C=O)R^{87}$, $NR^{77}(C=O)OR^{87}$, $NR^{77}(C=O)NR^{78}R^{87}$, $NR^{77}S(O)_{j5a}R^{87}$, $-(C=S)OR^{77}$, $-(C=O)SR^{77}$, $-NR^{77}(C=NR^{87})NR^{78}R^{88}$, $-NR^{77}(C=NR^{87})OR^{78}$, $-NR^{77}(C=NR^{87})SR^{78}$, $-O(C=O)OR^{77}$, $-O(C=O)NR^{77}R^{87}$, $-O(C=O)SR^{77}$, $-S(C=O)OR^{77}$, $-P(O)OR^{77}OR^{87}$, or $-S(C=O)NR^{77}R^{87}$ substituents; or R^5 with R^6 taken together with the respective carbon atom to which they are attached, form a 3-10 membered saturated or unsaturated ring, wherein said ring is optionally substituted with R^{69}; or R^5 with R^6 taken together with the respective carbon atom to which they are attached, form a 3-10 membered saturated or unsaturated heterocyclic ring, wherein said ring is optionally substituted with R^{69};

R^7 and R^8 are each independently H, acyl, alkyl, alkenyl, aryl, heteroaryl, heterocyclyl or cycloalkyl, any of which is optionally substituted by one or more G^{111} substituents;

R^4 is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, cycloalkenyl, or heterocycloalkenyl, any of which is optionally substituted by one or more G^{41} substituents;

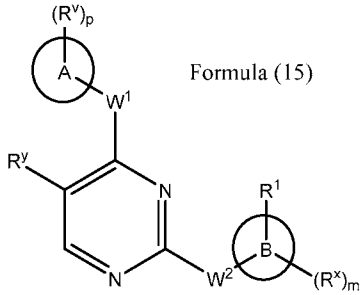
R^{69} is equal to halo, $-OR^{78}$, -SH, $-NR^{78}R^{88}$, $-CO_2R^{78}$, $-CONR^{78}R^{88}$, $-NO_2$, -CN, $-S(O)_{j8}R^{78}$, $-SO_2NR^{78}R^{88}$, $(C_{0\text{-}10})$alkyl, $(C_{2\text{-}10})$alkenyl, $(C_{2\text{-}10})$alkynyl, $(C_{1\text{-}10})$alkoxy$(C_{1\text{-}10})$alkyl, $(C_{1\text{-}10})$alkoxy$(C_{2\text{-}10})$alkenyl, $(C_{1\text{-}10})$alkoxy$(C_{2\text{-}10})$alkynyl, $(C_{1\text{-}10})$alkylthio$(C_{1\text{-}10})$alkyl, $(C_{1\text{-}10})$alkylthio$(C_{2\text{-}10})$alkenyl, $(C_{1\text{-}10})$alkylthio$(C_{2\text{-}10})$alkynyl, cyclo$(C_{3\text{-}8})$alkyl, cyclo$(C_{3\text{-}8})$alkenyl, cyclo$(C_{3\text{-}8})$alkyl$(C_{1\text{-}10})$alkyl, cyclo$(C_{3\text{-}8})$alkenyl$(C_{1\text{-}10})$alkyl, cyclo$(C_{3\text{-}8})$alkyl$(C_{2\text{-}10})$alkenyl, cyclo$(C_{3\text{-}8})$alkenyl$(C_{2\text{-}10})$alkenyl, cyclo$(C_{3\text{-}8})$alkyl$(C_{2\text{-}10})$alkynyl, cyclo$(C_{3\text{-}8})$alkenyl$(C_{2\text{-}10})$alkynyl, heterocyclyl-$(C_{0\text{-}10})$alkyl, heterocyclyl-$(C_{2\text{-}10})$alkenyl, or heterocyclyl-$(C_{2\text{-}10})$alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, $-OR^{778}$, $-SO_2NR^{778}R^{888}$, or $-NR^{778}R^{888}$ substituents; or aryl-$(C_{0\text{-}10})$alkyl, aryl-$(C_{2\text{-}10})$alkenyl, or aryl-$(C_{2\text{-}10})$alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, $-OR^{778}$, $(C_{1\text{-}10})$alkyl, $(C_{2\text{-}10})$alkenyl, $(C_{2\text{-}10})$alkynyl, halo$(C_{1\text{-}10})$alkyl, halo$(C_{2\text{-}10})$alkenyl, halo$(C_{2\text{-}10})$alkynyl, -COOH, $(C_{1\text{-}4})$alkoxycarbonyl, $-CONR^{778}R^{888}$, $-SO_2NR^{778}R^{888}$, or $-NR^{778}R^{888}$ substituents; or hetaryl-$(C_{0\text{-}10})$alkyl, hetaryl-$(C_{2\text{-}10})$alkenyl, or hetaryl-$(C_{2\text{-}10})$alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, $-OR^{778}$, $(C_{1\text{-}10})$alkyl, $(C_{2\text{-}10})$alkenyl, $(C_{2\text{-}10})$alkynyl, halo$(C_{1\text{-}10})$alkyl, halo$(C_{2\text{-}10})$alkenyl, halo$(C_{2\text{-}10})$alkynyl, -COOH, $(C_{1\text{-}4})$alkoxycarbonyl, $-CONR^{778}R^{888}$, $-SO_2NR^{778}R^{888}$, or $-NR^{778}R^{888}$ substituents; or mono$(C_{1\text{-}6}$alkyl)amino$(C_{1\text{-}6})$alkyl, di$((C_{1\text{-}6})$alkyl)amino$(C_{1\text{-}6})$alkyl, mono(aryl)amino$(C_{1\text{-}6})$alkyl, di(aryl)amino$(C_{1\text{-}6})$alkyl, or -N$((C_{1\text{-}6})$alkyl)-$(C_{1\text{-}6})$alkyl-aryl, any of which is optionally substituted with one or more independent halo, cyano, nitro, $-OR^{778}$, $(C_{1\text{-}10})$alkyl, $(C_{2\text{-}10})$alkenyl, $(C_{2\text{-}10})$alkynyl, halo$(C_{1\text{-}10})$alkyl, halo$(C_{2\text{-}10})$alkenyl, halo$(C_{2\text{-}10})$alkynyl, -COOH, $(C_{1\text{-}4})$alkoxycarbonyl, $-CONR^{778}R^{888}$ $SO_2NR^{778}R^{888}$, or $-NR^{778}R^{888}$ substituents; or in the case of $-NR^{78}R^{88}$, R^{78} and R^{88} taken together with the nitrogen atom to which they are attached form a 3-10 membered saturated ring, unsaturated ring, heterocyclic saturated ring, or heterocyclic unsaturated ring, wherein said ring is optionally substituted with one or more independent halo, cyano, hydroxy, nitro, $(C_{1\text{-}10})$alkoxy, $-SO_2NR^{778}R^{888}$, or $-NR^{778}R^{888}$ substituents;

R^{77}, R^{78}, R^{87}, R^{88}, R^{778}, and R^{888} are each independently (C_{0-10})alkyl, (C_{2-10})alkenyl, (C_{2-10})alkynyl, (C_{1-10})alkoxy(C_{1-10})alkyl, (C_{1-10})alkoxy$C_{2-10})$alkenyl, (C_{1-10})alkoxy(C_{2-10})alkynyl, (C_{1-10})alkylthio(C_{1-10})alkyl, (C_{1-10})alkylthio(C_{2-10})alkenyl, (C_{1-10})alkylthio(C_{2-10})alkynyl, cyclo(C_{3-8})alkyl, cyclo(C_{3-8})alkenyl, cyclo(C_{3-8})alkyl(C_{1-10})alkyl, cyclo(C_{3-8})alkenyl(C_{1-10})alkyl, cyclo(C_{3-8})alkyl(C_{2-10})alkenyl, cyclo(C_{3-8})alkenyl(C_{2-10})alkenyl, cyclo(C_{3-8})alkyl(C_{2-10})alkynyl, cyclo(C_{3-8})alkenyl(C_{2-10})alkynyl, heterocyclyl-(C_{0-10})alkyl, heterocyclyl-(C_{2-10})alkenyl, heterocyclyl-(C_{2-10})alkynyl, (C_{1-10})alkylcarbonyl, (C_{2-10})alkenylcarbonyl, (C_{2-10})alkynylcarbonyl, (C_{1-10})alkoxycarbonyl, (C_{1-10})alkoxycarbonyl(C_{1-10})alkyl, mono(C_{1-6})alkylaminocarbonyl, di(C_{1-6})alkylaminocarbonyl, mono(aryl)aminocarbonyl, di(aryl)aminocarbonyl, or (C_{1-10})alkyl(aryl)aminocarbonyl, any of which is optionally substituted with one or more independent halo, cyano, hydroxy, nitro, (C_{1-10})alkoxy, $-SO_2N((C_{0-4})alkyl)((C_{0-4})alkyl)$, or $-N((C_{0-4})alkyl)((C_{0-4})alkyl)$ substituents; or aryl-(C_{0-10})alkyl, aryl-(C_{2-10})alkenyl, or aryl-(C_{2-10})alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, $-O((C_{0-4})alkyl)$, (C_{1-10})alkyl, (C_{2-10})alkenyl, (C_{2-10})alkynyl, halo(C_{1-10})alkyl, halo(C_{2-10})alkenyl, halo(C_{2-10})alkynyl, -COOH, (C_{1-4})alkoxycarbonyl, $-CON((C_{0-4})alkyl)((C_{0-10})alkyl)$, $-SO_2N((C_{0-4})alkyl)((C_{0-4})alkyl)$, or $-N((C_{0-4})alkyl)((C_{0-4})alkyl)$ substituents; or hetaryl-(C_{0-10})alkyl, hetaryl-(C_{2-10})alkenyl, or hetaryl-(C_{2-10})alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, $-O((C_{0-4})alkyl)$, (C_{1-10})alkyl, (C_{2-10})alkenyl, (C_{2-10})alkynyl, halo(C_{1-10})alkyl, halo(C_{2-10})alkenyl, halo(C_{2-10})alkynyl, -COOH, (C_{1-4})alkoxycarbonyl, $-CON((C_{0-4})alkyl)((C_{0-4})alkyl)$, $-SO_2N((C_{0-4})alkyl)((C_{0-4})alkyl)$, or $-N((C_{0-4})alkyl)((C_{0-4})alkyl)$ substituents; or mono$((C_{1-6})$alkyl)amino(C_{1-6})alkyl, di$((C_{1-6})$alkyl)amino(C_{1-6})alkyl, mono(aryl)amino(C_{1-6})alkyl, di(aryl)amino(C_{1-6})alkyl, or $-N((C_{1-6})alkyl)-(C_{1-6})alkyl-aryl$, any of which is optionally substituted with one or more independent halo, cyano, nitro, $-O((C_{0-4})alkyl)$, (C_{1-10})alkyl, (C_{2-10})alkenyl, (C_{2-10})alkynyl, halo(C_{1-10})alkyl, halo(C_{2-10})alkenyl, halo(C_{2-10})alkynyl, -COOH, (C_{1-4})alkoxycarbonyl, $-CON((C_{0-4})alkyl)((C_{0-4})alkyl)$, $-SO_2N((C_{0-4})alkyl)((C_{0-4})alkyl)$, or $-N((C_{0-4})alkyl)((C_{0-4})alkyl)$ substituents; and

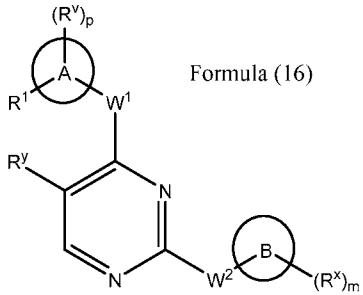
n, m, j1, j1a, j2a, j3a, j4, j4a, j5a, j6a, j7, and j8 are each independently equal to 0, 1, or 2.

[00278] 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 (15) or Formula (16):



Formula (15)



Formula (16)

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

Ring A is an optionally substituted group selected from phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated or aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an optionally substituted 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ring B is an optionally substituted group selected from phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated or aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an optionally substituted 7-10 membered bicyclic saturated or

partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^1 is a warhead group;

R^y is hydrogen, halogen, —CN, —CF_3, C_{1-4} aliphatic, C_{1-4} haloaliphatic, —OR, —C(O)R, or —$C(O)N(R)_2$;

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

W^1 and W^2 are each independently a covalent bond or a bivalent C_{1-3} alkylene chain wherein one methylene unit of W^1 or W^2 is optionally replaced by —NR^2—, —$N(R^2)C(O)$—, —$C(O)N(R^2)$—, —$N(R^2)SO_2$—, —$SO_2N(R^2)$—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —SO— or —SO_2—;

R^2 is hydrogen, optionally substituted C_{1-6} aliphatic, or —C(O)R, or:

R^2 and a substituent on Ring A are taken together with their intervening atoms to form a 4-6 membered saturated, partially unsaturated, or aromatic fused ring, or:

R^2 and R^y are taken together with their intervening atoms to form an optionally substituted 4-7 membered partially unsaturated or aromatic fused ring;

m and p are independently 0-4; and

R^x and R^v are independently selected from —R, halogen, —OR, —$O(CH_2)_qOR$, —CN, —NO_2, —SO_2R, —$SO_2N(R)_2$, —SOR, —C(O)R, —CO_2R, —$C(O)N(R)_2$, —NRC(O)R, —$NRC(O)NR_2$, —$NRSO_2R$, or —$N(R)_2$, wherein q is 1-4; or:

R^x and R^1 when concurrently present on Ring B are taken together with their intervening atoms to form an optionally substituted 5-7 membered saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with a warhead group and 0-3 groups independently selected from oxo, halogen, —CN, or C_{1-6} aliphatic; or

R^v and R^1 when concurrently present on Ring A are taken together with their intervening atoms to form an optionally substituted 5-7 membered saturated, partially unsaturated, or aryl ring

having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with a warhead group and 0-3 groups independently selected from oxo, halogen, —CN, or C_{1-6} aliphatic.

[00279] In an embodiment, the BTK inhibitor is a compound of Formula (15) or Formula (16), wherein:

Ring A is selected from phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated or aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an optionally substituted 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an optionally substituted 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ring B is selected from phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated or aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an optionally substituted 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an optionally substituted 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^1 is -L-Y, wherein:

L is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene units of L are optionally and independently replaced by cyclopropylene, —NR—, —N(R)C(O)—, —C(O)N(R)—, —N(R)SO_2—, —SO_2N(R)—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —SO—, —SO_2—, —C(=S)—, —C(=NR)—, —N=N—, or —C(=N_2)—;

Y is hydrogen, C_{1-6} aliphatic optionally substituted with oxo, halogen, or CN, or a 3-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aryl ring having 0-3

heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein said ring is substituted with at 1-4 groups independently selected from -Q-Z, oxo, NO_2, halogen, CN, or C_{1-6} aliphatic, wherein:

Q is a covalent bond or a bivalent C_{1-6} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one or two methylene units of Q are optionally and independently replaced by —NR—, —S—, —O—, —C(O)—, —SO—, or —SO_2—; and

Z is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, or CN;

R^y is hydrogen, halogen, —CN, —CF_3, C_{1-4} aliphatic, C_{1-4} haloaliphatic, —OR, —C(O)R, or —$C(O)N(R)_2$;

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

W^1 and W^2 are each independently a covalent bond or a bivalent C_{1-3} alkylene chain wherein one methylene unit of W^1 or W^2 is optionally replaced by —NR^2—, —$N(R^2)C(O)$—, —$C(O)N(R^2)$—, —$N(R^2)SO_2$—, —$SO_2N(R^2)$—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —SO— or —SO_2—;

R^2 is hydrogen, optionally substituted C_{1-6} aliphatic, or —C(O)R, or:

R^2 and a substituent on Ring A are taken together with their intervening atoms to form a 4-6 membered partially unsaturated or aromatic fused ring; or

R^2 and R^y are taken together with their intervening atoms to form a 4-6 membered saturated, partially unsaturated, or aromatic fused ring;

m and p are independently 0-4; and

R^x and R^v are independently selected from —R, halogen, —OR, —$O(CH_2)_qOR$, —CN, —NO_2, —SO_2R, —$SO_2N(R)_2$, —SOR, —C(O)R, —CO_2R, —$C(O)N(R)_2$, —NRC(O)R, —$NRC(O)NR_2$, —$NRSO_2R$, or —$N(R)_2$, wherein R is independently selected from the group consisting of hydrogen, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, and heterocycly; or:

R^x and R^1 when concurrently present on Ring B are taken together with their intervening atoms to form a 5-7 membered saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms

independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with a warhead group and 0-3 groups independently selected from oxo, halogen, —CN, or C_{1-6} aliphatic; or

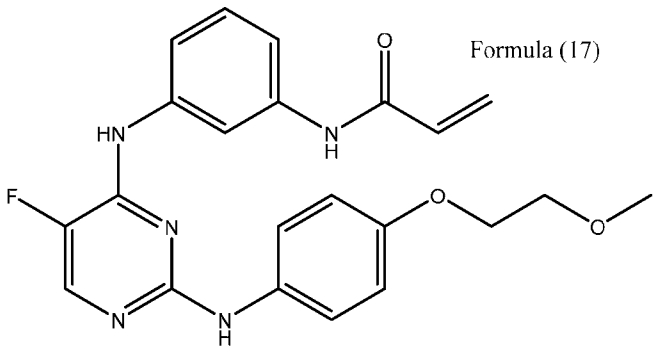
R^v and R^1 when concurrently present on Ring A are taken together with their intervening atoms to form a 5-7 membered saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with a warhead group and 0-3 groups independently selected from oxo, halogen, —CN, or C_{1-6} aliphatic.

[00280] 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.

[00281] 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.

[00282] In certain embodiments, Ring A in Formula (15) or Formula (16) is substituted as defined herein. In some embodiments, Ring A is substituted with one, two, or three groups independently selected from halogen, R^o, or $—(CH_2)_{0-4}OR^o$, or $—O(CH_2)_{0-4}R^o$, wherein each R^o is independently selected from the group consisting of cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl. Exemplary substituents on Ring A include Br, I, Cl, methyl, $—CF_3$, —C≡CH, $—OCH_2$phenyl, $—OCH_2$(fluorophenyl), or $—OCH_2$pyridyl.

[00283] In a preferred embodiment, the BTK inhibitor is CC-292 (also known as AVL-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 (17):



Formula (17)

,

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 an exemplary 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.

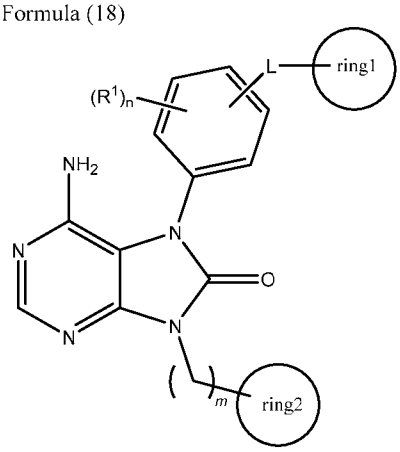
[00284] In a preferred embodiment, the BTK inhibitor is *N*-(3-((5-fluoro-2-((4-(2-methoxyethoxy)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, or a hydrochloride salt thereof. The preparation of this compound 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.

[00285] 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.

[00286] In an embodiment, the BTK inhibitor is a compound of Formula (18):

Formula (18)



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

L represents (1) –O–, (2) –S–, (3) –SO–, (4) –SO_2– (5) –NH–, (6) –C(O)–, (7) –CH_2O–, (8) –O–CH_2–, (9) –CH_2–, or (10) –CH(OH)–;

R^1 represents (1) a halogen atom, (2) a C_{1-4} alkyl group, (3) a C_{1-4} alkoxy group, (4) a C_{1-4} haloalkyl group, or (5) a C_{1-4} haloalkoxy group;

ring1 represents a 4- to 7-membered cyclic group, which may be substituted by from one to five substituents each independently selected from the group consisting of (1) halogen atoms, (2) C_{1-4} alkyl groups, (3) C_{1-4} alkoxy groups, (4) nitrile, (5) C_{1-4} haloalkyl groups, and (6) C_{1-4} haloalkoxy groups, wherein when two or more substituents are present on ring1, these substituents may form a 4- to 7-membered cyclic group together with the atoms in ring1 to which these substituents are bound;

ring2 represents a 4- to 7-membered saturated heterocycle, which may be substituted by from one to three –K–R^2; K represents (1) a bond, (2) a C_{1-4} alkylene, (3) –C(O)–, (4) –C(O)–CH_2–, (5) –CH_2–C(O)–, (6) –C(O)O–, or (7) –SO_2– (wherein the bond on the left is bound to the ring2);

R^2 represents (1) a C_{1-4} alkyl, (2) a C_{2-4} alkenyl, or (3) a C_{2-4} alkynyl group, each of which may be substituted by from one to five substituents each independently selected from the group consisting of (1) NR^3R^4, (2) halogen atoms, (3) $CONR^5R^6$, (4) CO_2R^7, and (5) OR^8;

R^3 and R^4 each independently represent (1) a hydrogen atom, or (2) a C_{1-4} alkyl group which may be substituted by OR^9 or $CONR^{10}R^{11}$; R^3 and R^4 may, together with the nitrogen atom to which they are bound, form a 4- to 7-membered nitrogenous saturated heterocycle, which may be substituted by an oxo group or a hydroxyl group;

R^5 and R^6 each independently represent (1) a hydrogen atom, (2) a C_{1-4} alkyl group, or (3) a phenyl group;

R^7 represents (1) a hydrogen atom or (2) a C_{1-4} alkyl group;

R^8 represents (1) a hydrogen atom, (2) a C_{1-4} alkyl group, (3) a phenyl group, or (4) a benzotriazolyl group; R^9 represents (1) a hydrogen atom or (2) a C_{1-4} alkyl group;

R^{10} and R^{11} each independently represent (1) a hydrogen atom or (2) a C_{1-4} alkyl group;

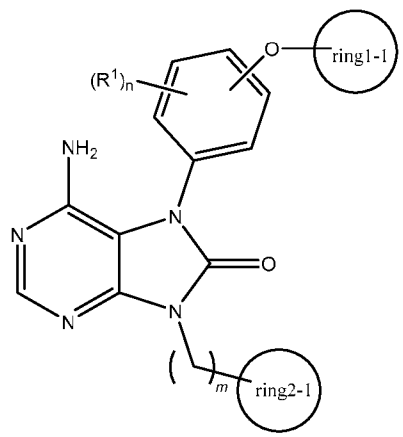
n represents an integer from 0 to 4;

m represents an integer from 0 to 2; and

when n is two or more, the R^1's may be the same as each other or may differ from one another).

[00287] In an exemplary embodiment, the BTK inhibitor is a compound of Formula (19):

Formula (19)



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

R^1 represents (1) a halogen atom, (2) a C_{1-4} alkyl group, (3) a C_{1-4} alkoxy group, (4) a C_{1-4} haloalkyl group, or (5) a C_{1-4} haloalkoxy group;

ring1 represents a benzene, cyclohexane, or pyridine ring, each of which may be substituted by from one to five substituents each independently selected from the group consisting of (1) halogen atoms, (2) C_{1-4} alkyl groups, (3) C_{1-4} alkoxy groups, (4) nitrile, (5) CF_3;

ring2 represents a 4- to 7-membered nitrogenous saturated heterocycle, which may be substituted by from one to three $–K–R^2$; wherein K represents (1) a bond, (2) a C_{1-4} alkylene, (3) –C(O)–, (4) $–C(O)–CH_2–$, (5) $–CH_2–C(O)–$, (6) –C(O)O–, or (7) $–SO_2–$ (wherein the bond on the left is bound to the ring2);

R^2 represents (1) a C_{1-4} alkyl, (2) a C_{2-4} alkenyl, or (3) a C_{2-4} alkynyl group, each of which may be substituted by from one to five substituents each independently selected from the group consisting of (1) NR^3R^4, (2) halogen atoms, (3) $CONR^5R^6$, (4) CO_2R^7, and (5) OR^8;

R^3 and R^4 each independently represent (1) a hydrogen atom, or (2) a C_{1-4} alkyl group which may be substituted by OR^9 or $CONR^{10}R^{11}$; R^3 and R^4 may, together with the nitrogen atom to which they are bound, form a 4- to 7-membered nitrogenous saturated heterocycle, which may be substituted by an oxo group or a hydroxyl group;

R^5 and R^6 each independently represent (1) a hydrogen atom, (2) a C_{1-4} alkyl group, or (3) a phenyl group;

R^7 represents (1) a hydrogen atom or (2) a C_{1-4} alkyl group;

R^8 represents (1) a hydrogen atom, (2) a C_{1-4} alkyl group, (3) a phenyl group, or (4) a benzotriazolyl group; R^9 represents (1) a hydrogen atom or (2) a C_{1-4} alkyl group;

R^{10} and R^{11} each independently represent (1) a hydrogen atom or (2) a C_{1-4} alkyl group;

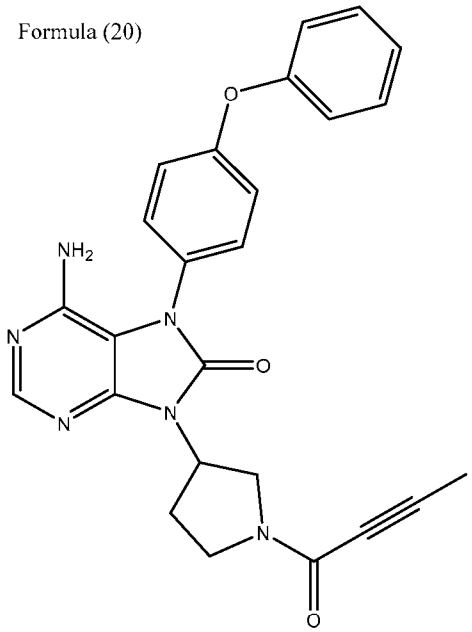
n represents an integer from 0 to 4;

m represents an integer from 0 to 2; and

when n is two or more, the R^1's may be the same as each other or may differ from one another).

[00288] In a preferred embodiment, the BTK inhibitor is a compound of Formula (20):

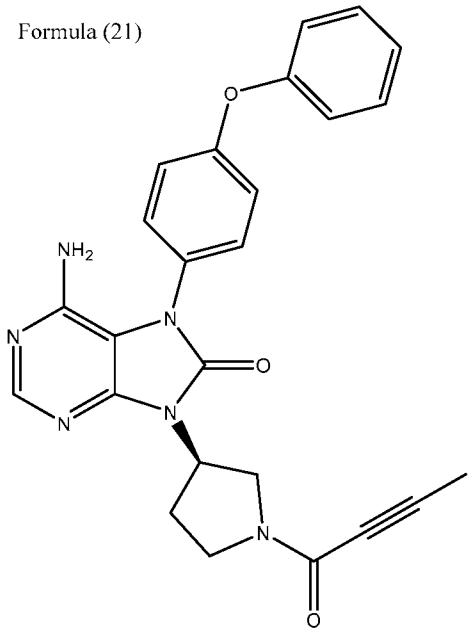
Formula (20)



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 and 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 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.

[00289] The *R*-enantiomer of Formula (20) is also known as ONO-4059, and is given by Formula (21). In a preferred embodiment, the BTK inhibitor is a compound of Formula (21):

Formula (21)



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

[00290] In an embodiment, the BTK inhibitor is 6-amino-9-[(3*R*)-1-(2-butynoyl)-3-pyrrolidinyl]-7-(4- phenoxyphenyl)-7,9-dihydro-8*H*-purin-8-one or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, preferably a hydrochloride salt thereof.

[00291] The preparation of Formula (21) 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 (21) can be prepared by the following procedure.

[00292] 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).

[00293] Step 2: The compound prepared in Step 1 (19 g) and tert-butyl (3*R*)-3-aminopyrrolidine-1-carboxylate (10.5 g) are dissolved in dioxane (58 mL). Triethylamine (8.1

mL) is added, and the mixture is stirred for 5 hours at 50 °C. The reaction mixture is returned to room temperature, the solvent is distilled off, water is added, and extraction is performed with ethyl acetate. The organic layer is washed with saturated aqueous sodium chloride solution, then dried over anhydrous sodium sulfate, and the solvent is distilled off. The residue is purified by silica gel column chromatography to obtain *tert*-butyl (3*R*)-3-{[6-(dibenzylamino)-5-nitropyrimidin-4-yl]amino}pyrrolidine-1-carboxylate (27.0 g).

[00294] Step 3: An ethyl acetate (360 mL) solution of the compound prepared in Step 2 (17.5 g) is dripped into a mixture of zinc (23.3 g) and a 3.0 M aqueous ammonium chloride solution (11.4 g) on an ice bath, and the temperature is immediately raised to room temperature. After stirring for 2 hours, the reaction mixture is filtered through CELITE and the solvent is distilled off. The residue is purified by silica gel column chromatography to obtain *tert*-butyl (3*R*)-3-{[5-amino-6-(dibenzylamino)pyrimidin-4-yl]amino}pyrrolidine-1-carboxylate (12.4 g).

[00295] Step 4: The compound prepared in Step 3 (8.4 g) and 1,1'-carbonyl diimidazole (5.9 g) are dissolved in tetrahydrofuran (120 mL) and the solution is stirred for 15 hours at 60 °C. The solvent is distilled off from the reaction mixture, water is added, and extraction with ethyl acetate is performed. The organic layer is washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and the solvent is distilled off. The residue is purified by silica gel column chromatography to obtain *tert*-butyl (3*R*)-3-[6-(dibenzylamino)-8-oxo-7,8-dihydro-9*H*-purin-9-yl]pyrrolidin-1-carboxylate (7.8 g).

[00296] Step 5: The compound prepared in Step 4 (7.8 g) is dissolved in methanol (240 mL) and ethyl acetate (50 mL), 20% Pearlman's catalyst ($Pd(OH)_2/C$) (8.0 g, 100 wt %) is added, hydrogen gas replacement is carried out, and stirring is performed for 7.5 hours at 60 °C. The reaction mixture is filtered through CELITE and the solvent is distilled off to obtain *tert*-butyl (3*R*)-3-(6-amino-8-oxo-7,8-dihydro-9*H*-purin-9-yl)pyrrolidine-1-carboxylate (5.0 g).

[00297] Step 6: At room temperature p-phenoxy phenyl boronic acid (2.1 g), copper(II) acetate (1.48 g), molecular sieve 4A (2.5 g), and pyridine (0.82 mL) are added to a dichloromethane suspension (200 mL) of the compound prepared in Step 5 (2.5 g), followed by stirring for 21 hours. The reaction mixture is filtered through CELITE and the residue is purified by silica gel column chromatography to obtain *tert*-butyl (3*R*)-3-[6-amino-8-oxo-7-(4-phenoxyphenyl)-7,8-dihydro-9*H*-purin-9-yl]pyrrolidine-1-carboxylate (1.3 g).

[00298] 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 (3*R*)-6-amino-9-pyrrolidin-3-yl-7-(4-phenoxyphenyl)-7,9-dihydro-8*H*-purin-8-one dihydrochloride (1.5 g).

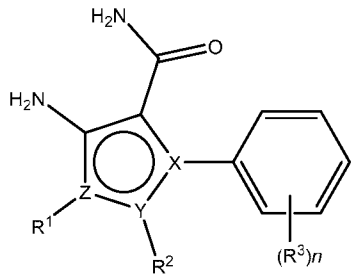
[00299] Step 8: After 2-butylnoic acid (34 mg), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC) (78 mg), 1-hydroxybenzotriazole (HOBt) (62 mg), and triethylamine (114 mL) are added to a solution of the compound prepared in Step 7 (100 mg) in dimethyl formamide (3 mL), the mixture is stirred at room temperature for 3 hours. Water is added to the reaction mixture and extraction with ethyl acetate is performed. The organic layer is washed with saturated sodium carbonate solution and saturated aqueous sodium chloride solution, then dried over anhydrous sodium sulfate, and the solvent is distilled off. The residue is purified by thin layer chromatography (dichloromethane:methanol:28% ammonia water=90:10:1) to obtain 6-amino-9-[(3*R*)-1-(2-butynoyl)-3-pyrrolidinyl]-7-(4-phenoxyphenyl)-7,9-dihydro-8*H*-purin-8-one (Formula (21)) (75 mg).

[00300] The hydrochloride salt of the compound of Formula (21) can be prepared as follows: 6-amino-9-[(3*R*)-1-(2-butynoyl)-3-pyrrolidinyl]-7-(4-phenoxyphenyl)-7,9-dihydro-8*H*-purin-8-one (3.0 g) (which may be prepared as described above) is placed in a 300 mL 3-neck pear-shaped flask, ethyl acetate (30 mL) and 1-propanol (4.5 mL) are added, and the external temperature is set at 70 °C (internal temperature 61 °C). After it is confirmed that the compound prepared in Step 8 has dissolved completely, 10% HCl/methanol (3.5 mL) is added, and after precipitation of crystals is confirmed, the crystals are ripened by the following sequence: external temperature 70 °C for 30 min, external temperature 60 °C for 30 min, external temperature 50 °C for 60 min, external temperature 40 °C for 30 min, room temperature for 30 min, and an ice bath for 30 min. The resulting crystals are filtered, washed with ethyl acetate (6 mL), and dried under vacuum at 50 °C to obtain white crystals of 6-amino-9-[(3*R*)-1-(2-butynoyl)-3-pyrrolidinyl]-7-(4-phenoxyphenyl)-7,9-dihydro-8*H*-purin-8-one hydrochloride (2.76 g).

[00301] 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.

[00302] In an embodiment, the BTK inhibitor is a compound of Formula (22):

Formula (22)



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

X-Y-Z is N-C-C and R^2 is present, or C-N-N and R^2 is absent;

R^1 is a 3-8 membered, N-containing ring, wherein the N is unsubstituted or substituted with R^4;

R^2 is H or lower alkyl, particularly methyl, ethyl, propyl or butyl; or

R^1 and R^2 together with the atoms to which they are attached, form a 4-8 membered ring, preferably a 5-6 membered ring, selected from cycloalkyl, saturated or unsaturated heterocycle, aryl, and heteroaryl rings unsubstituted or substituted with at least one substituent L-R^4;

R^3 is in each instance, independently halogen, alkyl, S-alkyl, CN, or OR^5;

n is 1, 2, 3, or 4, preferably 1 or 2;

L is a bond, NH, heteroalkyl, or heterocyclyl;

R^4 is COR', CO_2R', or SO_2R', wherein R' is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl;

R^5 is H or unsubstituted or substituted heteroalkyl, alkyl, cycloalkyl, saturated or unsaturated heterocyclyl, aryl, or heteroaryl.

[00303] In some embodiments, the BTK inhibitor is one of the following particular embodiments of Formula (22):

X--Y--Z is C--N--N and R^2 is absent; and R^1 is 3-8 membered, N-containing ring, N-substituted with R^4;

X--Y--Z is N--C--C and R^2 is present, R^1 is 3-8 membered, N-containing ring, N-substituted with R^4; and R^2 is H or lower alkyl;

X--Y--Z is N--C--C and R^2 is present; and R^1 and R^2 together with the atoms to which they are attached, form a 4-8 membered ring selected from cycloalkyl, saturated or unsaturated

heterocycle, aryl, and heteroaryl rings unsubstituted or substituted with at least one substituent L-R^4, wherein preferred rings of R^1 and R^2 are 5-6-membered, particularly dihydropyrrole, tetrahydropyridine, tetrahydroazepine, phenyl, or pyridine;

X--Y--Z is N--C--C and R^2 is present; and R^1 and R^2 together with the atoms to which they are attached, form a 5-6 membered ring, preferably (a) phenyl substituted with a single -L-R^4, or (b) dihydropyrrole or tetrahydropyridine, N-substituted with a single -L-R^4 wherein L is bond;

R^1 is piperidine or azaspiro[3.3]heptane, preferably N-substituted with R^4;

R^4 is COR' or SO_2R', particularly wherein R' is substituted or unsubstituted alkenyl, particularly substituted or unsubstituted ethenyl; or

R^5 is unsubstituted or substituted alkyl or aryl, particularly substituted or unsubstituted phenyl or methyl, such as cyclopropyl-substituted methyl with or tetrabutyl-substituted phenyl.

[00304] In some embodiments, the BTK inhibitor is one of the following particular embodiments of Formula (22):

R^1 is piperidine or azaspiro[3.3]heptane, N-substituted with R^4, wherein R^4 is H, COR' or SO_2R', and R' is substituted or unsubstituted alkenyl, particularly substituted or unsubstituted ethenyl;

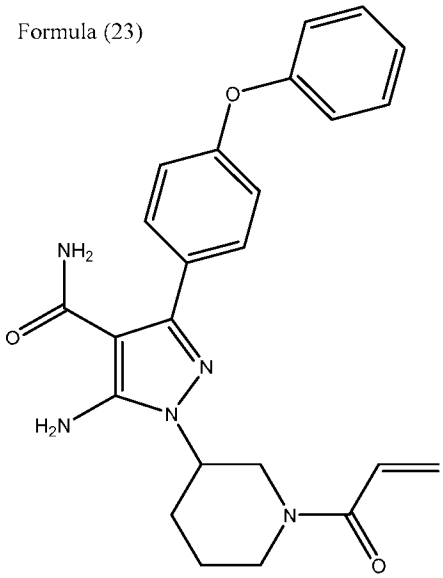
R^3 is $–OR^5$, R^5 is phenyl, and n is 1;

R^1 and R^2, together with the atoms to which they are attached, form a 5-6 membered ring, preferably (a) phenyl substituted with a single -L-R^4, or (b) dihydropyrrole or tetrahydropyridine, N-substituted with a single -L-R^4 wherein L is bond; R^3 is $–OR^5$; n is 1; R^4 is COR', and R' is ethenyl; and R^5 is phenyl; and

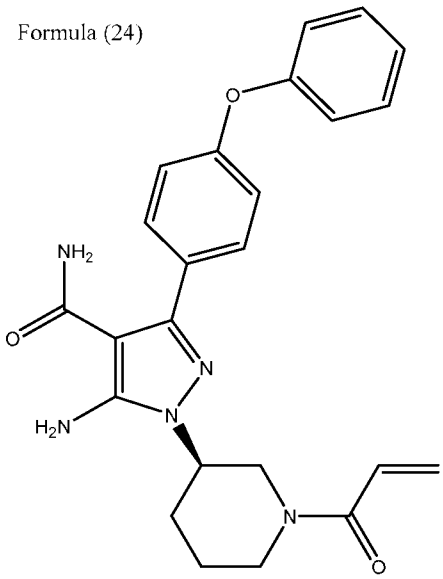
X--Y--Z is C--N--N and R^2 is absent; R^1 is piperidine, N-substituted with R^4; R^3 is $–OR^5$; n is 1; R^4 is COR', and R' is unsubstituted or substituted alkenyl, particularly ethenyl; and R^5 is substituted or unsubstituted aryl, particularly phenyl.

[00305] In some embodiments, the BTK inhibitor is a compound selected from the group consisting of Formula (23), Formula (24), or Formula (25):

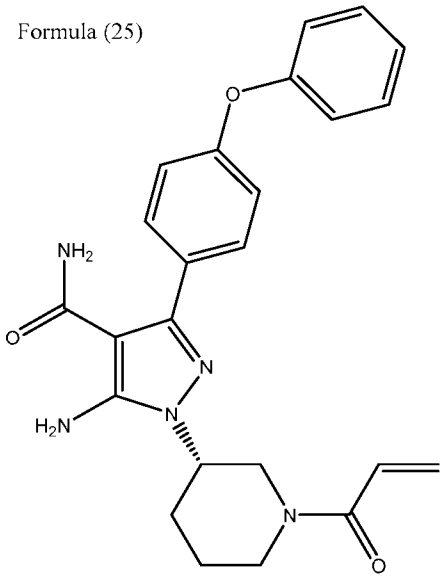
Formula (23)



Formula (24)



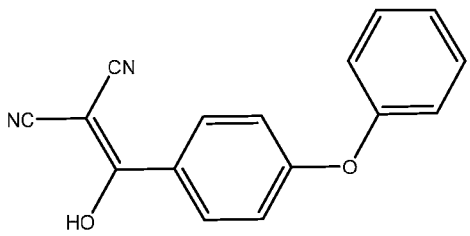
Formula (25)



or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. Formula (24) 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.

[00306] In brief, the BTK inhibitor of Formula (23) can be prepared by the following procedure.

[00307] Step 1. Preparation of 2-(hydroxy(4-phenoxyphenyl)methylene)malononitrile:

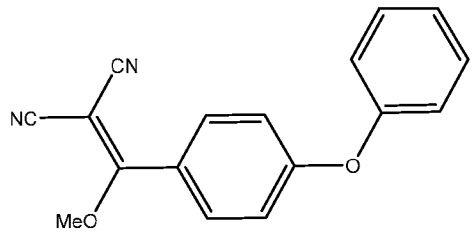


[00308] A solution of 4-phenoxybenzoic acid (300 g, 1.4 mol) in $SOCl_2$ (1.2 L) is stirred at 80° C under N_2 for 3 hours. The mixture is concentrated in vacuum to give the intermediate (315 g) which is used for next step without further purification.

[00309] To a solution of propanedinitrile (89.5 g, 1355 mmol) and *N,N*-diisopropylethylamine (DIEA) (350 g, 2710 mmol) in THF (800 mL) is added dropwise a solution of the intermediate (315 g) in toluene (800 mL) at 0-5 °C over 2 hours. The resultant mixture is allowed to warm to

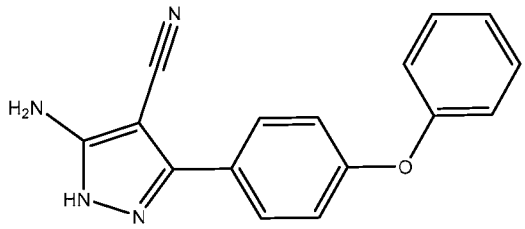
RT and stirred for 16 hours. The reaction is quenched with water (2.0 L) and extracted with of EA (2.0 L × 3). The combined organic layers are washed with 1000 mL of 3 N HCl aqueous solution, brine (2.0 L × 3), dried over Na_2SO_4 and concentrated to give the crude product (330 g, 93%).

[00310] Step 2. Preparation of 2-(methoxy(4-phenoxyphenyl)methylene)malononitrile:



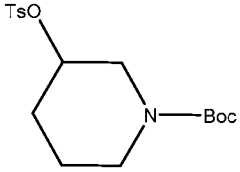
[00311] A solution of 2-(hydroxy(4-phenoxyphenyl)methylene)malononitrile (50 g, 190.8 mmol) in $CH(OMe_3)$ (500 mL) is heated to 75 °C for 16 hours. Then the mixture is concentrated to a residue and washed with MeOH (50 mL) to give 25 g (47.5%) of 2-(methoxy(4-phenoxyphenyl)methylene)malononitrile as a yellow solid.

[00312] Step 3. Preparation of 5-amino-3-(4-phenoxyphenyl)-1*H*-pyrazole-4-carbonitrile:



[00313] To a solution of 2-(methoxy(4-phenoxyphenyl)methylene)malononitrile (80 g, 290 mmol) in ethanol (200 mL) is added hydrazine hydrate (20 mL). The mixture is stirred at RT for 16 hours then is concentrated to give the crude product and washed with MeOH (30 mL) to afford 55 g (68.8%) of 5-amino-3-(4-phenoxyphenyl)-1*H*-pyrazole-4-carbonitrile as a off-white solid.

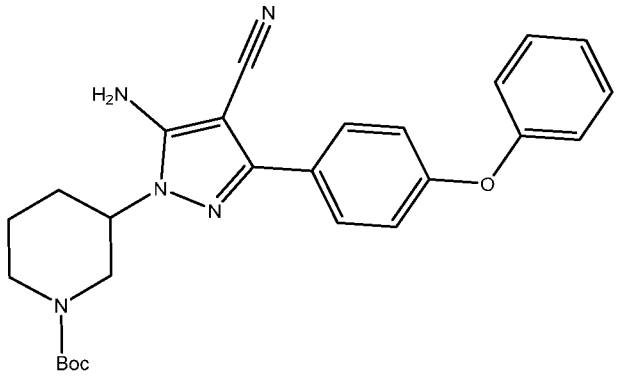
[00314] Step 4. Preparation of *tert*-butyl 3-(tosyloxy)piperidine-1-carboxylate:



wherein "Boc" represents a *tert*-butyloxycarbonyl protecting group.

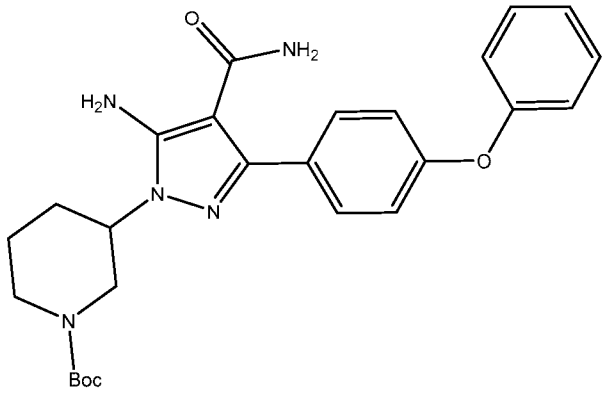
[00315] To a solution of *tert*-butyl 3-hydroxypiperidine-1-carboxylate (1.05 g, 5.0 mmol) in pyridine (8 mL) is added TsCl (1.425 g, 7.5 mmol). The mixture is stirred at RT under N_2 for two days. The mixture is concentrated and partitioned between 100 mL of EA and 100 mL of HCl (1 N) aqueous solution. The organic layer is separated from aqueous layer, washed with saturated $NaHCO_3$ aqueous solution (100 mL × 2), brine (100 mL × 3) and dried over Na_2SO_4. The organic layer is concentrated to afford 1.1 g (60%) of *tert*-butyl 3-(tosyloxy)piperidine-1-carboxylate as a colorless oil.

[00316] Step 5. Preparation of *tert*-butyl 3-(5-amino-4-cyano-3-(4-phenoxyphenyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate:



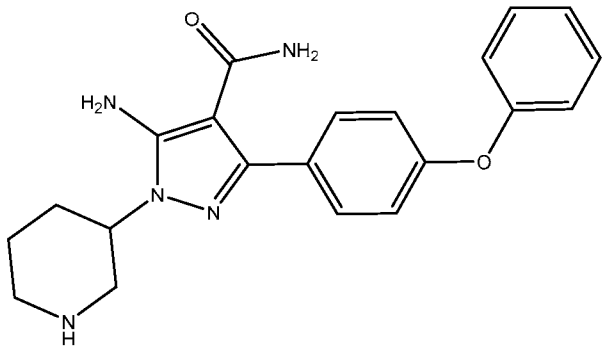
[00317] To a solution of *tert*-butyl 3-(tosyloxy)piperidine-1-carboxylate (355 mg, 1.0 mmol) and 5-amino-3-(4-phenoxyphenyl)-1*H*-pyrazole-4-carbonitrile (276 mg, 1.0 mmol) in 5 mL of DMF is added Cs_2CO_3 (650 mg, 2.0 mmol). A tosyloxy leaving group is employed in this reaction. The mixture is stirred at RT for 16 hours, 75 °C for 3 hours and 60 °C for 16 hours. The mixture is concentrated washed with brine (100 mL × 3) and dried over Na_2SO_4. The material is concentrated and purified by chromatography column on silica gel (eluted with petroleum ether/ethyl actate = 3/1) to afford 60 mg (13%) of *tert*-butyl 3-(5-amino-4-cyano-3-(4-phenoxyphenyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate as a yellow oil.

[00318] Step 6. Preparation of *tert*-butyl 3-(5-amino-4-carbamoyl-3-(4-phenoxyphenyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate:



[00319] To a solution of *tert*-butyl 3-(5-amino-4-cyano-3-(4-phenoxyphenyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate (100 mg, 0.22 mmol) in DMSO (2 mL) and ethanol (2 mL) was added the solution of NaOH (200 mg, 5 mmol) in water (1 mL) and H_2O_2 (1 mL). The mixture is stirred at 60 °C for 15 min and concentrated to remove EtOH, after which 10 mL of water and 50 mL of ethyl acetate are added. The organic layer is separated from aqueous layer, washed with brine (30 mL × 3) and dried over Na_2SO_4. After concentratation, 50 mg of residue is used directly in the next step, wherein 50 mg of residue is purified by pre-TLC (eluted with petroleum ether/ethyl actate = 1/1) to afford 12 mg (30%) of *tert*-butyl 3-(5-amino-4-carbamoyl-3-(4-phenoxyphenyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate as a white solid.

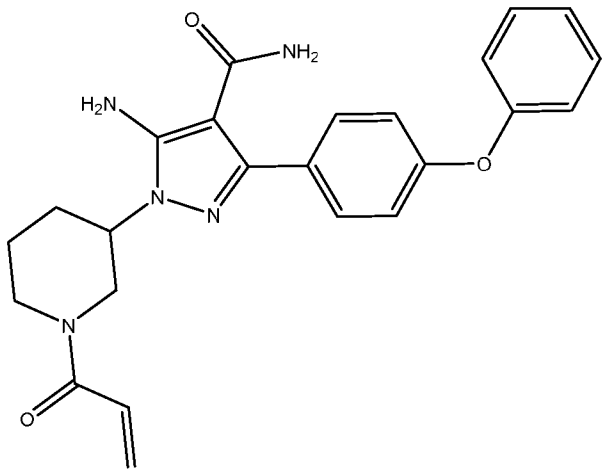
[00320] Step 7. Preparation of 5-amino-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1*H*-pyrazole-4-carboxamide:



[00321] To a solution of *tert*-butyl 3-(5-amino-4-carbamoyl-3-(4-phenoxyphenyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate (50 mg, 0.11 mmol) in ethyl acetate (1 mL) is added concentrated HCl (0.75 mL). The mixture is stirred at RT for 1 hour. Then saturated $NaHCO_3$ is added until pH > 7, followed by ethyl acetate (50 mL). The organic layer is separated from aqueous layer, washed with brine (50 mL × 3) and dried over Na_2SO_4. The resulting product is concentrated

and purified by Pre-TLC (eluted with dichloromethane/MeOH/NH_3-H_2O=5/1/0.01) to afford 10 mg (25%) of 5-amino-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1*H*-pyrazole-4-carboxamide as a white solid.

[00322] Step 8. Preparation of 1-(1-acryloylpiperidin-3-yl)-5-amino-3-(4-phenoxyphenyl)-1*H*-pyrazole-4-carboxamide:



[00323] To a solution of 5-amino-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1*H*-pyrazole-4-carboxamide (63 mg, 0.17 mmol) in dichloromethane (4 mL) is added pyridine (27 mg, 0.34 mmol). Then a solution of acryloyl chloride (12 mg, 0.17 mmol) in dichloromethane (1 mL) is added dropwise. After stirring at RT for 4 hours, the mixture is partitioned between 100 mL of dichloromethane and 100 mL of brine. The organic layer is separated from aqueous layer, washed with brine (100 mL × 2) and dried over Na_2SO_4. The material is concentrated and purified by Pre-TLC (eluted with dichloromethane/MeOH=10/1) to afford 4 mg (5.5%) of 1-(1-acryloylpiperidin-3-yl)-5-amino-3-(4-phenoxyphenyl)-1*H*-pyrazole-4-carboxamide as a white solid.

[00324] The enantiomers of Formula (23) provided by the procedure above may be prepared from 5-amino-3-(phenoxyphenyl)-1*H*-pyrazole-4-carbonitrile and (*S*)-*tert*-butyl 3-hydroxypiperidine-1-carboxylate using a similar procedure (step 4 to 8) for Formula (24), or from (*R*)-*tert*-butyl 3-hydroxypiperidine-1-carboxylate using a similar procedure (step 4 to 8) for Formula (25). Under appropriate conditions recognized by one of ordinary skill in the art, a racemic mixture of Formula (23) may be separated by chiral HPLC, the crystallization of chiral

salts, or other means described above to yield Formula (24) and Formula (25) of high enantiomeric purity.

[00325] 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.

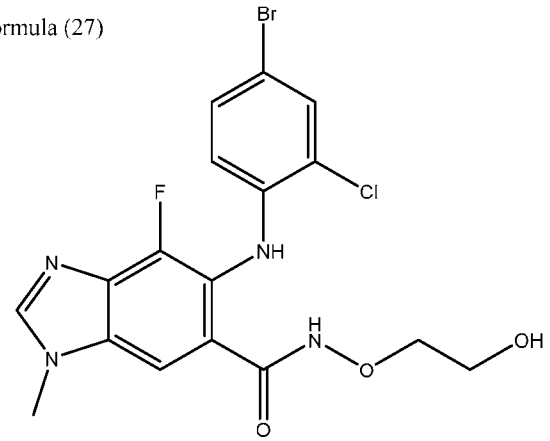
[00326] Other BTK inhibitors suitable for use in the described combination with a MEK inhibitor include, but are not limited to, those described in International Patent Application Publication Nos. WO 2013/010868, WO 2012/158843, WO 2012/135944, WO 2012/135937, U.S. Patent Application Publication No. 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.

MEK Inhibitors

[00327] The MEK inhibitor may be any MEK inhibitor known in the art. In particular, it is one of the MEK inhibitors described in more detail in the following paragraphs. In an embodiment, the MEK inhibitor is a MEK1 inhibitor. In an embodiment, the MEK inhibitor is a MEK2 inhibitor. In an embodiment, the MEK inhibitor is a MEK1/2 inhibitor. In an embodiment, the MEK inhibitor is an allosteric MEK1/2 inhibitor. In an embodiment, the MEK inhibitor is an MEK1/2 inhibitor capable of binding to an allosteric regulatory site independent of the adenosine triphosphate (ATP) binding site. In preferred embodiments, the compositions described herein provide a combination of a MEK inhibitor with a BTK inhibitor, or methods of using a combination of a MEK inhibitor with a BTK inhibitor.

[00328] In a preferred embodiment, the MEK inhibitor is selumetinib, also known as AZD6244. In a preferred embodiment, the MEK inhibitor is a compound of Formula (27):

Formula (27)

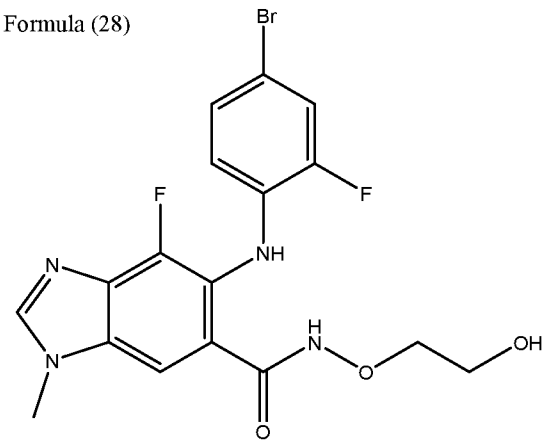


or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The properties of selumetinib are described, *e.g.*, in Davies, *et al.*, *Mol. Cancer Ther.* **2007,** *6,* 2209-19.

[00329] In a preferred embodiment, the MEK inhibitor is 5-((4-bromo-2-chlorophenyl)amino)-4-fluoro-*N*-(2-hydroxyethoxy)-1-methyl-1*H*-benzo[*d*]imidazole-6-carboxamide, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00330] In a preferred embodiment, the MEK inhibitor is binimetinib, also known as MEK162, ARRY-162, and ARRY-438162. In a preferred embodiment, the MEK inhibitor is a compound of Formula (28):

Formula (28)

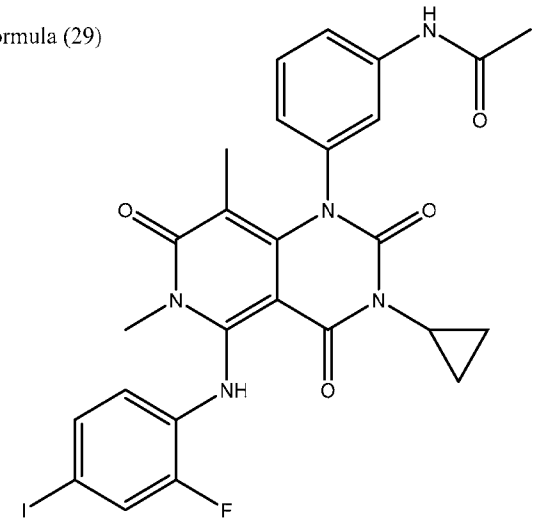


or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The properties of binimetinib are described, *e.g.*, in Gras, *Drugs Fut.* **2015,** *40,* 157.

[00331] In a preferred embodiment, the MEK inhibitor is 5-((4-bromo-2-fluorophenyl)amino)-4-fluoro-*N*-(2-hydroxyethoxy)-1-methyl-1*H*-benzo[*d*]imidazole-6-carboxamide, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00332] In a preferred embodiment, the MEK inhibitor is trametinib, also known as GSK-1120212 and JTP-74057. In a preferred embodiment, the MEK inhibitor is a compound of Formula (29):

Formula (29)

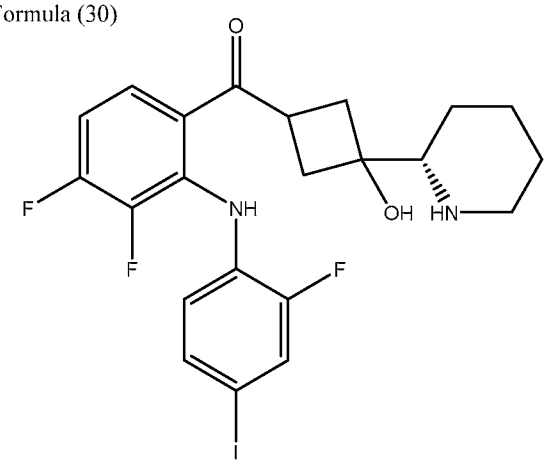


or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. In a preferred embodiment, the MEK inhibitor is a dimethylsulfoxide solvate of a compound of Formula (29). The properties of trametinib are described, *e.g.*, in Gilmartin, *Clin. Cancer Res.*. **2011,** *17,* 989-1000.

[00333] In a preferred embodiment, the MEK inhibitor is *N*-(3-(3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-*d*]pyrimidin-1(2*H*)-yl)phenyl)acetamide, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. In a preferred embodiment, the MEK inhibitor is *N*-(3-(3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-*d*]pyrimidin-1(2*H*)-yl)phenyl)acetamide dimethylsulfoxide solvate.

[00334] In a preferred embodiment, the MEK inhibitor is cobimetinib, also known as GDC-0973. In an embodiment, the MEK inhibitor is a compound of Formula (30):

Formula (30)

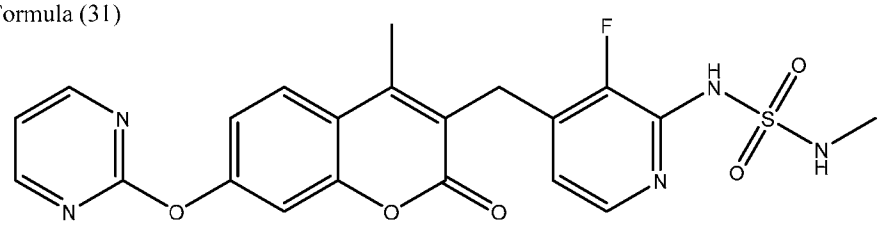


or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00335] In a preferred embodiment, the MEK inhibitor is (*S*)-(3,4-difluoro-2-((2-fluoro-4-iodophenyl)amino)phenyl)(3-hydroxy-3-(piperidin-2-yl)cyclobutyl)methanone, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00336] In a preferred embodiment, the MEK inhibitor is RO5126766, also known as CH5126766. In an embodiment, the MEK inhibitor is a compound of Formula (31):

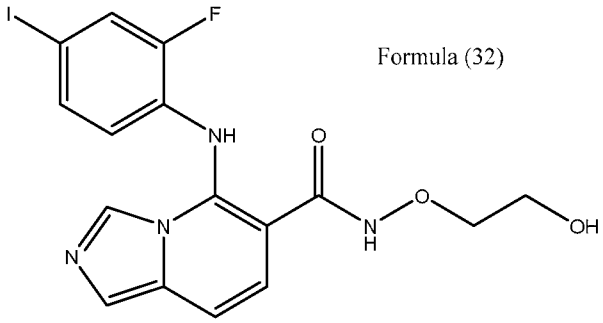
Formula (31)



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

[00337] In a preferred embodiment, the MEK inhibitor is 3-[[2-[(Methylaminosulfonyl)amino]-3-fluoropyridin-4-yl]methyl]-4-methyl-7-[(pyrimidin-2-yl)oxy]-2*H*-1-benzopyran-2-one, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00338] In a preferred embodiment, the MEK inhibitor is GDC-0623. In an embodiment, the MEK inhibitor is a compound of Formula (32):



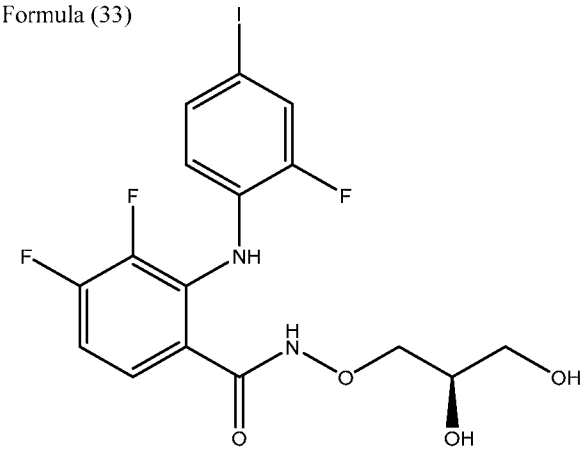
Formula (32)

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

[00339] In a preferred embodiment, the MEK inhibitor is 5-(2-fluoro-4-iodoanilino)-*N*-(2-hydroxyethoxy)imidazo[1,5-*a*]pyridine-6-carboxamide, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00340] In a preferred embodiment, the MEK inhibitor is PD-0325901. In an embodiment, the MEK inhibitor is a compound of Formula (33):

Formula (33)

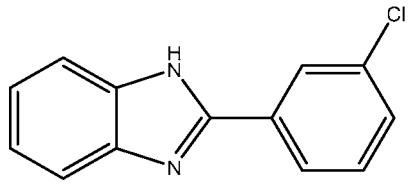


or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00341] In a preferred embodiment, the MEK inhibitor is (*R*)-*N*-(2,3-dihydroxypropoxy)-3,4-difluoro-2-((2-fluoro-4-iodophenyl)amino)benzamide, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. In a preferred embodiment, the MEK inhibitor is *N*-[(2*R*)-2,3-dihydroxypropoxy]-3,4-difluoro-2-(2-fluoro-4-iodoanilino)benzamide, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00342] In an embodiment, the MEK inhibitor is G-573. In an embodiment, the MEK inhibitor is a compound of Formula (34):

Formula (34)

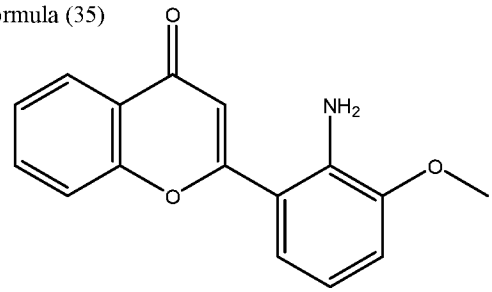


or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The properties of G-573 are described, *e.g.*, in Choo, *et al., Xenobiotica* **2010,** *40, 751-62.*

[00343] In an embodiment, the MEK inhibitor is 2-(3-chlorophenyl)-1*H*-benzo[*d*]imidazole, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00344] In an embodiment, the MEK inhibitor is PD98059 (Pfizer). In an embodiment, the MEK inhibitor is a compound of Formula (35):

Formula (35)

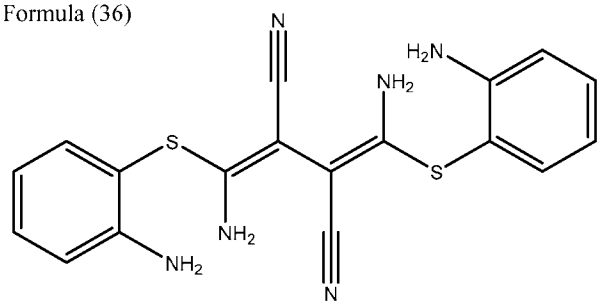


or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00345] In an embodiment, the MEK inhibitor is 2-(2-amino-3-methoxyphenyl)-4*H*-chromen-4-one, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00346] In an embodiment, the MEK inhibitor is U0126 (DuPont). In an embodiment, the MEK inhibitor is a compound of Formula (36):

Formula (36)

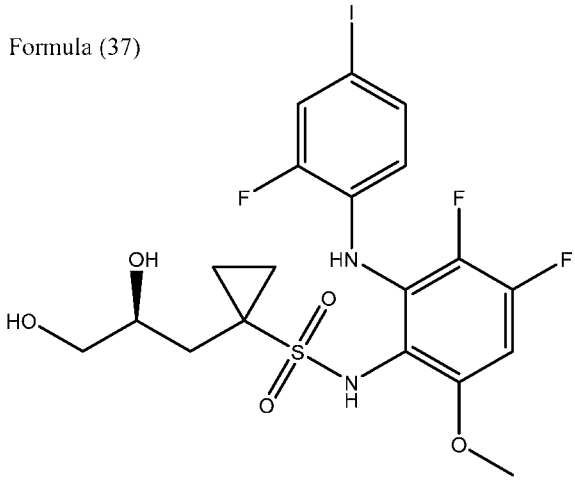


or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. In a preferred embodiment, the MEK inhibitor is an ethanol solvate of a compound of Formula (29).

[00347] In an embodiment, the MEK inhibitor is 2,3-bis(amino(2-aminophenylthio)methylene)succinonitrile, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. In an embodiment, the MEK inhibitor is 2,3-bis(amino(2-aminophenylthio)methylene)succinonitrile ethanol solvate.

[00348] In an embodiment, the MEK inhibitor is refametinib, also known as RDEA119 or Bay 86-9766. In an embodiment, the MEK inhibitor is a compound of Formula (37):

Formula (37)

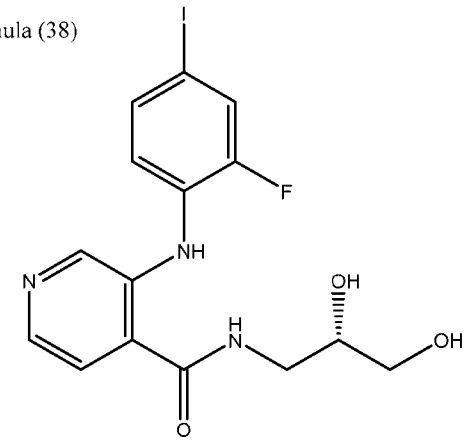


or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00349] In an embodiment, the MEK inhibitor is (*S*)-*N*-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00350] In an embodiment, the MEK inhibitor is pimasertib, also known as AS703026 or MSC1936369B. In an embodiment, the MEK inhibitor is a compound of Formula (38):

Formula (38)

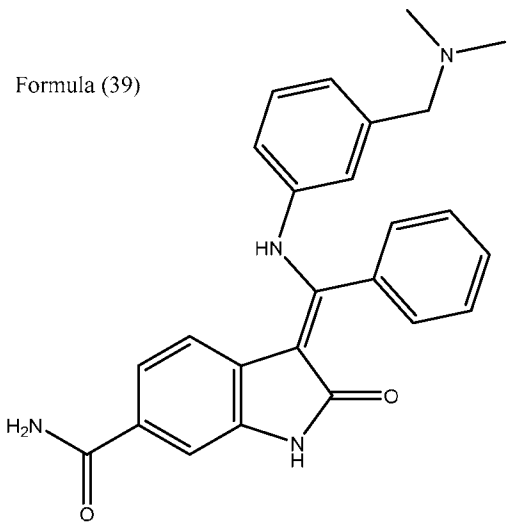


or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00351] In an embodiment, the MEK inhibitor is *N*-[(2*S*)-2,3-dihydroxypropyl]-3-(2-fluoro-4-iodoanilino)pyridine-4-carboxamide, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00352] In an embodiment, the MEK inhibitor is BIX02188. In an embodiment, the MEK inhibitor is a compound of Formula (39):

Formula (39)



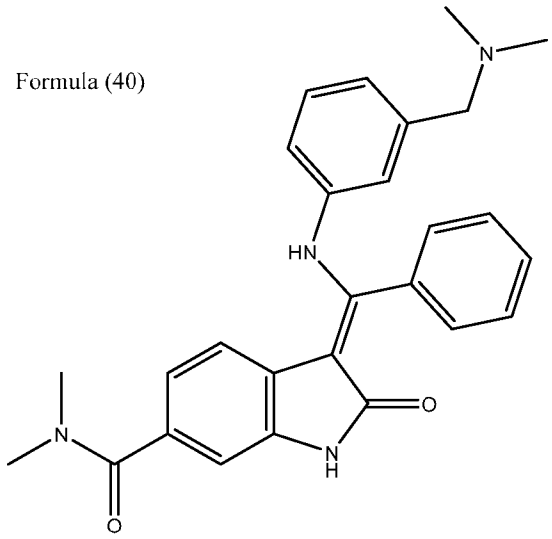
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00353] In an embodiment, the MEK inhibitor is *N*-[(2*S*)-2,3-dihydroxypropyl]-3-(2-fluoro-4-iodoanilino)pyridine-4-carboxamide, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. In an embodiment, the MEK inhibitor is (*E*)-3-(((3-

((dimethylamino)methyl)phenyl)amino)(phenyl)methylene)-2-oxoindoline-6-carboxamide, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00354] In an embodiment, the MEK inhibitor is BIX02189. In an embodiment, the MEK inhibitor is a compound of Formula (40):

Formula (40)

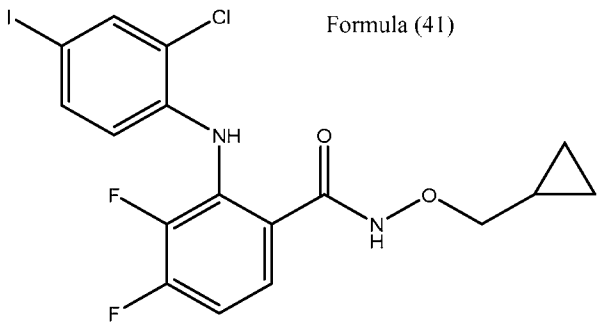


or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00355] In an embodiment, the MEK inhibitor is (*E*)-3-(((3-((dimethylamino)methyl)phenyl)amino)(phenyl)methylene)-*N*,*N*-dimethyl-2-oxoindoline-6-carboxamide, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00356] In an embodiment, the MEK inhibitor is PD184352, also known as CI-1040. In an embodiment, the MEK inhibitor is a compound of Formula (41):

Formula (41)

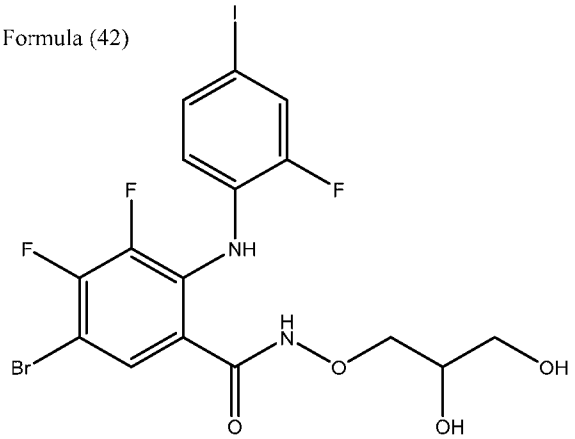


or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00357] In an embodiment, the MEK inhibitor is 2-(2-chloro-4-iodophenylamino)-*N*-(cyclopropylmethoxy)-3,4-difluorobenzamide, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00358] In an embodiment, the MEK inhibitor is PD318088, also known as CI-1040. In an embodiment, the MEK inhibitor is a compound of Formula (42):

Formula (42)

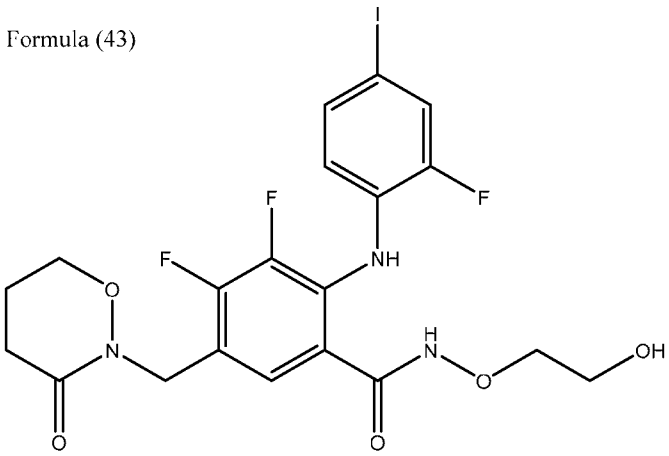


or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00359] In an embodiment, the MEK inhibitor is 5-bromo-*N*-(2,3-dihydroxypropoxy)-3,4-difluoro-2-(2-fluoro-4-iodoanilino)benzamide, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00360] In an embodiment, the MEK inhibitor is RO4987655. In an embodiment, the MEK inhibitor is a compound of Formula (43):

Formula (43)

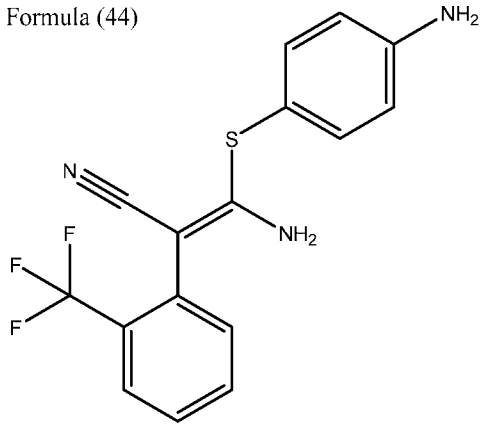


or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00361] In an embodiment, the MEK inhibitor is 3,4-difluoro-2-((2-fluoro-4-iodophenyl)amino)-N-(2-hydroxyethoxy)-5-((3-oxo-1,2-oxazinan-2-yl)methyl)benzamide, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00362] In an embodiment, the MEK inhibitor is SL327. In an embodiment, the MEK inhibitor is a compound of Formula (44):

Formula (44)

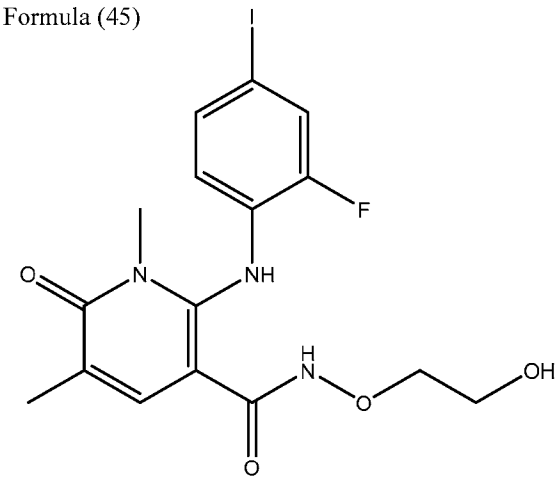


or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00363] In an embodiment, the MEK inhibitor is (*Z*)-3-amino-3-(4-aminophenylthio)-2-(2-(trifluoromethyl)phenyl) acrylonitrile, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00364] In an embodiment, the MEK inhibitor is AZD8330, also known as ARRY-424704 or ARRY-704. In an embodiment, the MEK inhibitor is a compound of Formula (45):

Formula (45)

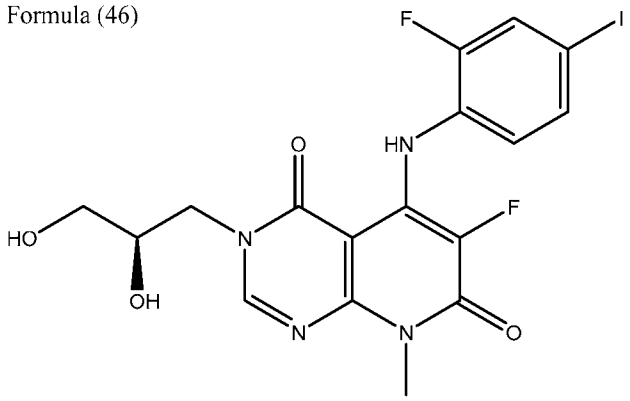


or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00365] In an embodiment, the MEK inhibitor is 2-((2-fluoro-4-iodophenyl)amino)-*N*-(2-hydroxyethoxy)-1,5-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00366] In an embodiment, the MEK inhibitor is TAK-733. In an embodiment, the MEK inhibitor is a compound of Formula (46):

Formula (46)

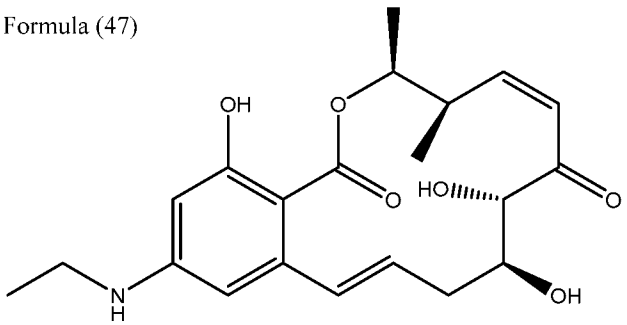


or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00367] In an embodiment, the MEK inhibitor is (*R*)-3-(2,3-dihydroxypropyl)-6-fluoro-5-((2-fluoro-4-iodophenyl)amino)-8-methylpyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00368] In an embodiment, the MEK inhibitor is E6201 (Eisai). In an embodiment, the MEK inhibitor is a compound of Formula (47):

Formula (47)



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

[00369] In an embodiment, the MEK inhibitor is (3*S*,4*R*,5*Z*,8*S*,9*S*,11*E*)-14-(ethylamino)-8,9,16-trihydroxy-3,4-dimethyl-3,4,9,10-tetrahydro-1*H*-benzo[*c*][1]oxacyclotetradecine-1,7(8*H*)-dione, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[00370] Additional examples of MEK inhibitors include, without limitation, those disclosed in U.S. Patent Nos. 7,745,663; 7,001,905; 8,575,391; 7,173,135; 8,604,051; 7,842,816; 7,772,233; 8,076,486; 7,576,114; 8,283,359; 6,469,004; 8,802,703; 8,487,101; 7,429,667; 8,003,805; 7,235,537; 8,637,491; 8,178,693; 6,703,420; 7,842,836; 7,973,170; 8,350,037; 7,425,637; 7,777,050; 8,394,822; 7,652,047; 9,034,861; 6,750,217; 8,716,318; 7,915,250; 8,362,002; 6,455,582; 6,835,749; 7,897,624; 6,440,966; 7,803,839; 8,673,919; 8,841,462; 8,084,645; 6,310,060; 6,821,963; 8,193,231; 6,506,798; 8,193,230; 7,820,664; 7,169,816; 8,063,049; 8,492,427; 8,101,611; 6,638,945; 7,923,456; 6,809,106; 7,307,071; 8,211,921; 7,485,643; 7,230,099; 7,772,234; 8,829,052; 8,431,574; 7,511,058; 7,598,383; 7,576,072; 8,268,852; 7,893,065; 7,271,178; 7,759,518; 7,144,907; 8,101,799; 7,517,994; 8,101,639; 8,211,920; 7,732,616; 8,791,118; 8,648,116; 8,466,289; 8,841,459; 8,404,725; 8,470,878; and 7,019,033; U.S. Patent Application Publication Nos. 2005/0256123, 2005/0143438, 2005/0049419, 2005/0250782, 2014/0051686, 2011/0183981, 2005/0054701, 2007/0112038, 2005/0153942, 2010/0267710, 2008/0171778, 2009/0209542, 2009/0143579, 2007/0238710, 2007/0293544, 2014/0378466, 2012/0022076, 2009/0082457, 2007/0244164, 2012/0107307, 2010/0331334, 2012/0245209, 2011/0112152, 2012/0316149, 2008/0255133, 2007/0021512, 2014/0135519, 2005/0049429, 2006/0052608, 2010/0179124, 2015/0073033, 2012/0329774, 2009/0149437, 2009/0264411, 2011/0021558, 2014/0080804, 2012/0238599, 2007/0299103, 2011/0224192, 2014/0187566, 2013/0273061, 2006/0189808, 2012/0295889, 2006/0189649, 2007/0299063, 2009/0131435, 2008/0177082, 2015/0017261, 2011/0178136, 2006/0106225, 2010/0261718, 2005/0130976, 2010/0063053, 2010/0261717, 2009/0143389, 2009/0093462, 2005/0256123, 2005/0143438, 2005/0049419, 2005/0130943, 2014/0051686, 2011/0183981, 2005/0054701, 2007/0112038, 2005/0153942, 2010/0267710, 2008/0171778, 2009/0209542, 2009/0143579, 2008/0058340, 2007/0238710, 2007/0293544, and 2014/0378466; and International Patent Application Publication Nos. 2015/022662, 2015/022664, 2015/022663, 2014/204263, 2014/063024, 2014/056894, 2014/078669, 2014/078669, 2014/169167, 2013/136249, 2012/095505, 2012/059041, 2011/067356, 2011/067348, 2011/067348, 2011/054828, 2011/047055, 2010/121646, 2010/068738, 2010/108652, 2010/003025, 2010/145197, 2010/020703, 2010/003022, 2009/013462, 2009/036020, 2009/093013, 2009/093008, 2009/093009, 2009/153554, 2009/080523, 2008/089459, 2007/121481, 2008/020206, 2008/020206, 2005/009975, 2005/007616, 2007/088345, 2007/121269, 2005/023251,

2006/133417, 2007/123939, 2007/121269, 2007/044515, 2006/061712, 2007/123936, 2007/121481, 2005/028426, 2005/000818, 2006/056427, 2007/071951, 2007/014011, 2005/051300, 2005/051906, 2005/023759, 2007/044084, 2005/051301, 2006/058752, 2005/051302, 2005/051302, 2011/070030, 2012/168884, 2013/107283, and 2009/018233.

Pharmaceutical Compositions

[00371] In one embodiment, the invention provides a pharmaceutical composition for use in the treatment of the diseases and conditions described herein. In a preferred embodiment, the invention provides pharmaceutical compositions, including those described below, for use in the treatment of a hyperproliferative disease. In a preferred embodiment, the invention provides pharmaceutical compositions, including those described below, for use in the treatment of cancer.

[00372] In some embodiments, the invention provides pharmaceutical compositions for treating solid tumor cancers, lymphomas and leukemia.

[00373] In preferred embodiments, the invention provides a composition comprising therapeutically effective amounts of (1) a MEK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (2) a BTK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in the treatment of cancer. This composition is typically a pharmaceutical composition.

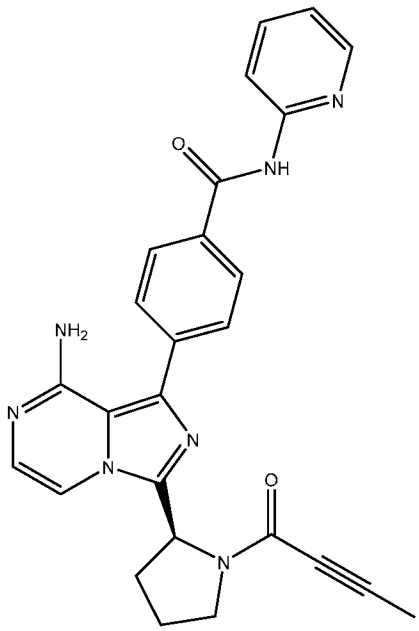
[00374] In preferred embodiments, the invention provides a composition comprising therapeutically effective amounts of (1) a MEK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a BTK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof. This composition is typically a pharmaceutical composition.

[00375] In some embodiments, the invention provides a composition comprising therapeutically effective amounts of (1) a MEK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a BTK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (3) a compound selected from the group consisting of

gemcitabine, albumin-bound paclitaxel, bendamustine, fludarabine, cyclophosphamide, chlorambucil, an anticoagulant or antiplatelet active pharmaceutical ingredient, or combinations thereof. This composition is typically a pharmaceutical composition.

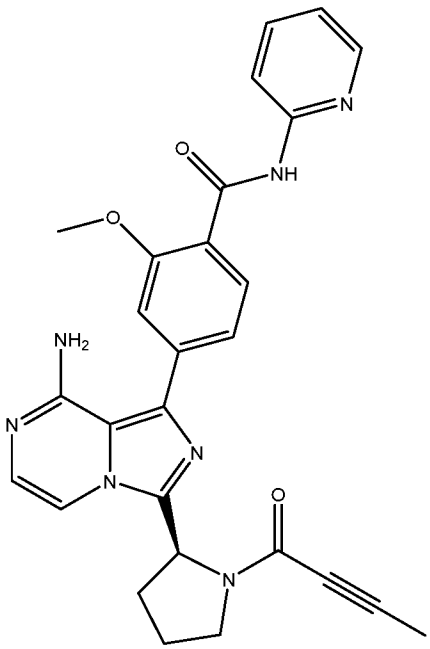
[00376] In some embodiments, the invention provides a composition comprising therapeutically effective amounts of (1) a MEK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a BTK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in the treatment of cancer; (3) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, biosimilars thereof, and combinations thereof; and (4) a compound selected from the group consisting of gemcitabine, albumin-bound paclitaxel, bendamustine, fludarabine, cyclophosphamide, chlorambucil, an anticoagulant or antiplatelet active pharmaceutical ingredient, and combinations thereof. This composition is typically a pharmaceutical composition.

[00377] In some embodiments, the invention provides a composition comprising therapeutically effective amounts of (1) a MEK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (2) a BTK inhibitor having the structure:



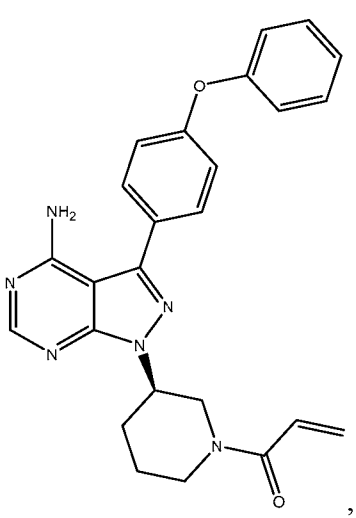
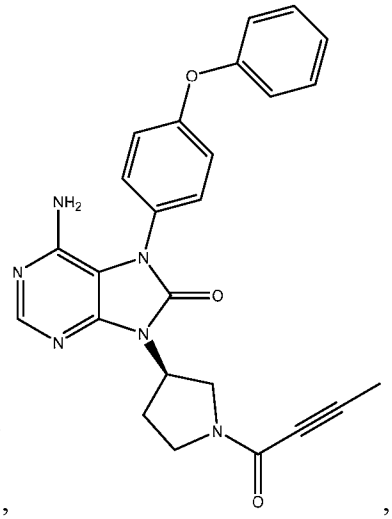
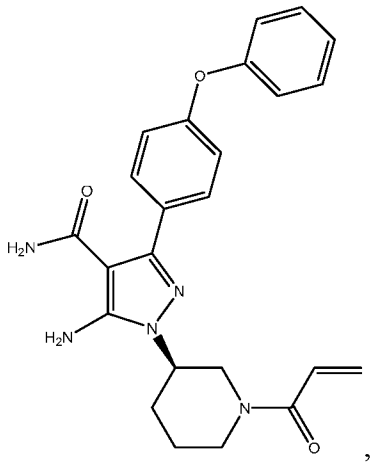
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.

[00378] In some embodiments, the invention provides a composition comprising therapeutically effective amounts of (1) a MEK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (2) a BTK inhibitor having the structure:



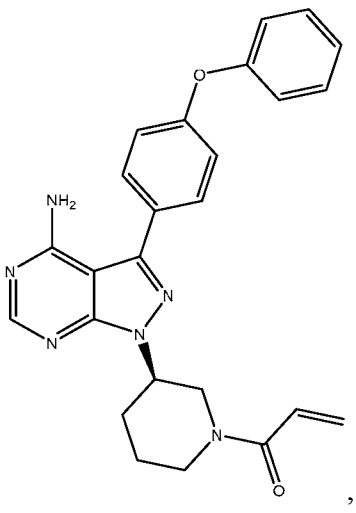
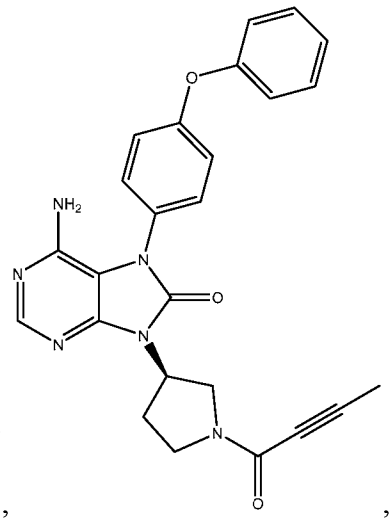
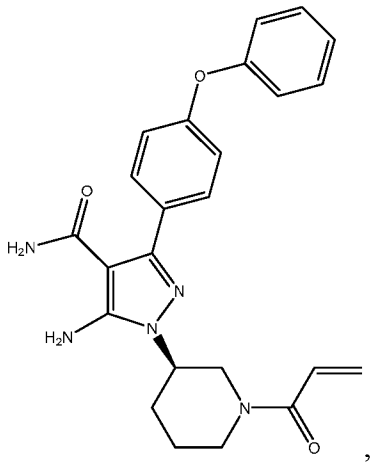
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.

[00379] In some embodiments, the invention provides a composition comprising therapeutically effective amounts of (1) a MEK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (2) a BTK inhibitor selected from the group consisting of:


,

,

,

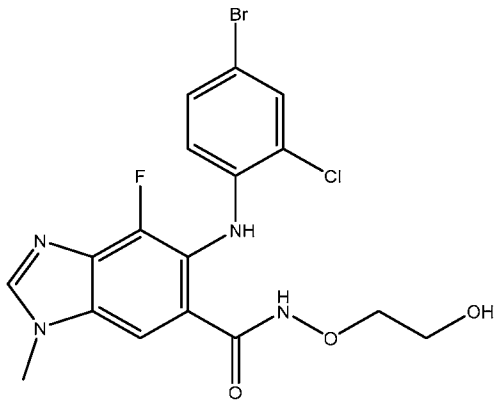
and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, and prodrugs thereof. This composition is typically a pharmaceutical composition.

[00380] In some embodiments, the invention provides a composition comprising therapeutically effective amounts of (1) a MEK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a BTK inhibitor selected from the group consisting of:

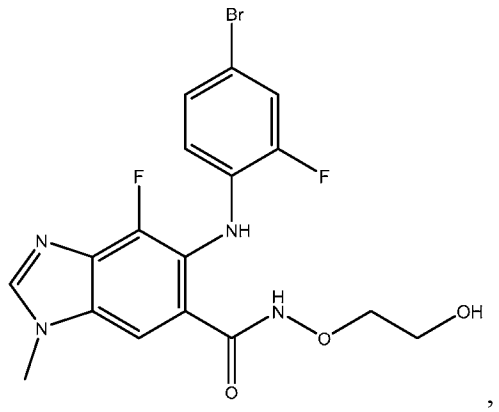

,

,

,

and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, and prodrugs thereof; and (3) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof. This composition is typically a pharmaceutical composition.

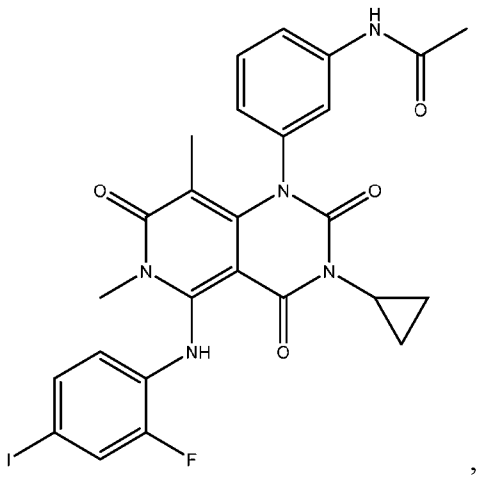
[00381] In some embodiments, the invention provides a composition comprising therapeutically effective amounts of (1) a MEK inhibitor selected from the group consisting of



,



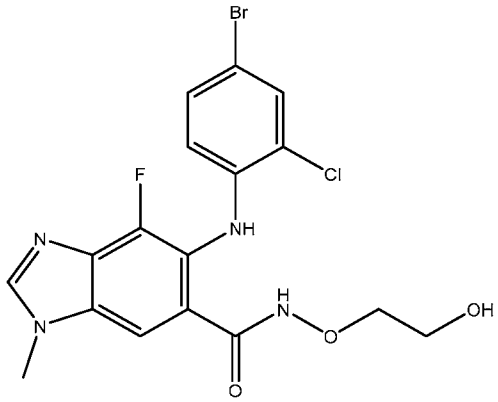
,



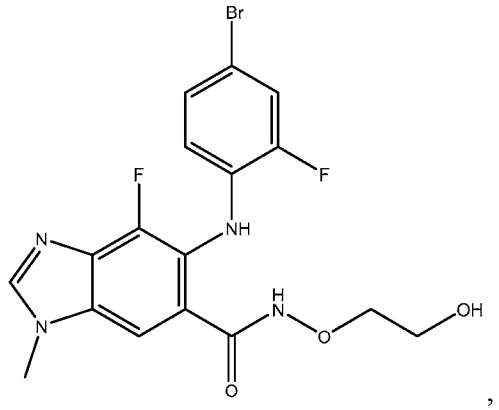
,

and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, and prodrugs thereof; and (2) a BTK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. This composition is typically a pharmaceutical composition.

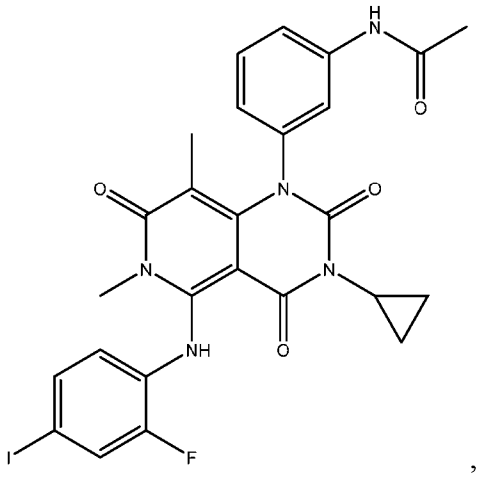
[00382] In some embodiments, the invention provides a composition comprising therapeutically effective amounts of (1) a MEK inhibitor selected from the group consisting of:



,



,



,

and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, and prodrugs thereof; (2) a BTK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in the treatment of cancer; and (3) an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof. This composition is typically a pharmaceutical composition.

[00383] The pharmaceutical compositions are typically formulated to provide a therapeutically effective amount of a combination as described herein, *i.e.*, a combination of a MEK inhibitor and a BTK inhibitor as the active ingredients, or pharmaceutically acceptable salts, prodrugs, solvates, or hydrates thereof. Where desired, the pharmaceutical compositions contain a pharmaceutically acceptable salt and/or coordination complex of one or more of the active ingredients. Typically, the pharmaceutical compositions also comprise 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.

[00384] The pharmaceutical compositions described above are preferably for use in the treatment of the diseases and conditions described below. In a preferred embodiment, the pharmaceutical compositions are for use in the treatment of cancer. In preferred embodiments, the pharmaceutical compositions are for use in treating solid tumor cancers, lymphomas, and leukemias.

[00385] In a preferred embodiment, the pharmaceutical compositions of the present invention are for use in the treatment of cancer. In one embodiment, the pharmaceutical compositions of the present invention are for use in the treatment of a cancer selected from the group consisting of bladder cancer, squamous cell carcinoma including head and neck cancer, pancreatic ductal adenocarcinoma (PDA), pancreatic cancer, colon carcinoma, mammary carcinoma, breast cancer, fibrosarcoma, mesothelioma, renal cell carcinoma, lung carcinoma, thyoma, prostate cancer, colorectal cancer, ovarian cancer, acute myeloid leukemia, thymus cancer, brain cancer, squamous cell cancer, skin cancer, eye cancer, retinoblastoma, melanoma, intraocular melanoma, oral cavity and oropharyngeal cancers, gastric cancer, stomach cancer, cervical cancer, renal cancer, kidney cancer, liver cancer, ovarian cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, acquired immune deficiency syndrome (AIDS)-related cancers (e.g., lymphoma and Kaposi's sarcoma), viral-induced cancer, glioblastoma, esophogeal tumors, hematological neoplasms, non-small-cell lung cancer, chronic myelocytic leukemia, diffuse large B-cell lymphoma, esophagus tumor, follicle center lymphoma, head and neck tumor, hepatitis C virus infection, hepatocellular carcinoma, Hodgkin's disease, metastatic colon cancer, multiple myeloma, non-Hodgkin's lymphoma, indolent non-Hodgkin's lymphoma, ovary tumor, pancreas tumor, renal cell carcinoma, small-cell lung cancer, stage IV melanoma, chronic lymphocytic leukemia, B-cell acute lymphoblastic leukemia (ALL), mature B-cell ALL, follicular lymphoma, mantle cell lymphoma, and Burkitt's lymphoma.

[00386] The pharmaceutical compositions may be administered as a combination of a MEK inhibitor with a BTK inhibitor. Where desired, other active pharmaceutical ingredient(s) may be mixed into a preparation or two or more components of the combination may be formulated into separate preparations for use in combination separately or at the same time. A kit containing the

components of the combination, formulated into separate preparations for said use, in also provided by the invention.

[00387] In an embodiment, the molar ratio of the MEK inhibitor to the BTK inhibitor in the pharmaceutical compositions is in the range from about 10:1 to about 1:10, preferably from about 2.5:1 to about 1:2.5, and more preferably about about 1:1. In an embodiment, the weight ratio of the MEK inhibitor to the BTK inhibitor in the pharmaceutical compositions is selected from the group consisting of about 20:1, about 19:1, about 18:1, about 17:1, about 16:1, about 15:1, about 14:1, about 13:1, about 12:1, about 11:1, about 10:1, about 9:1, about 8:1, about 7:1, about 6:1, about 5:1, about 4:1, about 3:1, about 2:1, about 1:1, about 1:2, about 1:3, about 1:4, about 1:5, about 1:6, about 1:7, about 1:8, about 1:9, about 1:10, about 1:11, about 1:12, about 1:13, about 1:14, about 1:15, about 1:16, about 1:17, about 1:18, about 1:19, and about 1:20.

[00388] In some embodiments, the concentration of each of the MEK or BTK inhibitors provided in the pharmaceutical compositions of the invention is independently less than, for example, 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002% or 0.0001% w/w, w/v or v/v of the pharmaceutical composition.

[00389] In some embodiments, the concentration of each of the MEK or 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 of the pharmaceutical composition.

[00390] In some embodiments, the concentration of each of the MEK or BTK inhibitors provided in the pharmaceutical compositions is independently in the range from about 0.0001% to about 50%, about 0.001% to about 40%, about 0.01% to about 30%, about 0.02% to about 29%, about 0.03% to about 28%, about 0.04% to about 27%, about 0.05% to about 26%, about 0.06% to about 25%, about 0.07% to about 24%, about 0.08% to about 23%, about 0.09% to about 22%, about 0.1% to about 21%, about 0.2% to about 20%, about 0.3% to about 19%, about 0.4% to about 18%, about 0.5% to about 17%, about 0.6% to about 16%, about 0.7% to about 15%, about 0.8% to about 14%, about 0.9% to about 12% or about 1% to about 10% w/w, w/v or v/v of the pharmaceutical composition.

[00391] In some embodiments, the concentration of each of the MEK or BTK inhibitors provided in the pharmaceutical compositions is independently in the range from about 0.001% to about 10%, about 0.01% to about 5%, about 0.02% to about 4.5%, about 0.03% to about 4%, about 0.04% to about 3.5%, about 0.05% to about 3%, about 0.06% to about 2.5%, about 0.07% to about 2%, about 0.08% to about 1.5%, about 0.09% to about 1%, about 0.1% to about 0.9% w/w, w/v or v/v of the pharmaceutical composition.

[00392] In some embodiments, the amount of each of the MEK or BTK inhibitors provided in the pharmaceutical compositions is independently equal to or less than 10 g, 9.5 g, 9.0 g, 8.5 g, 8.0 g, 7.5 g, 7.0 g, 6.5 g, 6.0 g, 5.5 g, 5.0 g, 4.5 g, 4.0 g, 3.5 g, 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.

[00393] In some embodiments, the amount of each of the MEK or BTK inhibitors provided in the pharmaceutical compositions 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, 3 g, 3.5, 4 g, 4.5 g, 5 g, 5.5 g, 6 g, 6.5 g, 7 g, 7.5 g, 8 g, 8.5 g, 9 g, 9.5 g, or 10 g.

[00394] Each of the MEK and BTK inhibitors according to the invention is effective over a wide dosage range. For example, in the treatment of adult humans, dosages independently ranging 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.

[00395] In a preferred embodiment, the pharmaceutical compositions of the present invention are for use in the treatment of cancer. In a preferred embodiment, the pharmaceutical compositions of the present invention are for use in the treatment of a cancer selected from the group consisting of bladder cancer, squamous cell carcinoma including head and neck cancer, pancreatic ductal adenocarcinoma (PDA), pancreatic cancer, colon carcinoma, mammary carcinoma, breast cancer, fibrosarcoma, mesothelioma, renal cell carcinoma, lung carcinoma, thyoma, prostate cancer, colorectal cancer, ovarian cancer, acute myeloid leukemia, thymus cancer, brain cancer, squamous cell cancer, skin cancer, eye cancer, retinoblastoma, melanoma, intraocular melanoma, oral cavity and oropharyngeal cancers, gastric cancer, stomach cancer, cervical cancer, renal cancer, kidney cancer, liver cancer, ovarian cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, acquired immune deficiency syndrome (AIDS)-related cancers (e.g., lymphoma and Kaposi's sarcoma), viral-induced cancer, glioblastoma, esophogeal tumors, hematological neoplasms, non-small-cell lung cancer, chronic myelocytic leukemia, diffuse large B-cell lymphoma, esophagus tumor, follicle center lymphoma, head and neck tumor, hepatitis C virus infection, hepatocellular carcinoma, Hodgkin's disease, metastatic colon cancer, multiple myeloma, non-Hodgkin's lymphoma, indolent non-Hodgkin's lymphoma, ovary tumor, pancreas tumor, renal cell carcinoma, small-cell lung cancer, stage IV melanoma, chronic lymphocytic leukemia, B-cell acute lymphoblastic leukemia (ALL), mature B-cell ALL, follicular lymphoma, mantle cell lymphoma, and Burkitt's lymphoma.

[00396] Described below are non-limiting pharmaceutical compositions and methods for preparing the same.

Pharmaceutical Compositions for Oral Administration

[00397] In preferred embodiments, the invention provides a pharmaceutical composition for oral administration containing the combination of a MEK inhibitor and BTK inhibitor, and a pharmaceutical excipient suitable for oral administration.

[00398] In preferred embodiments, the invention provides a solid pharmaceutical composition for oral administration containing: (i) an effective amount of each of a MEK inhibitor and a 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 active pharmaceutical ingredient.

[00399] In preferred embodiments, the invention provides a solid pharmaceutical composition for oral administration containing: (i) an effective amount of a MEK inhibitor in combination with a BTK inhibitor and (ii) a pharmaceutical excipient suitable for oral administration. In selected embodiments, the composition further contains (iii) an effective amount of a third active pharmaceutical ingredient.

[00400] In some embodiments, the pharmaceutical composition may be a liquid pharmaceutical composition suitable for oral consumption.

[00401] Pharmaceutical compositions of the invention suitable for oral administration can be presented as discrete dosage forms, such as capsules, sachets, tablets, 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.

[00402] 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.

[00403] Each of the MEK inhibitors and 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.

[00404] 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.

[00405] 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.

[00406] 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.

[00407] 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.

[00408] When aqueous suspensions and/or elixirs are desired for oral administration, the active pharmacetical ingredient(s) 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.

[00409] 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.

[00410] 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.

[00411] 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.

[00412] 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.

[00413] 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.

[00414] Ionic surfactants may be the ionized forms of lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidic acid, phosphatidylserine, lysophosphatidylcholine, lysophosphatidylethanolamine, lysophosphatidylglycerol, lysophosphatidic acid, lysophosphatidylserine, PEG-phosphatidylethanolamine, PVP-phosphatidylethanolamine, lactylic esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid esters of mono/diglycerides, cholylsarcosine, caproate, caprylate, caprate, laurate, myristate, palmitate, oleate, ricinoleate, linoleate, linolenate, stearate, lauryl sulfate, teracecyl sulfate, docusate, lauroyl carnitines, palmitoyl carnitines, myristoyl carnitines, and salts and mixtures thereof.

[00415] Hydrophilic non-ionic surfactants may include, but not limited to, alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; polyoxyalkylene alkyl ethers such as polyethylene glycol alkyl ethers; polyoxyalkylene alkylphenols such as polyethylene

glycol alkyl phenols; polyoxyalkylene alkyl phenol fatty acid esters such as polyethylene glycol fatty acids monoesters and polyethylene glycol fatty acids diesters; polyethylene glycol glycerol fatty acid esters; polyglycerol fatty acid esters; polyoxyalkylene sorbitan fatty acid esters such as polyethylene glycol sorbitan fatty acid esters; hydrophilic transesterification products of a polyol with at least one member of the group consisting of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids, and sterols; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylated vitamins and derivatives thereof; polyoxyethylene-polyoxypropylene block copolymers; and mixtures thereof; polyethylene glycol sorbitan fatty acid esters and hydrophilic transesterification products of a polyol with at least one member of the group consisting of triglycerides, vegetable oils, and hydrogenated vegetable oils. The polyol may be glycerol, ethylene glycol, polyethylene glycol, sorbitol, propylene glycol, pentaerythritol, or a saccharide.

[00416] Other hydrophilic-non-ionic surfactants include, without limitation, PEG-10 laurate, PEG-12 laurate, PEG-20 laurate, PEG-32 laurate, PEG-32 dilaurate, PEG-12 oleate, PEG-15 oleate, PEG-20 oleate, PEG-20 dioleate, PEG-32 oleate, PEG-200 oleate, PEG-400 oleate, PEG-15 stearate, PEG-32 distearate, PEG-40 stearate, PEG-100 stearate, PEG-20 dilaurate, PEG-25 glyceryl trioleate, PEG-32 dioleate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-20 glyceryl stearate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-40 palm kernel oil, PEG-50 hydrogenated castor oil, PEG-40 castor oil, PEG-35 castor oil, PEG-60 castor oil, PEG-40 hydrogenated castor oil, PEG-60 hydrogenated castor oil, PEG-60 corn oil, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polyglyceryl-10 laurate, PEG-30 cholesterol, PEG-25 phyto sterol, PEG-30 soya sterol, PEG-20 trioleate, PEG-40 sorbitan oleate, PEG-80 sorbitan laurate, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, POE-20 oleyl ether, POE-20 stearyl ether, tocopheryl PEG-100 succinate, PEG-24 cholesterol, polyglyceryl-10oleate, Tween 40, Tween 60, sucrose monostearate, sucrose monolaurate, sucrose monopalmitate, PEG 10-100 nonyl phenol series, PEG 15-100 octyl phenol series, and poloxamers.

[00417] 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.

[00418] 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.

[00419] Examples of suitable solubilizers include, but are not limited to, the following: alcohols and polyols, such as ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediols and isomers thereof, glycerol, pentaerythritol, sorbitol, mannitol, transcutol, dimethyl isosorbide, polyethylene glycol, polypropylene glycol, polyvinylalcohol, hydroxypropyl methylcellulose and other cellulose derivatives, cyclodextrins and cyclodextrin derivatives; ethers of polyethylene glycols having an average molecular weight of about 200 to about 6000, such as tetrahydrofurfuryl alcohol PEG ether (glycofurol) or methoxy PEG; amides and other nitrogen-containing compounds such as 2-pyrrolidone, 2-piperidone, Ɛ-caprolactam, N-alkylpyrrolidone, N-hydroxyalkylpyrrolidone, N-alkylpiperidone, N-alkylcaprolactam, dimethylacetamide and polyvinylpyrrolidone; esters such as ethyl propionate, tributylcitrate, acetyl triethylcitrate, acetyl tributyl citrate, triethylcitrate, ethyl oleate, ethyl caprylate, ethyl butyrate, triacetin, propylene glycol monoacetate, propylene glycol diacetate, .epsilon.-caprolactone and isomers thereof, δ-valerolactone and isomers thereof, β-butyrolactone and isomers thereof; and other solubilizers known in the art, such as dimethyl acetamide, dimethyl isosorbide, N-methyl pyrrolidones, monooctanoin, diethylene glycol monoethyl ether, and water.

[00420] 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.

[00421] 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.

[00422] 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.

[00423] In addition, an acid or a base may be incorporated into the composition to facilitate processing, to enhance stability, or for other reasons. Examples of pharmaceutically acceptable bases include amino acids, amino acid esters, ammonium hydroxide, potassium hydroxide, sodium hydroxide, sodium hydrogen carbonate, aluminum hydroxide, calcium carbonate, magnesium hydroxide, magnesium aluminum silicate, synthetic aluminum silicate, synthetic hydrocalcite, magnesium aluminum hydroxide, diisopropylethylamine, ethanolamine, ethylenediamine, triethanolamine, triethylamine, triisopropanolamine, trimethylamine, tris(hydroxymethyl)aminomethane (TRIS) and the like. Also suitable are bases that are salts of a

pharmaceutically acceptable acid, such as acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acid, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, uric acid, and the like. Salts of polyprotic acids, such as sodium phosphate, disodium hydrogen phosphate, and sodium dihydrogen phosphate can also be used. When the base is a salt, the cation can be any convenient and pharmaceutically acceptable cation, such as ammonium, alkali metals and alkaline earth metals. Example may include, but not limited to, sodium, potassium, lithium, magnesium, calcium and ammonium.

[00424] Suitable acids are pharmaceutically acceptable organic or inorganic acids. Examples of suitable inorganic acids include hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, nitric acid, boric acid, phosphoric acid, and the like. Examples of suitable organic acids include acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acids, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, methanesulfonic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid and uric acid.

Pharmaceutical Compositions for Injection

[00425] In preferred embodiments, the invention provides a pharmaceutical composition for injection containing the combination of the MEK inhibitors and BTK inhibitors, and a pharmaceutical excipient suitable for injection. Components and amounts of agents in the compositions are as described herein.

[00426] 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.

[00427] 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.

[00428] Sterile injectable solutions are prepared by incorporating the combination of the MEK and 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 vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Pharmaceutical Compositions for Topical Delivery

[00429] In preferred embodiments, the invention provides a pharmaceutical composition for transdermal delivery containing the combination of the MEK inhibitors and BTK inhibitors, and a pharmaceutical excipient suitable for transdermal delivery.

[00430] 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.

[00431] 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.

[00432] Another exemplary 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 MEK inhibitors and BTK inhibitors in controlled amounts, either with or without another active pharmaceutical ingredient.

[00433] The construction and use of transdermal patches for the delivery of pharmaceutical agents 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 pharmaceutical agents.

Pharmaceutical Compositions for Inhalation

[00434] Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described supra. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be inhaled directly from the nebulizing device or the nebulizing device may be attached to a face mask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices that deliver the formulation in an appropriate manner. Dry powder inhalers may also be used to provide inhaled delivery of the compositions.

Other Pharmaceutical Compositions

[00435] Pharmaceutical compositions may also be prepared from compositions described herein and one or more pharmaceutically acceptable excipients suitable for sublingual, buccal, rectal, intraosseous, intraocular, intranasal, epidural, or intraspinal administration. Preparations for such pharmaceutical compositions are well-known in the art. See, *e.g.*, Anderson, *et al.*, eds.,

Handbook of Clinical Drug Data, Tenth Edition, McGraw-Hill, 2002; and Pratt and Taylor, eds., Principles of Drug Action, Third Edition, Churchill Livingston, N.Y., 1990, each of which is incorporated by reference herein in its entirety.

[00436] Administration of the combination of the MEK 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.

[00437] The compositions of the invention may also be delivered via an impregnated or coated device such as a stent, for example, or an artery-inserted cylindrical polymer. Such a method of administration may, for example, aid in the prevention or amelioration of restenosis following procedures such as balloon angioplasty. Without being bound by theory, compounds of the invention may slow or inhibit the migration and proliferation of smooth muscle cells in the arterial wall which contribute to restenosis. A compound of the invention may be administered, for example, by local delivery from the struts of a stent, from a stent graft, from grafts, or from the cover or sheath of a stent. In some embodiments, a compound of the invention is admixed with a matrix. Such a matrix may be a polymeric matrix, and may serve to bond the compound to the stent. Polymeric matrices suitable for such use, include, for example, lactone-based polyesters or copolyesters such as polylactide, polycaprolactonglycolide, polyorthoesters, polyanhydrides, polyaminoacids, polysaccharides, polyphosphazenes, poly(ether-ester) copolymers (e.g. PEO-PLLA); polydimethylsiloxane, poly(ethylene-vinylacetate), acrylate-based polymers or copolymers (*e.g.*, polyhydroxyethyl methylmethacrylate, polyvinyl pyrrolidinone), fluorinated polymers such as polytetrafluoroethylene and cellulose esters. Suitable matrices may be nondegrading or may degrade with time, releasing the compound or compounds. The combination of the MEK and BTK inhibitors may be applied to the surface of the stent by various methods such as dip/spin coating, spray coating, dip-coating, and/or brush-coating. The compounds may be applied in a solvent and the solvent may be allowed to evaporate, thus forming a layer of compound onto the stent. Alternatively, the compound may be located in the body of the stent or graft, for example in microchannels or micropores. When implanted, the

compound diffuses out of the body of the stent to contact the arterial wall. Such stents may be prepared by dipping a stent manufactured to contain such micropores or microchannels into a solution of the compound of the invention in a suitable solvent, followed by evaporation of the solvent. Excess drug on the surface of the stent may be removed via an additional brief solvent wash. In yet other embodiments, compounds of the invention may be covalently linked to a stent or graft. A covalent linker may be used which degrades *in vivo*, leading to the release of the compound of the invention. Any bio-labile linkage may be used for such a purpose, such as ester, amide or anhydride linkages. The combination of the MEK and BTK inhibitors may additionally be administered intravascularly from a balloon used during angioplasty. Extravascular administration of the combination of the MEK and BTK inhibitors via the pericard or via advential application of formulations of the invention may also be performed to decrease restenosis.

[00438] Exemplary 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.

[00439] The invention also provides kits. The kits include each of the MEK 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 selected embodiments, the MEK and BTK inhibitors and another active pharmaceutical ingredient are provided as separate compositions in separate containers within the kit. In selected embodiments, the MEK and BTK inhibitors and the agent are provided as a single composition within a container in the kit. Suitable packaging and additional articles for use (*e.g.*, measuring cup for liquid preparations, foil wrapping to minimize exposure to air, and the like) are known in the art and may be included in the kit. Kits described herein can be provided, marketed and/or promoted to health providers,

including physicians, nurses, pharmacists, formulary officials, and the like. Kits may also, in selected embodiments, be marketed directly to the consumer.

[00440] In some embodiments, the invention provides a kit comprising (1) a composition comprising a therapeutically effective amount of a MEK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (2) a composition comprising a therapeutically effective amount of 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 the MEK and the BTK inhibitors, either simultaneously or separately.

[00441] In some embodiments, the invention provides a kit comprising (1) a composition comprising a therapeutically effective amount of MEK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a composition comprising a therapeutically effective amount of a BTK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and/or (3) a composition comprising a therapeutically effective amount of an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof. These compositions are typically pharmaceutical compositions. The kit is for co-administration of the MEK inhibitor, the BTK inhibitor, and/or the anti-CD20 antibody, either simultaneously or separately.

[00442] In some embodiments, the invention provides a kit comprising (1) a composition comprising a therapeutically effective amount of a MEK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a composition comprising a therapeutically effective amount of a BTK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and/or (3) a composition comprising a therapeutically effective amount of gemcitabine, albumin-bound paclitaxel, bendamustine, fludarabine, cyclophosphamide, chlorambucil, an anticoagulant or antiplatelet active pharmaceutical ingredient, or combinations thereof. These compositions are typically pharmaceutical compositions. The kit is for co-administration of the MEK inhibitor, BTK inhibitor, gemcitabine, albumin-bound paclitaxel, bendamustine, fludarabine, cyclophosphamide,

chlorambucil, and/or the anticoagulant or the antiplatelet active pharmaceutical ingredient, either simultaneously or separately.

[00443] In some embodiments, the invention provides a kit comprising (1) a composition comprising a therapeutically effective amount of a MEK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (2) a composition comprising a therapeutically effective amount of a BTK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; (3) a composition comprising a therapeutically effective amount of an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, biosimilars thereof, and combinations thereof; and/or (4) a composition comprising a therapeutically effective amount of gemcitabine, albumin-bound paclitaxel, bendamustine, fludarabine, cyclophosphamide, chlorambucil, an anticoagulant or antiplatelet active pharmaceutical ingredient, or combinations thereof. These compositions are typically pharmaceutical compositions. The kit is for co-administration of the MEK inhibitor, BTK inhibitor, anti-CD20 antibody, gemcitabine, albumin-bound paclitaxel, bendamustine, fludarabine, cyclophosphamide, chlorambucil, and/or the anticoagulant or the antiplatelet active pharmaceutical ingredient, either simultaneously or separately.

[00444] The kits described above are preferably for use in the treatment of the diseases and conditions described herein. In a preferred embodiment, the kits are for use in the treatment of cancer. In preferred embodiments, the kits are for use in treating solid tumor cancers, lymphomas and leukemias.

[00445] In a preferred embodiment, the kits of the present invention are for use in the treatment of cancer. In a preferred embodiment, the kits of the present invention are for use in the treatment of a cancer selected from the group consisting of bladder cancer, squamous cell carcinoma including head and neck cancer, pancreatic ductal adenocarcinoma (PDA), pancreatic cancer, colon carcinoma, mammary carcinoma, breast cancer, fibrosarcoma, mesothelioma, renal cell carcinoma, lung carcinoma, thyoma, prostate cancer, colorectal cancer, ovarian cancer, acute myeloid leukemia, thymus cancer, brain cancer, squamous cell cancer, skin cancer, eye cancer, retinoblastoma, melanoma, intraocular melanoma, oral cavity and oropharyngeal cancers, gastric

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

Dosages and Dosing Regimens

[00446] The amounts of BTK inhibitors and MEK inhibitors administered will be dependent on the human or 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 of each 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 - *e.g.*, by dividing such larger doses into several small doses for administration throughout the day. The dosage of BTK inhibitors and MEK inhibitors may be provided in units of mg/kg of body mass or in mg/m^2 of body surface area. In an embodiment, the ratio of the dose of the MEK inhibitor to the dose of the BTK inhibitor in mg/kg or in mg/m^2 is in the range from 10:1 to 1:10, preferably from 2.5:1 to 1:2.5, and more preferably about 1:1. In an embodiment, the ratio of the MEK inhibitor to the BTK inhibitor in mg/kg or in mg/m^2 is selected from the group consisting of about 20:1, about 19:1, about 18:1, about 17:1, about 16:1, about 15:1, about 14:1, about 13:1, about 12:1, about 11:1, about 10:1, about 9:1, about 8:1, about 7:1, about 6:1, about 5:1, about 4:1, about 3:1, about 2:1, about 1:1, about 1:2, about 1:3, about 1:4, about 1:5, about 1:6, about 1:7, about 1:8, about 1:9, about 1:10, about 1:11, about

1:12, about 1:13, about 1:14, about 1:15, about 1:16, about 1:17, about 1:18, about 1:19, and about 1:20.

[00447] In some embodiments, the combination of the MEK and BTK inhibitors is administered in a single dose. Such administration may be by injection, *e.g.*, intravenous injection, in order to introduce the MEK and BTK inhibitors quickly. However, other routes, including the preferred oral route, may be used as appropriate. A single dose of the combination of the MEK and BTK inhibitors may also be used for treatment of an acute condition.

[00448] In some embodiments, the combination of the MEK and BTK inhibitors is administered in multiple doses. In a preferred embodiment, the combination of the MEK and BTK inhibitors is administered in multiple doses. Dosing may be once, twice, three times, four times, five times, six times, or more than six times per day. Dosing may be once a month, once every two weeks, once a week, or once every other day. In other embodiments, the combination of the MEK and BTK inhibitors is administered about once per day to about 6 times per day. In some embodiments, the combination of the MEK, and BTK inhibitors is administered once daily, while in other embodiments, the combination of the MEK and BTK inhibitors is administered twice daily, and in other embodiments the combination of the MEK and BTK inhibitors is administered three times daily. In some embodiments, a BTK inhibitor disclosed herein is administered in combination with a MEK inhibitor once daily, while in other embodiments a BTK inhibitor disclosed herein is administered in combination with a MEK inhibitor twice daily, and in other embodiments a BTK inhibitor disclosed herein is administered in combination with a MEK inhibitor three times daily.

[00449] Administration of the active pharmaceutical ingredients of the invention may continue as long as necessary. In selected embodiments, the combination of the MEK and BTK inhibitors is administered for more than 1, 2, 3, 4, 5, 6, 7, 14, or 28 days. In some embodiments, the combination of the MEK and BTK inhibitors is administered for less than 28, 14, 7, 6, 5, 4, 3, 2, or 1 day. In selected embodiments, the combination of the MEK and BTK inhibitors is administered chronically on an ongoing basis - *e.g.*, for the treatment of chronic effects. In another embodiment the administration of the combination of the MEK and BTK 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.

[00450] In some embodiments, an effective dosage of a BTK inhibitor disclosed herein 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 a BTK inhibitor disclosed herein 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, or about 250 mg.

[00451] In some embodiments, an effective dosage of a BTK inhibitor disclosed herein is in the range of about 0.01 mg/kg to about 4.3 mg/kg, about 0.15 mg/kg to about 3.6 mg/kg, about 0.3 mg/kg to about 3.2 mg/kg, about 0.35 mg/kg to about 2.85 mg/kg, about 0.15 mg/kg to about 2.85 mg/kg, about 0.3 mg to about 2.15 mg/kg, about 0.45 mg/kg to about 1.7 mg/kg, about 0.15 mg/kg to about 1.3 mg/kg, about 0.3 mg/kg to about 1.15 mg/kg, about 0.45 mg/kg to about 1 mg/kg, about 0.55 mg/kg to about 0.85 mg/kg, about 0.65 mg/kg to about 0.8 mg/kg, about 0.7 mg/kg to about 0.75 mg/kg, about 0.7 mg/kg to about 2.15 mg/kg, about 0.85 mg/kg to about 2 mg/kg, about 1 mg/kg to about 1.85 mg/kg, about 1.15 mg/kg to about 1.7 mg/kg, about 1.3 mg/kg mg to about 1.6 mg/kg, about 1.35 mg/kg to about 1.5 mg/kg, about 2.15 mg/kg to about 3.6 mg/kg, about 2.3 mg/kg to about 3.4 mg/kg, about 2.4 mg/kg to about 3.3 mg/kg, about 2.6 mg/kg to about 3.15 mg/kg, about 2.7 mg/kg to about 3 mg/kg, about 2.8 mg/kg to about 3 mg/kg, or about 2.85 mg/kg to about 2.95 mg/kg. In some embodiments, an effective dosage of a BTK inhibitor disclosed herein 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.

[00452] In some embodiments, an effective dosage of a MEK inhibitor disclosed herein 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 1 mg to about 50 mg, about 5 mg to about 45 mg, about 10 mg to about 40 mg, about 15 mg to about 35 mg, about 20 mg to about 30 mg, about 23 mg to about 28 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, or about 95 mg to about 105 mg, about 98 mg to about 102 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 207 mg. In some embodiments, an effective dosage of a MEK inhibitor disclosed herein 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, or about 250 mg.

[00453] In some embodiments, an effective dosage of a MEK inhibitor disclosed herein 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 0.01 mg/kg to about 0.7 mg/kg, about 0.07 mg/kg to about 0.65 mg/kg, about 0.15 mg/kg to about 0.6 mg/kg, about 0.2 mg/kg to about 0.5 mg/kg, about 0.3 mg/kg to about 0.45 mg/kg, about 0.3 mg/kg to about 0.4 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 1.4 mg/kg to about 1.45 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 a MEK inhibitor disclosed herein is about 0.4 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.

[00454] In some embodiments, a combination of a BTK inhibitor and a MEK inhibitor is administered at a dosage of 10 to 200 mg BID, including 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, or 150 mg BID, for the BTK inhibitor, and 1 to 500 mg BID, including 1, 5, 10, 15, 25, 50, 75, 100, 150, 200, 300, 400, or 500 mg BID for the MEK inhibitor.

[00455] In some instances, dosage levels below the lower limit of the aforesaid ranges may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect - *e.g.*, by dividing such larger doses into several small doses for administration throughout the day.

[00456] An effective amount of the combination of the MEK and BTK inhibitors may be administered in either single or multiple doses by any of the accepted modes of administration of agents 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, Hematological Malignancies, Inflammation, Immune and Autoimmune Disorders, and Other Diseases

[00457] The compositions and combinations of inhibitors described above can be used in a method for treating BTK-mediated disorders and diseases. In a preferred embodiment, they are for use in treating hyperproliferative disorders. They may also be used in treating other disorders as described herein and in the following paragraphs.

[00458] In some embodiments, the invention provides a method of treating a hyperproliferative disorder in a mammal that comprises administering to said mammal a therapeutically effective amount of a MEK inhibitor and a BTK inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug of either or both the MEK inhibitor or the BTK inhibitor. In some embodiments, the invention provides a method of treating a hyperproliferative disorder in a mammal that comprises administering to said mammal a therapeutically effective amount of a MEK inhibitor and a BTK inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug of either or both the MEK inhibitor or the BTK inhibitor.

[00459] In some embodiments, the invention provides a method of treating a hyperproliferative disorder in a mammal that comprises administering to said mammal a therapeutically effective amount of a MEK inhibitor and a BTK inhibitor, wherein the BTK inhibitor is selected from wherein the BTK inhibitor is selected from the group consisting of Formula (2), Formula (3), Formula (4), Formula (5), Formula (6), and Formula (7), or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug of either or both the MEK inhibitor or the BTK inhibitor. In some embodiments, the invention provides a method of treating a hyperproliferative disorder

in a mammal that comprises administering to said mammal a therapeutically effective amount of a MEK inhibitor and a BTK inhibitor, where the BTK inhibitor is selected from the group consisting of wherein the BTK inhibitor is selected from the group consisting of Formula (2), Formula (3), Formula (4), Formula (5), Formula (6), and Formula (7), or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug of either or both the MEK inhibitor or the BTK inhibitor.

[00460] In some embodiments, the hyperproliferative disorder is a solid tumor cancer 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, esophogeal tumors, head and neck tumor, metastatic colon cancer, head and neck squamous cell carcinoma, ovary tumor, pancreas tumor, renal cell carcinoma, hematological neoplasms, small-cell lung cancer, non-small-cell lung cancer, stage IV melanoma, and glioma.

[00461] In some embodiments, the hyperproliferative disorder is a B cell hematological malignancy selected from the group consisting of chronic lymphocytic leukemia (CLL), small lymphocytic leukemia (SLL), non-Hodgkin's lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Hodgkin's lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Burkitt's lymphoma, Waldenström's macroglobulinemia (WM), Burkitt's lymphoma, multiple myeloma, myelodysplatic syndromes, or myelofibrosis. In an embodiment, the invention relates to a method of treating a cancer in a mammal, wherein the cancer is chronic myelocytic leukemia, acute myeloid leukemia, DLBCL

(including activated B-cell (ABC) and germinal center B-cell (GCB) subtypes), follicle center lymphoma, Hodgkin's disease, multiple myeloma, indolent non-Hodgkin's lymphoma, and mature B-cell ALL.

[00462] In some embodiments, the hyperproliferative disorder is a subtype of CLL. A number of subtypes of CLL have been characterized. CLL is often classified for immunoglobulin heavy-chain variable-region (IgV_H) mutational status in leukemic cells. R. N. Damle, *et al.*, *Blood* **1999,** *94,* 1840-47; T. J. Hamblin, *et al.*, *Blood* **1999**, *94,* 1848-54. Patients with IgV_H mutations generally survive longer than patients without IgV_H mutations. ZAP70 expression (positive or negative) is also used to characterize CLL. L. Z. Rassenti, *et al.*, *N. Engl. J. Med.* **2004,** *351,* 893-901. The methylation of ZAP-70 at CpG3 is also used to characterize CLL, for example by pyrosequencing. R. Claus, *et al.*, *J. Clin. Oncol.* **2012,** *30,* 2483-91; J. A. Woyach, *et al.*, *Blood* **2014,** *123,* 1810-17. CLL is also classfied 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 11q 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, 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.

[00463] In some embodiments, the hyperproliferative disorder is a CLL 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.

[00464] In some embodiments, the hyperproliferative disorder is a 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.

[00465] In some embodiments, the hyperproliferative disorder is selected from the group consisting of myeloproliferative disorders (MPDs), myeloproliferative neoplasms, polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), myelodysplastic syndrome, chronic myelogenous leukemia (BCR-ABL1-positive), chronic neutrophilic leukemia, chronic eosinophilic leukemia, or mastocytosis.

[00466] In some embodiments, the hyperproliferative disorder is an inflammatory, immune, or autoimmune disorder. In some embodiments, the hyperproliferative disorder 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, glioma and melanoma, ulcerative colitis, atopic dermatitis, pouchitis, spondylarthritis, uveitis, Behcet's disease, polymyalgia rheumatica, giant-cell arteritis, sarcoidosis, Kawasaki disease, juvenile idiopathic arthritis, hidratenitis suppurativa, Sjögren's syndrome, psoriatic arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, lupus, and lupus nephritis.

[00467] In some embodiments, the hyperproliferative disorder is a disease related to vasculogenesis or angiogenesis in a mammal which can manifest as tumor angiogenesis, chronic inflammatory disease such as rheumatoid arthritis, inflammatory bowel disease, atherosclerosis, skin diseases such as psoriasis, eczema, and scleroderma, diabetes, diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, glioma, melanoma, Kaposi's sarcoma and ovarian, breast, lung, pancreatic, prostate, colon and epidermoid cancer.

[00468] In some embodiments, provided herein is a method of treating, preventing and/or managing asthma. As used herein, "asthma" encompasses airway constriction regardless of the cause. Common triggers of asthma include, but are not limited to, exposure to an environmental stimulants (*e.g.*, allergens), cold air, warm air, perfume, moist air, exercise or exertion, and emotional stress. Also provided herein is a method of treating, preventing and/or managing one

or more symptoms associated with asthma. Examples of the symptoms include, but are not limited to, severe coughing, airway constriction and mucus production.

[00469] Efficacy of the methods, compounds, and combinations of compounds described herein in treating, preventing and/or managing the indicated diseases or disorders can be tested using various animal 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 described in Varicchio, *et al.*, *Expert Rev. Hematol.* **2009,** *2(3),* 315-334. Efficacy in treating, preventing and/or managing scleroderma can be assessed using a mouse model induced by repeated local injections of bleomycin described, for example, in Yamamoto, *et al.*, *J. Invest. Dermatol.* **1999,** *112,* 456-462. Efficacy in treating, preventing and/or managing dermatomyositis can be assessed using a myositis mouse model induced by immunization with rabbit myosin as described, for example, in Phyanagi, *et al.*, *Arthritis & Rheumatism*, **2009,** *60(10),* 3118-3127. Efficacy in treating, preventing and/or managing lupus can be assessed using various animal models described, for example, in Ghoreishi, *et al.*, *Lupus*, **2009,** *19,* 1029-1035; Ohl, *et al.*, *J. Biomed. Biotechnol.*, **2011,** Article ID 432595; Xia, *et al.*, *Rheumatology*, **2011,** *50,* 2187-2196; Pau, *et al.*, *PLoS*

ONE, **2012,** *7(5),* e36761; Mustafa, *et al.*, *Toxicology*, **2011,** *290,* 156-168; Ichikawa, *et al.*, *Arthritis & Rheumatism*, **2012,** *62(2),* 493-503; Rankin, *et al.*, *J. Immunology*, **2012,** *188,* 1656-1667. Efficacy in treating, preventing and/or managing Sjögren's syndrome can be assessed using various mouse models described, for example, in Chiorini, *et al.*, *J. Autoimmunity*, **2009,** *33,* 190-196. 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, *e.g.*, 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, *e.g.*, in Damsky, *et al.*, *Pigment Cell & Melanoma Res.* **2010,** *23,* 853–859. Models for determining efficacy of treatments for lung cancer are described, *e.g.*, in Meuwissen, *et al.*, *Genes & Development*, **2005,** *19,* 643-664. Models for determining efficacy of treatments for lung cancer are described, *e.g.*, 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 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.

[00470] In an embodiment, the invention provides a method of treating a solid tumor cancer with a composition including a combination of a MEK inhibitor and a BTK 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 selected embodiments, the invention provides 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 and a MEK 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, a MEK 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, a MEK inhibitor, and gemcitabine, or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof, wherein the BTK inhibitor is a compound of Formula (1).

[00471] In some embodiments, the invention provides pharmaceutical compositions of a combination of a MEK inhibitor and a BTK inhibitor for the treatment of hyperproliferative disorders as described herein. In some embodiments, the invention provides pharmaceutical compositions of a combination of a MEK inhibitor and a BTK inhibitor for the treatment of disorders such as myeloproliferative disorders (MPDs), myeloproliferative neoplasms, polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), myelodysplastic syndrome, chronic myelogenous leukemia (BCR-ABL1-positive), chronic neutrophilic leukemia, chronic eosinophilic leukemia, or mastocytosis, wherein the BTK inhibitor is selected from the group consisting of wherein the BTK inhibitor is selected from the group consisting of Formula (1), Formula (2), Formula (3), Formula (4), Formula (5), Formula (6), and Formula (7). The invention further provides a composition as described herein for the prevention of blastocyte implantation in a mammal.

Methods of Treating Patients Intolerant to Bleeding Events

[00472] In selected embodiments, the invention provides a method of treating a disease in a human sensitive to or intolerant to bleeding events, comprising the step of administering a therapeutically effective amount of a BTK inhibitor, or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof, and a MEK inhibitor, or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof. In a preferred embodiment, the invention provides a method of treating a cancer in a human sensitive to or intolerant to bleeding events, comprising the step of administering a therapeutically effective amount of a BTK inhibitor, wherein the BTK inhibitor is selected from the group consisting of Formula (1), Formula (2), Formula (3), Formula (4), Formula (5), Formula (6), and Formula (7), and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, and prodrugs thereof. In a

preferred embodiment, the invention provides a method of treating a cancer in a human sensitive to or intolerant to bleeding events, comprising the step of administering a therapeutically effective amount of a BTK inhibitor and a MEK inhibitor, wherein the BTK inhibitor is selected from the group consisting of Formula (1), Formula (2), Formula (3), Formula (4), Formula (5), Formula (6), and Formula (7), and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, and prodrugs thereof, and wherein the MEK inhibitor is selected from the group consisting of selumetinib, binimetinib, trametinib, and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, and prodrugs thereof. In some embodiments, the invention provides a method of treating a disease in a human sensitive to or intolerant to ibrutinib.

[00473] In selected embodiments, the invention provides a method of treating a disease in a human sensitive to or intolerant to bleeding events, comprising the step of administering a therapeutically effective amount of a BTK inhibitor, or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof, and a MEK inhibitor, or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof. In a preferred embodiment, the invention provides a method of treating a cancer in a human sensitive to or intolerant to bleeding events, comprising the step of administering a therapeutically effective amount of a BTK inhibitor, wherein the BTK inhibitor is selected from the group consisting of Formula (1), Formula (2), Formula (3), Formula (4), Formula (5), Formula (6), and Formula (7), and a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, and prodrug thereof. In a preferred embodiment, the invention provides a method of treating a cancer in a human sensitive to or intolerant to bleeding events, comprising the step of administering a therapeutically effective amount of a BTK inhibitor and a MEK inhibitor, wherein the BTK inhibitor is selected from the group consisting of Formula (1), Formula (2), Formula (3), Formula (4), Formula (5), Formula (6), and Formula (7), and a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, and prodrug thereof, and wherein the MEK inhibitor is selected from the group consisting of [insert compound structures], and a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, and prodrug thereof.

[00474] In an embodiment, the invention provides a method of treating a cancer in a human intolerant to bleeding events, comprising the step of administering a therapeutically effective amount of a BTK inhibitor, wherein the BTK inhibitor is is selected from the group consisting of Formula (1), Formula (2), Formula (3), Formula (4), Formula (5), Formula (6), and Formula (7),

or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof, and a MEK inhibitor, or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof, further comprising the step of administering a therapeutically effective amount of an anticoagulant or antiplatelet active pharmaceutical ingredient.

[00475] In selected embodiments, the invention provides a method of treating a cancer in a human intolerant to bleeding events, comprising the step of administering a therapeutically effective amount of a BTK inhibitor, wherein the BTK inhibitor is preferably is selected from the group consisting of Formula (1), Formula (2), Formula (3), Formula (4), Formula (5), Formula (6), and Formula (7), and wherein the cancer is selected from the group consisting of bladder cancer, squamous cell carcinoma including head and neck cancer, pancreatic ductal adenocarcinoma (PDA), pancreatic cancer, colon carcinoma, mammary carcinoma, breast cancer, fibrosarcoma, mesothelioma, renal cell carcinoma, lung carcinoma, thyoma, prostate cancer, colorectal cancer, ovarian cancer, acute myeloid leukemia, thymus cancer, brain cancer, squamous cell cancer, skin cancer, eye cancer, retinoblastoma, melanoma, intraocular melanoma, oral cavity and oropharyngeal cancers, gastric cancer, stomach cancer, cervical cancer, head, neck, renal cancer, kidney cancer, liver cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, acquired immune deficiency syndrome (AIDS)-related cancers (e.g., lymphoma and Kaposi's sarcoma), viral-induced cancer, glioblastoma, esophogeal tumors, hematological neoplasms, non-small-cell lung cancer, chronic myelocytic leukemia, diffuse large B-cell lymphoma, esophagus tumor, follicle center lymphoma, head and neck tumor, hepatitis C virus infection, hepatocellular carcinoma, Hodgkin's disease, metastatic colon cancer, multiple myeloma, non-Hodgkin's lymphoma, indolent non-Hogkin's lymphoma, ovary tumor, pancreas tumor, renal cell carcinoma, small-cell lung cancer, stage IV melanoma, chronic lymphocytic leukemia, B-cell acute lymphoblastic leukemia (ALL), mature B-cell ALL, follicular lymphoma, mantle cell lymphoma, and Burkitt's lymphoma.

[00476] In some embodiments, the invention provides a method of treating a cancer in a human intolerant to platelet-mediated thrombosis comprising the step of administering a therapeutically effective amount of a BTK inhibitor, wherein the BTK inhibitor is is selected from the group consisting of Formula (1), Formula (2), Formula (3), Formula (4), Formula (5), Formula (6), and Formula (7), or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof, and a MEK inhibitor, or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate,

or prodrug thereof.

[00477] 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 selected embodiments, the BTK inhibitor is administered before the anticoagulant or the antiplatelet active pharmaceutical ingredient. In selected embodiments, the BTK inhibitor is administered after the anticoagulant or the antiplatelet active pharmaceutical ingredient. In selected embodiments, a MEK 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.

[00478] Selected anti-platelet and anticoagulant 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), and adenosine reuptake inhibitors (*e.g.*, dipyridamole). 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.

[00479] In an embodiment, the invention provides 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 MEK inhibitor, or pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, further comprising the step of administering a therapeutically effective amount of an anticoagulant or antiplatelet active pharmaceutical ingredient, wherein the anticoagulant or antiplatelet active pharmaceutical ingredient is selected from the group consisting of acenocoumarol, anagrelide, anagrelide hydrochloride, abciximab, aloxiprin, antithrombin, apixaban, argatroban, aspirin, aspirin with

extended-release dipyridamole, beraprost, betrixaban, bivalirudin, carbasalate calcium, cilostazol, clopidogrel, clopidogrel bisulfate, cloricromen, dabigatran etexilate, darexaban, dalteparin, dalteparin sodium, defibrotide, dicumarol, diphenadione, dipyridamole, ditazole, desirudin, edoxaban, enoxaparin, enoxaparin sodium, eptifibatide, fondaparinux, fondaparinux sodium, heparin, heparin sodium, heparin calcium, idraparinux, idraparinux sodium, iloprost, indobufen, lepirudin, low molecular weight heparin, melagatran, nadroparin, otamixaban, parnaparin, phenindione, phenprocoumon, prasugrel, picotamide, prostacyclin, ramatroban, reviparin, rivaroxaban, sulodexide, terutroban, terutroban sodium, ticagrelor, ticlopidine, ticlopidine hydrochloride, tinzaparin, tinzaparin sodium, tirofiban, tirofiban hydrochloride, treprostinil, treprostinil sodium, triflusal, vorapaxar, warfarin, warfarin sodium, ximelagatran, salts thereof, solvates thereof, hydrates thereof, prodrugs thereof, and combinations thereof.

Combinations of BTK Inhibitors and MEK Inhibitors with Anti-CD20 Antibodies

[00480] The BTK inhibitors of the present invention and combinations of the BTK inhibitors with MEK 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. In an embodiment, the foregoing combinations exhibit synergistic effects that may result in greater efficacy, less side effects, the use of less active pharmaceutical ingredient to achieve a given clinical result, or other synergistic effects.

[00481] 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 selected from the group consisting of Formula (1), Formula (2), Formula (3), Formula (4), Formula (5), Formula (6), and Formula (7), 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 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 selected from the group consisting of Formula (1), Formula (2), Formula

(3), Formula (4), Formula (5), Formula (6), and Formula (7), 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 1×10^{-7} M or less, 5×10^{-8} M or less, 1×10^{-8} M or less, and 5×10^{-9} M or less. Anti-CD20 monoclonal antibodies are classified as Type I or Type II, as described in Klein, *et al.*, *mAbs* **2013,** *5,* 22-33. Type I anti-CD20 monoclonal antibodies are characterized by binding to the Class I epitope, localization of CD20 to lipid rafts, high complement-dependent cytotoxicity, full binding capacity, weak homotypic aggregation, and moderate cell death induction. Type II anti-CD20 monoclonal antibodies are characterized by binding to the Class I epitope, a lack of localization of CD20 to lipid rafts, low complement-dependent cytotoxicity, half binding capacity, homotypic aggregation, and strong cell death induction. Both Type I and Type II anti-CD20 monoclonal antibodies exhibit antibody-dependent cytotoxiticy (ADCC) and are thus useful with BTK inhibitors described herein. Type I anti-CD20 monoclonal antibodies include but are not limited to rituximab, ocrelizumab, and ofatumumab. Type II anti-CD20 monoclonal antibodies include but are not limited to obinutuzumab and tositumomab. In an embodiment, the foregoing methods exhibit synergistic effects that may result in greater efficacy, less side effects, the use of less active pharmaceutical ingredient to achieve a given clinical result, or other synergistic effects.

[00482] 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 selected from the group consisting of Formula (1), Formula (2), Formula (3), Formula (4), Formula (5), Formula (6), and Formula (7), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and a MEK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug 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 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 selected from the group consisting of Formula (1),

Formula (2), Formula (3), Formula (4), Formula (5), Formula (6), and Formula (7), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, a MEK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug 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 1×10^{-7} M or less, 5×10^{-8} M or less, 1×10^{-8} M or less, and 5×10^{-9} M or less.

[00483] 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 selected from the group consisting of Formula (1), Formula (2), Formula (3), Formula (4), Formula (5), Formula (6), and Formula (7), 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 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 selected from the group consisting of Formula (1), Formula (2), Formula (3), Formula (4), Formula (5), Formula (6), and Formula (7), 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 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 selected from the group consisting of Formula (1), Formula (2), Formula (3), Formula (4), Formula (5), Formula (6), and Formula (7), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and a MEK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug 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 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

selected from the group consisting of Formula (1), Formula (2), Formula (3), Formula (4), Formula (5), Formula (6), and Formula (7), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and a MEK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug 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.

[00484] In selected embodiments, the combinations of the BTK inhibitors with MEK inhibitors and the anti-CD20 monoclonal antibody are administered sequentially. In selected embodiments, the combinations of the BTK inhibitors with MEK inhibitors and the anti-CD20 monoclonal antibody are administered concomitantly. In selected embodiments, the combinations of the BTK inhibitors with MEK inhibitors are administered before the anti-CD20 monoclonal antibody. In selected embodiments, the combinations of the BTK inhibitors with MEK inhibitors are administered after the anti-CD20 monoclonal antibody. In selected embodiments, the combinations of the BTK inhibitors with MEK inhibitors and the anti-CD20 monoclonal antibody are administered over the same time period, and the BTK inhibitor and MEK inhibitor administration continues after the anti-CD20 monoclonal antibody administration is completed.

[00485] 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:1. The amino acid sequence for the light chains of rituximab is set forth in SEQ ID NO:2. 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:1. In an embodiment, the anti-CD20 monoclonal

antibody has a light chain sequence identity of greater than 90% to SEQ ID NO:2. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 95% to SEQ ID NO:1. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 95% to SEQ ID NO:2. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 98% to SEQ ID NO:1. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 98% to SEQ ID NO:2. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 99% to SEQ ID NO:1. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 99% to SEQ ID NO:2.

[00486] 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:3. The amino acid sequence for the light chains of obinutuzumab is set forth in SEQ ID NO:4. 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:3. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 90% to SEQ ID NO:4. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 95% to SEQ ID NO:3. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 95% to SEQ ID NO:4. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 98% to SEQ ID NO:3. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 98% to SEQ ID NO:4. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 99% to SEQ ID NO:3. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 99% to SEQ ID NO:4. In an embodiment, the anti-CD20 monoclonal antibody

obinutuzumab is an immunoglobulin G1, anti-(human B-lymphocyte antigen CD20 (membrane-spanning 4-domains subfamily A member 1, B-lymphocyte surface antigen B1, Leu-16 or Bp35)), humanized mouse monoclonal obinutuzumab des-CH3107-K-γ1 heavy chain (222-219')-disulfide with humanized mouse monoclonal obinutuzumab κ light chain dimer (228-228":231-231")-bisdisulfide antibody.

[00487] 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:5. In an embodiment, the anti-CD20 monoclonal antibody has a variable light chain sequence identity of greater than 90% to SEQ ID NO:6. In an embodiment, the anti-CD20 monoclonal antibody has a variable heavy chain sequence identity of greater than 95% to SEQ ID NO:5. In an embodiment, the anti-CD20 monoclonal antibody has a variable light chain sequence identity of greater than 95% to SEQ ID NO:6. In an embodiment, the anti-CD20 monoclonal antibody has a variable heavy chain sequence identity of greater than 98% to SEQ ID NO:5. In an embodiment, the anti-CD20 monoclonal antibody has a variable light chain sequence identity of greater than 98% to SEQ ID NO:6. In an embodiment, the anti-CD20 monoclonal antibody has a variable heavy chain sequence identity of greater than 99% to SEQ ID NO:5. In an embodiment, the anti-CD20 monoclonal antibody has a variable light chain sequence identity of greater than 99% to SEQ ID NO:6. In an embodiment, the anti-CD20 monoclonal antibody has a Fab fragment heavy chain sequence identity of greater than 90% to SEQ ID NO:7. In an embodiment, the anti-CD20 monoclonal antibody has a Fab fragment light chain sequence identity of greater than 90% to SEQ ID NO:8. In an embodiment, the anti-CD20 monoclonal antibody has a Fab fragment heavy chain sequence identity of greater than 95% to SEQ ID NO:7. In an embodiment, the anti-CD20

monoclonal antibody has a Fab fragment light chain sequence identity of greater than 95% to SEQ ID NO:8. In an embodiment, the anti-CD20 monoclonal antibody has a Fab fragment heavy chain sequence identity of greater than 98% to SEQ ID NO:7. In an embodiment, the anti-CD20 monoclonal antibody has a Fab fragment light chain sequence identity of greater than 98% to SEQ ID NO:8. In an embodiment, the anti-CD20 monoclonal antibody has a Fab fragment heavy chain sequence identity of greater than 99% to SEQ ID NO:7. In an embodiment, the anti-CD20 monoclonal antibody has a Fab fragment light chain sequence identity of greater than 99% to SEQ ID NO:8. In an embodiment, the anti-CD20 monoclonal antibody ofatumumab is an immunoglobulin G1, anti-(human B-lymphocyte antigen CD20 (membrane-spanning 4-domains subfamily A member 1, B-lymphocyte surface antigen B1, Leu-16 or Bp35)); human monoclonal ofatumumab-CD20 γ1 heavy chain (225-214')-disulfide with human monoclonal ofatumumab-CD20 κ light chain, dimer (231-231":234-234")-bisdisulfide antibody.

[00488] In an embodiment, the anti-CD20 monoclonal antibody is veltuzumab, or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof. Veltuzumab is also known as hA20. Veltuzumab is described in Goldenberg, *et al.*, *Leuk. Lymphoma* **2010,** *51,* 747-55. In an embodiment, the anti-CD20 monoclonal antibody is an anti-CD20 biosimilar monoclonal antibody approved by drug regulatory authorities with reference to veltuzumab. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 90% to SEQ ID NO:9. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 90% to SEQ ID NO:10. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 95% to SEQ ID NO:9. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 95% to SEQ ID NO:10. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 98% to SEQ ID NO:9. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 98% to SEQ ID NO:10. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 99% to SEQ ID NO:9. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 99% to SEQ ID NO:10. In an embodiment, the anti-CD20 monoclonal antibody ofatumumab is an immunoglobulin G1, anti-(human B-lymphocyte antigen CD20 (membrane-spanning 4-domains subfamily A member 1, Leu-16, Bp35)); [218- arginine,360-glutamic

acid,362-methionine]humanized mouse monoclonal hA20 γ1 heavy chain (224-213')-disulfide with humanized mouse monoclonal hA20 κ light chain (230-230":233-233")-bisdisulfide dimer

[00489] In an embodiment, the anti-CD20 monoclonal antibody is tositumomab, or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof. In an embodiment, the anti-CD20 monoclonal antibody is ^{131}I-labeled tositumomab. In an embodiment, the anti-CD20 monoclonal antibody is an anti-CD20 biosimilar monoclonal antibody approved by drug regulatory authorities with reference to tositumomab. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 90% to SEQ ID NO:11. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 90% to SEQ ID NO:12. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 95% to SEQ ID NO:11. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 95% to SEQ ID NO:12. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 98% to SEQ ID NO:11. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 98% to SEQ ID NO:12. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 99% to SEQ ID NO:11. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 99% to SEQ ID NO:12.

[00490] In an embodiment, the anti-CD20 monoclonal antibody is ibritumomab, or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof. The active form of ibritumomab used in therapy is ibritumomab tiuxetan. When used with ibritumomab, the chelator tiuxetan (diethylene triamine pentaacetic acid) is complexed with a radioactive isotope such as ^{90}Y or ^{111}In. In an embodiment, the anti-CD20 monoclonal antibody is ibritumomab tiuxetan, or radioisotope-labeled complex thereof. In an embodiment, the anti-CD20 monoclonal antibody is an anti-CD20 biosimilar monoclonal antibody approved by drug regulatory authorities with reference to tositumomab. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 90% to SEQ ID NO:13. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 90% to SEQ ID NO:14. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 95% to SEQ ID NO:13. In an embodiment, the

anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 95% to SEQ ID NO:14. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 98% to SEQ ID NO:13. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 98% to SEQ ID NO:14. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 99% to SEQ ID NO:13. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 99% to SEQ ID NO:14.

[00491] 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 infusing a dose selected from the group consisting of about 10 mg, about 20 mg, about 25 mg, about 50 mg, about 75 mg, 100 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, about 1100 mg, about 1200 mg, about 1300 mg, about 1400 mg, about 1500 mg, about 1600 mg, about 1700 mg, about 1800 mg, about 1900 mg, and about 2000 mg. In an embodiment, the anti-CD20 antibody is admininstered weekly. In an embodiment, the anti-CD20 antibody is admininstered every two weeks. In an embodiment, the anti-CD20 antibody is admininstered every three weeks. In an embodiment, the anti-CD20 antibody is admininstered monthly. In an embodiment, the anti-CD20 antibody is administered at a lower initial dose, which is escalated when administered at subsequent intervals admininstered monthly. For example, the first infusion can deliver 300 mg of anti-CD20 antibody, and subsequent weekly doses could deliver 2,000 mg of anti-CD20 antibody for eight weeks, followed by monthly doses of 2,000 mg of anti-CD20 antibody. During any of the foregoing embodiments, the combinations of the BTK inhibitors with MEK inhibitors may be administered daily, twice daily, or at different intervals as described above, at the dosages described above.

[00492] In an embodiment, the invention provides a kit comprising a first composition comprising a combination of a BTK inhibitor with a MEK inhibitor and a second composition comprising an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, and ibritumomab, or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof, for use in the treatment of CLL or SLL, hematological malignancies, B cell malignancies or, or any of the

other diseases described herein. The compositions are typically both pharmaceutical compositions. The kit is for use in co-administration of the anti-CD20 antibody and the BTK inhibitor, either simultaneously or separately, in the treatment of CLL or SLL, hematological malignancies, B cell malignancies, or any of the other diseases described herein.

[00493] The anti-CD20 antibody sequences referenced in the foregoing are summarized in Table 1.

TABLE 1. Anti-CD20 antibody sequences.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:1 rituximab heavy chain	QVQLQQPGAE LVKPGASVKM SCKASGYTFT SYNMHWVKQT PGRGLEWIGA IYPGNGDTSY NQKFKGKATL TADKSSSTAY MQLSSLTSED SAVYYCARST YYGGDWYFNV WGAGTTVTVS AASTKGPSVF PLAPSSKSTS GGTAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV TVPSSSLGTQ TYICNVNHKP SNTKVDKKVE PKSCDKTHTC PPCPAPELLG GPSVFLFPPK PKDTLMISRT PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN AKTKPREEQY NSTYRVVSVL TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP QVYTLPPSRD ELTKNQVSLT CLVKGFYPSD IAVEWESNGQ PENNYKTTPP VLDSDGSFFL YSKLTVDKSR WQQGNVFSCS VMHEALHNHY TQKSLSLSPG K	60 120 180 240 300 360 420 451
SEQ ID NO:2 rituximab light chain	QIVLSQSPAI LSASPGEKVT MTCRASSSVS YIHWFQQKPG SSPKPWIYAT SNLASGVPVR FSGSGSGTSY SLTISRVEAE DAATYYCQQW TSNPPTFGGG TKLEIKRTVA APSVFIFPPS DEQLKSGTAS VVCLLNNFYP REAKVQWKVD NALQSGNSQE SVTEQDSKDS TYSLSSTLTL SKADYEKHKV YACEVTHQGL SSPVTKSFNR GEC	60 120 180 213
SEQ ID NO:3 obinutuzumab heavy chain	QVQLVQSGAE VKKPGSSVKV SCKASGYAFS YSWINWVRQA PGQGLEWMGR IFPGDGDTDY NGKFKGRVTI TADKSTSTAY MELSSLRSED TAVYYCARNV FDGYWLVYWG QGTLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPGK	60 120 180 240 300 360 420 449
SEQ ID NO:4 obinutuzumab light chain	DIVMTQTPLS LPVTPGEPAS ISCRSSKSLL HSNGITYLYW YLQKPGQSPQ LLIYQMSNLV SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCAQNLELP YTFGGGTKVE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC	60 120 180 219
SEQ ID NO:5 ofatumumab variable heavy chain	EVQLVESGGG LVQPGRSLRL SCAASGFTFN DYAMHWVRQA PGKGLEWVST ISWNSGSIGY ADSVKGRFTI SRDNAKKSLY LQMNSLRAED TALYYCAKDI QYGNYYYGMD VWGQGTTVTV SS	60 120 122
SEQ ID NO:6 ofatumumab variable light chain	EIVLTQSPAT LSLSPGERAT LSCRASQSVS SYLAWYQQKP GQAPRLLIYD ASNRATGIPA RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ RSNWPITFGQ GTRLEIK	60 107
SEQ ID NO:7 ofatumumab Fab fragment heavy chain	EVQLVESGGG LVQPGRSLRL SCAASGFTFN DYAMHWVRQA PGKGLEWVST ISWNSGSIGY ADSVKGRFTI SRDNAKKSLY LQMNSLRAED TALYYCAKDI QYGNYYYGMD VWGQGTTVTV SSASTKGPSV FPLAPGSSKS TSGTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSSLGT QTYICNVNHK PSNTKVDKKV EP	60 120 180 222
SEQ ID NO:8 ofatumumab Fab fragment light chain	EIVLTQSPAT LSLSPGERAT LSCRASQSVS SYLAWYQQKP GQAPRLLIYD ASNRATGIPA RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ RSNWPITFGQ GTRLEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN R	60 120 180 211
SEQ ID NO:9 veltuzumab heavy chain	QVQLQQSGAE VKKPGSSVKV SCKASGYTFT SYNMHWVKQA PGQGLEWIGA IYPGMGDTSY NQKFKGKATL TADESTNTAY MELSSLRSED TAFYYCARST YYGGDWYFDV WGQGTTVTVS SASTKGPSVF PLAPSSKSTS GGTAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV TVPSSSLGTQ TYICNVNHKP SNTKVDKRVE PKSCDKTHTC PPCPAPELLG GPSVFLFPPK PKDTLMISRT PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN AKTKPREEQY NSTYRVVSVL TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP QVYTLPPSRE EMTKNQVSLT CLVKGFYPSD IAVEWESNGQ PENNYKTTPP VLDSDGSFFL YSKLTVDKSR WQQGNVFSCS VMHEALHNHY TQKSLSLSPG K	60 120 180 240 300 360 420 451

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:10 veltuzumab light chain	DIQLTQSPSS LSASVGDRVT MTCRASSSVS YIHWFQQKPG KAPKPWIYAT SNLASGVPVR FSGSGSGTDY TFTISSLQPE DIATYYCQQW TSNPPTFGGG TKLEIKRTVA APSVFIFPPS DEQLKSGTAS VVCLLNNFYP REAKVQWKVD NALQSGNSQE SVTEQDSKDS TYSLSSTLTL SKADYEKHKV YACEVTHQGL SSPVTKSFNR GEC	60 120 180 213
SEQ ID NO:11 tositumomab heavy chain	QAYLQQSGAE LVRPGASVKM SCKASGYTFT SYNMHWVKQT PRQGLEWIGA IYPGNGDTSY NQKFKGKATL TVDKSSSTAY MQLSSLTSED SAVYFCARVV YYSNSYWYFD VWGTGTTVTV SGPSVFPLAP SSKSTSGGTA ALGCLVKDYF PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTQTYIC NVNHKPSNTK VDKKAEPKSC DKTHTCPPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK GQPREPQVYT LPPSRDELTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGK	60 120 180 240 300 360 420 447
SEQ ID NO:12 tositumomab light chain	QIVLSQSPAI LSASPGEKVT MTCRASSSVS YMHWYQQKPG SSPKPWIYAP SNLASGVPAR FSGSGSGTSY SLTISRVEAE DAATYYCQQW SFNPPTFGAG TKLELKRTVA APSVFIFPPS DEQLKSGTAS VVCLLNNFYP REAKVQWKVD NALQSGNSQE SVTEQDSKDS TYSLSSTLTL SKADYEKHKV YACEVTHQGL SSPVTKSFNR	60 120 180 210
SEQ ID NO:13 ibritumomab heavy chain	QAYLQQSGAE LVRPGASVKM SCKASGYTFT SYNMHWVKQT PRQGLEWIGA IYPGNGDTSY NQKFKGKATL TVDKSSSTAY MQLSSLTSED SAVYFCARVV YYSNSYWYFD VWGTGTTVTV SAPSVYPLAP VCGDTTGSSV TLGCLVKGYF PEPVTLTWNS GSLSSGVHTF PAVLQSDLYT LSSSVTVTSS TWPSQSITCN VAHPASSTKV DKKIEPRGPT IKPCPPCKCP APNLLGGPSV FIFPPKIKDV LMISLSPIVT CVVVDVSEDD PDVQISWFVN NVEVHTAQTQ THREDYNSTL RVVSALPIQH QDWMSGKEFK CKVNNKDLPA PIERTISKPK GSVRAPQVYV LPPPEEEMTK KQVTLTCMVT DFMPEDIYVE WTNNGKTELN YKNTEPVLDS DGSYFMYSKL RVEKKNWVER NSYSCSVVHE GLHNHHTTKS FSR	60 120 180 240 300 360 420 443
SEQ ID NO:14 ibritumomab light chain	QIVLSQSPAI LSASPGEKVT MTCRASSSVS YMHWYQQKPG SSPKPWIYAP SNLASGVPAR FSGSGSGTSY SLTISRVEAE DAATYYCQQW SFNPPTFGAG TKLELKRADA APTVFIFPPS DEQLKSGTAS VVCLLNNFYP REAKVQWKVD NALQSGNSQE SVTEQDSKDS TYSLSSTLTL SKADYEKHKV YACEVTHQGL SSPVTKSFN	60 120 180 209

Combinations of BTK Inhibitors with Chemotherapeutic Active Pharmaceutical Ingredients

[00494] The combinations of the BTK inhibitors with MEK inhibitors may also be safely co-administered with chemotherapeutic active pharmaceutical ingredients such as gemcitabine, albumin-bound paclitaxel (nab-paclitaxel), and bendamustine or bendamustine hydrochloride. In a preferred 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 and a MEK inhibitor, and further comprising the step of administering a therapeutically-effective amount of gemcitabine, or a pharmaceutically acceptable salt, prodrug, cocrystal, solvate or hydrate thereof. 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 selected from the group consisting of Formula (1), Formula (2), Formula (3), Formula (4), Formula (5), Formula (6), and Formula (7), or a pharmaceutically acceptable salt, prodrug, cocrystal, solvate or hydrate thereof, and/or a MEK inhibitor, and further comprising the step of administering a therapeutically-effective amount of gemcitabine, or a pharmaceutically acceptable salt, prodrug, cocrystal, solvate or hydrate thereof. In an embodiment, the solid tumor cancer in any of the foregoing embodiments is pancreatic

cancer.

[00495] 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 and a MEK inhibitor, and further comprising the step of administering a therapeutically-effective amount of albumin-bound paclitaxel. 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 selected from the group consisting of Formula (1), Formula (2), Formula (3), Formula (4), Formula (5), Formula (6), and Formula (7), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and/or a MEK inhibitor, and further comprising the step of administering a therapeutically-effective amount of albumin-bound paclitaxel. In an embodiment, the solid tumor cancer in any of the foregoing embodiments is pancreatic cancer.

[00496] 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 and a MEK 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 (1), Formula (2), Formula (3), Formula (4), Formula (5), Formula (6), and Formula (7), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and/or a MEK inhibitor, and further comprising the step of administering a therapeutically-effective amount of bendamustine hydrochloride.

[00497] 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 and a MEK 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 (1), Formula (2), Formula (3), Formula (4), Formula (5), Formula (6), and Formula (7),

or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and further comprising the step of administering a therapeutically-effective amount of FCR chemotherapy. In an embodiment, the invention provides a hematological malignancy or a solid tumor cancer comprising the step of administering to said human a BTK inhibitor and a MEK 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.

[00498] 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 and a MEK inhibitor, and further comprising the step of administering a therapeutically-effective amount of a combination of rituximab, cyclophosphamide, doxorubicin hydrochloride (also referred to as hydroxydaunomycin), vincristine sulfate (also referred to as oncovin), and prednisone (which collectively may be referred to as "R-CHOP" or "R-CHOP chemotherapy"). In an embodiment, the invention provides a method of treating a hematological malignancy or a solid tumor cancer in a human comprising the step of administering to said human a BTK inhibitor of Formula (1), Formula (2), Formula (3), Formula (4), Formula (5), Formula (6), and Formula (7), 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 a MEK inhibitor, and further comprising the step of administering a therapeutically-effective amount of R-CHOP chemotherapy. 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.

[00499] 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 and a MEK inhibitor, further comprising the step of administering a therapeutically-effective amount of bendamustine or bendamustine hydrochloride and a therapeutically-effective amount of rituximab or a biosimilar thereof ("BR" or "BR 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 selected from the group consisting of Formula (1), Formula (2), Formula (3), Formula (4), Formula (5), Formula (6), Formula (7), Formula (10), and Formula (21), and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof, and a MEK inhibitor or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof, further comprising the step of administering a therapeutically-effective amount of bendamustine hydrochloride, and further comprising the step of administering a therapeutically-effective amount of rituximab or a biosimilar thereof. BR chemotherapy has been shown to improve overall response rates in non-Hodgkin's lymphoma and mantle cell lymphomas and also demonstrated improved safety in comparison to alternative regimens, as described in Flinn, *et al.*, *Blood* **2014,** *123*, 2944-52.

[00500] In any of the foregoing embodiments, the chemotherapeutic active pharmaceutical ingredient or combinations thereof may be administered before, concurrently, or after administration of the MEK inhibitors and the BTK inhibitors.

[00501] 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

[00502] 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 – Preclinical Characteristics of BTK Inhibitors

[00503] The BTK inhibitor ibrutinib (Formula (10), (1-[(3*R*)-3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidin-1-yl]prop-2-en-1-one) is a first-generation BTK inhibitor. In clinical testing as a monotherapy in subjects with hematologic malignancies, ibrutinib was generally well tolerated at dose levels through 840 mg (the highest dose tested). Advani, *et al.*, *J. Clin. Oncol.* **2013,** *31,* 88-94; Byrd, *et al.*, *N. Engl. J. Med.* **2013**, *369,* 32-42; Wang, *et al.*, *N. Engl. J. Med.* **2013,** *369,* 507-16. No maximum tolerated dose (MTD) was

apparent within the tested dose range. Furthermore, subjects typically found the drug tolerable over periods extending to > 2 years. No subject had tumor lysis syndrome. No overt pattern of myelosuppression was associated with ibrutinib treatment. No drug-related reductions in circulating $CD4^+$ T cells or serum immunoglobulins were noted. Adverse events with an apparent relationship to study drug included diarrhea and rash.

[00504] 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.

[00505] 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.

[00506] The preclinical selectivity and potency characteristics of the second-generation BTK inhibitor of Formula (2) were compared to the first-generation BTK inhibitor of Formula (10) (ibrutinib). In Table 2, a kinome screen (performed by Life Technologies or based on literature data) is shown that compares these compounds.

TABLE 2. Kinome Screen for BTK Inhibitors (IC_{50}, nM)

3F-Cys Kinase	Formula (2)	Ibrutinib (Formula (10))
Btk	3.1	0.5
Tec	29	78
Bmx	39	0.80
ITK	>1000	10.7
Txk	291	2.0
EGFR	>1000	5.6
ErbB2	912	9.4
ErbB4	13.2	2.7
Blk	>1000	0.5
JAK-3	>1000	16.1

[00507] The results shown in Table 2 are obtained from a 10 point biochemical assay generated from 10 point concentration curves. The BTK inhibitor of Formula (2) shows much greater selectivity for BTK compared to other kinases than ibrutinib.

[00508] A comparison of the *in vivo* potency results for the BTK inhibitors of Formula (2) and ibrutinib is shown in FIG. 1. 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 hours post-dose). BCR was stimulated with IgM and the expression of activation marker CD69 and CD86 are monitored by flow cytometry to determine EC_{50} values.

[00509] *In vitro* and *in vivo* safety pharmacology studies with Formula (2) 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 (2) shows significant activity only against the A3 adenosine receptor; follow-up dose-response experiments indicated an IC_{50} of 2.7 μM, suggesting a low clinical risk of off-target effects. Formula (2) 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 (2) 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 (2) inhibited hERG channel activity by 25% at 10 μM,

suggesting a low clinical risk that Formula (2) would induce clinical QT prolongation as predicted by this assay. Formula (2) was well tolerated in standard *in vivo* Good Laboratory Practices (GLP) studies of pharmacologic safety. A functional observation battery in rats at doses 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 (2) 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 (2) is unlikely to cause serious off-target effects or adverse effects on critical organ systems.

[00510] The drug-drug interaction potential of Formula (2) was also evaluated. *In vitro* experiments evaluating loss of parent drug as catalyzed by CYPs indicated that Formula (2) is metabolized by CYP3A4. *In vitro* metabolism studies using mouse, rat, dog, rabbit, monkey, and human hepatocytes incubated with ^{14}C-labeled Formula (2) 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 (2) binds to glutathione but does not deplete glutathione *in vitro*. Nonclinical CYP interaction studies data indicate that Formula (2) is very unlikely to cause clinical drug-drug interactions through alteration of the metabolism of drugs that are substrates for CYP enzymes.

[00511] The *in vitro* potency in whole blood of Formula (2), Formula (10) (ibrutinib), and Formula (17) (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. 2. 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 (2), Formula (10) (ibrutinib), and Formula (17) (CC-292), respectively.

[00512] The EGF receptor phosphorylation *in vitro* was also determined for Formula (2) and Formula (10) (ibrutinib). Epidermoid carcinoma A431 cells were incubated for 2h with a dose titration of Formula (2) or Formula (10) (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. 3. EGF-induced p-EGFR inhibition was determined to be 7% at 10 μM for Formula (2), 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 2 – BTK Inhibitory Effects on Solid Tumor Microenvironment in an Orthotopic Pancreatic Cancer Model

[00513] An orthotopic pancreatic cancer model was used to investigate the therapeutic efficacy of the combination of the BTK inhibitor of Formula (2) and a PI3K-δ inhibitor through treatment of the solid tumor microenvironment. Mice were dosed orally with 15 mg/kg of Formula (2), 15 mg/kg of a PI3K-δ inhibitor, or a combination of 15 mg/kg of both drugs.

[00514] Cell lines derived from KrasG12D;Trp53R172H;Pdx1-Cre (KPC) mice were orthotopically implanted into the head of the pancreas after 35 passages. Based on the mice background from where the cell lines were generated, 1×10^6 cells were injected in C57BL/6 mice. Throughout the experiment, animals were provided with food and water *ad libitum* and subjected to a 12 hour 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.

[00515] Results of the experiments are shown in FIG. 4, 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 agent 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.

[00516] Additional results of the experiments relating to treatment of the tumor microenvironment are shown in FIG. 5 to FIG. 7. FIG. 5 shows the effects of oral dosing with 15 mg/kg of the BTK inhibitor of Formula (2), 15 mg/kg of a PI3K inhibitor, or a combination of both drugs on myeloid tumor-associated macrophages (TAMs) in pancreatic tumor-bearing mice. FIG. 6 illustrates the effects of oral dosing with 15 mg/kg of the BTK inhibitor of Formula (2), 15 mg/kg of a PI3K inhibitor, or a combination of both inhibitors on myeloid-derived suppressor cells (MDSCs) in pancreatic tumor-bearing mice. FIG. 7 illustrates the effects of oral dosing with 15 mg/kg of the BTK inhibitor of Formula (2), 15 mg/kg of a PI3K inhibitor, or a combination of both inhibitors on regulatory T cells (Tregs) in pancreatic tumor-bearing mice. The results demonstrate that administration of the BTK inhibitor of Formula (2) and the combination of the BTK inhibitor of Formula (2) and the PI3K inhibitor reduce immunosuppressive tumor associated myeloid cells and Tregs in pancreatic tumor-bearing mice. Overall, BTK inhibition with Formula (2) or a combination of Formula (2) and the PI3K inhibitor 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 3 – BTK Inhibitory Effects on Solid Tumor Microenvironment in an Orthotopic Pancreatic Cancer Model and Synergistic Combination of a BTK Inhibitor and Gemcitabine

[00517] A study was performed to observe potential reduction in tumor burden through modulation of tumor infiltrating MDSCs and TAMs using the BTK inhibitor of Formula (2) and/or gemcitabine ("Gem"). In this study, KPC derived mouse pancreatic cancer cells (KrasG12D;Trp53R172H;Pdx1-Cre) were injected into the pancreases. Animals were treated with (1) vehicle; (2) Formula (2), 15 mg/kg/BID given orally; (3) gemcitabine 15 mg/kg intravenous (IV) administered every 4 days for 3 injections; or (4) Formula (2), 15 mg/kg/BID given orally together with gemcitabine, 15 mg/kg IV administered every 4 days for 3 injections.

[00518] Single cell suspensions from tumor samples. Mouse tumor tissue was collected and stored in PBS/0.1% soybean trypsin inhibitor prior to enzymatic dissociation. Samples were finely minced with a scissors and mouse tissue was transferred into DMEM containing 1.0

mg/mL collagenase IV (Gibco), 0.1% soybean trypsin inhibitor, and 50 U/ml DNase (Roche) and incubated at 37 °C for 30 min. with constant stirring while human tissue was digested in 2.0 mg/ml collagenase IV, 1.0 mg/ml hyluronidase, 0.1% soybean trypsin inhibitor, and 50 U/ml DNase for 45 minutes. Suspensions were filtered through a 100 micron filter and washed with FACS buffer (PBS/0.5% BSA/2.0 mM EDTA) prior to staining. Two million total cells were stained with antibodies as indicated. Intracellular detection of FoxP3 was achieved following permeabilization with BD Perm Buffer III (BD Biosciences) and eBioscience Fix/Perm respectively. Following surface staining, samples were acquired on a BD Fortessa and analyzed using FlowJo (Treestar) software.

[00519] In FIG. 8, 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. 9, FIG. 10, FIG. 11, and FIG. 12.

[00520] The results shown in FIG. 8 to FIG. 12 illustrate reduction in tumor burden by modulating the tumor infiltrating MDSCs and TAMs, which affects Treg and $CD8^+$ T cell levels, through inhibition of BTK using Formula (2). A synergistic effect using the combination of Formula (2) and gemcitabine is observed in the tumor volumes shown in FIG. 8, which are reduced well beyond the level observed with either Formula (2) or gemcitabine alone or expected from their additive combination.

Example 4 – BTK Inhibitory Effects on Solid Tumor Microenvironment in an Ovarian Cancer Model

[00521] The ID8 syngeneic orthotopic ovarian cancer murine model was used to investigate the therapeutic efficacy of the BTK inhibitor of Formula (2) 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 (2), 15 mg/kg/BID given orally. The results of the study are shown in FIG. 13, FIG. 14, FIG. 15, FIG. 16, FIG. 17, FIG. 18, FIG. 19, and FIG. 20.

[00522] FIG. 13 and FIG. 14 demonstrate that the BTK inhibitor of Formula (2) impairs ID8

ovarian cancer growth in the ID8 syngeneic murine model. FIG. 15 shows that tumor response to treatment with the BTK inhibitor of Formula (2) correlates with a significant reduction in immunosuppressive tumor-associated lymphocytes in tumor-bearing mice. FIG. 16 shows treatment with the BTK inhibitor of Formula (2) impairs ID8 ovarian cancer growth (through reduction in tumor volume) in the syngeneic murine model. FIG. 17 and FIG. 18 show that the tumor response induced by treatment with the BTK inhibitor of Formula (2) correlates with a significant reduction in immunosuppressive B cells, including Bregs, in tumor-bearing mice. FIG. 19 and FIG. 20 show that the tumor response induced by treatment with the BTK inhibitor of Formula (2) correlates with a significant reduction in immunosuppressive tumor associated Tregs and an increase in $CD8^+$ T cells.

[00523] The results shown in FIG. 13 to FIG. 20 illustrate the surprising performance of the BTK inhibitor of Formula (2) in modulating tumor microenvironment in a model predictive of efficacy of a treatment for ovarian cancer in humans.

Example 5 – BTK Inhibitory Effects on Solid Tumor Microenvironment in a KPC Pancreatic Cancer Model

[00524] Given the potential for BTK inhibition to affect TAMs and MDSCs, single-active pharmaceutical ingredient Formula (2) was evaluated in mice with advanced pancreatic cancer arising as the result of genetic modifications of oncogenes KRAS and p53, and the pancreatic differentiation promoter PDX-1 (KPC mice). The KPC mouse model recapitulates many of the molecular, histopathologic, and clinical features of human disease (Westphalen and Olive, *Cancer J.* **2012,** *18,* 502-510). Combination therapy with gemcitabine was also evaluated in this model. Mice were enrolled after identification of spontaneously appearing tumors in the pancreas that were $\geq$ 100 mm^3 (as assessed by high-resolution ultrasonography). Mice were treated with (1) vehicle (N=6); or (2) Formula (2), 15 mg/kg BID given orally (N=6).

[00525] As shown in FIG. 21, treatment with single-active pharmaceutical ingredient Formula (2) 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 (2), 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 (2), survival at day 14 was 6/6 animals, and at day 28 was 5/6 animals.

[00526] 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 (2) treatment (FIG. 22, FIG. 23, and FIG. 24). As expected, the decrease in these immunosuppressive cell subsets correlated with a significant increase in $CD8^{+}$ cells (FIG. 25).

Example 6 – BTK Inhibitory Effects on Solid Tumor Microenvironment in a Non-small Cell Lung Cancer (NSCLC) Model

[00527] A genetic tumor model of NSCLC (KrasLA2) was studied as a model for lung cancer using the treatment schema shown in FIG. 26. 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 (2) showed a significant decrease in tumor volumes versus vehicle (FIG. 27) and fewer overall tumors with dosing of 15 mg/kg. The effects on TAMs (FIG. 28), MDSCs (FIG. 29), Tregs (FIG. 30), and CD8+ cells (FIG. 31) were consistent with suppression of the solid tumor microenviroment as demonstrated previously.

Example 7 – BTK Inhibitory Effects on MDSCs in the Solid Tumor Microenvironment

[00528] 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 (2). Complete BTK occupancy is observed for both the granulocytic and monocytic MDSC compartments on Day 8 at 4 hours post dose (N=5). The results are shown in FIG. 32.

Example 8 – Effects of BTK Inhibitors on Antibody-Dependent NK Cell Mediated Cytotoxicity Using Rituximab

[00529] 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.

[00530] In this example, the effects of Formula (2) and ibrutinib on NK cell function were

evaluated in cell lines and primary NK cells from healthy volunteers and CLL patients. In summary, the results show that the activation of NK cells co-cultured with antibody-coated target cells was strongly inhibited by ibrutinib. The secretion of IFN-γ was reduced by 48% ($p = 0.018$) and 72% ($p = 0.002$) in cultures treated with ibrutinib at 0.1 and 1.0 μM respectively and NK cell degranulation was significantly ($p = 0.002$) reduced, compared with control cultures. Formula (2) treatment at 1 μM, a clinically relevant concentration, did not inhibit IFN-γ or NK cell degranulation. Rituximab-mediated ADCC was evaluated in NK cells from healthy volunteers as well as assays of NK cells from CLL patients targeting autologous CLL cells. In both cases, ADCC was not inhibited by Formula (2) treatment at 1 μM. In contrast, addition of ibrutinib to the ADCC assays strongly inhibited the rituximab-mediated cytotoxicity of target cells, and no increase over natural cytotoxicity was observed at any rituximab concentration. This result indicates that the combination of rituximab and Formula (2) provides an unexpected benefit in the treatment of B cell malignancies and other diseases where NK cell inhibition is undesirable.

[00531] BTK is a non-receptor enzyme in the Tec kinase family that is expressed among cells of hematopoietic origin, including B cells, myeloid cells, mast cells and platelets, where it regulates multiple cellular processes including proliferation, differentiation, apoptosis, and cell migration. Khan, *Immunol Res.* **2001,** *23,* 147-56; Mohamed, *et al.*, *Immunol Rev.* **2009,** *228,* 58-73; Bradshaw, *Cell Signal.* **2010,** *22,* 1175-84. Functional null mutations of BTK in humans cause the inherited disease, X linked agammaglobulinemia, which is characterized by a lack of mature peripheral B cells. Vihinen, *et al., Front Biosci.* **2000,** *5,* D917-28. Conversely, BTK activation is implicated in the pathogenesis of several B-cell malignancies. Herman, *et al., Blood* **2011,** *117,* 6287-96; Kil, *et al., Am. J. Blood Res.* **2013,** *3,* 71-83; Tai, *et al., Blood* **2012,** *120,* 1877-87; Buggy, and Elias, *Int. Rev. Immunol.* **2012,** *31,* 119-32 (Erratum in: *Int. Rev. Immunol.* **2012,** *31,* 428). In addition, BTK-dependent activation of mast cells and other immunocytes in peritumoral inflammatory stroma has been shown to sustain the complex microenvironment needed for lymphoid and solid tumor maintenance. Soucek, *et al., Neoplasia* **2011,** *13,* 1093-100; Ponader, *et al., Blood* **2012,** *119,* 1182-89; de Rooij, *et al., Blood* **2012**, *119,* 2590-94. Taken together, these findings have suggested that inhibition of BTK may offer an attractive strategy for treating B cell neoplasms, other hematologic malignancies, and solid tumors.

[00532] Ibrutinib (PCI-32765, IMBRUVICA), is a first-in-class therapeutic BTK inhibitor. This

orally delivered, small-molecule drug is being developed by Pharmacyclics, Inc. for the therapy of B cell malignancies. As described above, in patients with heavily pretreated indolent non-Hodgkin lymphoma (iNHL), mantle cell lymphoma (MCL), and CLL, ibrutinib showed substantial antitumor activity, inducing durable regressions of lymphadenopathy and splenomegaly in the majority of patients. Advani, *et al.*, *J. Clin. Oncol.* **2013,** *31,* 88-94; Byrd, *et al.*, *N. Engl. J. Med.* **2013**, *369,* 32-42; Wang, *et al.*, *N. Engl. J. Med.* **2013,** *369,* 507-16; O'Brien, *et al.*, *Blood* **2012,** *119,* 1182-89. The pattern of changes in CLL was notable. Inhibition of BTK with ibrutinib caused rapid and substantial mobilization of malignant CLL cells from tissue sites into the peripheral blood, as described in Woyach, *et al.*, *Blood* **2014,** *123,* 1810-17; this effect was consistent with decreased adherence of CLL to protective stromal cells. Ponader, *et al.*, *Blood* **2012,** *119,* 1182-89; de Rooij, *et al.*, *Blood* **2012**, *119,* 2590-94. Ibrutinib has been generally well tolerated. At dose levels associated with total BTK occupancy, no dose-limiting toxicities were identified and subjects found the drug tolerable over periods extending to >2.5 years.

[00533] Given the homology between BTK and ITK, it has been recently confirmed that ibrutinib irreversibly binds ITK. Dubovsky, *et al.*, *Blood* **2013,** *122,* 2539-2549. ITK expression in Fc receptor (FcR)-stimulated NK cells leads to increased calcium mobilization, granule release, and cytotoxicity. Khurana, *et al.*, *J. Immunol.* **2007,** *178,* 3575-3582. As rituximab is a backbone of lymphoma therapy, with mechanisms of action including ADCC, as well as direct induction of apoptosis and complement-dependent cytotoxicity, and FcR stimulation is requisite for ADCC, we investigated if ibrutinib or Formula (2) (the latter lacking ITK inhibition) influenced rituximab's anti-lymphoma activity *in vitro* by assessing NK cell IFN-γ secretion, degranulation by CD107a mobilization, and cytotoxicity by chromium release using $CD20^+$ cell lines and autologous patient samples with chronic lymphocytic leukemia (CLL).

[00534] Formula (2) is a more selective inhibitor than ibrutinib, as shown previously. Formula (2) is not a potent inhibitor of ITK in contrast to ibrutinib, as shown herein (see, *e.g.*, Table 2). ITK is required for FcR-stimulated NK cell function including calcium mobilization, granule release, and overall ADCC. Anti-CD20 antibodies like rituximab are currently the standard of care for the treatment of many $CD20^+$ B cell malignancies, often as part of combination regimens with older chemotherapeutic agents. The potential of ibrutinib or Formula (2) to antagonize ADCC was evaluated *in vitro*. Previous studies have determined that ibrutinib undesirably

antagonizes rituximab ADCC effects mediated by NK cells. Kohrt, *et al.*, *Blood* **2014,** *123,* 1957-60. We hypothesized that the BTK inhibitor of Formula (2), 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.

[00535] 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.

[00536] 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 (2), or DMSO vehicle control). NK cells from healthy donors were enriched as described above and then added to the target cells and incubated for 4 hours at 37 °C. Triplicate cultures were performed on NK cells from donors. After incubation, supernatants were harvested, centrifuged briefly, and then analyzed for interferon-γ using an enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Minneapolis, MN, USA).

[00537] Lytic granule release was determined as follows. NK cells from healthy donors were

enriched and cultured in the presence of target cells, monoclonal antibodies and test articles as described above. After 4 hours, the cultures were harvested and cells were pelleted, washed, and then stained for flow cytometry evaluation. Degranulation was evaluated via by flow cytometery by externalization of CD107a, a protein normally present on the inner leaflet of lytic granules, and gating on NK cells (CD3-$CD16^+$ lymphocytes). The percentage of CD107a positive NK cells was quantified by comparison with a negative control (isotype control, unstained cells/FMO). Control cultures (NK cells cultured without target cells, or NK, target cell co-cultures in the absence of appropriate monoclonal antibody) were also evaluated; all experiments were performed in triplicate.

[00538] ADCC assays were performed as follows. Briefly, target cells (Raji or primary CLL) were labeled by incubation at 37 °C with 100 μCi ^{51}Cr for 4 hours prior to co-culture with NK cells. Cells were washed, enumerated, and then added in triplicate to prepared 96-well plates containing treated NK cells at an effector:target (E:T) ratio of 25:1. Rituximab (Genentech) was added to ADCC wells at concentrations of 0.1, 1.0 or 10 μg/mL and the assays were briefly mixed and then centrifuged to collect cells at the bottom of the wells. The effect of NK cell natural cytotoxicity was assessed in wells containing no rituximab. Cultures were incubated at 37 °C for 4 hours, and then centrifuged. Supernatants were harvested and ^{51}Cr release was measured by liquid scintillation counting. All experiments were performed in triplicate.

[00539] Ibrutinib inhibited rituximab-induced NK cell cytokine secretion in a dose-dependent manner (0.1 and 1 μM) (FIG. 33: 48% $p = 0.018$; 72% $p = 0.002$, respectively). At 1 μM, Formula (2) did not significantly inhibit cytokine secretion (FIG. 33: 3.5%). Similarly, Formula (2) had no inhibitory effect on rituximab-stimulated NK cell degranulation (< 2%) while ibrutinib reduced degranulation by ~50% ($p = 0.24$, FIG. 34). Formula (2) had no inhibitory effect while ibrutinib prevented trastuzumab-stimulated NK cell cytokine release and degranulation by ~92% and ~84% at 1 μM, respectively (FIG. 33 and FIG. 34: ***$p = 0.004$, **$p = 0.002$).

[00540] In Raji cell samples, *ex vivo* NK cell activity against autologous tumor cells was not inhibited by addition of Formula (2) at 1 μM, and increased cell lysis was observed with increasing concentrations of rituximab at a constant E:T ratio (FIG. 35). In primary CLL samples, *ex vivo* NK cell activity against autologous tumor cells was not inhibited by addition of

Formula (2) at 1 μM, and increased cell lysis was observed with increasing concentrations of rituximab at a constant E:T ratio (FIG. 36). 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. A graph highlighting the significant differences between Formula (2) and ibrutinib is shown in FIG. 37 (where "Ab" refers to rituximab). The difference between Formula (2) and ibrutinib was highly significant in this assay ($p = 0.001$).

[00541] In ADCC assays using healthy donor NK cells, antibody-dependent lysis of rituximab-coated Raji cells was not inhibited by addition of 1 μM of Formula (2) (FIG. 37). 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.

[00542] 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 (2), is superior to ibrutinib. These results provide support for the unexpected property of Formula (2) as a synergistic and superior active pharmaceutical ingredient than ibrutinib to use in combinations with antibodies that have ADCC as a mechanism of action. The improved performance of Formula (2) in combination with anti-CD20 antibody therapies is expected to extend to its use in combination with other kinase inhibitors and checkpoint inhibitors in both hematological malignancies and solid tumors, as these combinations would also benefit from reduced inhibition of NK cell function.

Example 9 – Effects of BTK Inhibition on Antibody-Dependent NK Cell Mediated Cytotoxicity Using Obinutuzumab

[00543] It has been shown above that ibrutinib undesirably antagonizes rituximab ADCC effects mediated by NK cells, and that Formula (2) 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 (2).

[00544] 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 (2) 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 (2) 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% CO_2 incubator for 4 hours at 37 °C. The experimental conditions thus achieved a WBC:MEC-1 cell ratio of 1:1, with final concentrations of the BTK inhibitors in the assay of 10 μM, 1 μM and 0.1 μM and final concentrations of the antibodies of 1 μg/mL.

[00545] After 4 hours, the samples were mixed gently and 50 μL aliquots were removed from each well and placed in fluorescence-activated cell sorting (FACS) test tubes. A 20 μL aliquot of anti-CD56-APC antibody and anti-CD107a-PE antibody was added. The samples were incubated for 20 minutes at room temperature in the dark. An aliquot of 2 mL of FACS lysing solution (BD Biosceinces) was added. The samples were again incubated for 5 minutes, and then centrifuged at 2000 rpm for 5 minutes. Supernatant was discarded and the cell pellet was

resuspended in 500 μL of PBS. The samples were analyzed on the flow cytometer for $CD107a^+$ NK cells ($CD56^+$).

[00546] The NK cell degranulation results are summarized in FIG. 38 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 (2) shows little antagonism towards NK cells, and had a minimal effect on obinutuzumab-stimulated NK cell degranulation while ibrutinib reduced obinutuzumab-stimulated NK degranulation by greater than 40%. These results support the synergistic combination of obinutuzumab and Formula (2) in treatment of human B cell malignancies.

Example 10 – Effects of BTK Inhibition on Generalized NK Cell Mediated Cytotoxicity

[00547] An assay was performed to assess the effects of BTK inhibition using Formula (2) on generalized NK killing (non-ADCC killing). The targets (K562 cells) do not express major histocompatibility complex (MHC) class I, so they do not inactivate NK cells. Target cells were grown to mid-log phase, and 5×10^5 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. 39.

Example 11 – Effects of BTK Inhibition on T Cells

[00548] An assay was performed to assess the effects of BTK inhibition using Formula (2) on T cells. Enriched $CD4^+$ T cells are plated on 24-well culture dishes that have been precoated 2

hr with 250 μL anti-TCRβ (0.5 μg/mL) plus anti-CD28 (5 μg/mL) at 37 °C in PBS. The cells are then supplemented with media containing BTK inhibitors along with the skewing cytokines as indicated in the following. The Th17 and Treg cultures are grown for 4 days before analysis. The cells are maintained for an additional 3 days with skewing cytokines (Th17; 20 ng/mL IL-6, 0.5 ng/mL TGF-β, 5 μg/mL IL-4, 5 μg/mL IFN-γ and Treg; 0.5 ng/mL TGF-β, 5 μg/mL IL-4, 5 μg/mL IFN-γ) and are supplemented with IL2 as a growth factor.

[00549] The results are shown in FIG. 40 and FIG. 41, and further illustrate the surprising properties of Formula (2) in comparison to Formula (10) (ibrutinib). Because of the lack of activity of Formula (2) on ITK and Txk, no adverse effect 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.

[00550] The effects of ibrutinib in comparison to Formula (2) 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. 42, indicate that higher concentrations of Formula (10) (ibrutinib) have a strong, negative effect on $CD8^+$ T cell viability that is not observed with Formula (2) at any concentration.

[00551] Without being bound by any theory, $CD8^+$ T cells have two primary effector functions: (1) produce large amounts of IFN-γ (which activates macrophages), and (2) cytolytic activity. A cytotoxic T cell (CTL) assay was performed to compare the BTK inhibitors of Formula (2) and Formula (10) (ibrutinib). Effectors were prepared by generating CTL by culturing MHC mismatched splenocytes for 4 days with (500 nM) and without Formula (2) or Formula (10) (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. 43, the results show that Formula (10) (ibrutinib) affects $CD8^+$ T cell function as measured by % cytotoxicity. Formula (2), in contrast, has no effect on $CD8^+$ T cell function as measured by % cytotoxicity relative to vehicle. The effect on $CD8^+$ T cell function can also be observed by

measurement of IFN-γ levels, as shown in FIG. 44, where Formula (10) (ibrutinib) again results in a significant loss of function relative to Formula (2) and vehicle.

Example 12 – Clinical Study of a BTK Inhibitor in Leukemia/Lymphoma and Effects on Bone Marrow and Lymphoid Microenvironments

[00552] 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 (2), 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 (2) in treating subjects with chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL).

[00553] 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 (2). 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 (2) 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 (2) nonclinical safety pharmacology and toxicology studies support the safety of testing Formula (2) in subjects with B cell malignancies.

[00554] The primary objectives of the clinical study are as follows: (1) establish the safety and the MTD of orally administered Formula (2) in subjects with CLL/SLL; (2) determine pharmacokinetics (PK) of orally administered Formula (2) 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.

[00555] The secondary objective of the clinical study is to evaluate tumor responses in patients treated with Formula (2).

[00556] 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)

[00557] 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 (2) 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.

[00558] Treatment with Formula (2) 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.

[00559] 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.

[00560] 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.

[00561] 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.

[00562] The schedule of assessments is as follows, with all days stated in the following meaning the given day or +/- 2 days from the given day. A physical examination, including vital signs

and weight, are performed at screening, during cycle 1 at 1, 8, 15, 22, and 28 days, during cycle 2 at 15 and 28 days, during cycles 3 to 24 at 28 days, and at follow up (after the last dose). The screening physical examination includes, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. Symptom-directed physical exams are done thereafter. Vital signs (blood pressure, pulse, respiratory rate, and temperature) are assessed after the subject has rested in the sitting position. Eastern Cooperative Oncology Group (ECOG) status is assessed at screening, during cycle 1 at 1, 8, 15, 22, and 28 days, during cycle 2 at 15 and 28 days, during cycles 3 to 24 at 28 days, and at follow up, using the published ECOG performance status indications described in Oken, *et al.*, *Am. J. Clin. Oncol.* **1982,** *5,* 649-655. ECG testing is performed at screening, during cycle 1 at 1, 2, 8, 15, 22, and 28 days, during cycle 2 at 15 and 28 days, during cycles 3 to 24 at 28 days, and at follow up. The 12-lead ECG test will be done in triplicate (≥ 1 minute apart) at screening. The calculated QTc average of the 3 ECGs must be <480 ms for eligibility. On cycle 1, day 1 and cycle 1, day 8, single ECGs are done predose and at 1, 2, 4, and 6 hours 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 assesed at screening, during cycle 1 at 1, 8, 15, 22, and 28 days, during cycle 2 at 15 and 28 days, during cycles 3 to 24 at 28 days, and at follow up. Serum chemistry is assesed at screening, during cycle 1 at 1, 8, 15, 22, and 28 days, during cycle 2 at 15 and 28 days, during cycles 3 to 24 at 28 days, and at follow up. Serum chemistry includes albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphate, potassium, sodium, total bilirubin, total protein, and uric acid. Cell counts and serum immunoglobulin are performed at screening, at cycle 2, day 28, and at every 6 months thereafter until last dose and include T/B/NK/monocyte cell counts (CD3, CD4, CD8, CD14, CD19, CD19, CD16/56, and others as needed) and serum immunoglobulin (IgG, IgM, IgA, and total immunoglobulin). Bone marrow aspirates are performed at cycle 12. Pharmacodynamics samples are drawn during cycle 1 at 1,

2, and 8 days, and at follow up. On days 1 and 8, pharmacodynamic samples are drawn pre-dose and 4 hours (±10 minutes) post-dose, and on day 2, pharmacodynamic samples are drawn pre-dose. Pharmacokinetics samples are drawn during cycle 1 at 1, 2, 8, 15, 22, and 28 days. Pharmacokinetic samples for Cycle 1 Day 1 are drawn pre-dose and at 0.5, 1, 2, 4, 6 and 24 hours (before dose on Day 2) post-dose. Samples for Cycle 1 Day 8 are drawn pre-dose and at 0.5, 1, 2, 4, and 6 hours post-dose. On Cycle 1 Day 15, 22, and 28, a PK sample is drawn pre-dose and the second PK sample must be drawn before (up to 10 minutes before) the ECG acquisition, which is 2 hours postdose. Pretreatment radiologic tumor assessments are performed within 30 days before the first dose. A computed tomography (CT) scan (with contrast unless contraindicated) is required of the chest, abdomen, and pelvis. In addition, a positron emission tomography (PET) or PET/CT must done for subjects with SLL. Radiologic tumor assessments are mandatory at the end of Cycle 2 (-7 days), Cycle 4 (- 7days), and Cycle 12 (-7 days). Otherwise, radiologic tumor assessments are done at investigator discretion. A CT (with contrast unless contraindicated) scan of the chest, abdomen, and pelvis is required for subjects with CLL. In addition, a PET/CT is required in subjects with SLL. Bone marrow and radiologic assessments are both required for confirmation of a complete response (CR). Clinical assessments of tumor response should be done at the end of Cycle 6 and every 3 months thereafter. Molecular markers are measured at screening, and include interphase cytogenetics, stimulated karyotype, IgHV mutational status, Zap-70 methylation, and beta-2 microglobulin levels. Urinalysis is performed at screening, and includes pH, ketones, specific gravity, bilirubin, protein, blood, and glucose. Other assessments, including informed consent, eligibility, medical history, and pregnancy test are done at the time of screening.

[00563] The investigator rates the subject's response to treatment based on recent guidelines for CLL, as given in Hallek, *et al.*, *Blood* **2008,** *111,* 5446-56, and for SLL, as given in Cheson, *et al., J. Clin. Oncol.* **2007,** *25,* 579-586. The response assessment criteria for CLL are summarized in Table 3.

TABLE 3. Response Assessment Criteria for CLL. Abbreviations: ANC = absolute neutrophil count; CR = complete remission; CRi = CR with incomplete blood count recovery; PR = partial remission.

Response	Peripheral Blood	Bone Marrow (if performed)	Nodes, Liver, and Spleen[a]
CR	Lymphocytes < 4 x 10^9/L ANC >1.5 x 10^9/L[b] Platelets > 100 x 10^9/L[b] Hemoglobin > 11.0 g/dL (untransfused)[b]	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[b] or Hemoglobin > 11.0 g/dL or 50% improvement over baseline (untransfused)[b]	Not assessed	≥50% reduction in lymphadenopathy[c] and/or in spleen or liver enlargement

a. Computed tomography (CT) scan of abdomen, pelvis, and chest is required for this evaluation

b. Without need for exogenous growth factors

c. In the sum products of ≤ 6 lymph nodes or in the largest diameter of the enlarged lymph node(s) detected before therapy and no increase in any lymph node or new enlarged lymph nodes

[00564] The response assessment criteria for SLL are summarized in Table 4.

TABLE 4. Response Assessment Criteria for SLL. Abbreviations: CR = complete remission, CT = computed tomography, FDG = [^{18}F]fluorodeoxyglucose, PET = positron-emission tomography, PR = partial remission, SD = stable disease, SPD = sum of the product of the diameters.

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

[00565] The PK parameters of the study are as follows. The plasma PK of Formula (2) and a metabolite is characterized using noncompartmental analysis. The following PK parameters are calculated, whenever possible, from plasma concentrations of Formula (2):

$AUC_{(0-t)}$: 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 (Ct),

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

$AUC_{(0-\infty)}$: Area under the plasma concentration-time curve from 0 to infinity, calculated using the formula: $AUC_{(0-\infty)} = AUC_{(0-t)} + Ct / \lambda z$, where λz is the apparent terminal elimination rate constant,

C_{max}: Maximum observed plasma concentration,

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

$t_{½}$: Terminal elimination half-life (whenever possible),

λ_z: Terminal elimination rate constant (whenever possible),

Cl/F: Oral clearance.

[00566] The PD parameters of the study are as follows. The occupancy of BTK by Formula (2) are measured in peripheral blood mononuclear cells (PBMCs) with the aid of a biotin-tagged Formula (2) analogue probe. The effect of Formula (2) on biologic markers of B cell function will also be evaluated.

[00567] 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.

[00568] The following definitions are used for the safety and efficacy analysis sets: Safety analysis set: All enrolled subjects who receive ≥ 1 dose of study drug; Per-protocol (PP) analysis set: All enrolled subjects who receive ≥ 1 dose of study drug and with ≥ 1 tumor response assessment after treatment. The safety analysis set will be used for evaluating the safety parameters in this study. The PP analysis sets will be analyzed for efficacy parameters in this study.

[00569] 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.

[00570] 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.

[00571] 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.

[00572] 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).

[00573] The study scheme is a seqential 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 (2), 100 mg QD for 28 days. Cohort 2 (N = 6) consists of Formula (2), 175 mg QD for 28 days. Cohort 3 (N = 6) consists of Formula (2), 250

mg QD for 28 days. Cohort 4 (N = 6) consists of Formula (2), 350 mg QD for 28 days. Cohort 5 (N = 6) consists of Formula (2), 450 mg QD for 28 days. Cohort 6 (N = 6) consists of Formula (2), 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 (2) may be continued for greater than 28 days until disease progression or an unacceptable drug-related toxicity occurs.

[00574] 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).

[00575] The dosage form and strength of Formula (2) used in the clinical study is a hard gelatin capsules prepared using standard pharmaceutical grade excipients (microcrystalline cellulose) and containing 25 mg of Formula (2) 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).

[00576] The baseline characteristics for the patients enrolled in the clinical study are given in Table 5.

TABLE 5. Relapsed/refractory CLL baseline characteristics.

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

[00577] The results of the clinical study in relapsed/refractory CLL patients are summarized in Table 6.

TABLE 6. Activity of Formula (2) in relapsed/refractory CLL. (PR = partial response; PR+L = partial response with lymphocytosis; SD = stable disease; PD = progressive disease.)

n (%)	**All Cohorts (N=31)**	**100 mg QD (N=8)**	**175 mg QD (N=8)**	**250 mg QD (N=7)**	**100 mg BID (N=3)**	**400 mg QD (N=5)**
PR	22 (71)	7 (88)	5 (63)	5 (71)	3 (100)	2 (40)
PR+L	7 (23)	0 (0)	3 (37)	2 (29)	0 (0)	2 (40)
SD	2 (6)	1 (12)	0 (0)	0 (0)	0 (0)	1 (20)
PD	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Median (range) Cycles						
	7.3 (3.0-10.8)	**10.0 (9.0-10.8)**	**8.6 (3.0-8.8)**	**7.0 (7.0-7.3)**	**5.2 (4.7-5.5)**	**5.0 (4.8-5.5)**

[00578] FIG. 45 shows the median % change in ALC and SPD from baseline in the clinical study of Formula (2), 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 (2) 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 (2) 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. 46, and in all cases shows significant responses.

[00579] A Kaplan-Meier curve showing PFS from the clinical CLL study of Formula (2) is shown in FIG. 47. 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. 48. Both FIG. 47 and FIG. 48 show the results for Formula (2) in comparison to the results reported for Formula (10) (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 (2) in comparison to patients treated with ibrutinib.

[00580] Based on the data and comparisons shown above, the CLL study showed that the efficacy of Formula (2) was surprisingly superior to that of Formula (10) (ibrutinib).

[00581] 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. 49, the PFS is shown for Formula (2) 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. 50, the number of patients at risk with the 17p deletion is compared. To date, no 17p patients have progressed on Formula (2).

[00582] The adverse events observed in the clinical study in relapsed/refractory CLL are given in Table 7. 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 7. Treatment-related adverse events reported in the clinical study of Formula (2) in relapsed/refractory CLL. (Reported in ≥ 5% of patients.)

Adverse Events (Treatment-Related), n (%)	**Grade**	**All (N=44)**
Headache	1/2	7 (16)
Increased tendency to bruise	1	6 (14)
Diarrhea	1	4 (9)
Petechiae	1	3 (7)

[00583] The clinical study of Formula (2) 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 (2).

[00584] BTK target occupany was measured for relapsed/refractory CLL patients with the results shown in FIG. 51. For 200 mg QD dosing of the BTK inhibitor of Formula (2), about 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 (2) achieves superior BTK occupancy in CLL patients than ibrutinib.

[00585] The effects of Formula (2) on cell subset percentages were also evaluated using flow cytometry analysis of peripheral blood, with the results shown in FIG. 52, FIG. 53, FIG. 54, FIG. 55, FIG. 56, and FIG. 57. PBMC samples from CLL patient samples drawn prior to (predose) and after 28 days of dosing with Formula (2) were compared for potential changes in cell subsets. PBMCs were stained with monoclonal antibodies conjugated to fluorescent tags (flourochromes) to identify cell subsets via flow cytometry. Non-viable cells were excluded from the analysis using the dye 7-aminoactinomycin D (7-AAD). To produce the metric of percent change, the following steps were taken. First, each cell subset was defined by hierarchical flow cytometry gating. Then, the change in frequency (between day 1 and day 28) was calculated for each cell subset. MDSC subsets were measured as a % of all myeloid cells. T cell subsets were measured as a % of all $CD3^+$ cells, and NK cells were measured as a % of all live $CD45^+$ cells. In FIG. 52 and FIG. 53, 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 (2) mobilizes MDSCs and thus affects the CLL tumor microenvironment in marrow and lymph nodes, which is an unexpected indication of superior efficacy. In FIG. 54 and FIG. 55, 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. 52 to FIG. 55 are observed in multiple cohorts, at doses including 100 mg BID, 200 mg QD, and 400 mg QD. In FIG. 56 and FIG. 57, 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.

[00586] These results suggest that after Formula (2) 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.

[00587] Updated clinical results from the CLL study are shown in FIG. 58 to FIG. 63. FIG. 58 shows an update of the data presented in FIG. 45. FIG. 59 shows an update of the data presented in FIG. 51, and includes BID dosing results. Formula (2) 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 (2) 100 mg BID dosing resulted in 97% - 99% BTK occupancy,

complete BTK coverage, and less inter-patient variability. The PFS for patients with 11q deletions and 17p deletions are illustrated in FIG. 60, FIG. 61, and FIG. 62. Updated SPD results are illustrated in FIG. 63, and again show significant results across all cohorts and dosing regimens.

[00588] Treatment of CLL patients with Formula (2) also resulted in increased apoptotis, as illustrated in FIG. 64. 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 (2) 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 (2), as shown in FIG. 65 and FIG. 66, respectively.

[00589] Overall, Formula (2) shows superior efficacy to first generation BTK inhibitors such as ibrutinib, or to monotherapy with PI3K-δ inhibitors such as idelalisib. Formula (2) has better target occupancy and better pharmacokinetic and metabolic parameters than ibrutinib, leading to improved B cell apoptosis. Furthermore, unlike treatment with ibrutinib and PI3K-δ inhibitors, treatment with Formula (2) does not affect NK cell function. Finally, treatment with Formula (2) leads to a CLL tumor microenvironmental effect by excluding MDSC cells from the marrow and lymph nodes and reducing their number.

Example 13 – Effects of BTK Inhibitors on Thrombosis

[00590] 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(1),* 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 about half of patients treated with ibrutinib (IMBRUVICA package insert and prescribing information, revised July 2014, U.S. Food and Drug Administration).

[00591] 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 (17) (CC-292), and Formula (10) (ibrutinib), in clinical development. Importantly, early stage clinical trials have found ibrutinib to be particularly active in chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL), suggesting that this class of inhibitors may play a significant role in various types of cancers (Aalipour and Advani, *Br. J. Haematol.* **2013,** *163,* 436-43). However, their effects are not limited to leukemia or lymphomas as platelets also rely on the Tec kinases family members BTK and Tec for signal transduction in response to various thrombogenic stimuli (Oda, *et al.*, *Blood* **2000**, *95(5),* 1663-70; Atkinson, *et al.*, *Blood* **2003**, *102(10),* 3592-99). In fact, both Tec and BTK play an important role in the regulation of phospholipase Cγ2 (PLCγ2) downstream of the collagen receptor glycoprotein VI (GPVI) in human platelets. In addition, BTK is activated and undergoes tyrosine phosphorylation upon challenge of the platelet thrombin receptor, which requires the engagement of αIIbβ3 integrin and PI3K activity (Laffargue, *et al.*, *FEBS Lett.* **1999,** *443(1),* 66-70). It has also been implicated in GPIbα-dependent thrombus stability at sites of vascular injury (Liu, *et al.*, *Blood* **2006**, *108(8),* 2596-603). Thus, BTK and Tec are involved in several processes important in supporting the formation of a stable hemostatic plug, which is critical for preventing significant blood loss in response to vascular injury. Hence, the effects of the BTK inhibitors of Formula (2) and Formula (10) (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.

[00592] 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 aperature (NA)) of a Zeiss Axiotech vario microscope. Human platelet and wall interactions were visualized by fluorescence microscopy using a system equipped with a Yokogawa CSU-22 spinning disk confocal scanner, iXON EM camera, and 488 nm and 561 nm laser lines to detect BCECF-labeled and rhodamine-labeled platelets, respectively (Revolution XD, Andor Technology). The extent of thrombus

formation was assessed for 2 minutes after injury and the area (μm^2) of coverage determined (Image IQ, Andor Technology). For the Formula (2), Formula (17) (CC-292), and Formula (10) (ibrutinib) inhibition studies, the BTK inhibitors were were added to purified human platelets for 30 minutes before administration.

[00593] The *in vivo* throbus effects of the BTK inhibitors, Formula (2), Formula (17) (CC-292), and Formula (10) (ibrutinib), were evaluated on human platelet-mediated thrombosis by utilizing the *in vivo* human thrombus formation in the VWF HA1 mice model, which has been previously described (Chen, *et al.*, *Nat Biotechnol.* **2008,** *26(1),* 114-19). Purified human platelets were preincubated with various concentrations of the BTK inhibitors (0.1 μM, 0.5 μM, or 1 μM) or DMSO and then administered to VWF HA1 mice, followed by laser-induced thrombus formation. The BTK inhibitor-treated human platelets were fluorescently labeled and infused continuously through a catheter inserted into the femoral artery. Their behavior in response to laser-induced vascular injury was monitored in real time using two-channel confocal intravital microscopy (Furie and Furie, *J. Clin. Invest.* **2005,** *115(12),* 2255-62). Upon induction of arteriole injury untreated platelets rapidly formed thrombi with an average thrombus size of 6,450 ± 292 mm^2 (mean ± s.e.m.), as shown in FIG. 67 and FIG. 68. Similarly, Formula (2) (1 μM) treated platelets formed a slightly smaller but not significantly different thrombi with an average thrombus size of 5733 ± 393 mm^2 (mean ± s.e.m.). In contrast, a dramatic reduction in thrombus size occured in platelets pretreated with 1 μM of Formula (10) (ibrutinib), 2600 ± 246 mm^2 (mean ± s.e.m.), resulting in a reduction in maximal thrombus size by about 61% compared with control ($P > 0.001$) (FIG. 67 and FIG. 69). Similar results were obtained with platelets pretreated with 500 nM of Formula (2) or ibrutinib: thrombus size of 5946 ± 283 mm^2, and 2710 ± 325 mm^2 respectively. These initial results may provide some mechanic background and explaination on the reported 44% bleeding related adverse event rates in the Phase III RESONATE study comparing ibrutinib with ofatumumab. The results obtained for Formula (17) (CC-292) were similar to that for Formula (10) (ibrutinib), as shown in FIG. 67, 68, and 69. The effect of the BTK inhibitor concentration is shown in FIG. 70. These results demonstrate the surprising advantage of the BTK inhibitor of Formula (2), which does not interfere with thrombus formation, while the BTK inhibitors of Formula (17) (CC-292) and Formula (10) (ibrutinib) interfere with thrombus formation.

[00594] The objective of this study was to evaluate *in vivo* thrombus formation in the presence

of BTK inhibitors. *In vivo* testing of novel antiplatelet agents 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 (2), Formula (17) (CC-292), and Formula (10) (ibrutinib) on thrombus formation. These results show that Formula (2) had no significant effect on human platelet-mediated thrombus formation while Formula (10) (ibrutinib) was able to limit this process, resulting in a reduction in maximal thrombus size by 61% compared with control. Formula (17) (CC-292) showed an effect similar to Formula (10) (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 $\leq 6\%$ of patients treated with Formula (10) (ibrutinib).

[00595] GPVI platelet aggregation was measured for Formula (2) and Formula (10) (ibrutinib). Blood was obtained from untreated humans, and platelets were purified from plasma-rich protein by centrifugation. Cells were resuspended to a final concentration of 350,000/μL in buffer containing 145 mmol/L NaCl, 10 mmol/L HEPES, 0.5 mmol/L Na_2HPO_4, 5 mmol/L KCl, 2 mmol/L $MgCl_2$, 1 mmol/L $CaCl_2$, and 0.1% glucose, at pH 7.4. Stock solutions of Convulxin (CVX) GPVI were prepared on the day of experimentation and added to platelet suspensions 5 minutes (37 °C, 1200 rpm) before the induction of aggregation. Aggregation was assessed with a Chronolog Lumi-Aggregometer (model 540 VS; Chronolog, Havertown, PA) and permitted to proceed for 6 minutes after the addition of agonist. The results are reported as maximum percent change in light transmittance from baseline with platelet buffer used as a reference. The results are shown in FIG. 71.

[00596] In FIG. 72, 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.

[00597] The results depicted in FIG. 71 and FIG. 72 indicate that the BTK inhibitor of Formula (10) (ibrutinib) significantly inhibits GPVI platelet aggregation, while the BTK inhibitor of Formula (2) does not, further illustrating the surprising benefits of the latter compound.

Example 14 – Synergistic Combinations of BTK Inhibitors and MEK Inhibitors

[00598] Combination experiments were performed to determine the synergistic, additive, or antagonistic behavior of drug combinations of BTK inhibitors and MEK inhibitors using the Chou-Talalay method of determining combination indexes for drug combinations. Cell lines and inhibitors were commercially obtained or synthesized as described herein or in the art. Single drug activities may be first determined in the various cell lines and subsequently, the combination indexes may be established using equimolar ratios taking the single agent drug EC50s into consideration. For individual drugs that displayed no single drug activity, equimolar ratios may be used at fixed concentrations to establish combination indexes. The MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium) substrate was Cell Titer 96 (Promega). Incubations were performed for 72 or 96 hours. The readout from 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)). The synergy of the combinations was calculated using CalcuSyn software (Biosoft), which is based on the Median Effect methods described by Chou and Talalay, *Trends Pharmacol. Sci.* **1983,** *4,* 450-454.

[00599] The combination index obtained may be ranked according to Table 8.

TABLE 8. Combination Index (CI) Ranking Scheme

Range of CI	**Description**
<0.1	Very strong synergism
0.1-0.3	Strong synergism
0.3-0.7	Synergism
0.7-0.85	Moderate synergism
0.85-0.9	Slight synergism
0.9-1.1	Nearly additive
1.1-1.2	Slight antagonism
1.2-1.45	Moderate antagonism
1.45-3.3	Antagonism
3.3-10	Strong antagonism
>10	Very strong antagonism

[00600] The detailed results of the cell line studies for the BTK inhibitor of Formula (2) (acalabrutinib) and the MEK inhibitor of Formula (27) (selumetinib) are given in FIG. 73 to FIG. 76. The results of the cell line studies are summarized in Table 9.

TABLE 9. Summary of results of the combination of the BTK inhibitor of Formula (2) (acalabrutinib) with the MEK inhibitor of Formula (27) (selumetinib) (S = synergistic, A = additive, X = no effect).

Cell Line	Indication	ED25	ED50	ED75	ED90
TMD-8	DLBCL-ABC	S	S	S	S/A
RI-1	B-NHL	S	S	S	S
Mino	MCL	S	S	S	S

[00601] Synergistic effects of the combination of a BTK inhibitor of Formula (2) (acalabrutinib) with the MEK inhibitor of Formula (27) (selumetinib) are observed in cell lines representative of B cell non-Hodgkin's lymphoma (B-NHL), mantle cell lymphoma (MCL), and activated B cell like diffuse large B-cell lymphoma (DLBCL-ABC).

[00602] The detailed results of the cell line studies for the BTK inhibitor of Formula (10) (ibrutinib) and the MEK inhibitor of Formula (27) (selumetinib) are given in FIG. 77 to FIG. 80. The results of the cell line studies are summarized in Table 10.

TABLE 10. Summary of results of the combination of the BTK inhibitor of Formula (10) (ibrutinib) with the MEK inhibitor of Formula (27) (selumetinib) (S = synergistic, A = additive, X = no effect).

Cell Line	Indication	ED25	ED50	ED75	ED90
RI-1	B-NHL	X	X/A	S	S
Mino	MCL	S/A	S	S	S

[00603] Synergistic effects of the combination of a BTK inhibitor of Formula (10) (ibrutinib) with the MEK inhibitor of Formula (27) (selumetinib) are observed in cell lines representative of B cell non-Hodgkin's lymphoma (B-NHL) and mantle cell lymphoma (MCL).

[00604] The detailed results of the cell line studies for the BTK inhibitor of Formula (21) (ONO-4059) and the MEK inhibitor of Formula (27) (selumetinib) are given in FIG. 81 to FIG. 84. The results of the cell line studies are summarized in Table 11.

TABLE 11. Summary of results of the combination of the BTK inhibitor of Formula (21) (ONO-4059) with the MEK inhibitor of Formula (27) (selumetinib) (S = synergistic, A = additive, X = no effect).

Cell Line	Indication	ED25	ED50	ED75	ED90
RI-1	B-NHL	X	S/A	S	S
Mino	MCL	S	S	S	S

[00605] Synergistic effects of the combination of a BTK inhibitor of Formula (21) (ONO-4059) with the MEK inhibitor of Formula (27) (selumetinib) are observed in cell lines representative of B cell non-Hodgkin's lymphoma (B-NHL) and mantle cell lymphoma (MCL).

CLAIMS

We claim:

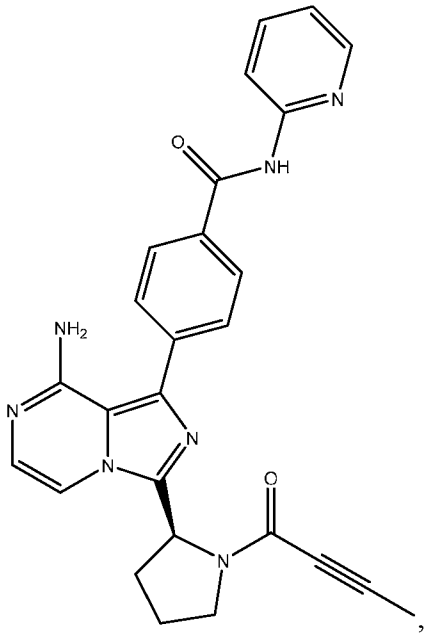
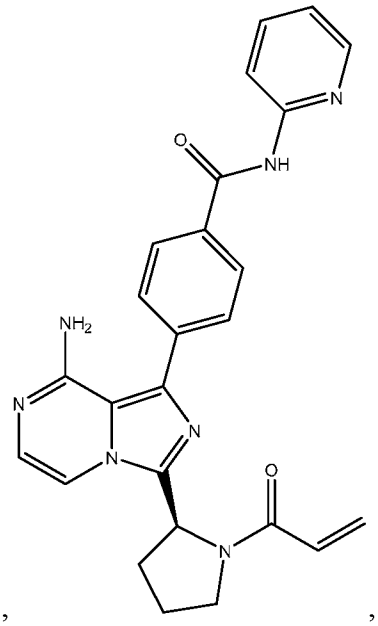
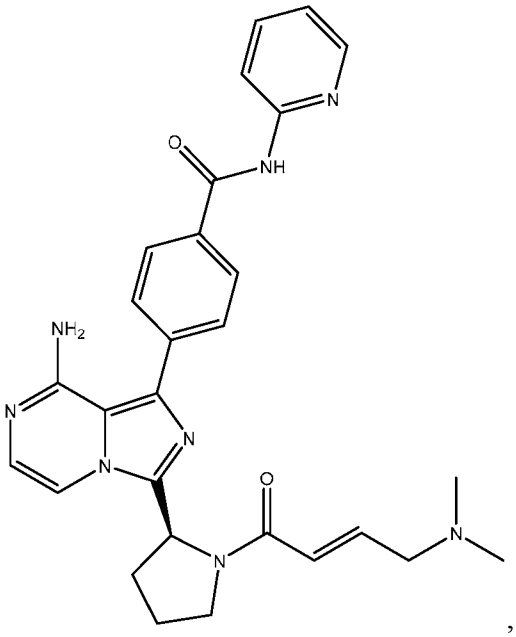
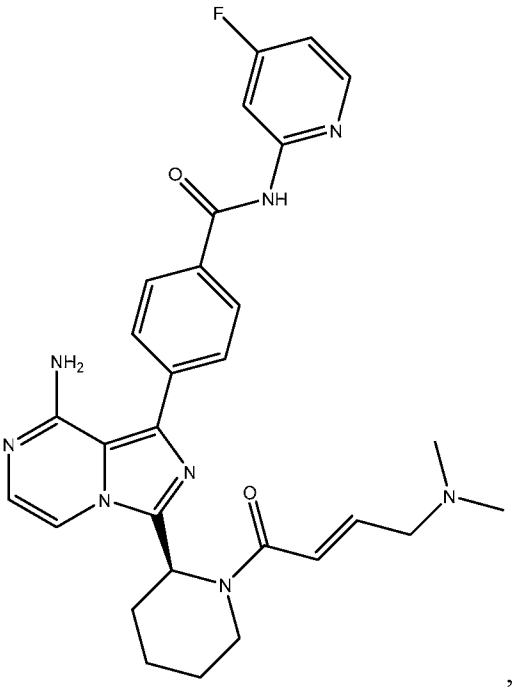
1. A method of treating a hyperproliferative disease, comprising co-administering, to a mammal in need thereof, therapeutically effective amounts of (1) a MEK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and (2) a Bruton's tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

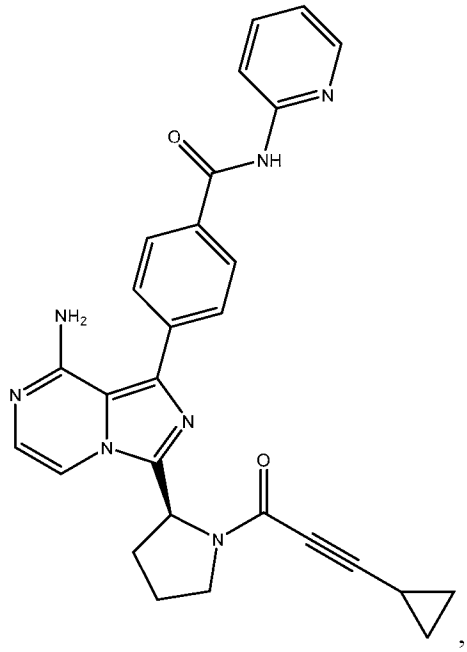
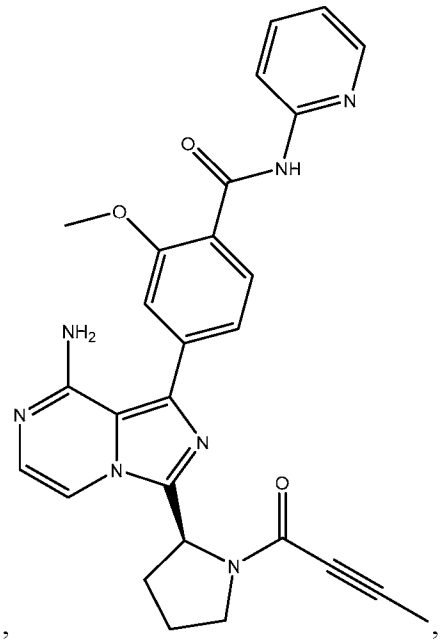
2. The method of Claim 1, wherein the MEK inhibitor is administered to the mammal before administration of the BTK inhibitor.

3. The method of Claim 1, wherein the MEK inhibitor is administered to the mammal simultaneously with the administration of the BTK inhibitor.

4. The method of Claim 1, wherein the MEK inhibitor is administered to the mammal after administration of the BTK inhibitor.

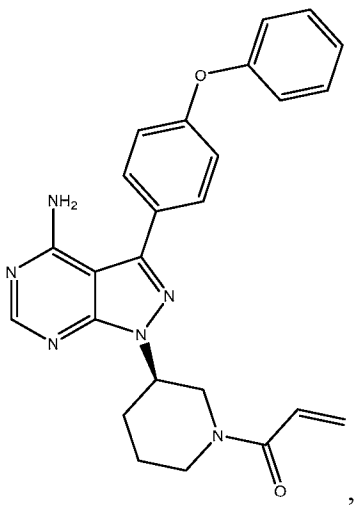
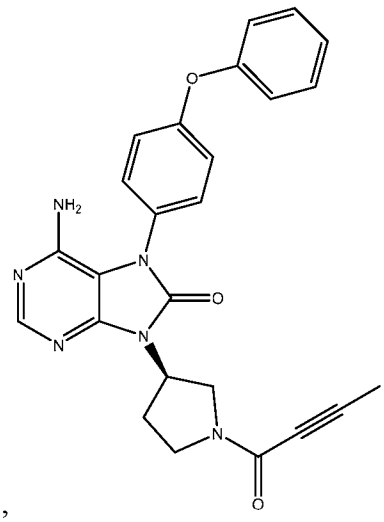
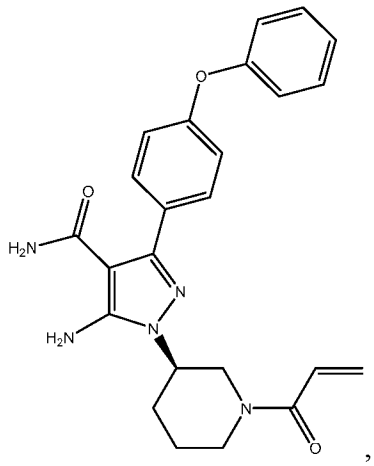
5. The method of any one of Claims 1 to 4, wherein the BTK inhibitor is selected from the group consisting of:


,

,

,

,


,

,

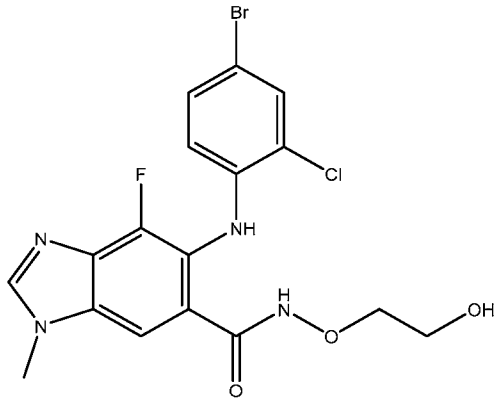
and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, and prodrugs thereof.

6. The method of any one of Claims 1 to 4, wherein the BTK inhibitor is selected from the group consisting of:

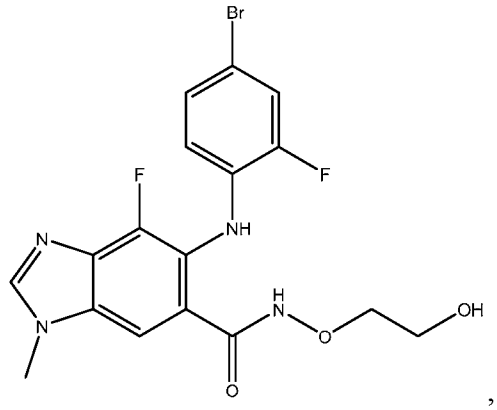

,

,

,

and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, and prodrugs thereof.

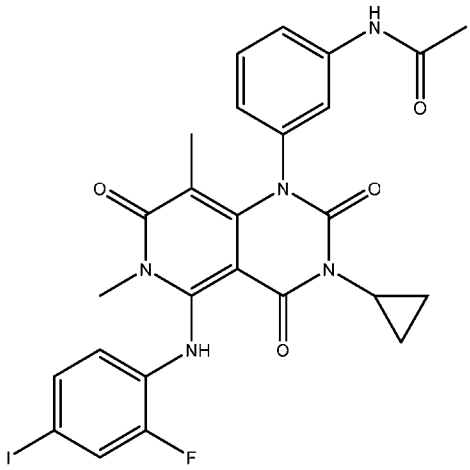
7. The method of any one of Claims 1 to 6, wherein the MEK inhibitor is selected from the group consisting of:



,



,



,

and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof.

8. The method of any one of Claims 1 to 7, further comprising the step of administering a therapeutically effective amount of an anti-CD20 antibody.

9. The method of Claim 8, wherein the anti-CD20 antibody is selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, biosimilars thereof, and combinations thereof.

10. The method of any one of Claims 1 to 9, further comprising the step of administering a therapeutically effective amount of fludarabine, cyclophosphamide, and rituximab (FCR chemotherapy).

11. The method of any one of Claims 1 to 9, further comprising the step of administering a therapeutically effective amount of rituximab, cyclophosphamide, doxorubicin, vincristine, and

prednisone (R-CHOP chemotherapy).

12. The method of any one of Claims 1 to 9, further comprising the step of administering a therapeutically effective amount of bendamustine and rituximab (BR chemotherapy).

13. The method of any one of Claims 1 to 12, wherein the hyperproliferative disease is a cancer.

14. The method of Claim 13, wherein the cancer is a B cell hematological malignancy.

15. The method of Claim 14, wherein the B cell 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, and myelofibrosis.

16. The method of Claim 13, wherein the cancer is a solid tumor cancer.

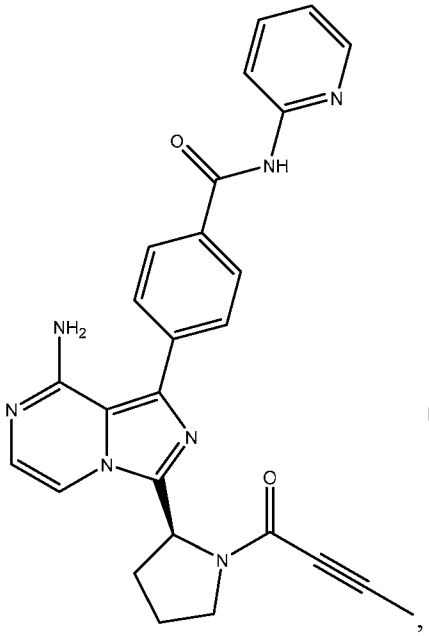
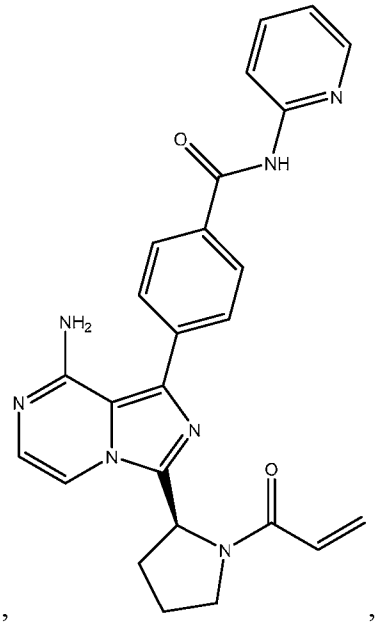
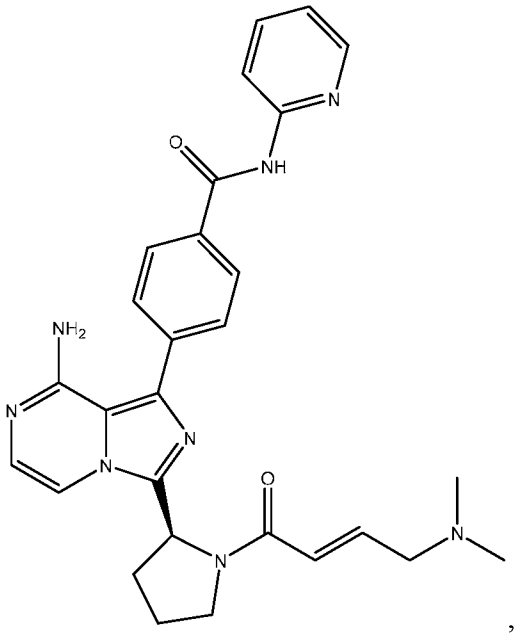
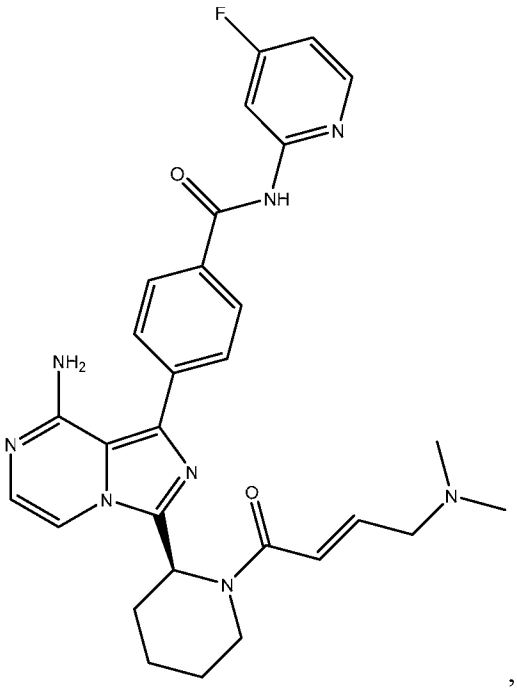
17. The method of Claim 16, wherein the solid tumor cancer is selected from the group consisting of bladder cancer, non-small cell lung cancer, cervical cancer, anal cancer, pancreatic cancer, squamous cell carcinoma including head and neck cancer, renal cell carcinoma, melanoma, ovarian cancer, small cell lung cancer, glioblastoma, 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, esophageal cancer, testicular cancer, gynecological cancer, colon cancer, and brain cancer.

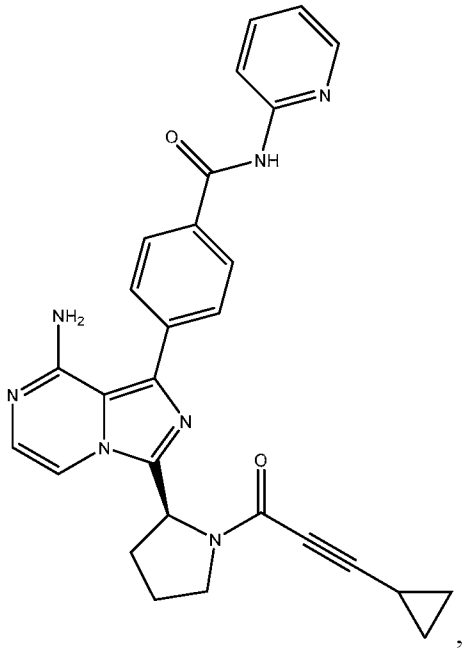
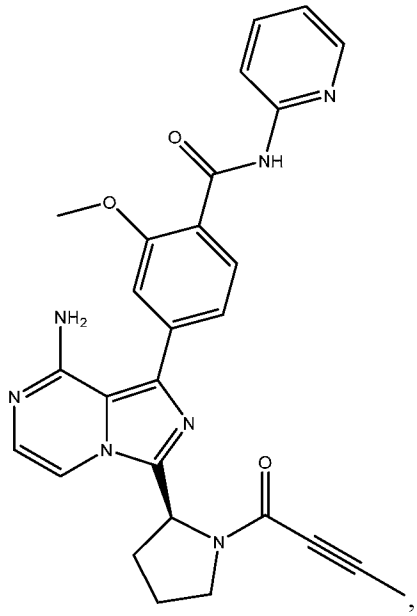
18. The method of any of Claims 16 to 17, further comprising the step of administering a therapeutically effective amount of gemcitabine.

19. The method of any of Claims 16 to 17, further comprising the step of administering a therapeutically effective amount of albumin-bound paclitaxel.

20. A method of treating a cancer in a human intolerant to a bleeding event comprising the step of administering (1) a therapeutically effective amount of a MEK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and (2) a therapeutically effective amount of a Bruton's tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein the

BTK inhibitor is selected from the group consisting of:

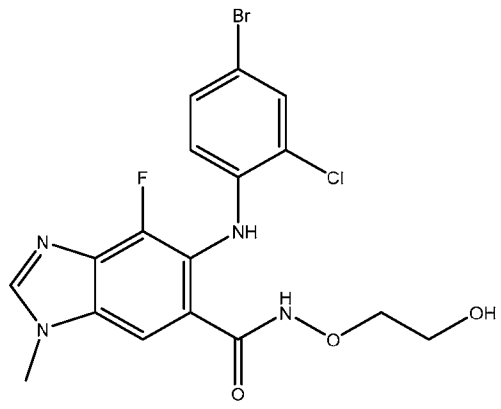
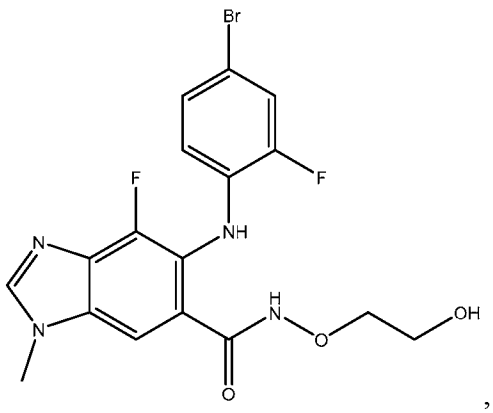

,

,

,

,

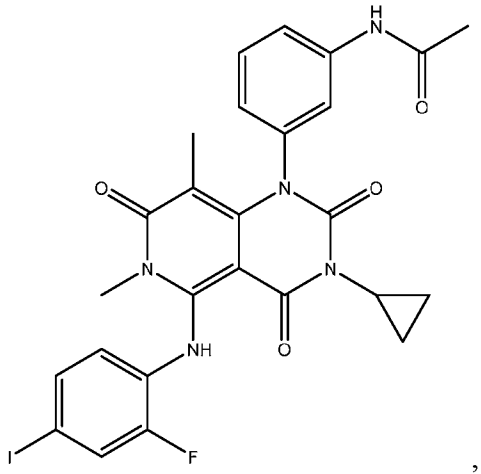

,

,

and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, or prodrugs thereof.

21. The method of Claim 20, wherein the bleeding event is selected from the group consisting of subdural hematoma, gastrointestinal bleeding, hematuria, post-procedural hemorrhage, bruising, petechiae, and combinations thereof.

22. The method of Claims 20 or 21, wherein the MEK inhibitor is selected from the group consisting of:


,

,



and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, and prodrugs thereof.

23. The method of any one of Claims 20 to 22, further comprising the step of administering a therapeutically effective amount of fludarabine, cyclophosphamide, and rituximab (FCR chemotherapy).

24. The method of any one of Claims 20 to 22, further comprising the step of administering a therapeutically effective amount of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP chemotherapy).

25. The method of any one of Claims 20 to 22, further comprising the step of administering a therapeutically effective amount of bendamustine and rituximab (BR chemotherapy).

26. The method of any one of Claims 20 to 25, further comprising the step of administering a therapeutically effective amount of an anticoagulant or antiplatelet active pharmaceutical ingredient.

27. The method of Claim 26, wherein the anticoagulant or antiplatelet active pharmaceutical ingredient is selected from the group consisting of acenocoumarol, anagrelide, anagrelide hydrochloride, abciximab, aloxiprin, antithrombin, apixaban, argatroban, aspirin, aspirin with extended-release dipyridamole, beraprost, betrixaban, bivalirudin, carbasalate calcium, cilostazol, clopidogrel, clopidogrel bisulfate, cloricromen, dabigatran etexilate, darexaban, dalteparin, dalteparin sodium, defibrotide, dicumarol, diphenadione, dipyridamole, ditazole, desirudin, edoxaban, enoxaparin, enoxaparin sodium, eptifibatide, fondaparinux, fondaparinux sodium, heparin, heparin sodium, heparin calcium, idraparinux, idraparinux sodium, iloprost,

indobufen, lepirudin, low molecular weight heparin, melagatran, nadroparin, otamixaban, parnaparin, phenindione, phenprocoumon, prasugrel, picotamide, prostacyclin, ramatroban, reviparin, rivaroxaban, sulodexide, terutroban, terutroban sodium, ticagrelor, ticlopidine, ticlopidine hydrochloride, tinzaparin, tinzaparin sodium, tirofiban, tirofiban hydrochloride, treprostinil, treprostinil sodium, triflusal, vorapaxar, warfarin, warfarin sodium, ximelagatran, salts thereof, solvates thereof, hydrates thereof, and combinations thereof.

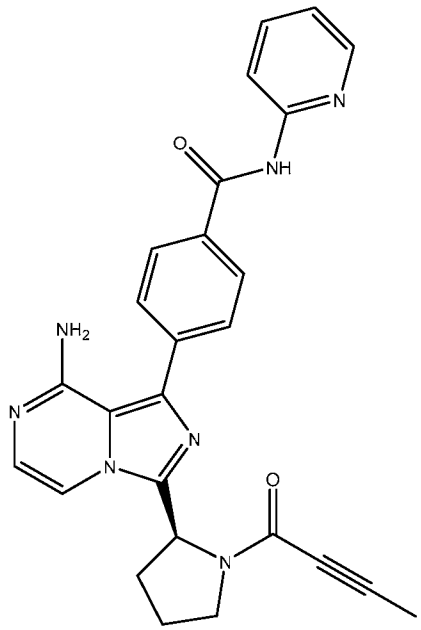
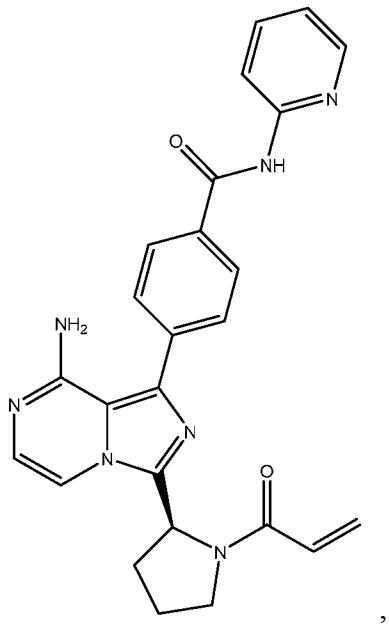
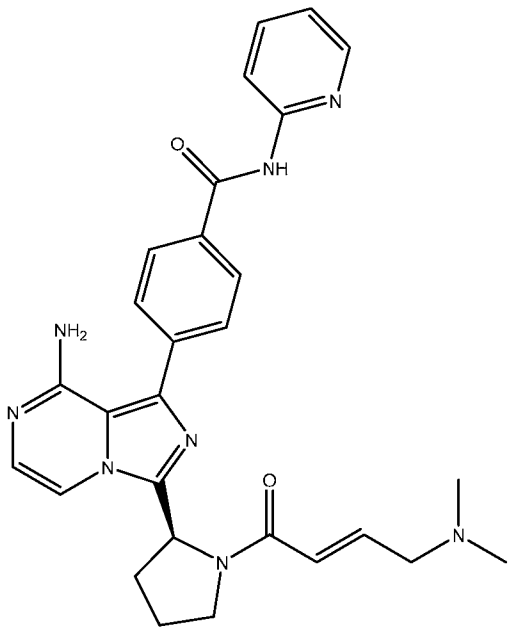
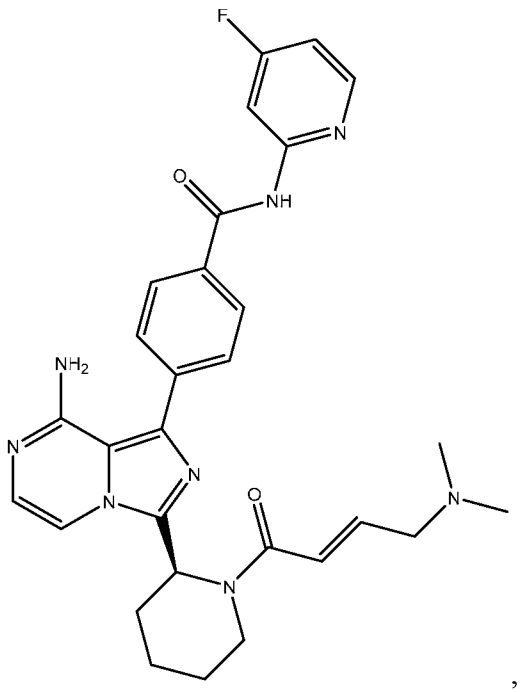
28. The method of any one of Claims 20 to 27, wherein the cancer is selected from the group consisting of bladder cancer, squamous cell carcinoma including pancreatic ductal adenocarcinoma (PDA), pancreatic cancer, colon carcinoma, mammary carcinoma, breast cancer, fibrosarcoma, mesothelioma, renal cell 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 and neck cancer, renal cancer, kidney cancer, liver cancer, ovarian cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, acquired immune deficiency syndrome (AIDS)-related cancers (e.g., lymphoma and Kaposi's sarcoma), viral-induced cancer, glioblastoma, esophogeal tumors, hematological neoplasms, non-small-cell lung cancer, chronic myelocytic leukemia, diffuse large B-cell lymphoma, esophagus tumor, follicle center lymphoma, head and neck tumor, hepatitis C virus infection, hepatocellular carcinoma, Hodgkin's disease, metastatic colon cancer, multiple myeloma, non-Hodgkin's lymphoma, indolent non-Hogkin'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, Burkitt's lymphoma, and myelofibrosis.

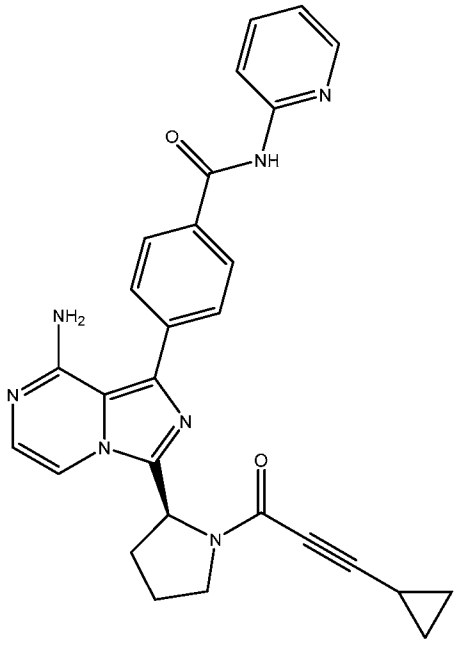
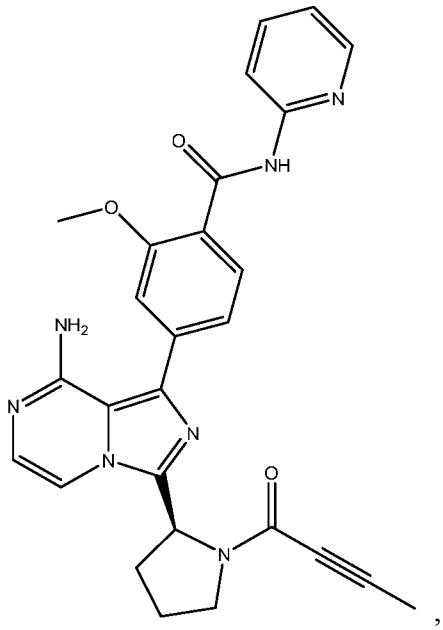
29. A composition comprising (1) a therapeutically effective amount of a MEK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof; and (2) a therapeutically effective amount of a Bruton's tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, for use in the treatment of cancer.

30. The composition of Claim 29, for use as a medicament.

31. The composition of any one of Claims 29 to 30, for use in the treatment of cancer.

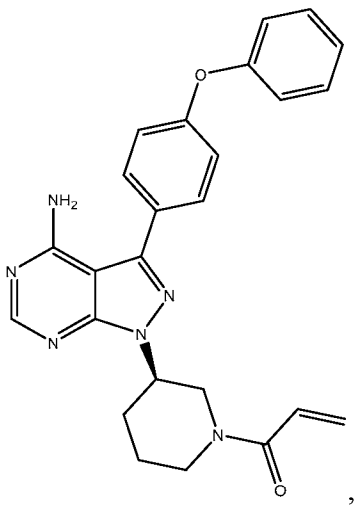
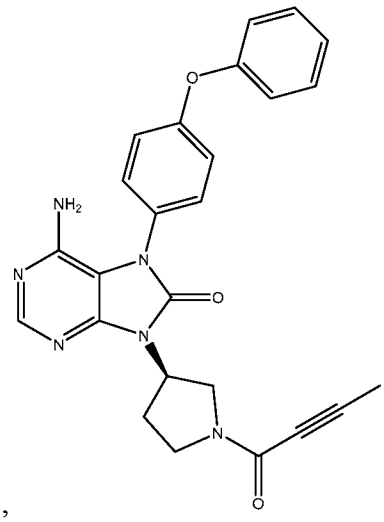
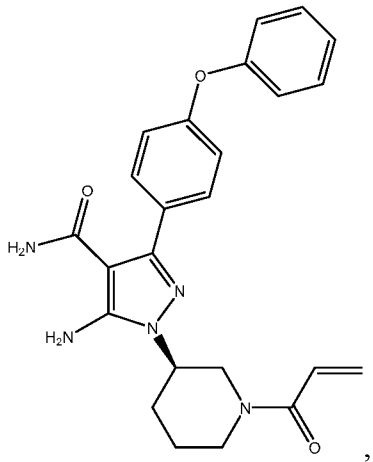
32. The composition of any one of Claims 29 to 31, wherein the BTK inhibitor is selected from the group consisting of:


,

,

,

,


,

,

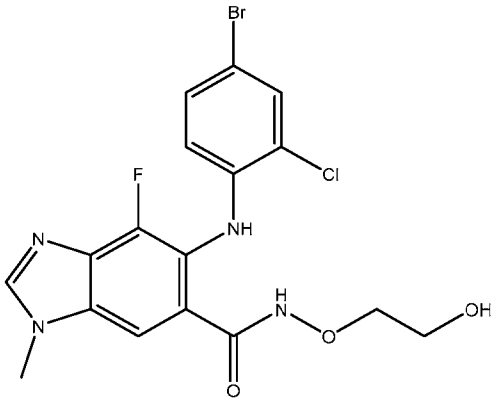
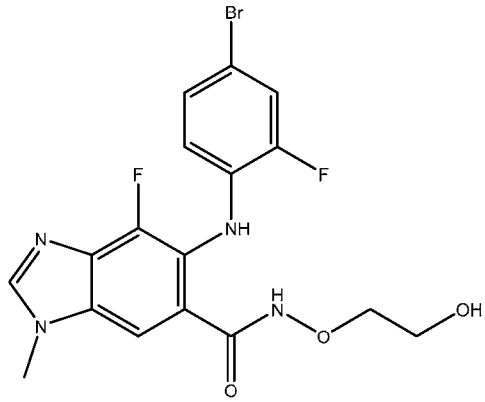
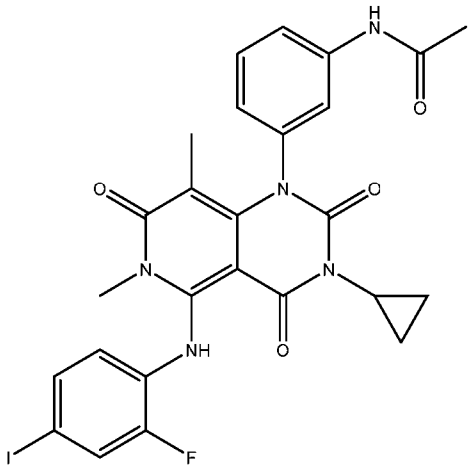
and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, and prodrugs thereof.

33. The composition of any one of Claims 29 to 31, wherein the BTK inhibitor is selected from the group consisting of:


,

,

,

and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, and prodrugs thereof.

34. The composition of any one of Claims 29 to 33, wherein the MEK inhibitor is selected from the group consisting of:

and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, and prodrugs thereof.

35. The composition of any one of Claims 29 to 34, further comprising a therapeutically effective amount of an anti-CD20 antibody.

36. The composition of Claim 35, wherein the anti-CD20 antibody is selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof.

37. The composition of any one of Claims 29 to 36, further comprising a therapeutically effective amount of fludarabine, cyclophosphamide, and rituximab (FCR chemotherapy).

38. The composition of any one of Claims 29 to 36, further comprising a therapeutically effective amount of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP chemotherapy).

39. The composition of any one of Claims 29 to 36, further comprising a therapeutically effective amount of bendamustine and rituximab (BR chemotherapy).

40. The composition of any one of Claims 29 to 39, for use in the treatment of cancer.

41. The composition of Claim 40, wherein the cancer is a B cell hematological malignancy.

42. The composition of Claim 41, wherein the B cell 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, and myelofibrosis.

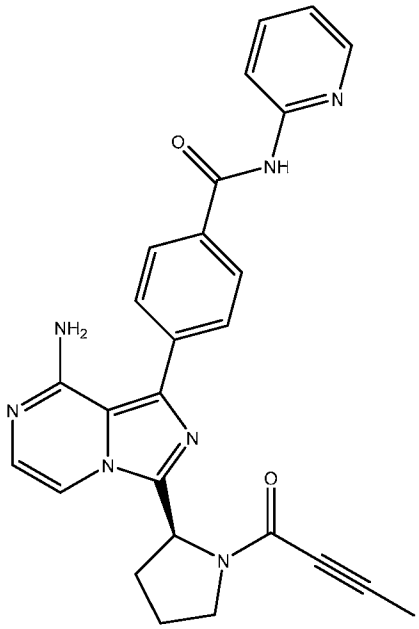
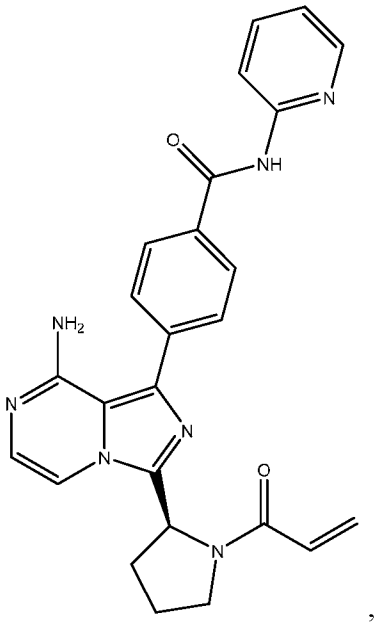
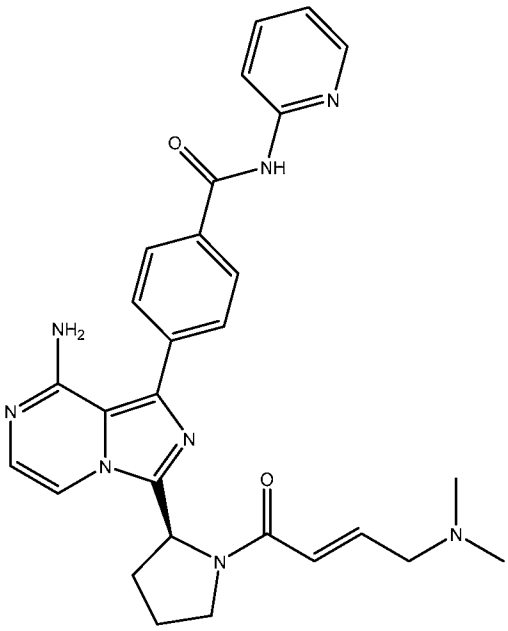
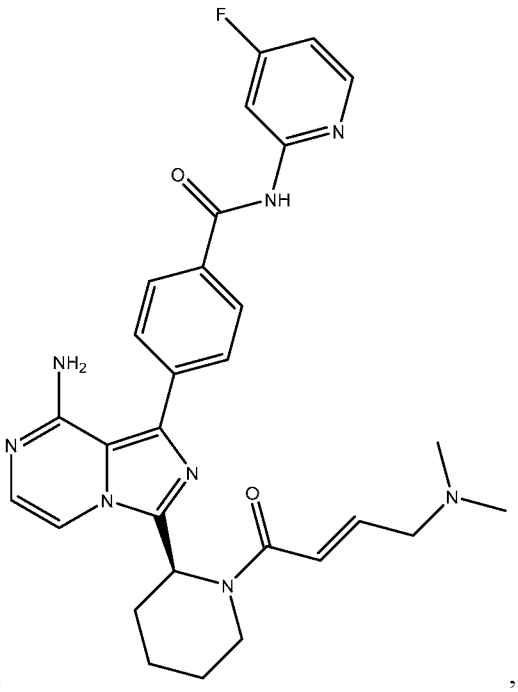
43. The composition of Claim 40, wherein the cancer is a solid tumor cancer.

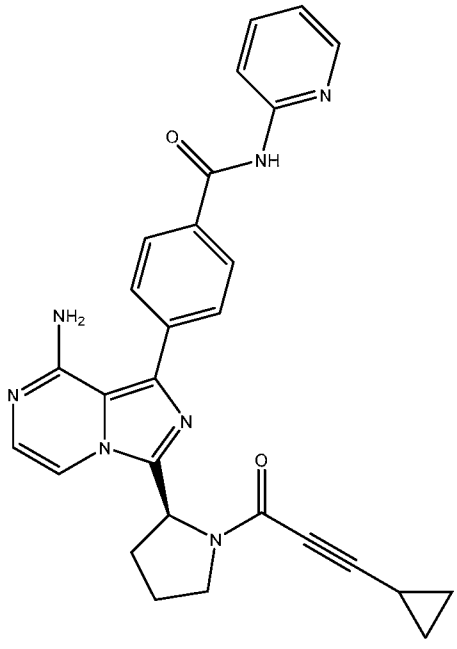
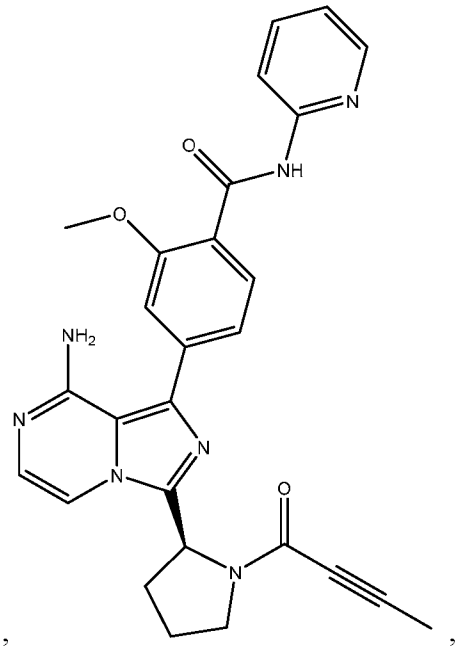
44. The composition of Claim 43, wherein the solid tumor cancer is selected from the group consisting of bladder cancer, non-small cell lung cancer, cervical cancer, anal cancer, pancreatic cancer, squamous cell carcinoma including head and neck cancer, renal cell carcinoma, melanoma, ovarian cancer, small cell lung cancer, glioblastoma, 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, esophageal cancer, testicular cancer, gynecological cancer, colon cancer, and brain cancer.

45. The composition of any one of Claims 43 to 44, further comprising a therapeutically effective amount of gemcitabine.

46. The composition of any one of Claims 43 to 44, further comprising a therapeutically effective amount of albumin-bound paclitaxel.

47. A composition comprising (1) a therapeutically effective amount of a MEK inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and (2) a therapeutically effective amount of a Bruton's tyrosine kinase (BTK) inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein the BTK inhibitor is selected from the group consisting of:

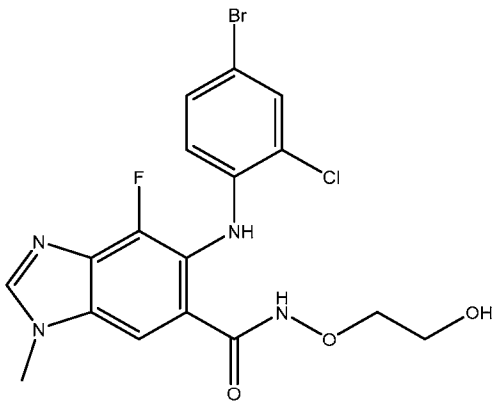
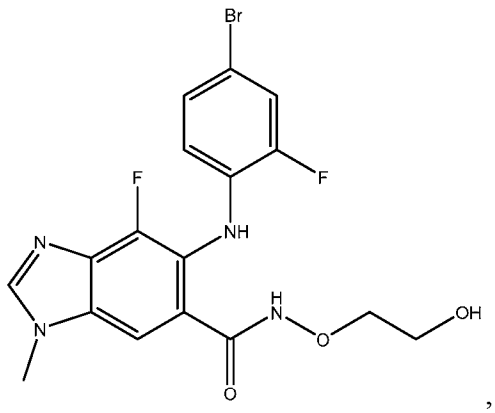

,

,

,

,

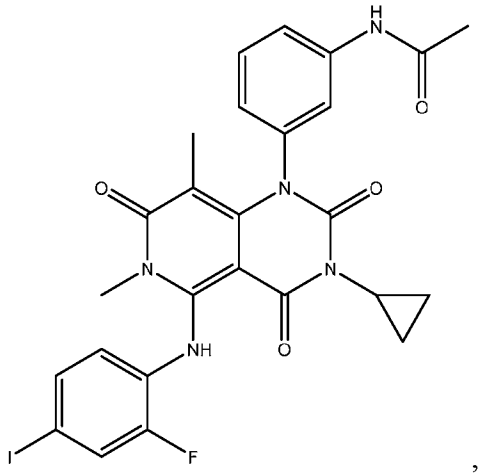

,

,

and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, and prodrugs thereof, for use in the treatment of a cancer in a human intolerant to a bleeding event.

48. The composition of Claim 47, wherein the bleeding event is selected from the group consisting of subdural hematoma, gastrointestinal bleeding, hematuria, post-procedural hemorrhage, bruising, petechiae, and combinations thereof.

49. The composition of any one of Claims 47 to 48, wherein the MEK inhibitor is selected from the group consisting of:


,

,



and pharmaceutically-acceptable salts, cocrystals, hydrates, solvates, and prodrugs thereof.

50. The composition of any one of Claims 47 to 49, further comprising a therapeutically effective amount of fludarabine, cyclophosphamide, and rituximab (FCR chemotherapy).

51. The composition of any one of Claims 47 to 49, further comprising a therapeutically effective amount of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP chemotherapy).

52. The composition of any one of Claims 47 to 49, further comprising a therapeutically effective amount of bendamustine and rituximab (BR chemotherapy).

53. The composition of any one of Claims 47 to 52, further comprising a therapeutically effective dose of an anticoagulant or antiplatelet active pharmaceutical ingredient.

54. The composition of Claim 53, wherein the anticoagulant or antiplatelet active pharmaceutical ingredient is selected from the group consisting of acenocoumarol, anagrelide, anagrelide hydrochloride, abciximab, aloxiprin, antithrombin, apixaban, argatroban, aspirin, aspirin with extended-release dipyridamole, beraprost, betrixaban, bivalirudin, carbasalate calcium, cilostazol, clopidogrel, clopidogrel bisulfate, cloricromen, dabigatran etexilate, darexaban, dalteparin, dalteparin sodium, defibrotide, dicumarol, diphenadione, dipyridamole, ditazole, desirudin, edoxaban, enoxaparin, enoxaparin sodium, eptifibatide, fondaparinux, fondaparinux sodium, heparin, heparin sodium, heparin calcium, idraparinux, idraparinux sodium, iloprost, indobufen, lepirudin, low molecular weight heparin, melagatran, nadroparin, otamixaban, parnaparin, phenindione, phenprocoumon, prasugrel, picotamide, prostacyclin,

ramatroban, reviparin, rivaroxaban, sulodexide, terutroban, terutroban sodium, ticagrelor, ticlopidine, ticlopidine hydrochloride, tinzaparin, tinzaparin sodium, tirofiban, tirofiban hydrochloride, treprostinil, treprostinil sodium, triflusal, vorapaxar, warfarin, warfarin sodium, ximelagatran, salts thereof, solvates thereof, hydrates thereof, and combinations thereof.

55. The composition of any one of Claims 47 to 54, wherein the cancer is selected from the group consisting of bladder cancer, squamous cell carcinoma including 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 and neck cancer, renal cancer, kidney cancer, liver cancer, ovarian cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, acquired immune deficiency syndrome (AIDS)-related cancers (e.g., lymphoma and Kaposi's sarcoma), viral-induced cancer, glioblastoma, esophogeal tumors, hematological neoplasms, non-small-cell lung cancer, chronic myelocytic leukemia, diffuse large B-cell lymphoma, esophagus tumor, follicle center lymphoma, head and neck tumor, hepatitis C virus infection, hepatocellular carcinoma, Hodgkin's disease, metastatic colon cancer, multiple myeloma, non-Hodgkin's lymphoma, indolent non-Hogkin's lymphoma, ovary tumor, pancreas tumor, renal cell carcinoma, small-cell lung cancer, stage IV melanoma, chronic lymphocytic leukemia, B-cell acute lymphoblastic leukemia (ALL), mature B-cell ALL, follicular lymphoma, mantle cell lymphoma, and Burkitt's lymphoma.

56. A pharmaceutical composition comprising a MEK inhibitor in combination with a BTK inhibitor and at least one pharmaceutically acceptable excipient.

57. The pharmaceutical composition of Claim 56, for use in treating a hyperproliferative disorder.

58. A kit comprising a pharmaceutical composition comprising a MEK inhibitor and a pharmaceutical composition comprising a BTK inhibitor, for co-administration of the MEK inhibitor and the BTK inhibitor, either simultaneously or separately.

59. The kit of Claim 58, for use in treating a hyperproliferative disorder.

60. A MEK inhibitor in combination with a BTK inhibitor for use in treating a hyperproliferative disorder.

61. A combination according to Claim 60 in the form of a kit comprising two or more compositions (for example two or more pharmaceutical compositions) and optionally a package insert or label providing directions for administering the compositions simultaneously, separately or sequentially, wherein:

each composition comprises at least one ingredient selected from a BTK inhibitor, a MEK inhibitor, or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

62. A combination according to Claim 60 further comprising an anti-coagulant or antiplatelet active pharmaceutical ingredient.

63. A combination according to any one of Claims 60 to 62 comprising FCR chemotherapy or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

64. A combination according to any one of Claims 60 to 62 comprising R-CHOP chemotherapy or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

65. A combination according to any one of Claims 60 to 62 comprising BR chemotherapy or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

66. A combination according to any one of Claims 60 to 62 comprising bendamustine hydrochloride or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

67. A combination of a BTK inhibitor and a MEK inhibitor, wherein the BTK inhibitor is a compound of Formula (2) or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof and the MEK inhibitor is a compound selected from the group consisting of Formula (27), Formula (28), Formula (29), and pharmaceutically acceptable salts, solvates, hydrates, cocrystals, or prodrugs thereof.

68. A combination according to any of Claims 60 to 67 for use in the treatment of hyperproliferative disease such as cancer.

69. A combination according to any of Claims 60 to 67 for use in the treatment of a cancer selected from the group consisting of bladder cancer, squamous cell carcinoma including head and neck cancer, pancreatic ductal adenocarcinoma (PDA), pancreatic cancer, colon carcinoma, mammary carcinoma, breast cancer, fibrosarcoma, mesothelioma, renal cell carcinoma, lung carcinoma, thyoma, prostate cancer, colorectal cancer, ovarian cancer, acute myeloid leukemia, thymus cancer, brain cancer, squamous cell cancer, skin cancer, eye cancer, retinoblastoma, melanoma, intraocular melanoma, oral cavity and oropharyngeal cancers, gastric cancer, stomach cancer, cervical cancer, head, neck, renal cancer, kidney cancer, liver cancer, ovarian cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, acquired immune deficiency syndrome (AIDS)-related cancers (e.g., lymphoma and Kaposi's sarcoma), viral-induced cancer, glioblastoma, esophogeal tumors, hematological neoplasms, non-small-cell lung cancer, chronic myelocytic leukemia, diffuse large B-cell lymphoma, esophagus tumor, follicle center lymphoma, head and neck tumor, hepatitis C virus infection, hepatocellular carcinoma, Hodgkin's disease, metastatic colon cancer, multiple myeloma, non-Hodgkin's lymphoma, indolent non-Hodgkin's lymphoma, ovary tumor, pancreas tumor, renal cell carcinoma, small-cell lung cancer, stage IV melanoma, chronic lymphocytic leukemia, B-cell acute lymphoblastic leukemia (ALL), mature B-cell ALL, follicular lymphoma, mantle cell lymphoma, and Burkitt's lymphoma.

70. A combination according to any of Claims 60 to 67 for use in the treatment of:

solid tumor cancer selected from the group consisting of breast, lung, colorectal, thyroid, bone sarcoma and stomach cancers;

leukemia selected from the group consisting of acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), and acute lymphoblastic leukemia (ALL); and/or

lymphoma is follicular lymphoma, mantle cell lymphoma, diffuse large B cell lymphoma (DLBCL), B cell chronic lyphocytic leukemia, or Burkitt's lymphoma.

71. Use of a combination according to any one of Claims 56 to 70 as a research tool in the discovery and/or development of a pharmaceutical product.

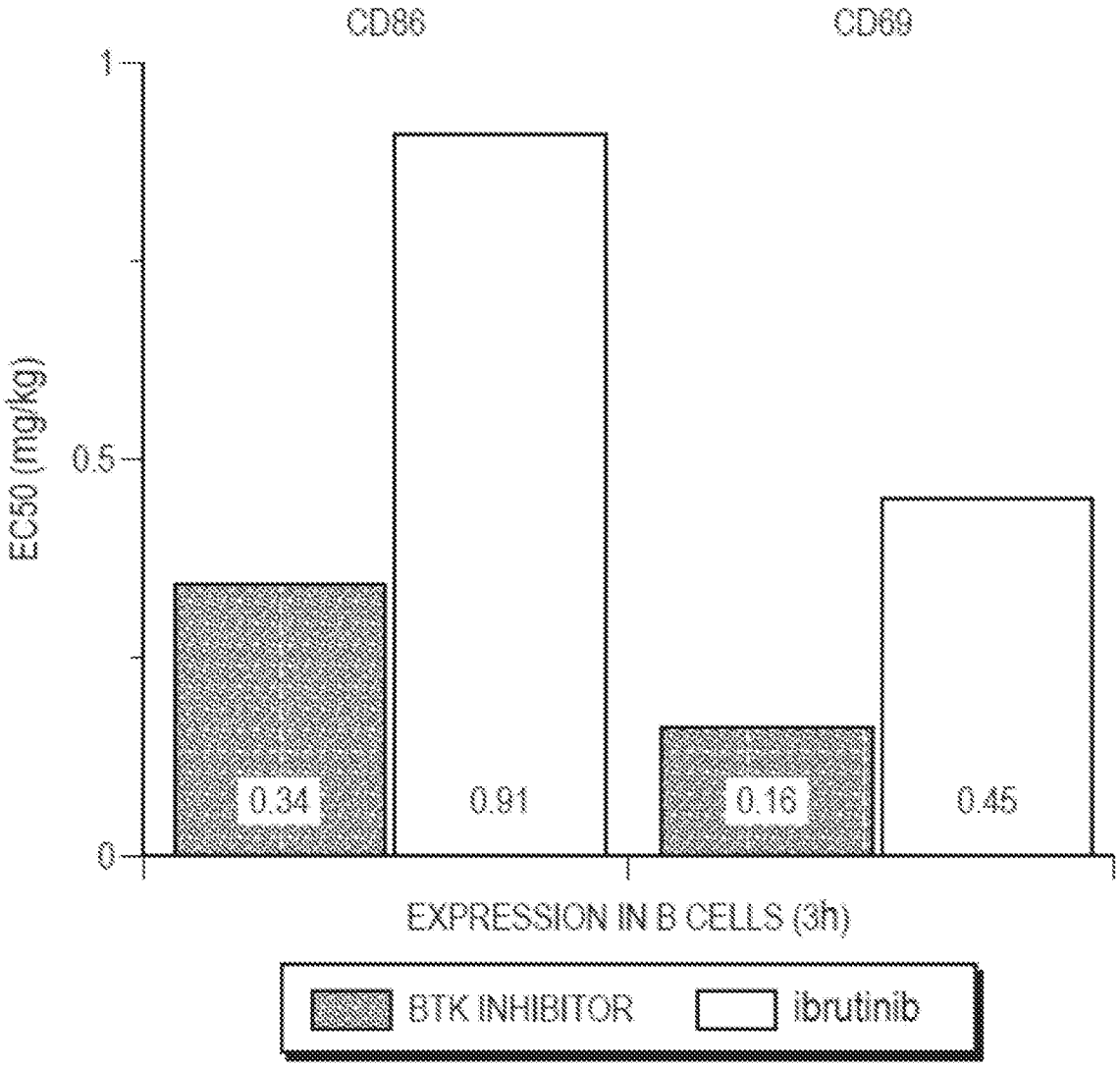

CD86
CD69
1
0.5
0
EC50 (mg/kg)
0.34
0.91
0.16
0.45
EXPRESSION IN B CELLS (3h)
BTK INHIBITOR
ibrutinib

FIG. 1

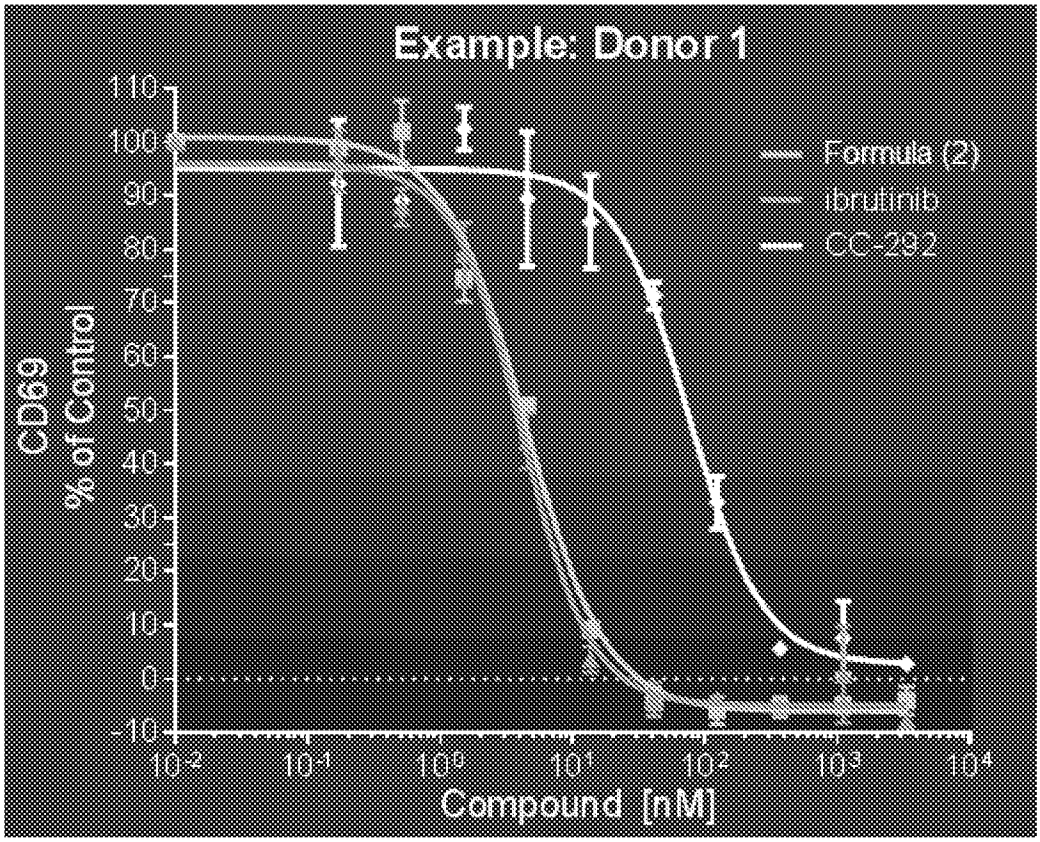

Example: Donor 1
Formula (2)
ibrutinib
CC-292
CD69
% of Control
110
100
90
80
70
60
50
40
30
20
10
0
-10
10-2
10-1
100
101
102
103
104
Compound [nM]

FIG. 2

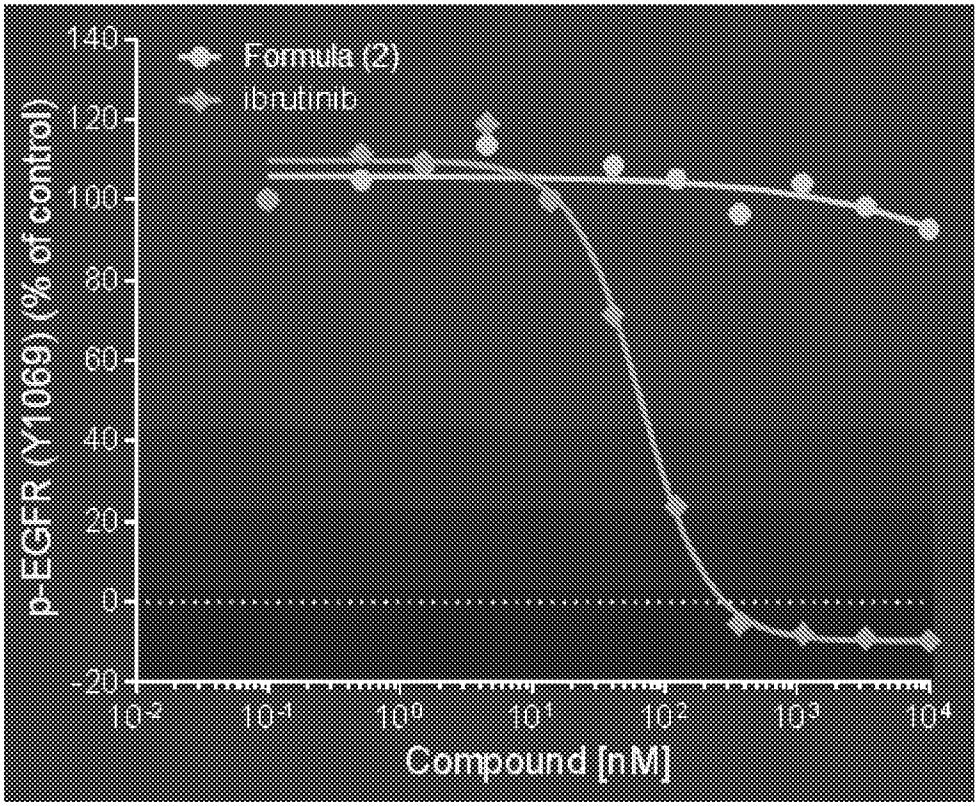

Formula (2)
ibrutinib
p-EGFR (Y1069) (% of control)
140
120
100
80
60
40
20
0
-20
10^{-2}
10^{-1}
10^{0}
10^{1}
10^{2}
10^{3}
10^{4}
Compound [nM]

FIG. 3

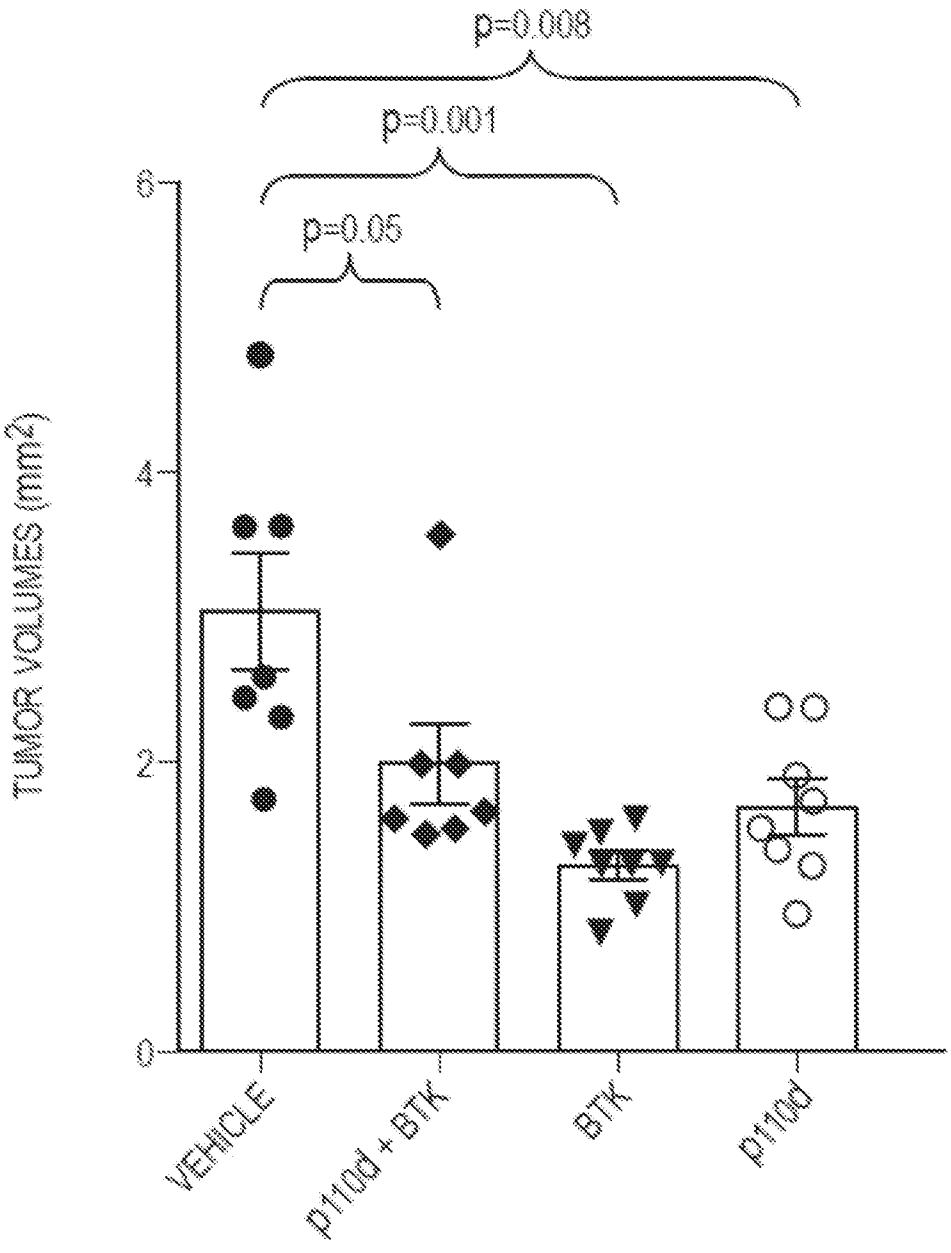

p=0.008
p=0.001
p=0.05
TUMOR VOLUMES (mm3)
6
4
2
0
VEHICLE
p110d + BTK
BTK
p110d

FIG. 4

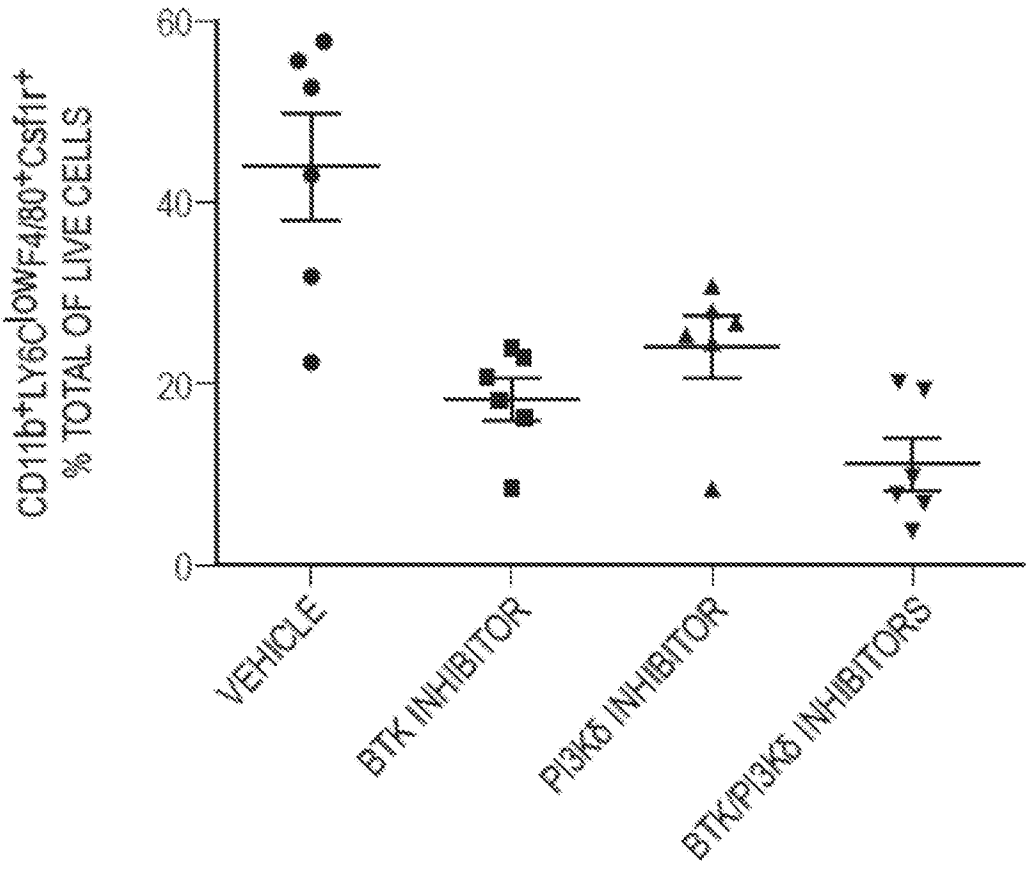

CD11b+LY6CLOWF4/80+Csf1r+
% TOTAL OF LIVE CELLS
60
40
20
0
VEHICLE
BTK INHIBITOR
PI3Kδ INHIBITOR
BTK/PI3Kδ INHIBITORS

FIG. 5

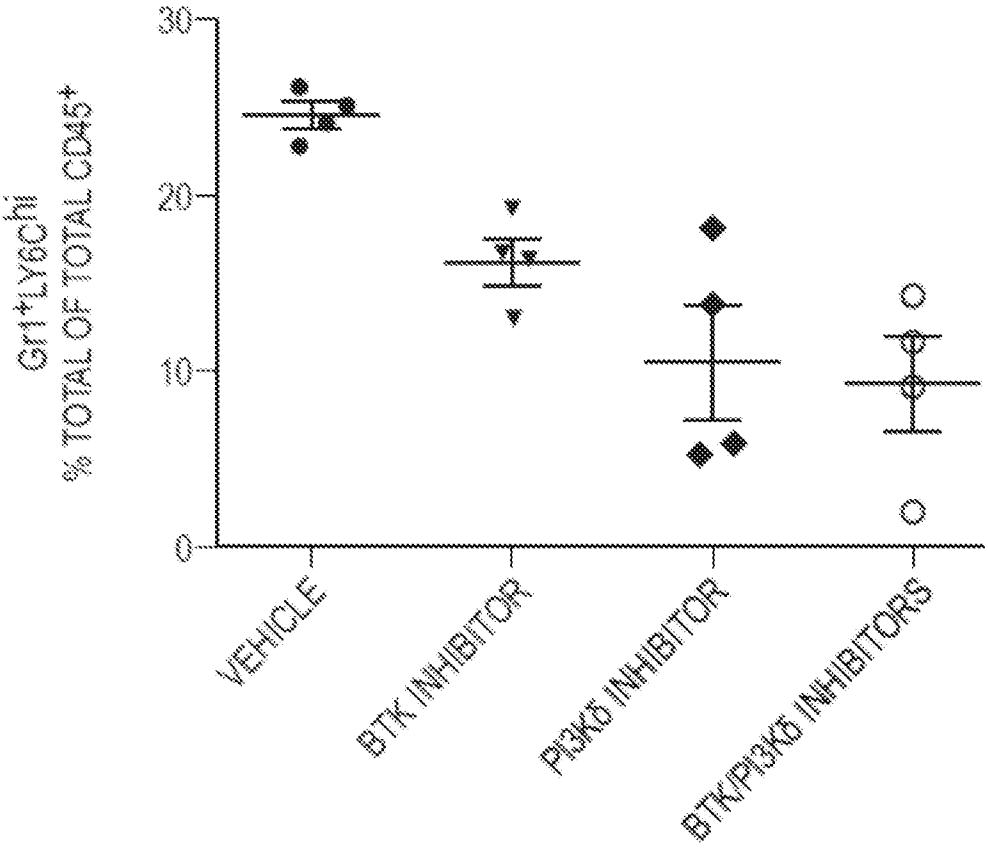

Gr1+LY6Chi
% TOTAL OF TOTAL CD45+
30
20
10
0
VEHICLE
BTK INHIBITOR
PI3Kδ INHIBITOR
BTK/PI3Kδ INHIBITORS

FIG. 6

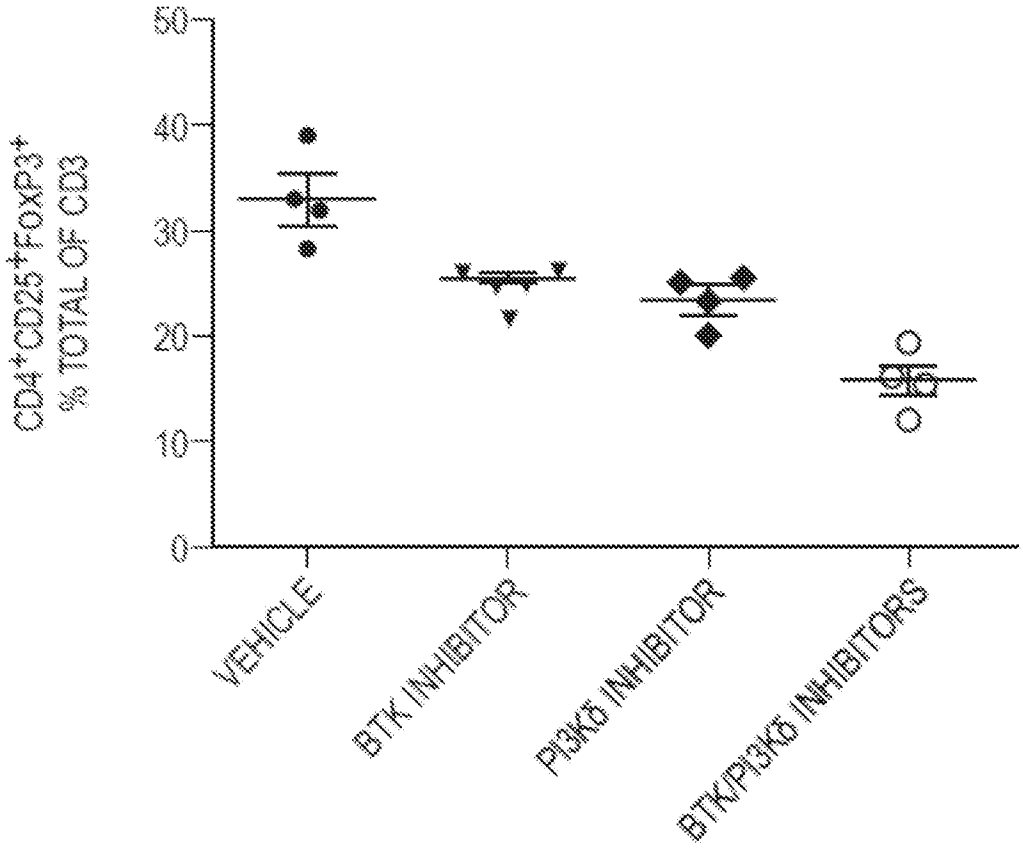

CD4+CD25+FoxP3+
% TOTAL OF CD3
50
40
30
20
10
0
VEHICLE
BTK INHIBITOR
PI3Kδ INHIBITOR
BTK/PI3Kδ INHIBITORS

FIG. 7

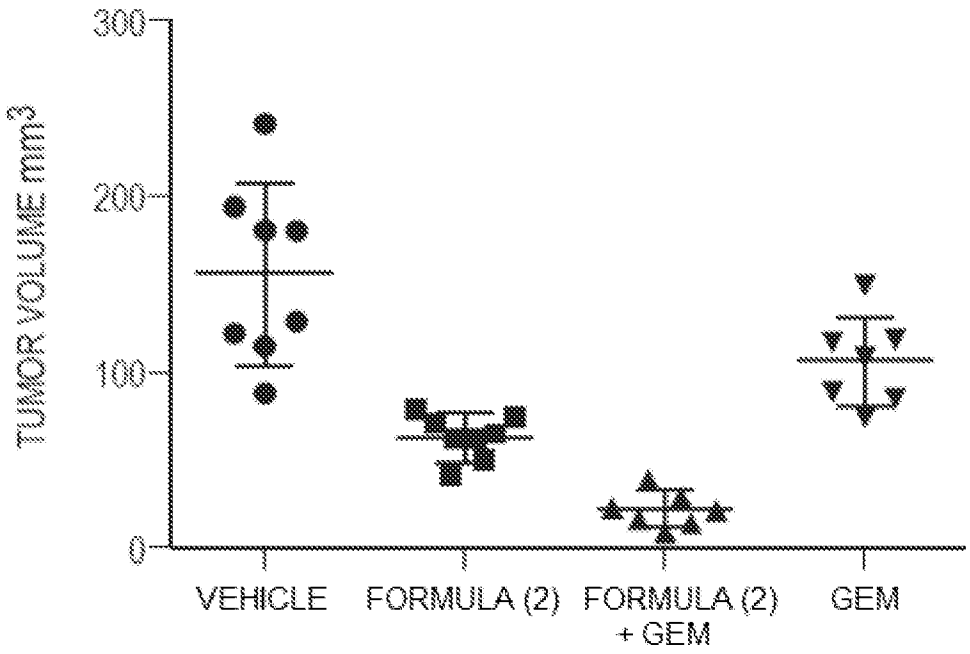

300
200
100
0
TUMOR VOLUME mm3
VEHICLE
FORMULA (2)
FORMULA (2) + GEM
GEM

FIG. 8

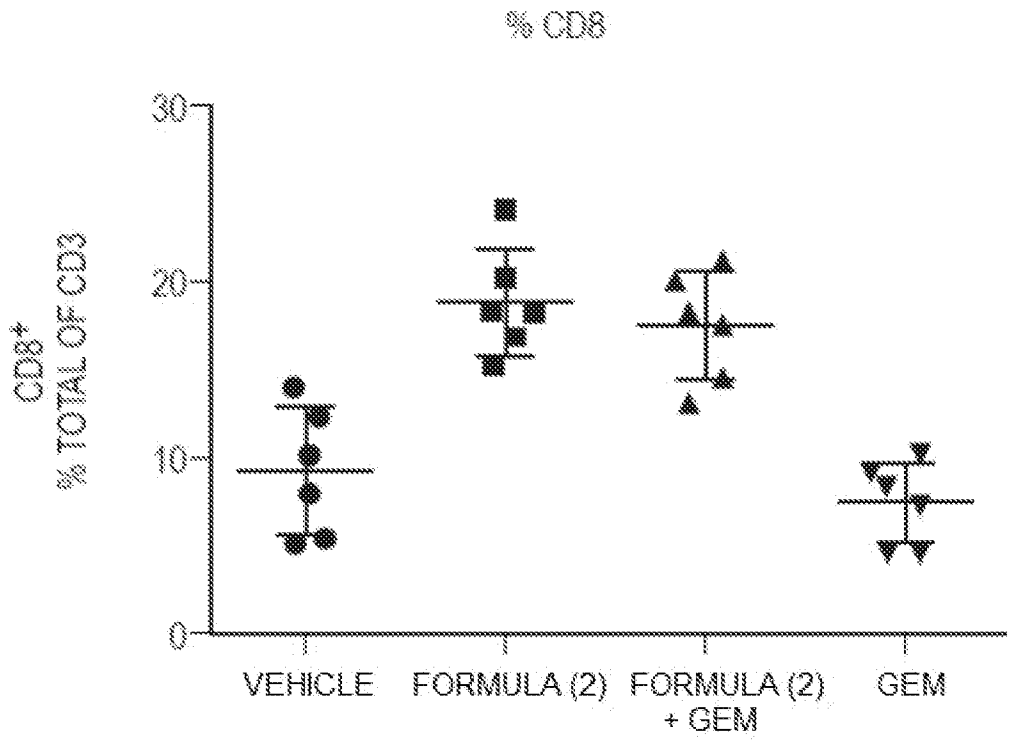

% CD8
CD8+
% TOTAL OF CD3
30
20
10
0
VEHICLE
FORMULA (2)
FORMULA (2)
+ GEM
GEM

FIG. 9

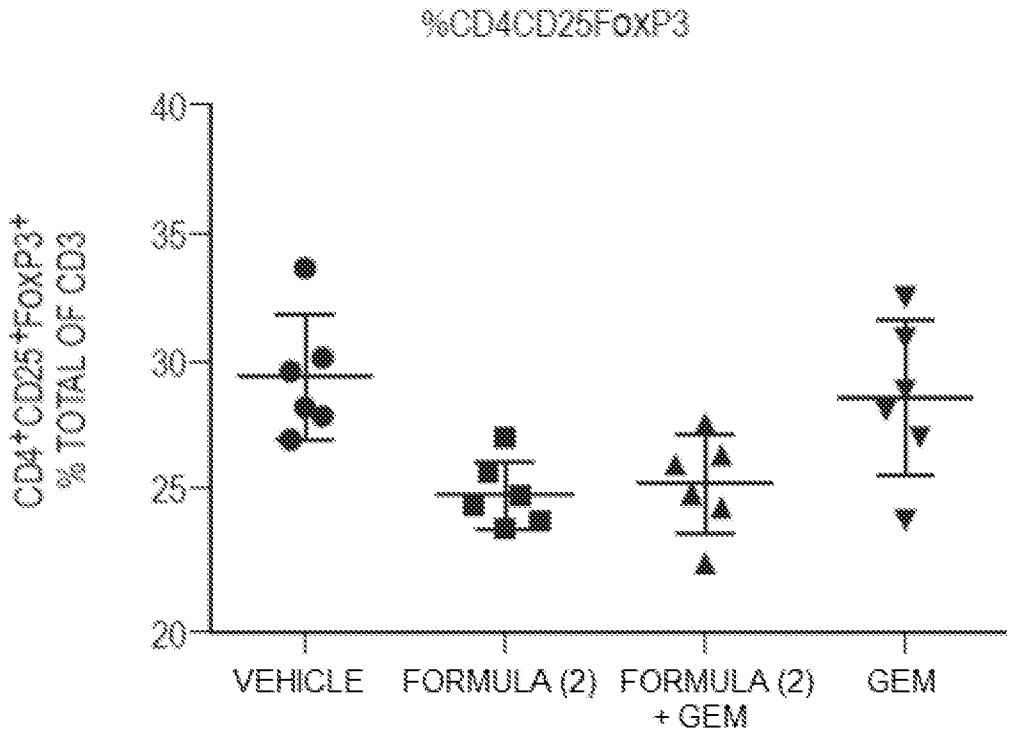

%CD4CD25FoxP3
CD4+CD25+FoxP3+
% TOTAL OF CD3
40
35
30
25
20
VEHICLE
FORMULA (2)
FORMULA (2) + GEM
GEM

FIG. 10

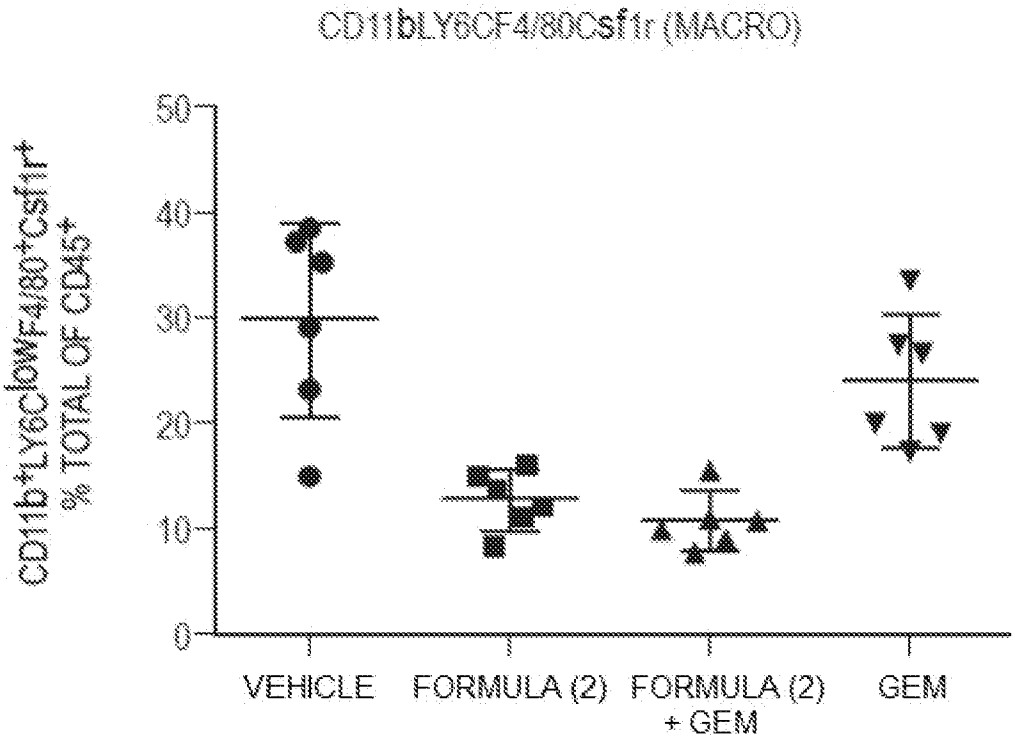

CD11bLY6CF4/80Csf1r (MACRO)
CD11b+LY6Clow F4/80+Csf1r+
% TOTAL OF CD45+
50
40
30
20
10
0
VEHICLE
FORMULA (2)
FORMULA (2) + GEM
GEM

FIG. 11

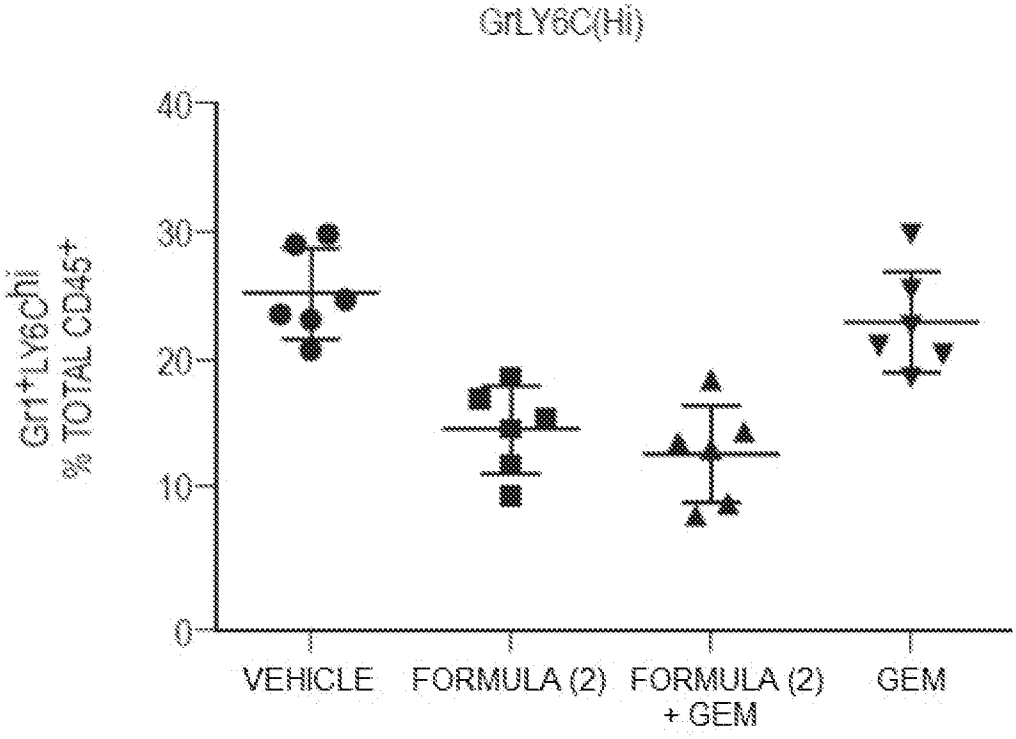

Gr1LY6C(Hi)
Gr1+Ly6Chi
% TOTAL CD45+
40
30
20
10
0
VEHICLE
FORMULA (2)
FORMULA (2) + GEM
GEM

FIG. 12

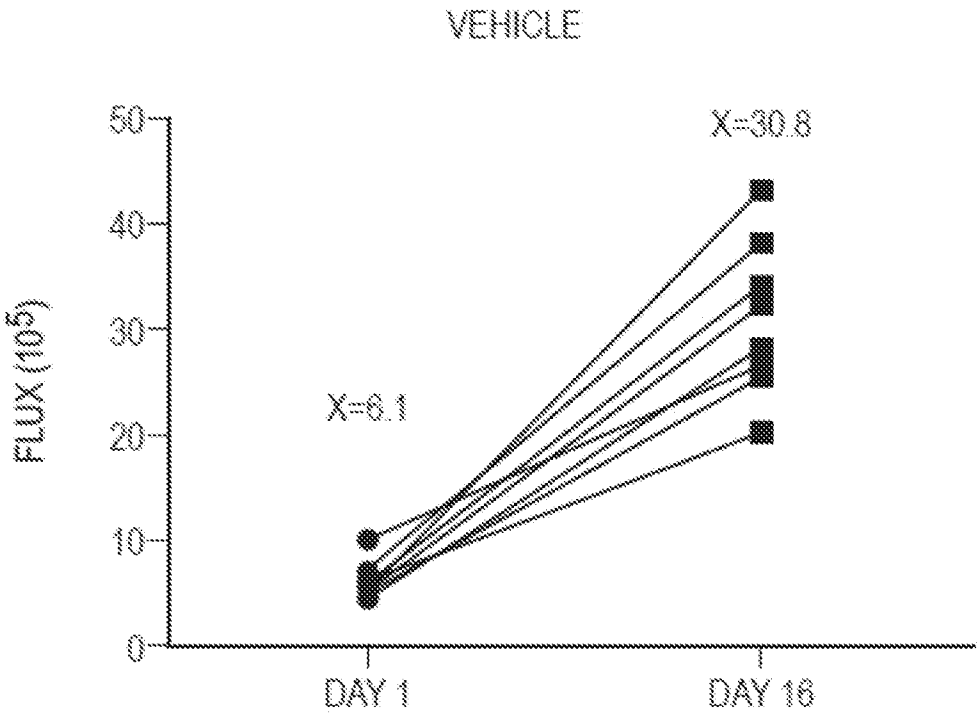


FIG. 13

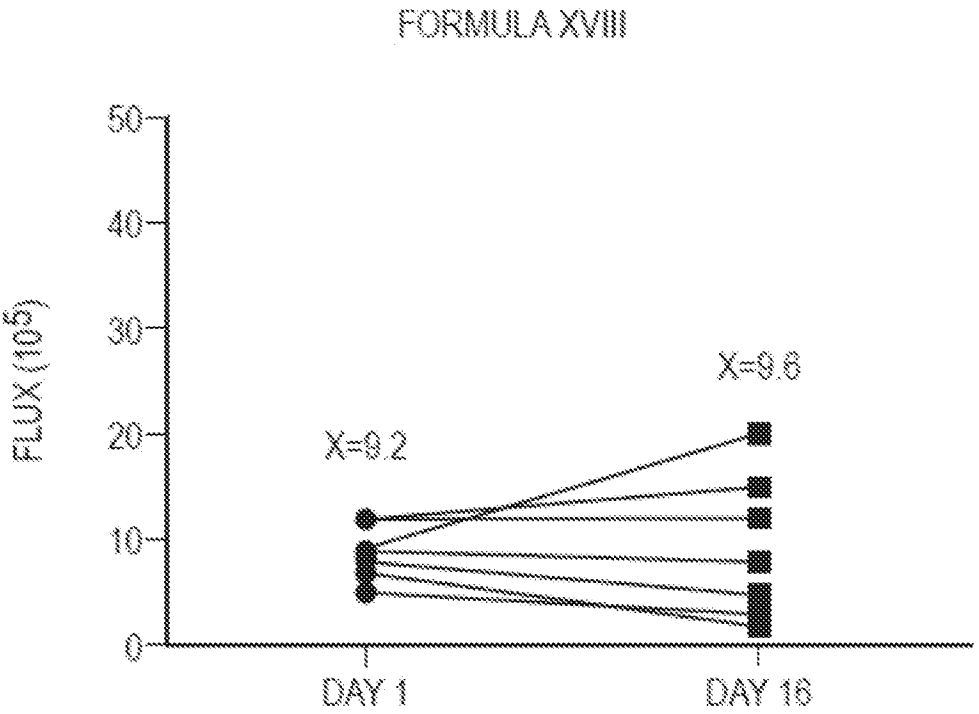


FIG. 14

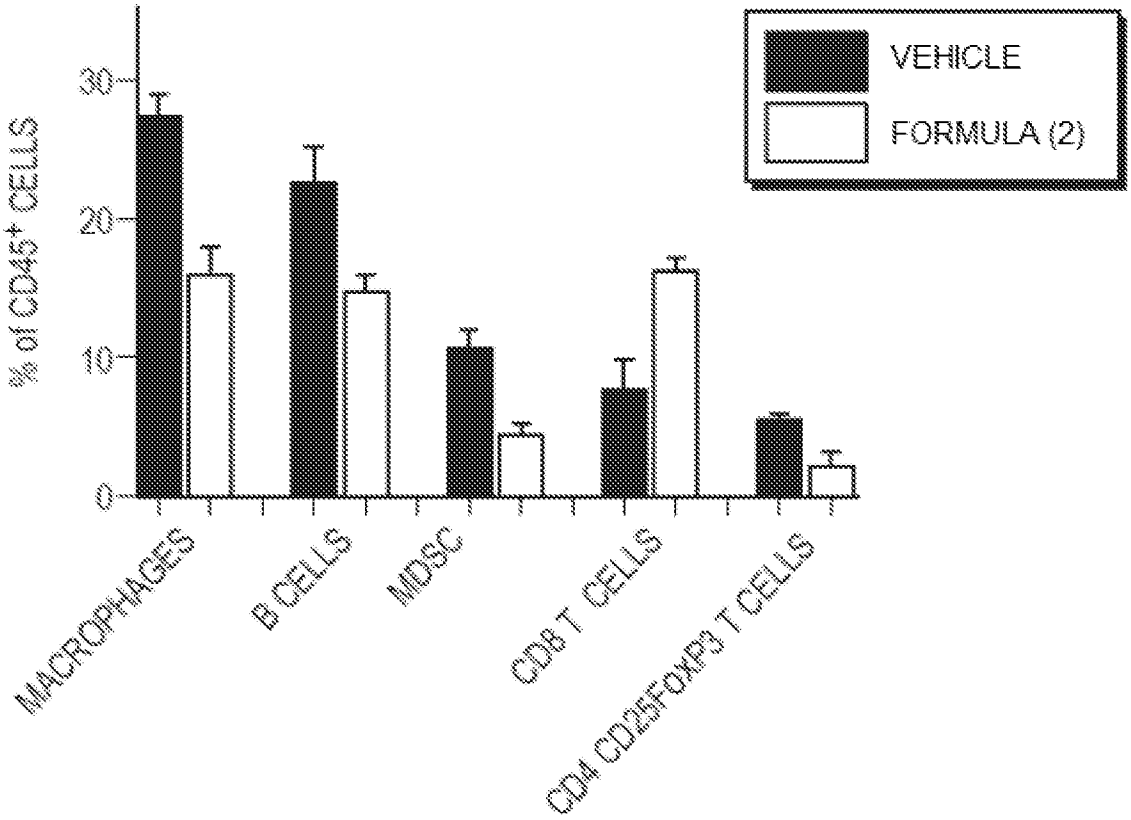

VEHICLE
FORMULA (2)
% of CD45+ CELLS
30
20
10
0
MACROPHAGES
B CELLS
MDSC
CD8 T CELLS
CD4 CD25FOXP3 T CELLS

FIG. 15

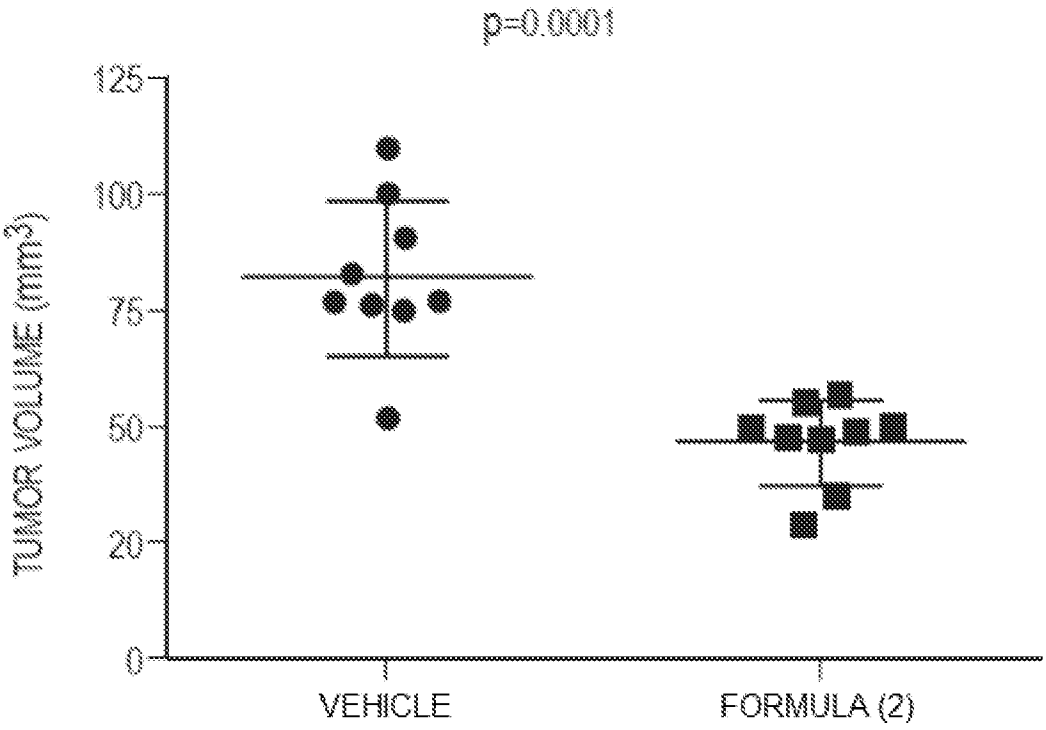


FIG. 16

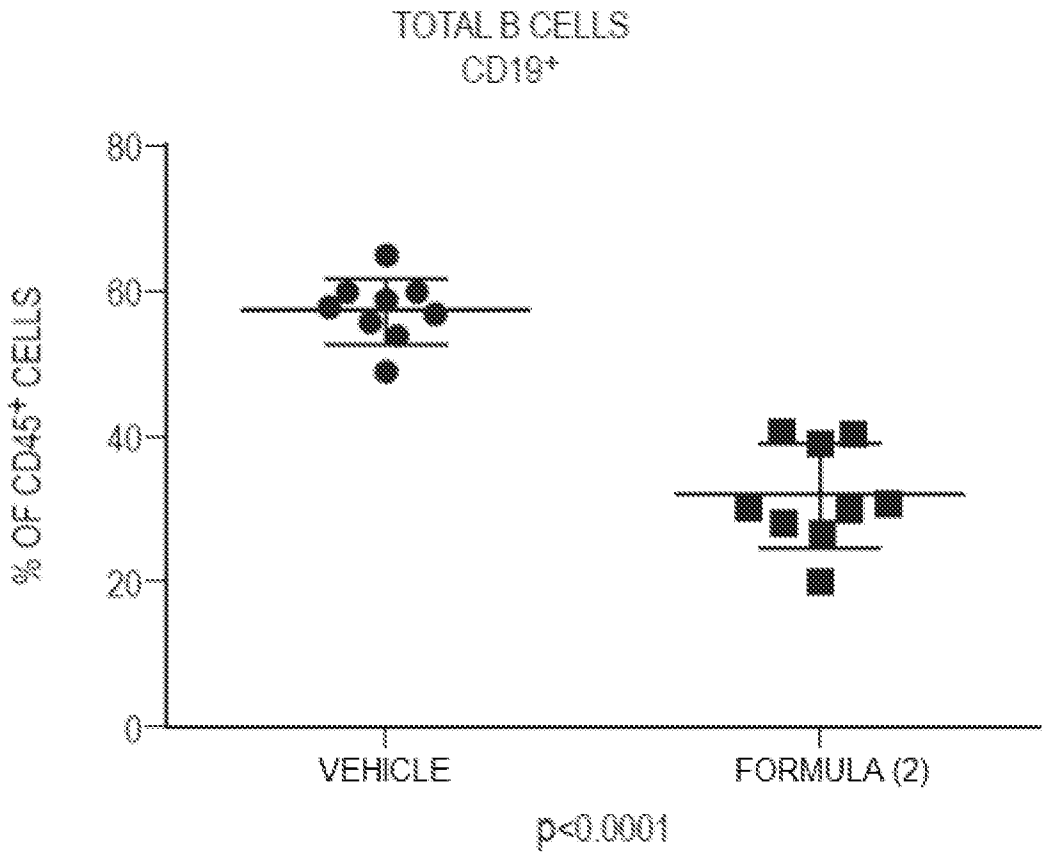

TOTAL B CELLS
CD19+
% OF CD45+ CELLS
80
60
40
20
0
VEHICLE
FORMULA (2)
p<0.0001

FIG. 17

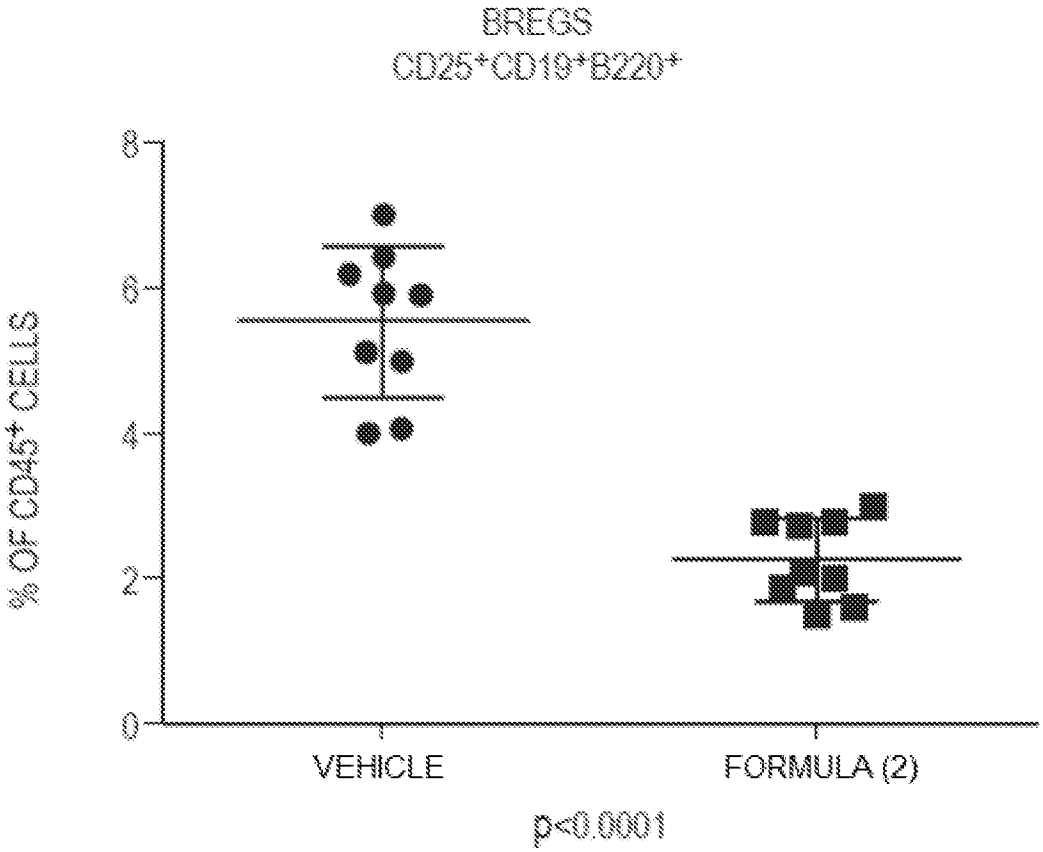

BREGS
CD25+CD19+B220+
% OF CD45+ CELLS
8
6
4
2
0
VEHICLE
FORMULA (2)
p<0.0001

FIG. 18

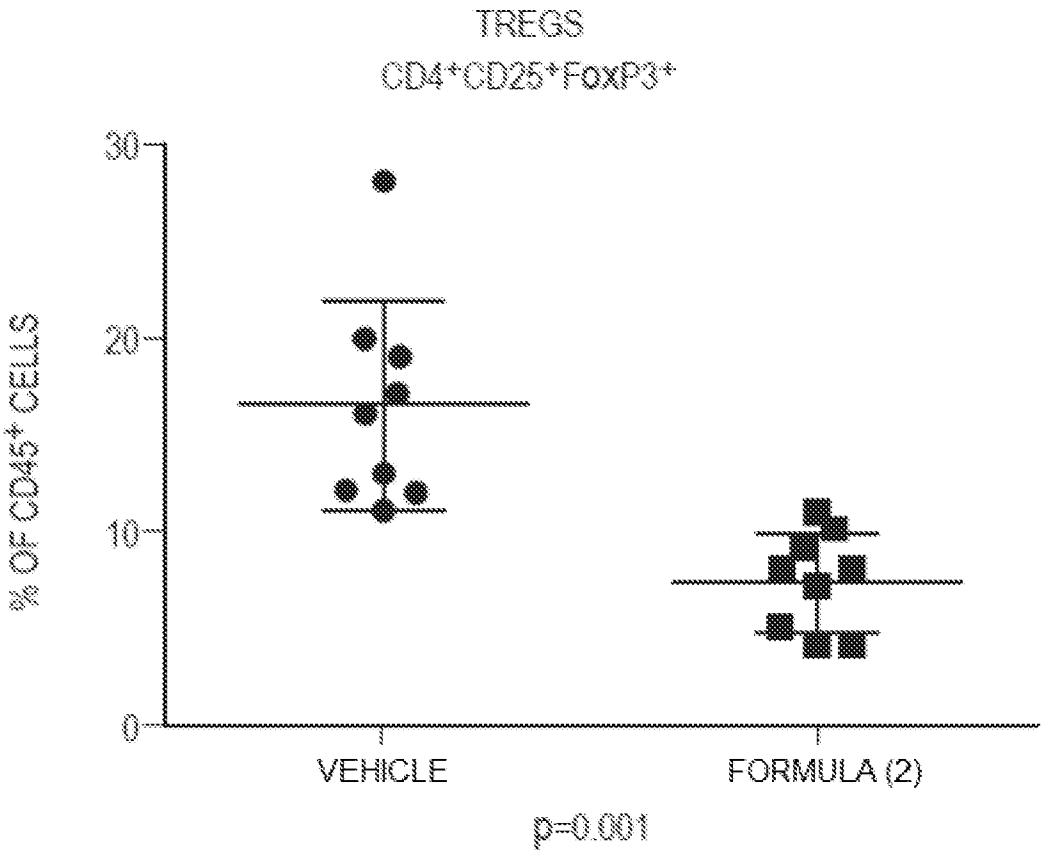

TREGS
CD4+CD25+FoxP3+
% OF CD45+ CELLS
30
20
10
0
VEHICLE
FORMULA (2)
p=0.001

FIG. 19

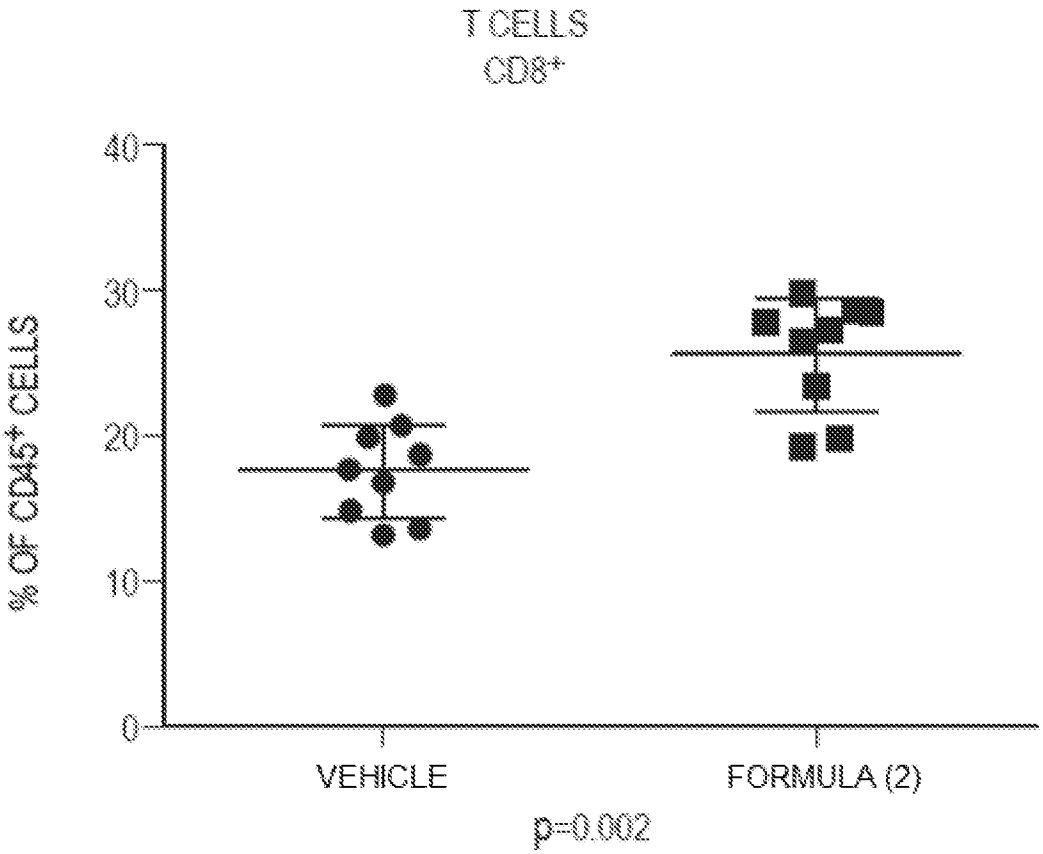


FIG. 20

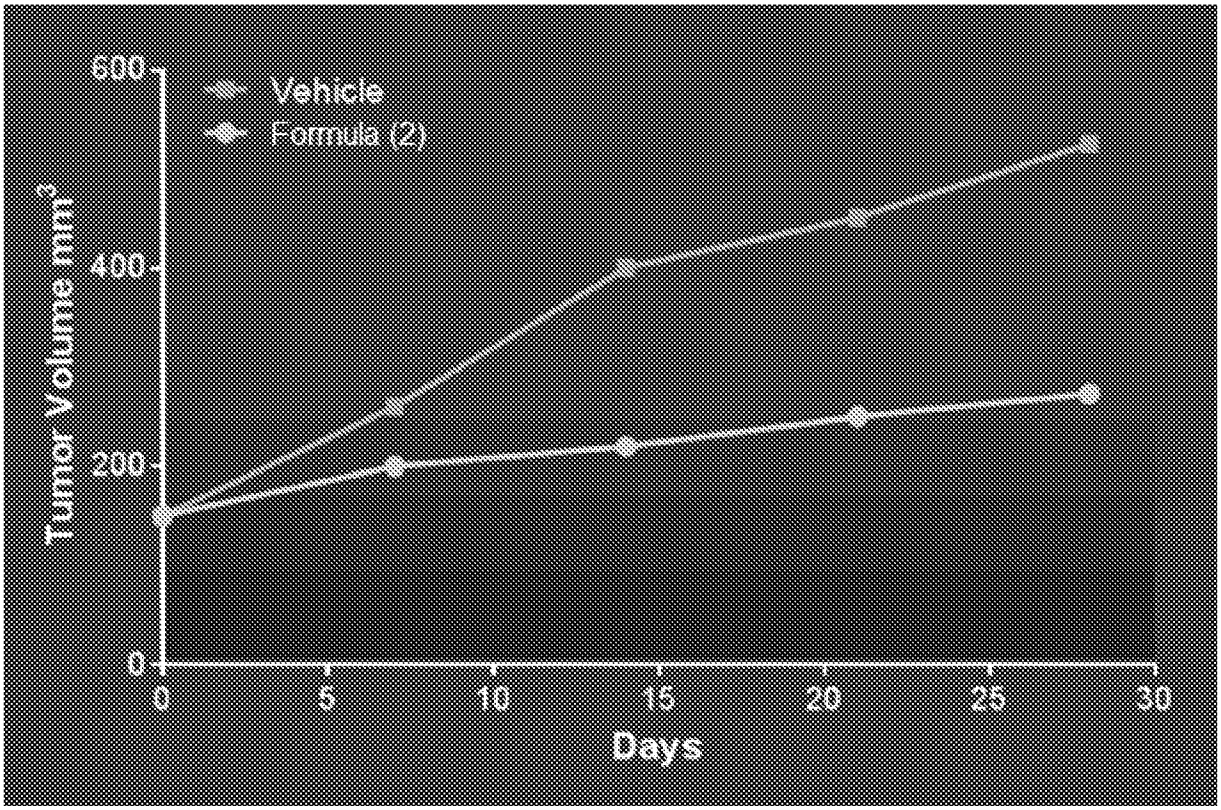

600
400
200
0
Tumor Volume mm3
Vehicle
Formula (2)
0
5
10
15
20
25
30
Days

FIG. 21

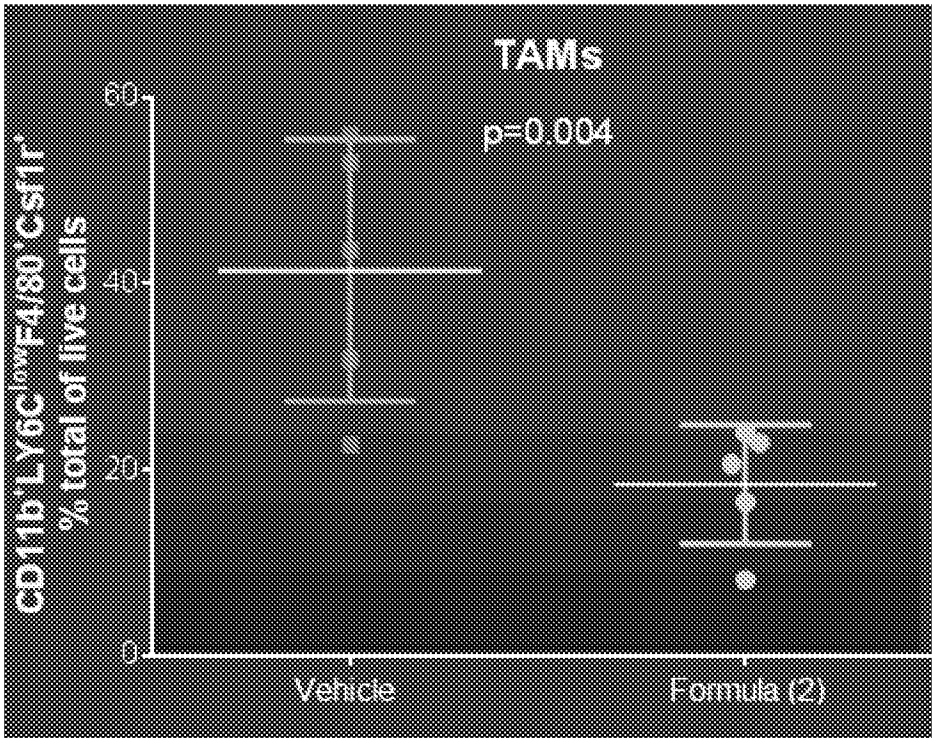

TAMs
p=0.004
CD11b+Ly6C-/lowF4/80+Csf1r+
% total of live cells
60
40
20
0
Vehicle
Formula (2)

FIG. 22

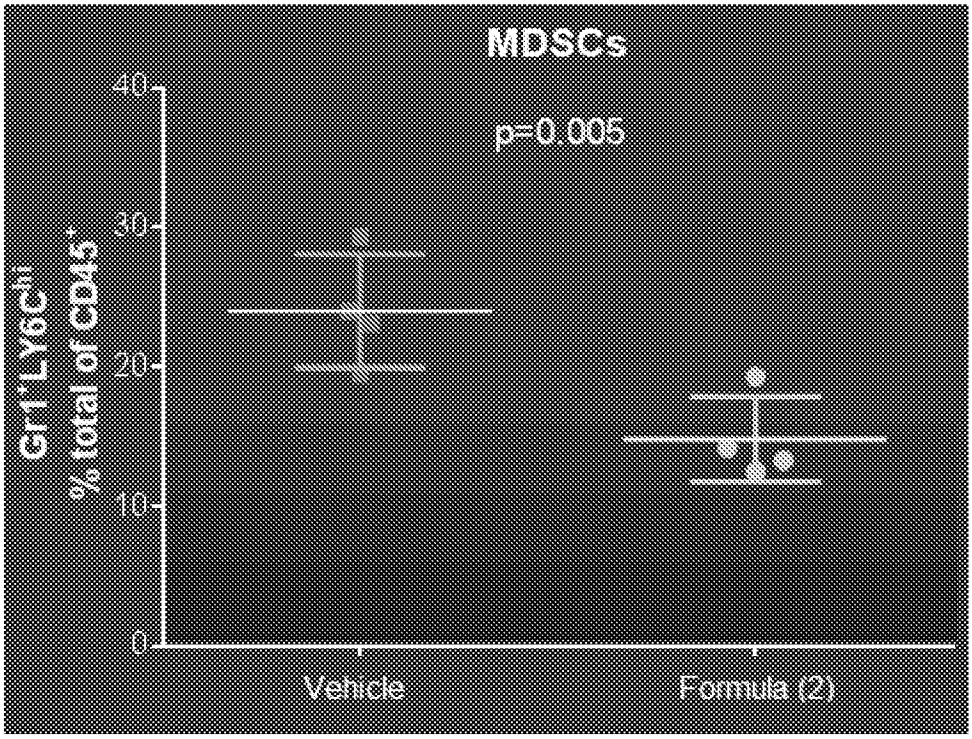

MDSCs
p=0.005
Gr1+Ly6C+
% total of CD45+
40
30
20
10
0
Vehicle
Formula (2)

FIG. 23

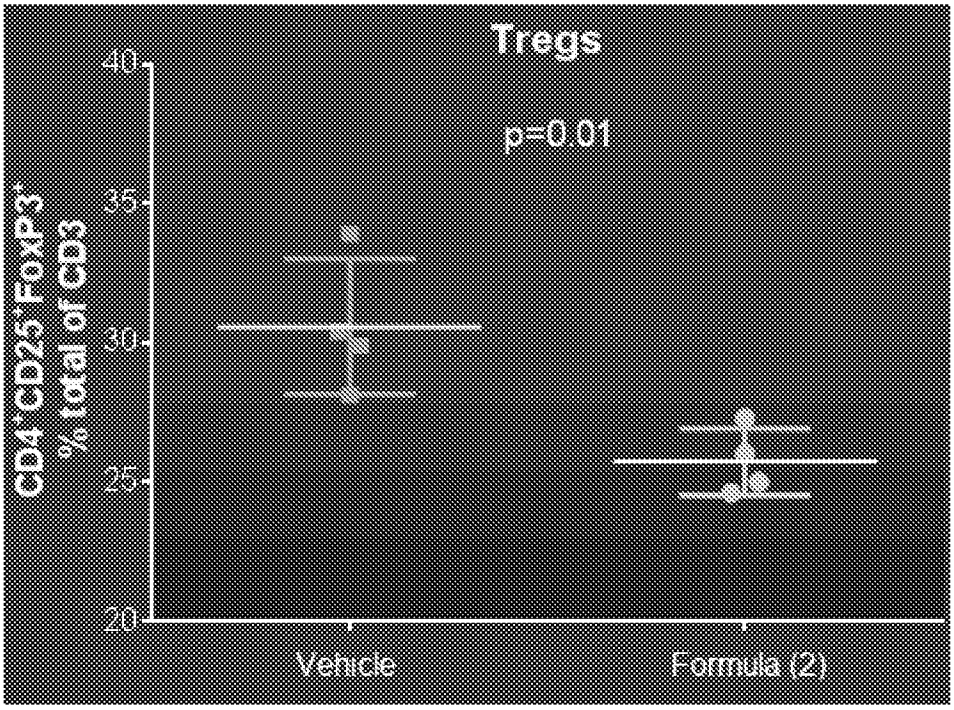

Tregs
p=0.01
CD4+CD25+FoxP3+
% total of CD3
40
35
30
25
20
Vehicle
Formula (2)

FIG. 24

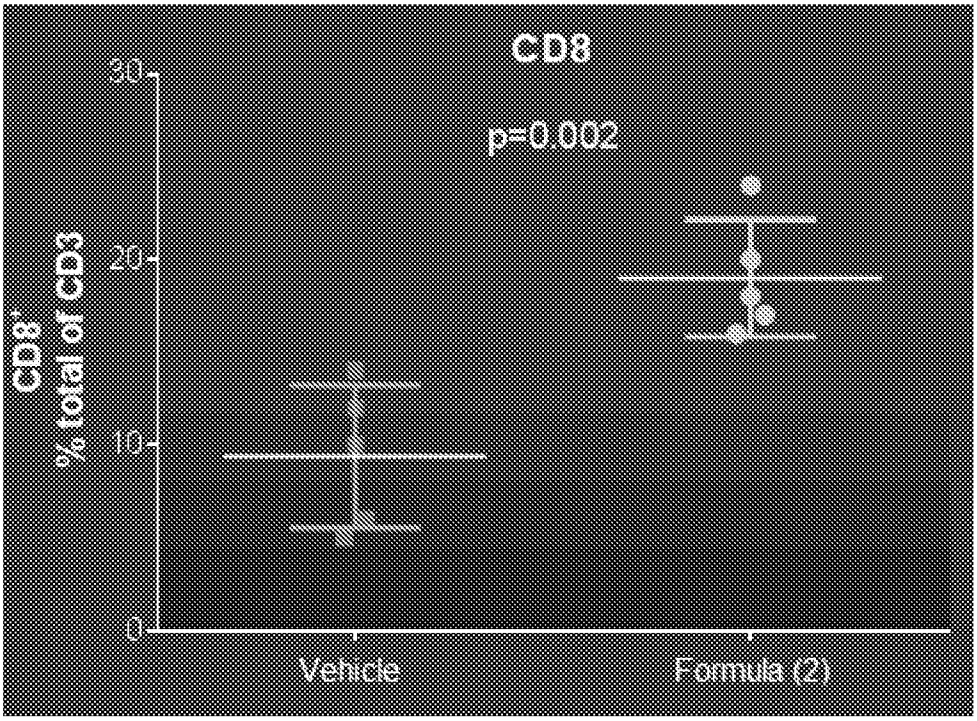


FIG. 25

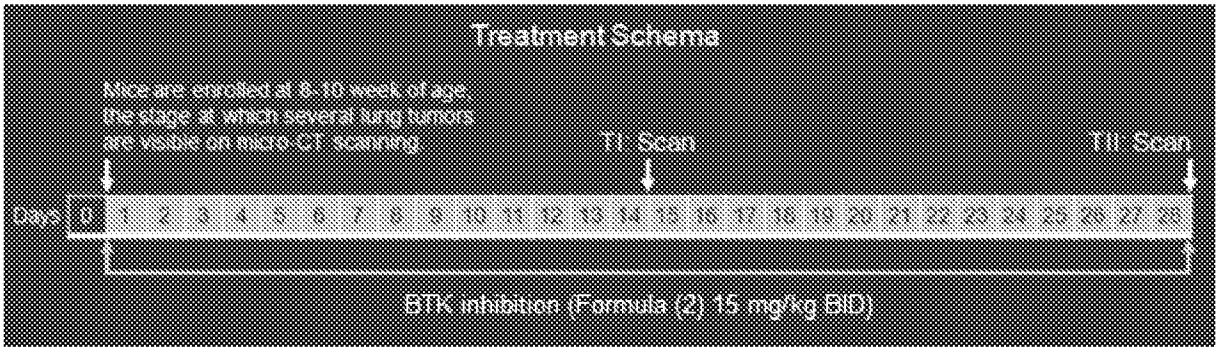

Treatment Schema
Mice are enrolled at 8-10 week of age,
the stage at which several lung tumors
are visible on micro-CT scanning
T1 Scan
T11 Scan
Days
0
BTK inhibition (Formula (2) 15 mg/kg BID)

FIG. 26

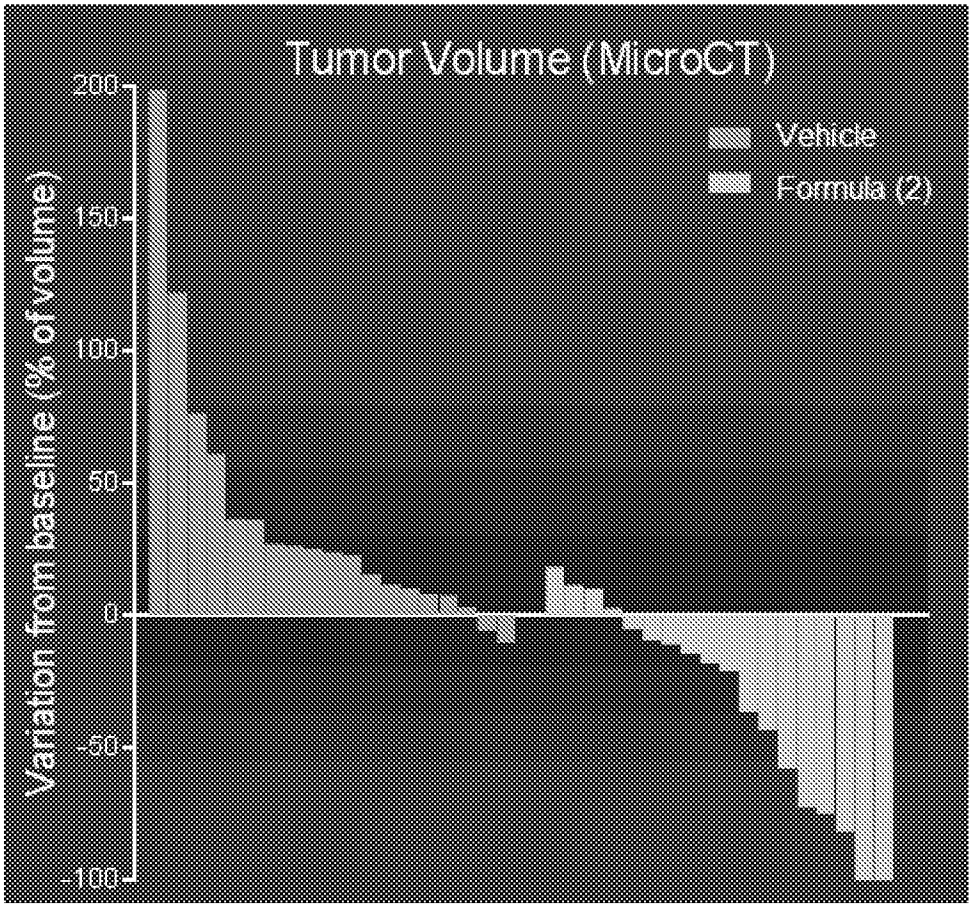

Tumor Volume (MicroCT)
Vehicle
Formula (2)
Variation from baseline (% of volume)
200
150
100
50
0
-50
-100

FIG. 27

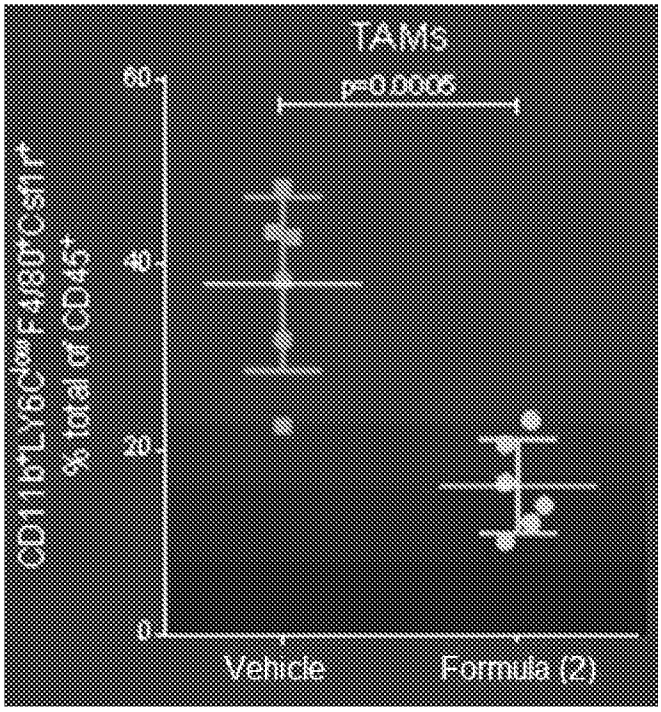

TAMs
p=0.0006
CD11b+Ly6C-lowF4/80+CSF1R+
% total of CD45+
60
40
20
0
Vehicle
Formula (2)

FIG. 28

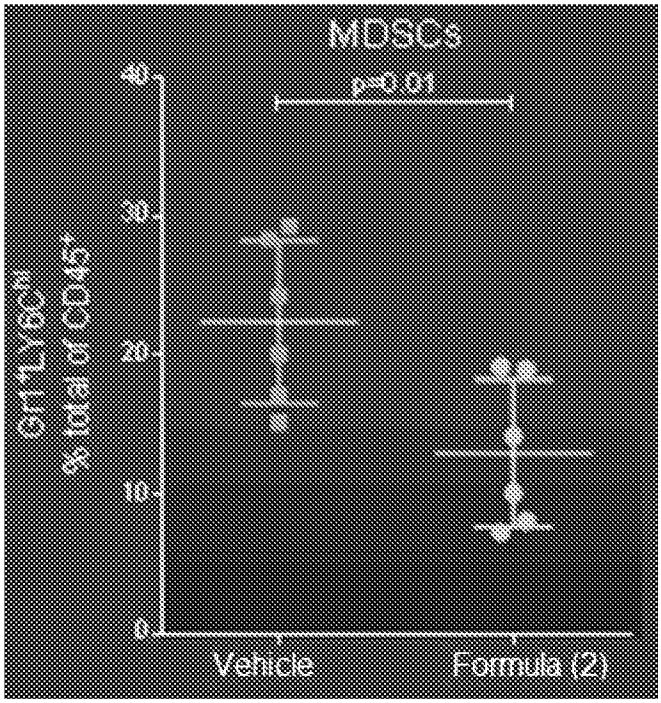


FIG. 29

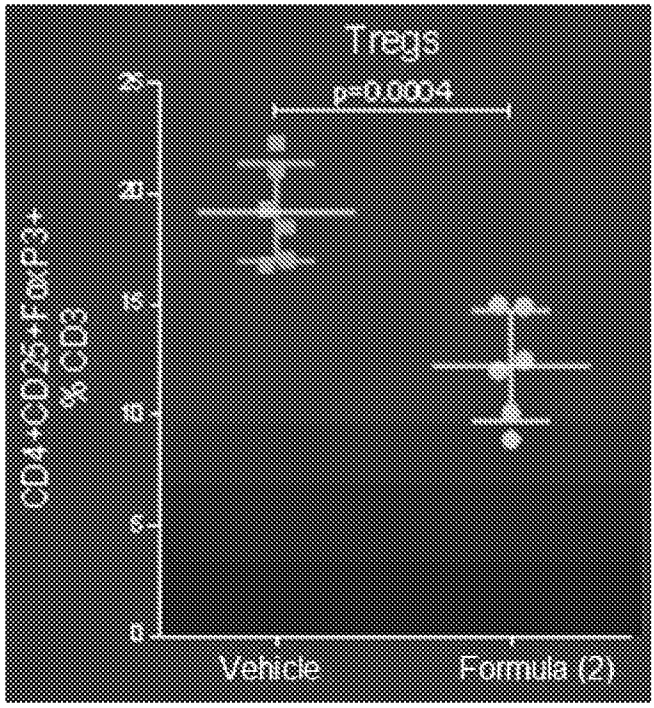

Tregs
p=0.0004
CD4+CD25+Foxp3+
% CD3
25
20
15
10
5
0
Vehicle
Formula (2)

FIG. 30

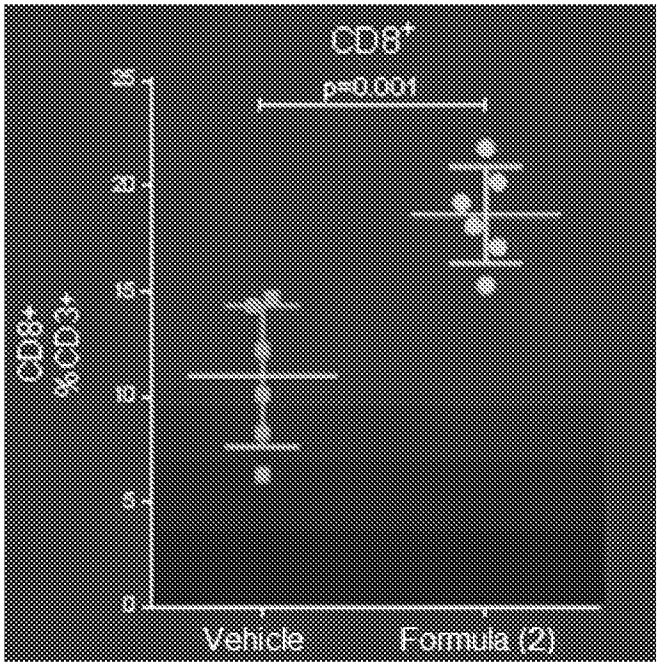


FIG. 31

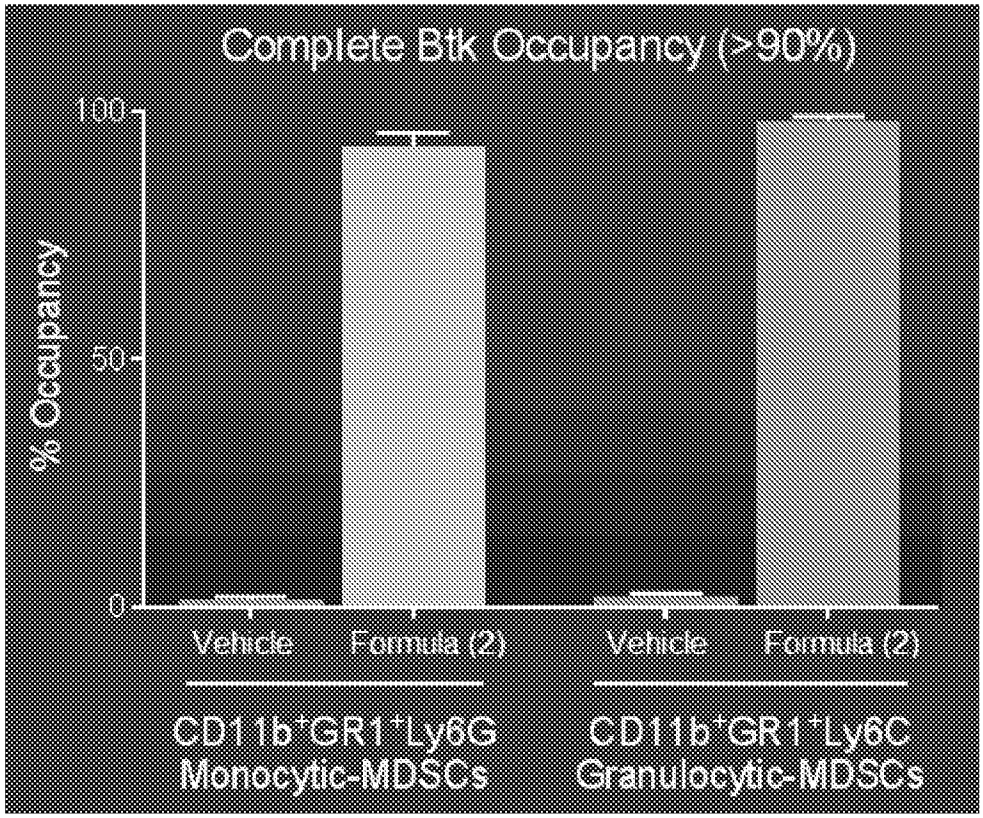

Complete Btk Occupancy (>90%)
% Occupancy
100
50
0
Vehicle
Formula (2)
Vehicle
Formula (2)
CD11b+GR1+Ly6G
Monocytic-MDSCs
CD11b+GR1+Ly6C
Granulocytic-MDSCs

FIG. 32

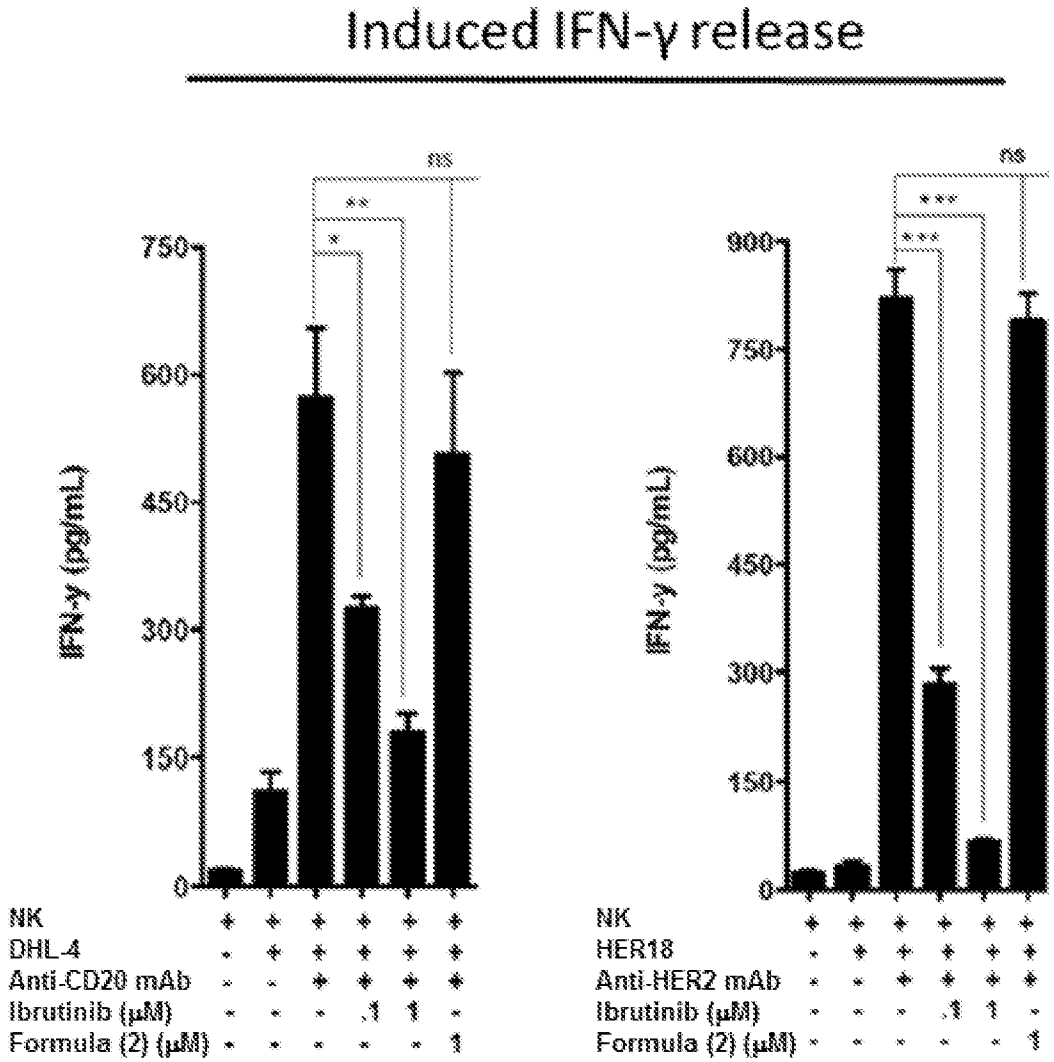

Induced IFN-γ release
IFN-γ (pg/mL)
750
600
450
300
150
0
ns
**
*
NK + + + + + +
DHL-4 - + + + + +
Anti-CD20 mAb - - + + + +
Ibrutinib (μM) - - - .1 1 -
Formula (2) (μM) - - - - - 1
IFN-γ (pg/mL)
900
750
600
450
300
150
0
ns
***
***
NK + + + + + +
HER18 - + + + + +
Anti-HER2 mAb - - + + + +
Ibrutinib (μM) - - - .1 1 -
Formula (2) (μM) - - - - - 1

FIG. 33

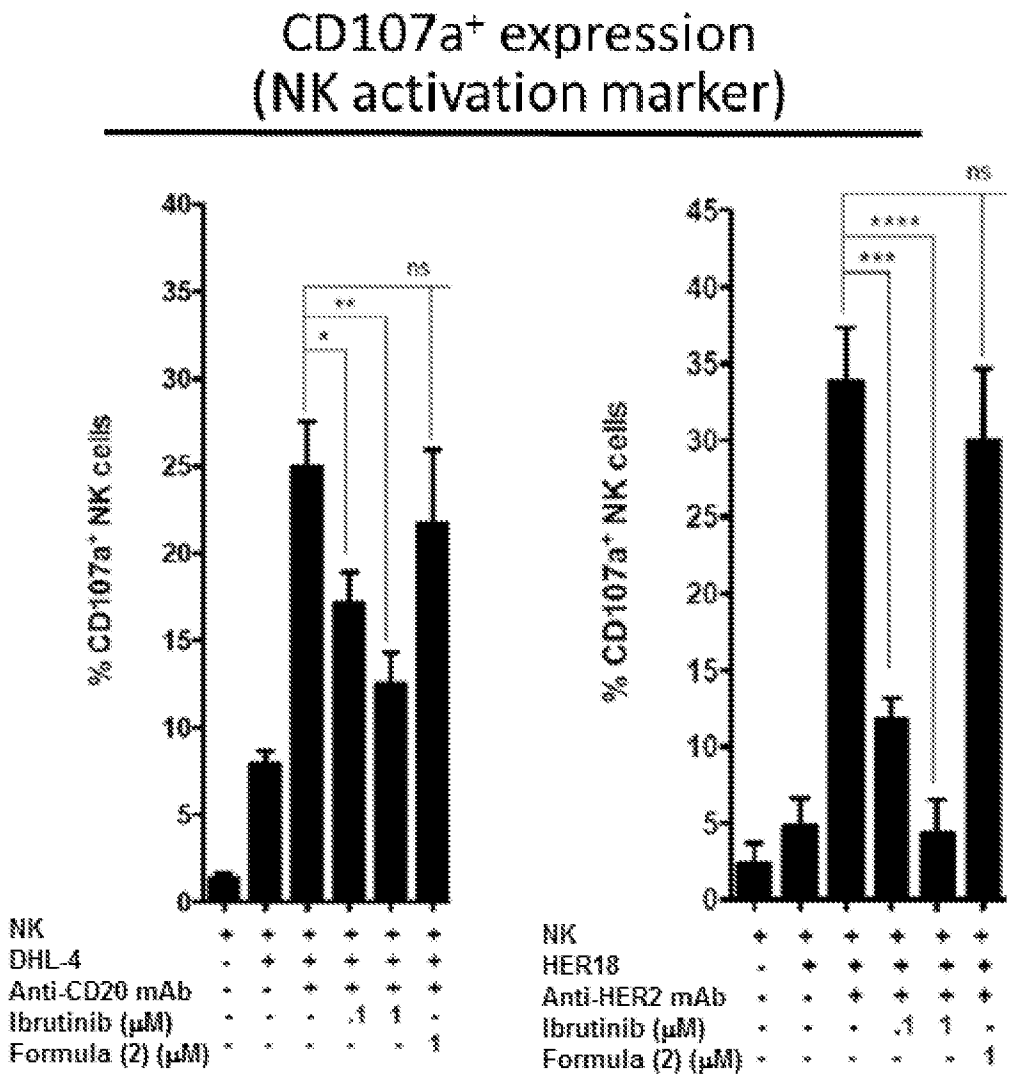

CD107a+ expression
(NK activation marker)
% CD107a+ NK cells
40
35
30
25
20
15
10
5
0
ns
**
*
NK + + + + + +
DHL-4 - + + + + +
Anti-CD20 mAb - - + + + +
Ibrutinib (μM) - - - .1 1 -
Formula (2) (μM) - - - - - 1
% CD107a+ NK cells
45
40
35
30
25
20
15
10
5
0
ns
****
***
NK + + + + + +
HER18 - + + + + +
Anti-HER2 mAb - - + + + +
Ibrutinib (μM) - - - .1 1 -
Formula (2) (μM) - - - - - 1

FIG. 34

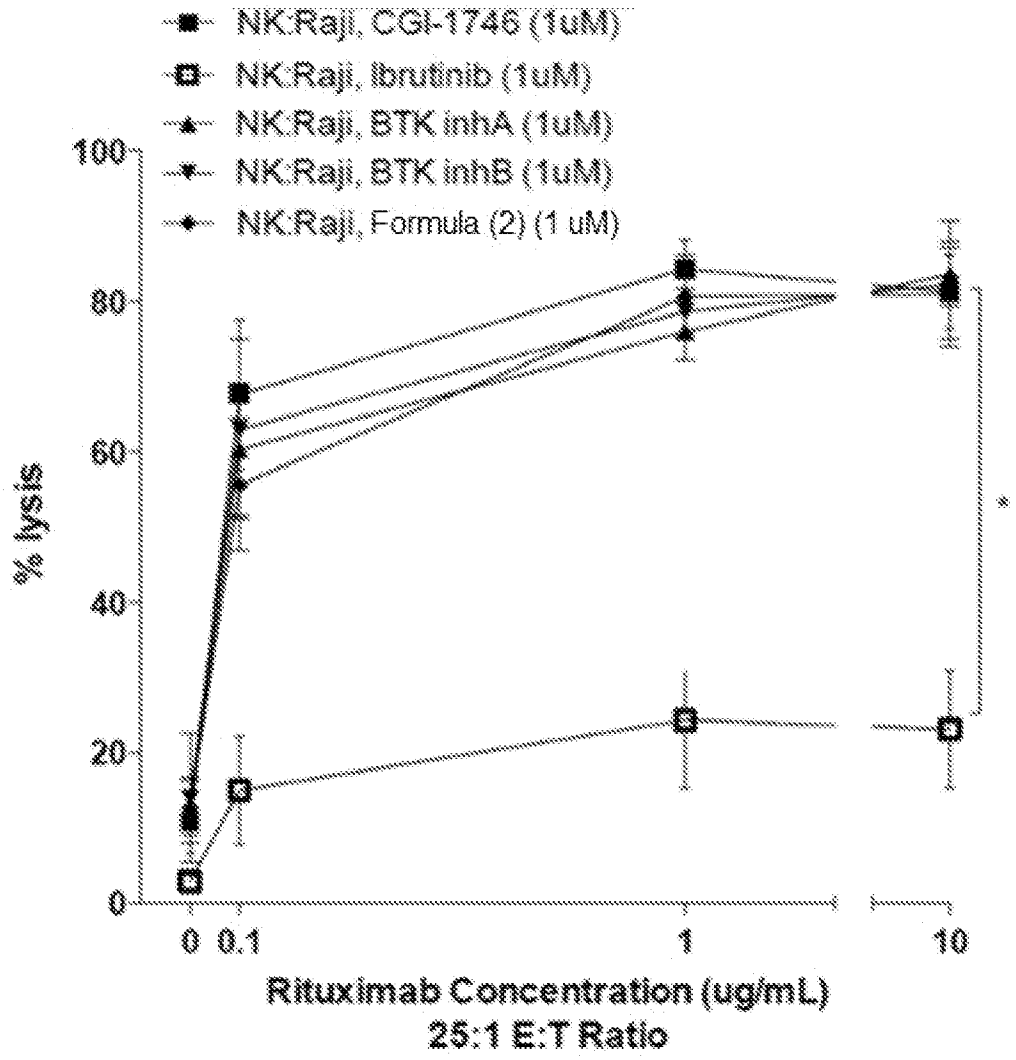

NK:Raji, CGI-1746 (1uM)
NK:Raji, Ibrutinib (1uM)
NK:Raji, BTK inhA (1uM)
NK:Raji, BTK inhB (1uM)
NK:Raji, Formula (2) (1 uM)
100
80
60
40
20
0
% lysis
0
0.1
1
10
*
Rituximab Concentration (ug/mL)
25:1 E:T Ratio

FIG. 35

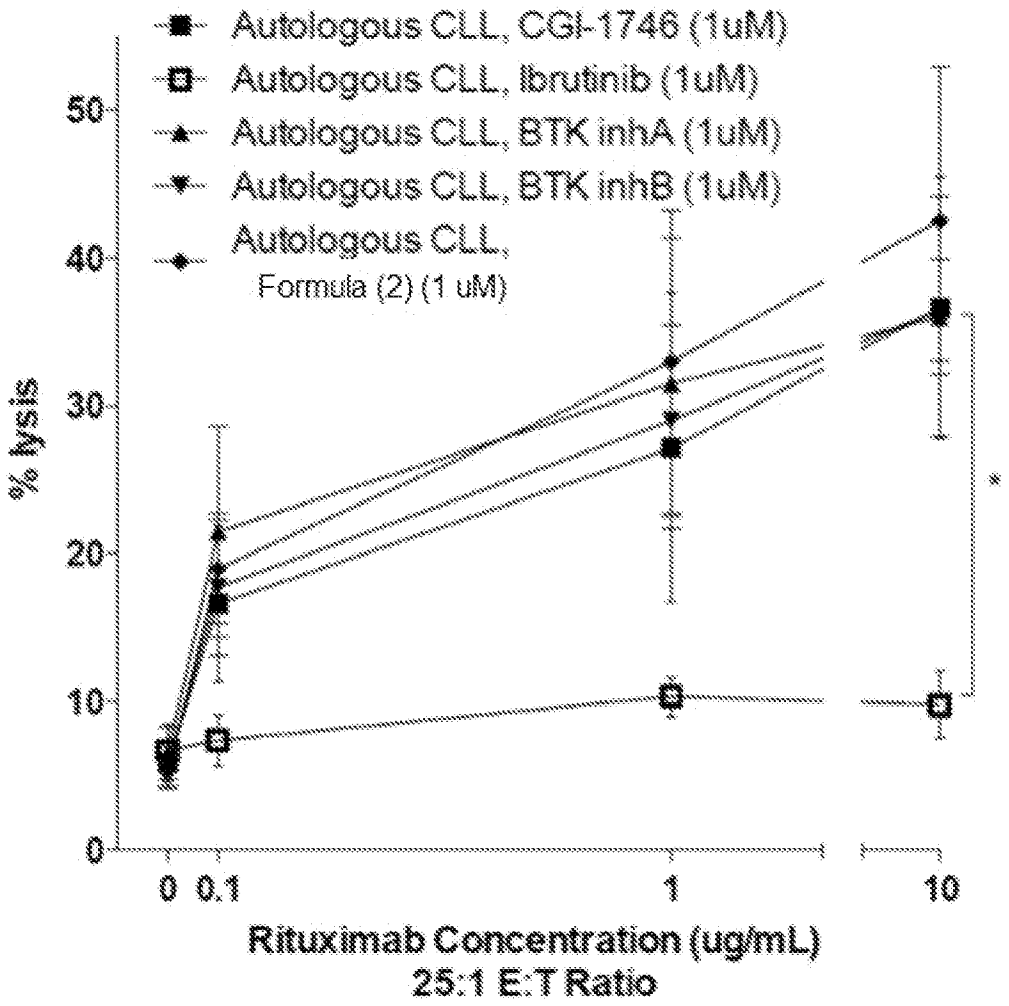

Autologous CLL, CGI-1746 (1uM)
Autologous CLL, Ibrutinib (1uM)
Autologous CLL, BTK inhA (1uM)
Autologous CLL, BTK inhB (1uM)
Autologous CLL, Formula (2) (1 uM)
% lysis
0
10
20
30
40
50
0
0.1
1
10
*
Rituximab Concentration (ug/mL)
25:1 E:T Ratio

FIG. 36

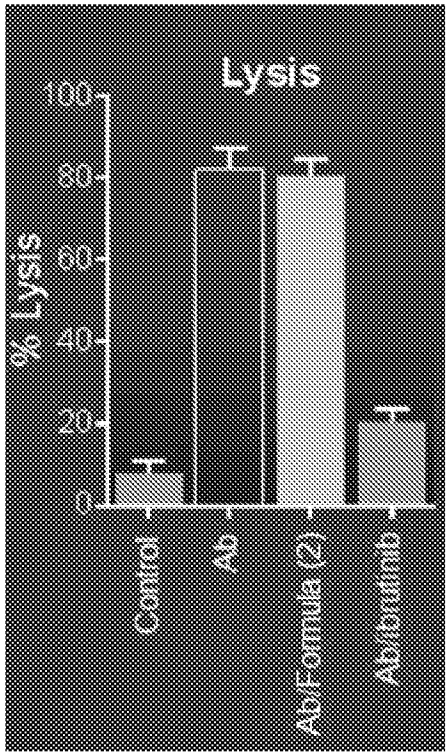

Lysis
% Lysis
100
80
60
40
20
0
Control
Ab
Ab/Formula (2)
Ab/Formula

FIG. 37

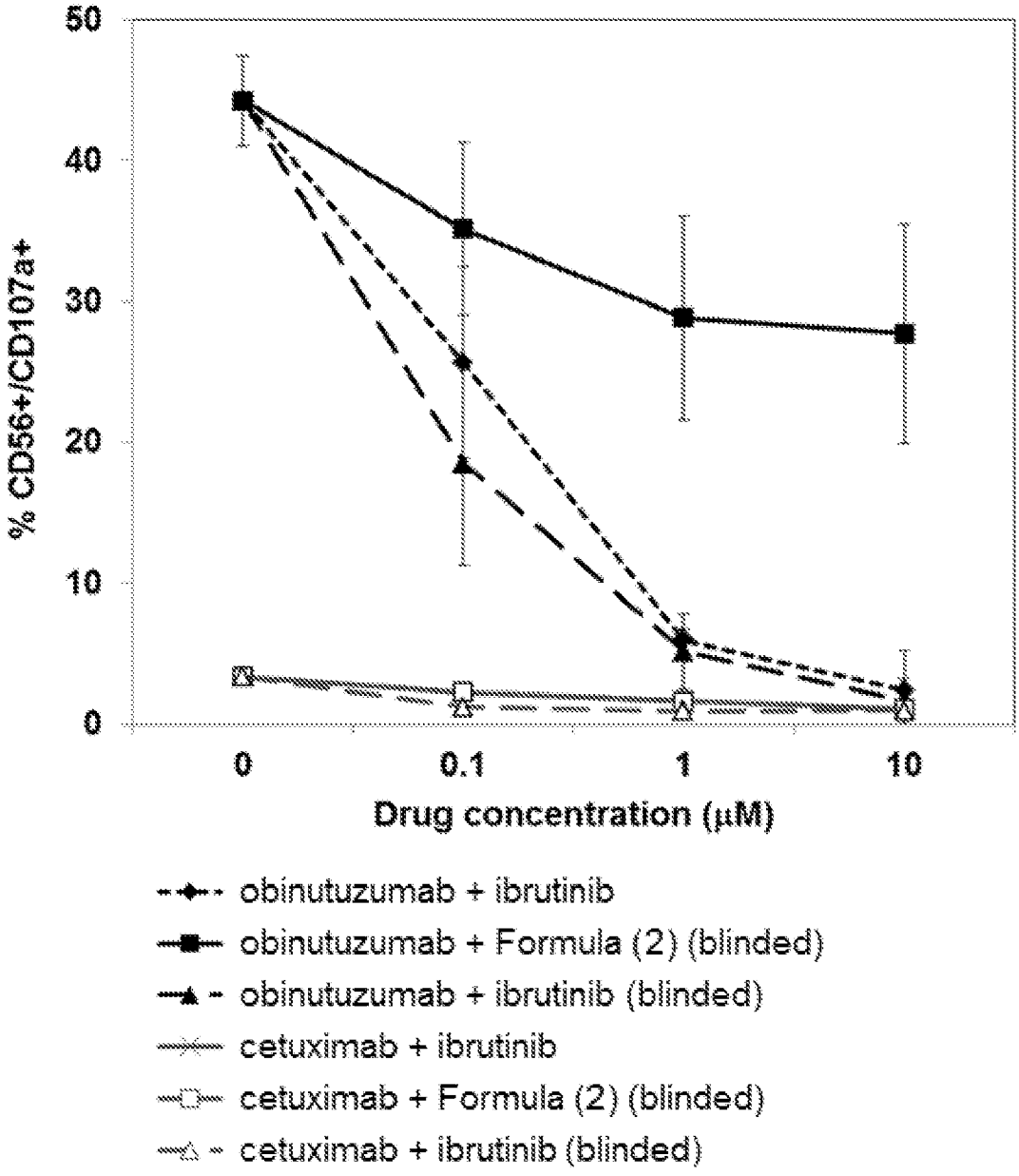

50
40
30
20
10
0
% CD56+/CD107a+
0
0.1
1
10
Drug concentration (μM)
obinutuzumab + ibrutinib
obinutuzumab + Formula (2) (blinded)
obinutuzumab + ibrutinib (blinded)
cetuximab + ibrutinib
cetuximab + Formula (2) (blinded)
cetuximab + ibrutinib (blinded)

FIG. 38

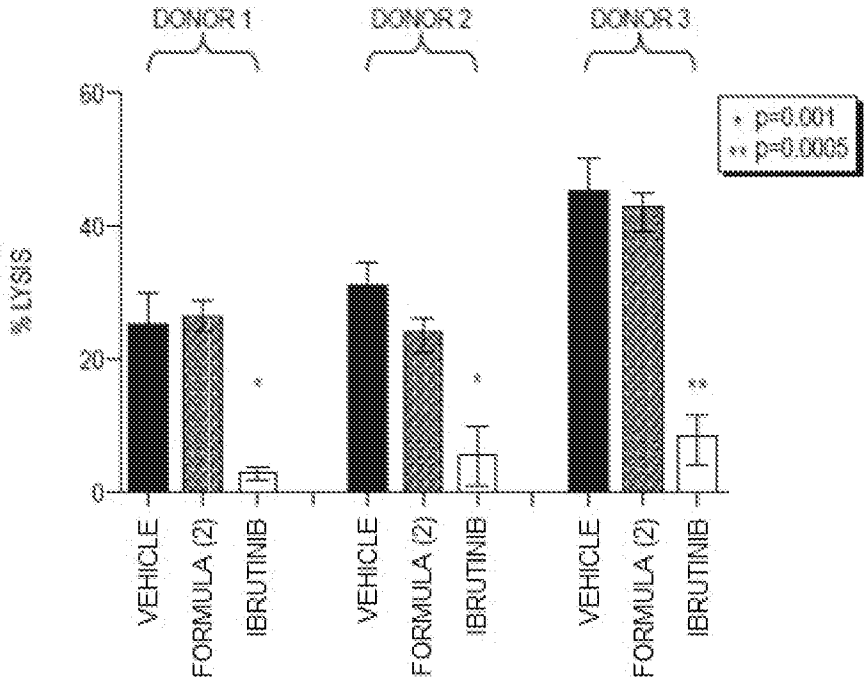

DONOR 1
DONOR 2
DONOR 3
* p=0.001
** p=0.0005
% LYSIS
0
20
40
60
VEHICLE
FORMULA (2)
IBRUTINIB
VEHICLE
FORMULA (2)
IBRUTINIB
VEHICLE
FORMULA (2)
IBRUTINIB

FIG. 39

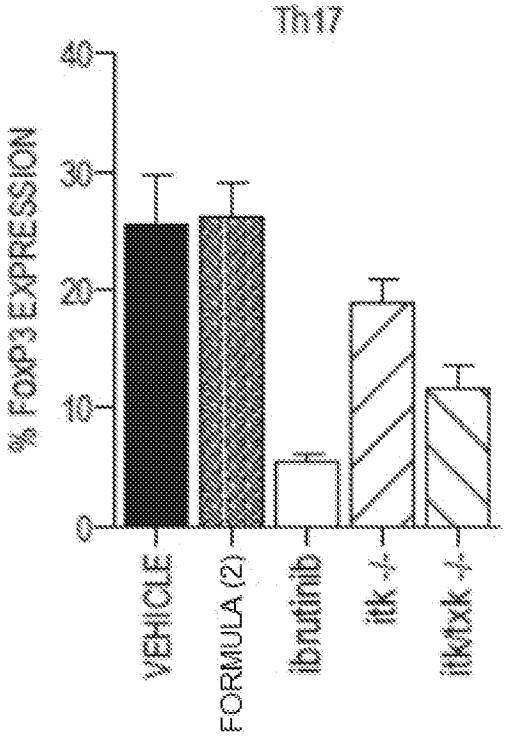

Th17
% FoxP3 EXPRESSION
0
10
20
30
40
VEHICLE
FORMULA (2)
ibrutinib
itk -/-
itkrlxk -/-

FIG. 40

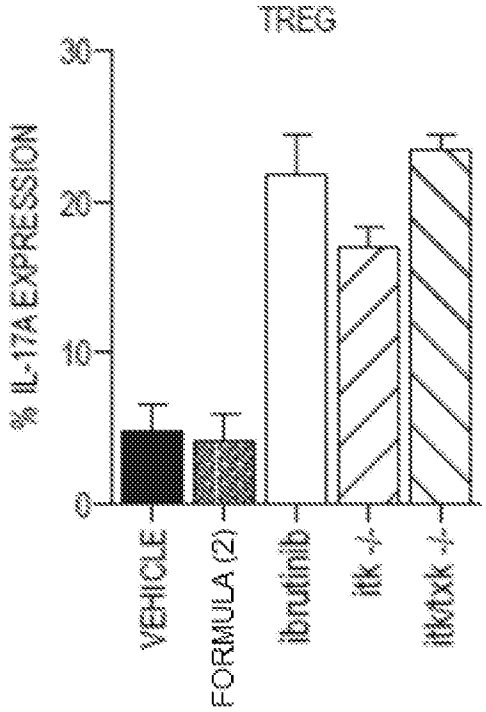

TREG
% IL-17A EXPRESSION
30
20
10
0
VEHICLE
FORMULA (2)
ibrutinib
itk -/-
itkrlyk -/-

FIG. 41

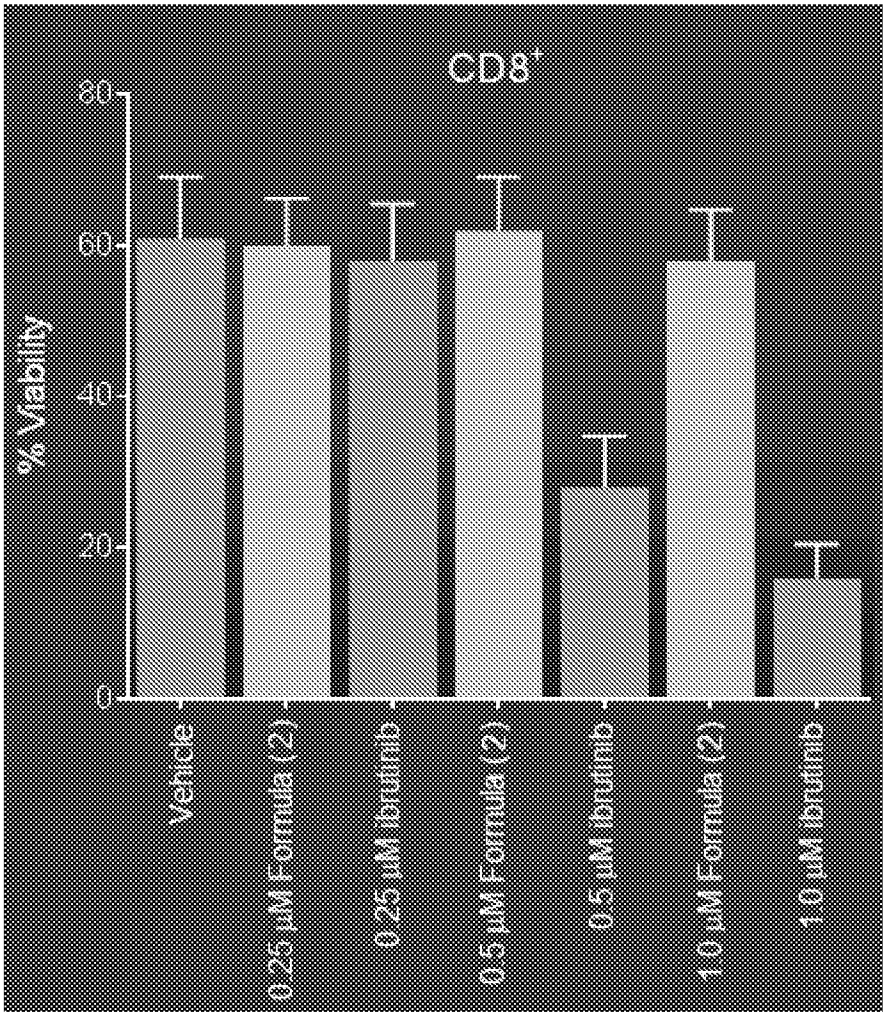

CD8+
% Viability
0
20
40
60
80
Vehicle
0.25 uM Formula (2)
0.25 uM Ibrutinib
0.5 uM Formula (2)
0.5 uM Ibrutinib
1.0 uM Formula (2)
1.0 uM Ibrutinib

FIG. 42

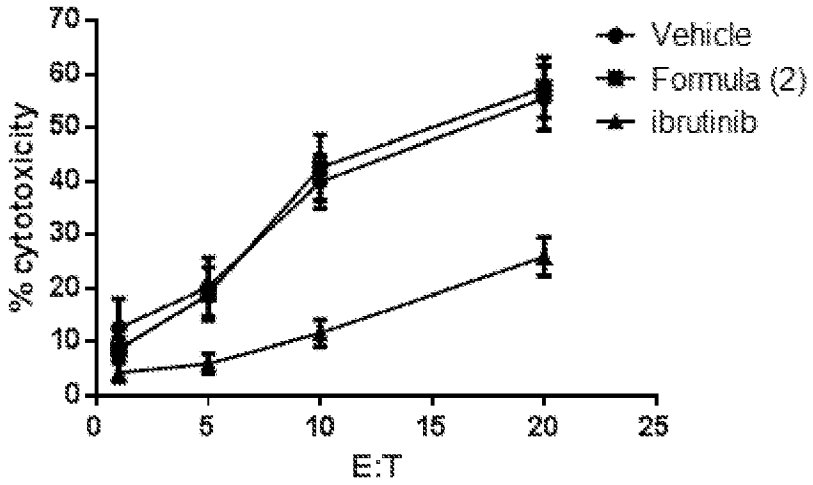

70
60
50
40
30
20
10
0
% cytotoxicity
0
5
10
15
20
25
E:T
Vehicle
Formula (2)
ibrutinib

FIG. 43

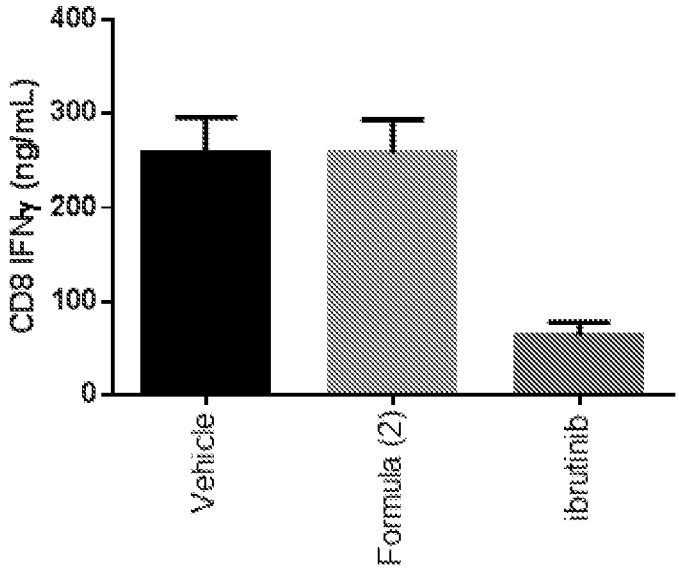


FIG. 44

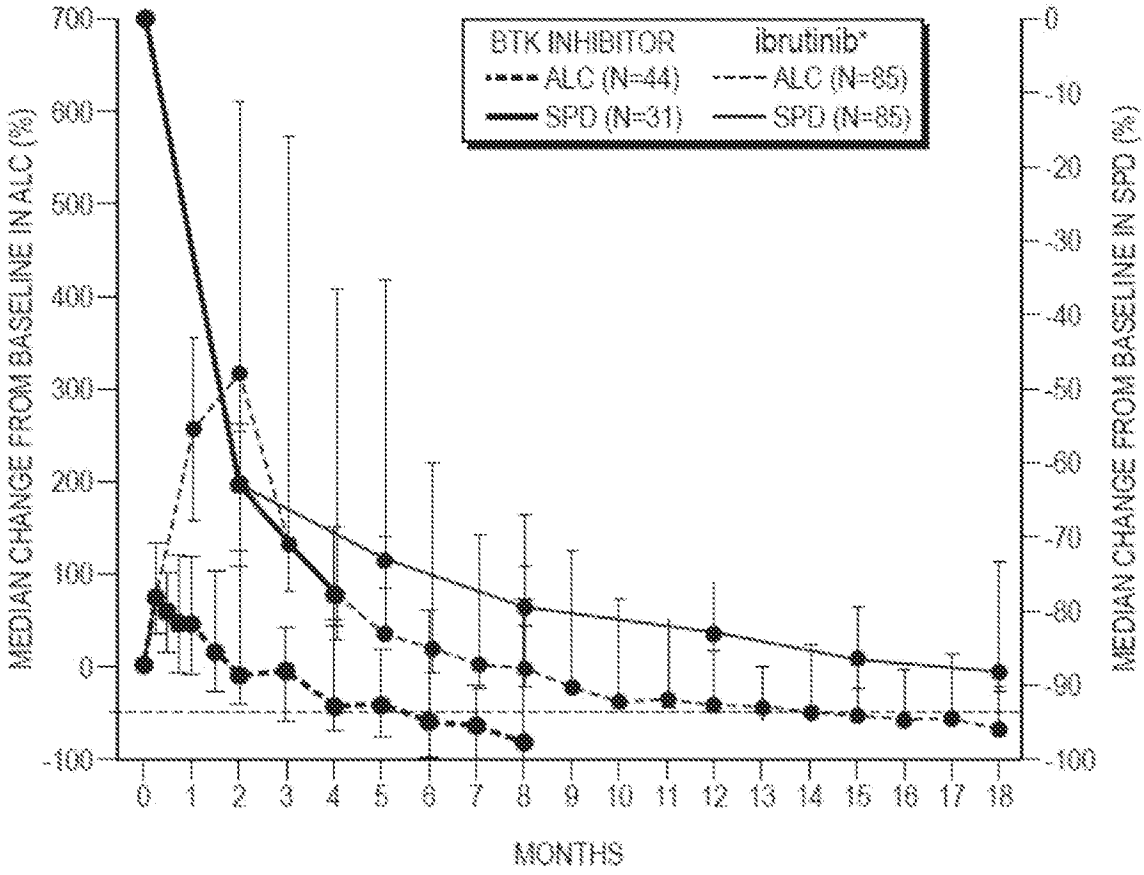

BTK INHIBITOR
ibrutinib*
ALC (N=44)
SPD (N=31)
ALC (N=85)
SPD (N=85)
MEDIAN CHANGE FROM BASELINE IN ALC (%)
MEDIAN CHANGE FROM BASELINE IN SPD (%)
MONTHS
700
600
500
400
300
200
100
0
-100
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

FIG. 45

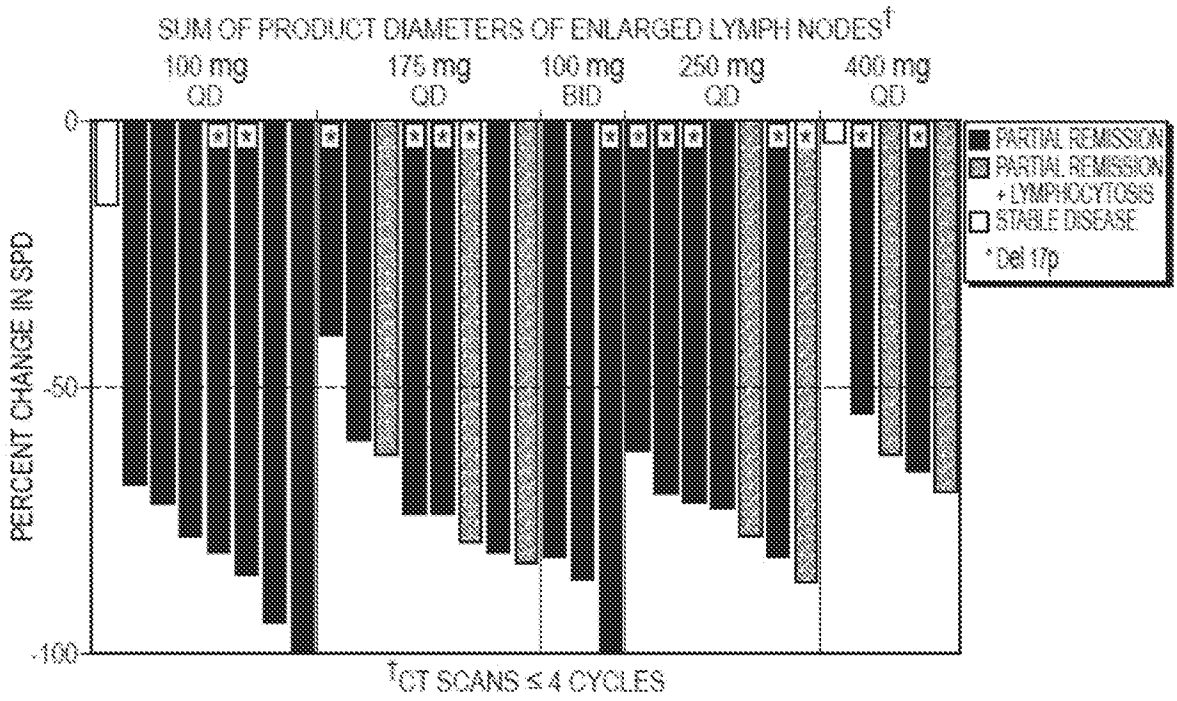

SUM OF PRODUCT DIAMETERS OF ENLARGED LYMPH NODES†
100 mg QD
175 mg QD
100 mg BID
250 mg QD
400 mg QD
0
-50
-100
PERCENT CHANGE IN SPD
PARTIAL REMISSION
PARTIAL REMISSION + LYMPHOCYTOSIS
STABLE DISEASE
* Del 17p
†CT SCANS ≤ 4 CYCLES

FIG. 46

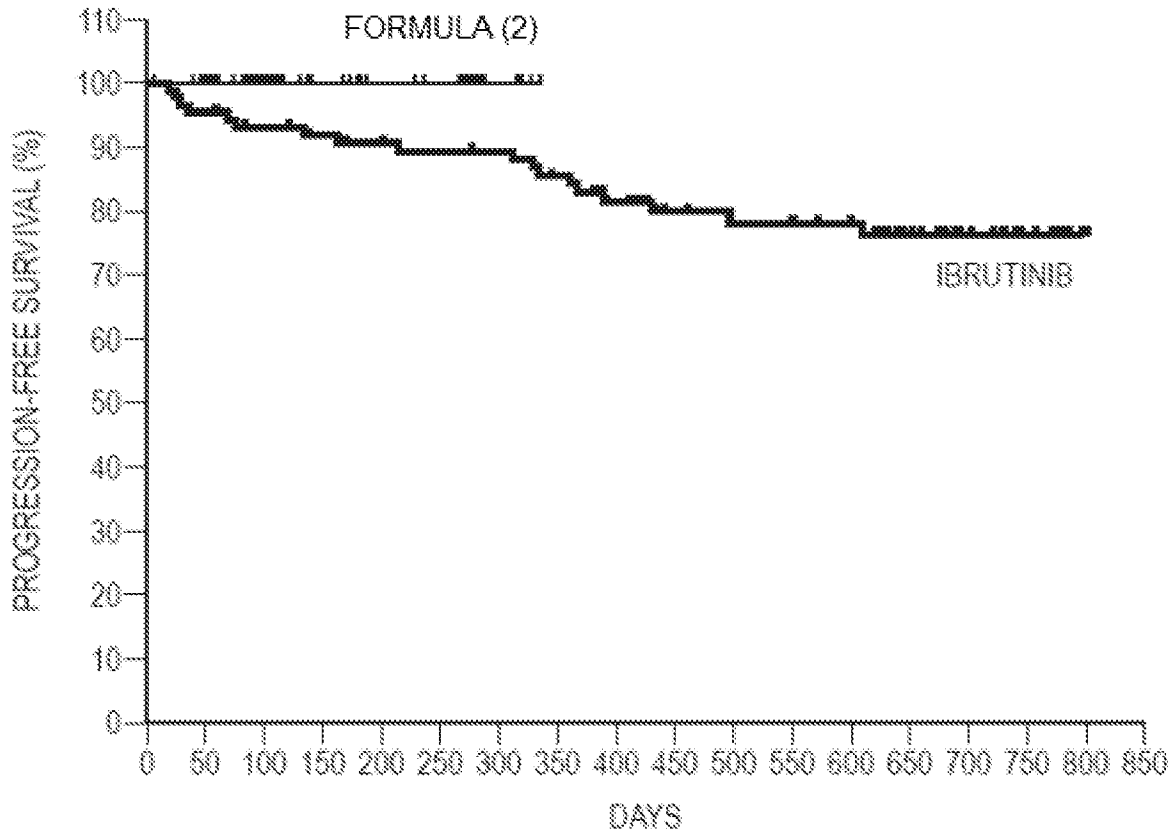

FORMULA (2)
IBRUTINIB
PROGRESSION-FREE SURVIVAL (%)
110
100
90
80
70
60
50
40
30
20
10
0
0 50 100 150 200 250 300 350 400 450 500 550 600 650 700 750 800 850
DAYS

FIG. 47

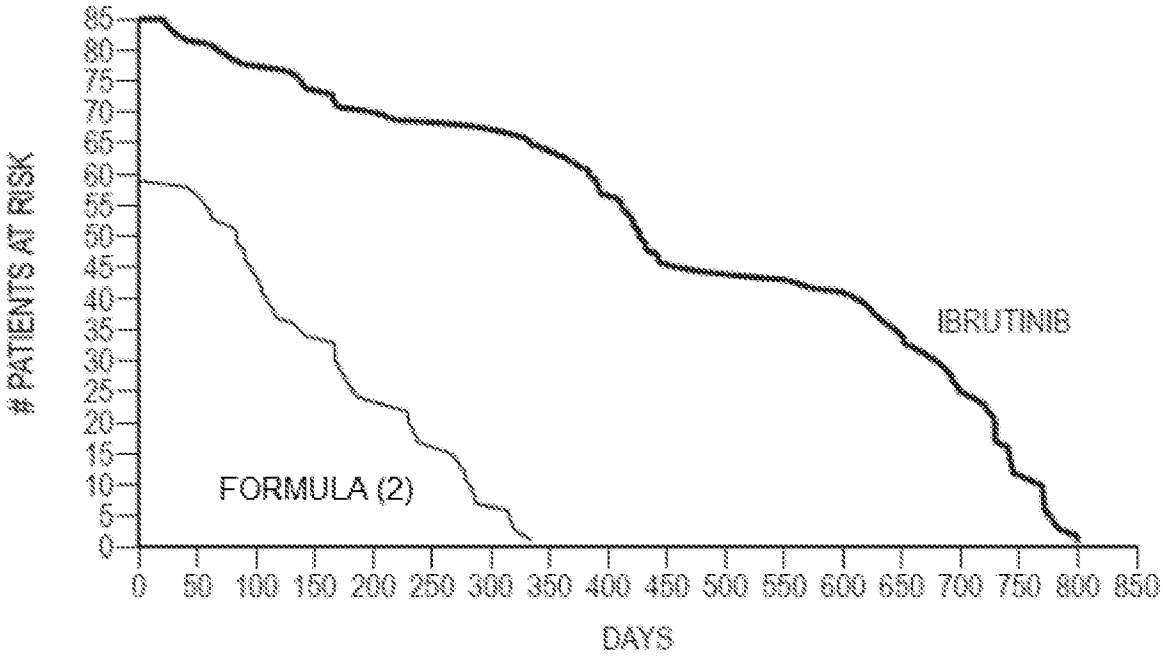

PATIENTS AT RISK
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
IBRUTINIB
FORMULA (2)
0 50 100 150 200 250 300 350 400 450 500 550 600 650 700 750 800 850
DAYS

FIG. 48

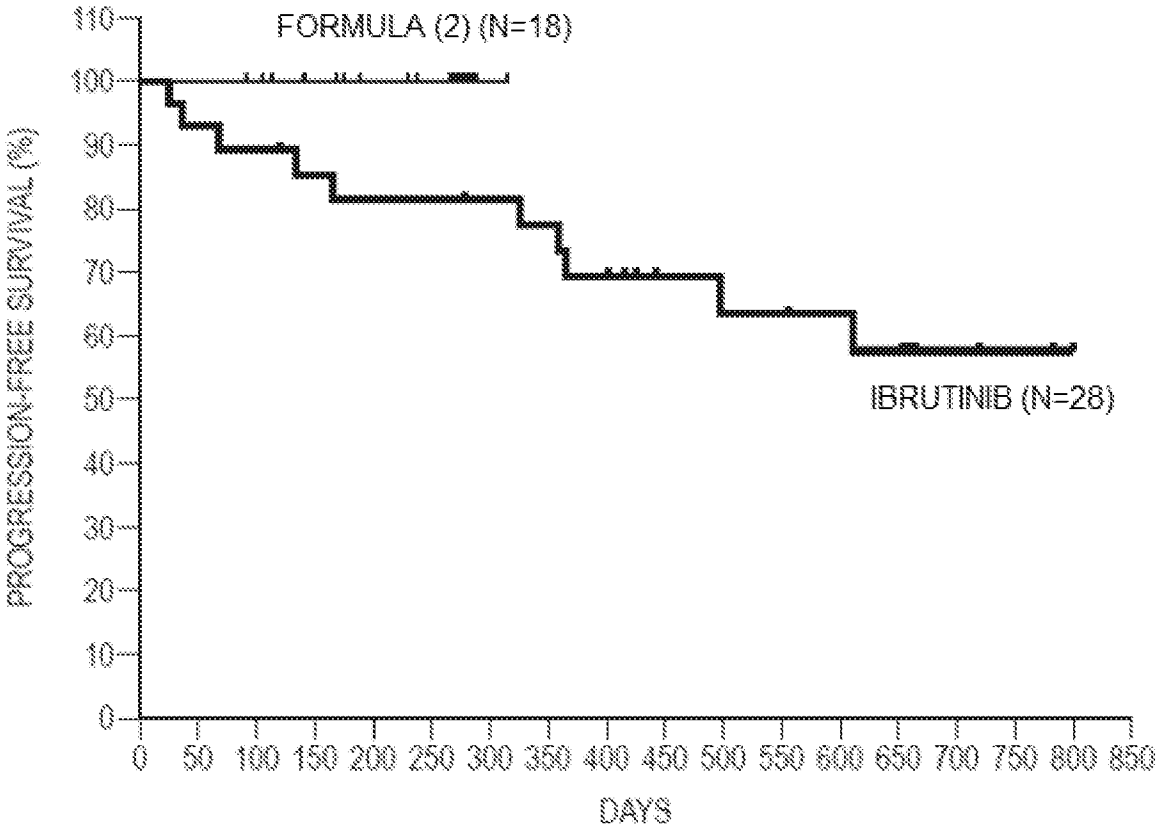

FORMULA (2) (N=18)
IBRUTINIB (N=28)
PROGRESSION-FREE SURVIVAL (%)
110
100
90
80
70
60
50
40
30
20
10
0
0 50 100 150 200 250 300 350 400 450 500 550 600 650 700 750 800 850
DAYS

FIG. 49

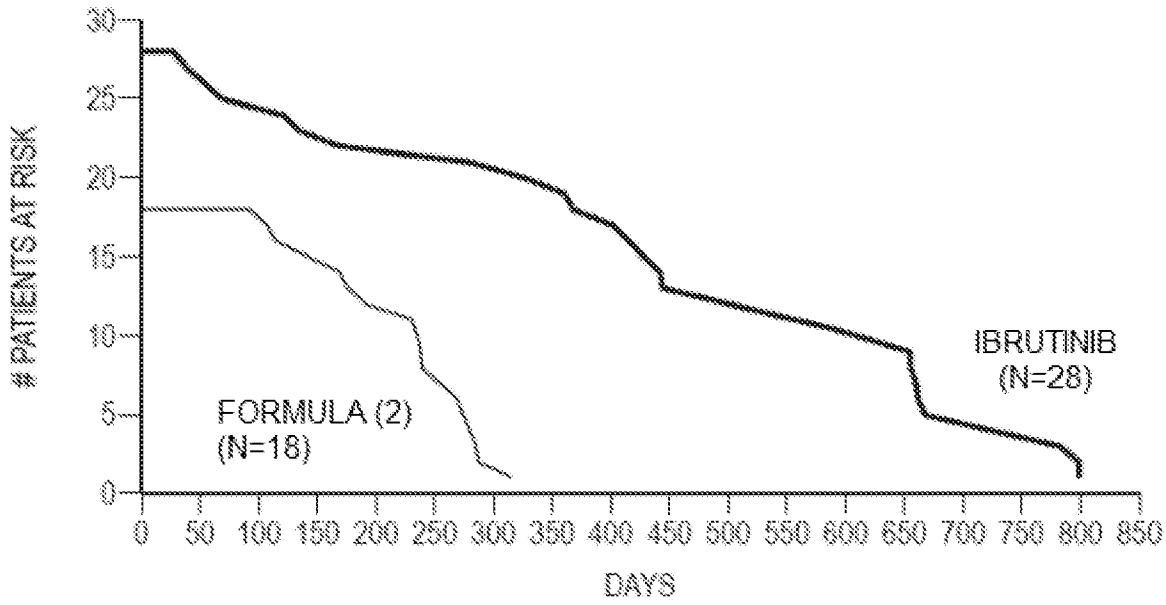

PATIENTS AT RISK
30
25
20
15
10
5
0
FORMULA (2)
(N=18)
IBRUTINIB
(N=28)
0 50 100 150 200 250 300 350 400 450 500 550 600 650 700 750 800 850
DAYS

FIG. 50

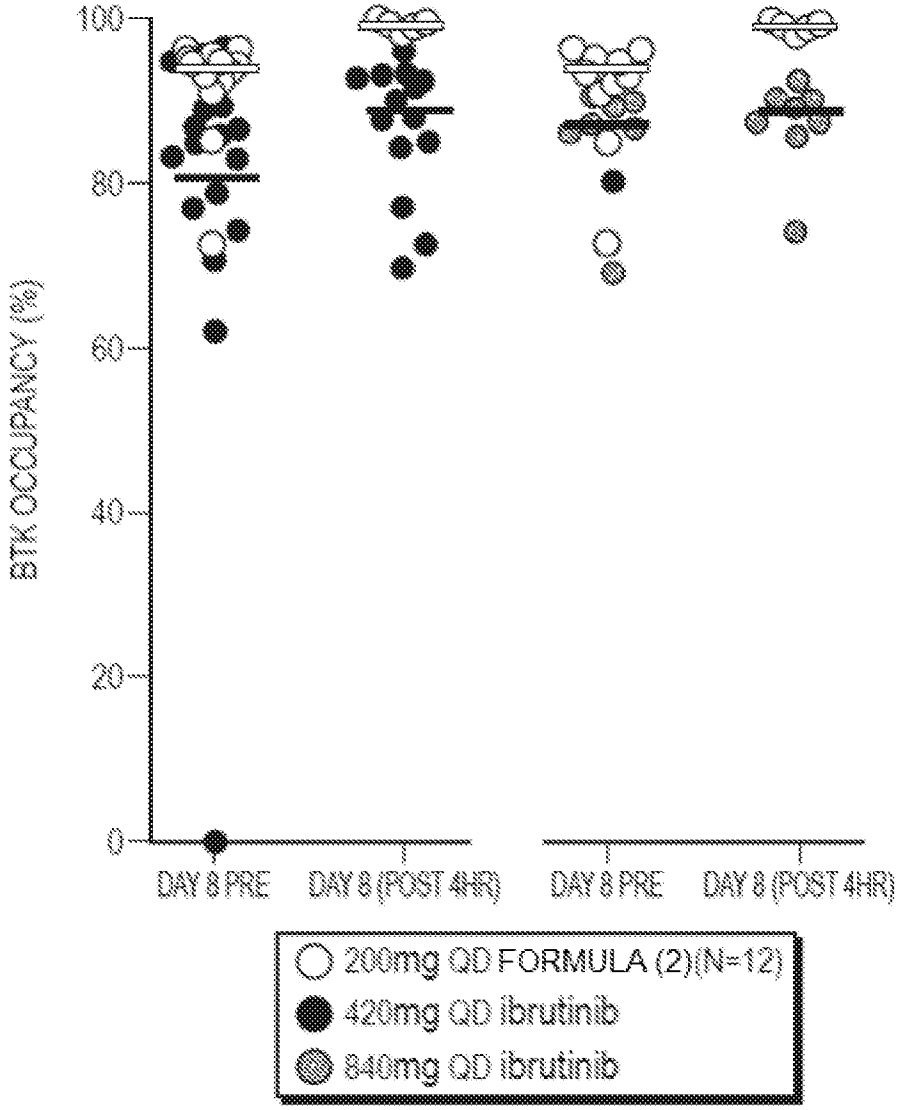

100
80
60
40
20
0
BTK OCCUPANCY (%)
DAY 8 PRE
DAY 8 (POST 4HR)
DAY 8 PRE
DAY 8 (POST 4HR)
200mg QD FORMULA (2)(N=12)
420mg QD ibrutinib
840mg QD ibrutinib

FIG. 51

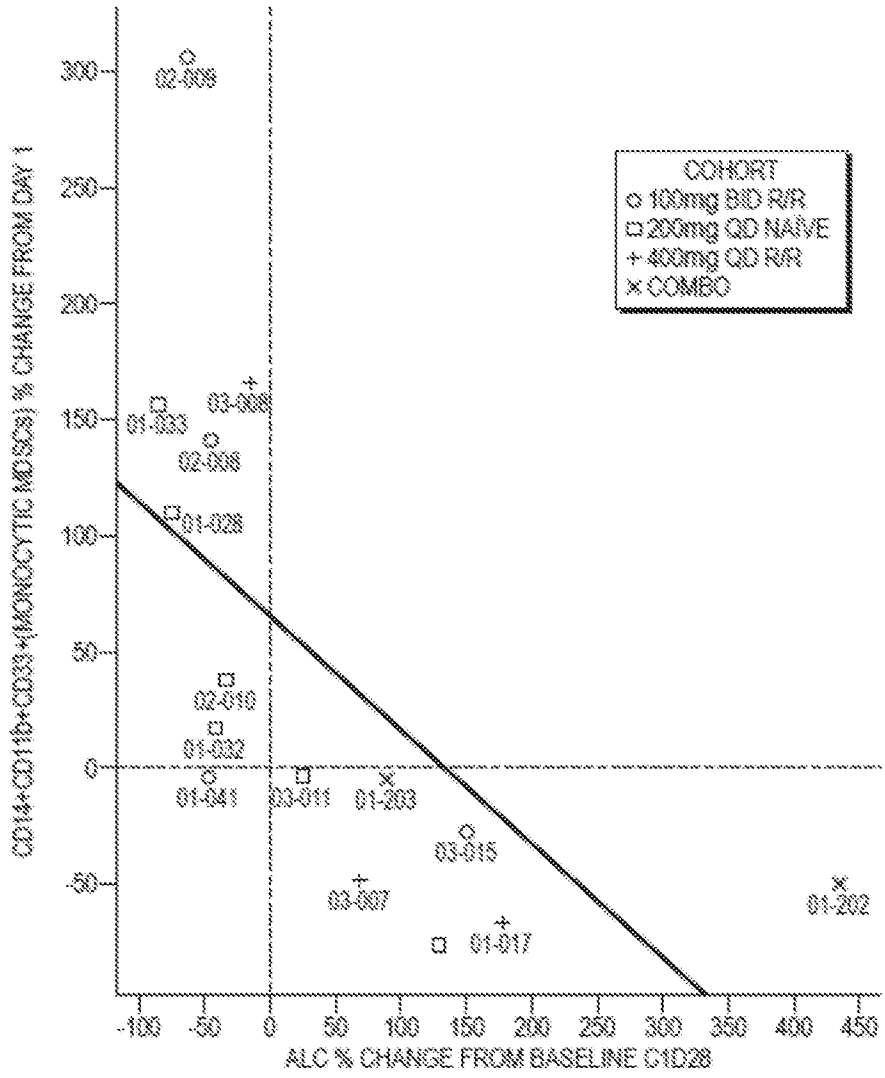

COHORT
100mg BID R/R
200mg QD NAIVE
400mg QD R/R
COMBO
CD14+CD16+CD33+(MONOCYTIC MDSC's) % CHANGE FROM DAY 1
ALC % CHANGE FROM BASELINE C1D28
300
250
200
150
100
50
0
-50
-100
-50
0
50
100
150
200
250
300
350
400
450
02-008
03-008
01-033
02-006
01-028
02-010
01-032
01-041
03-011
01-203
03-015
03-007
01-017
01-202

FIG. 52

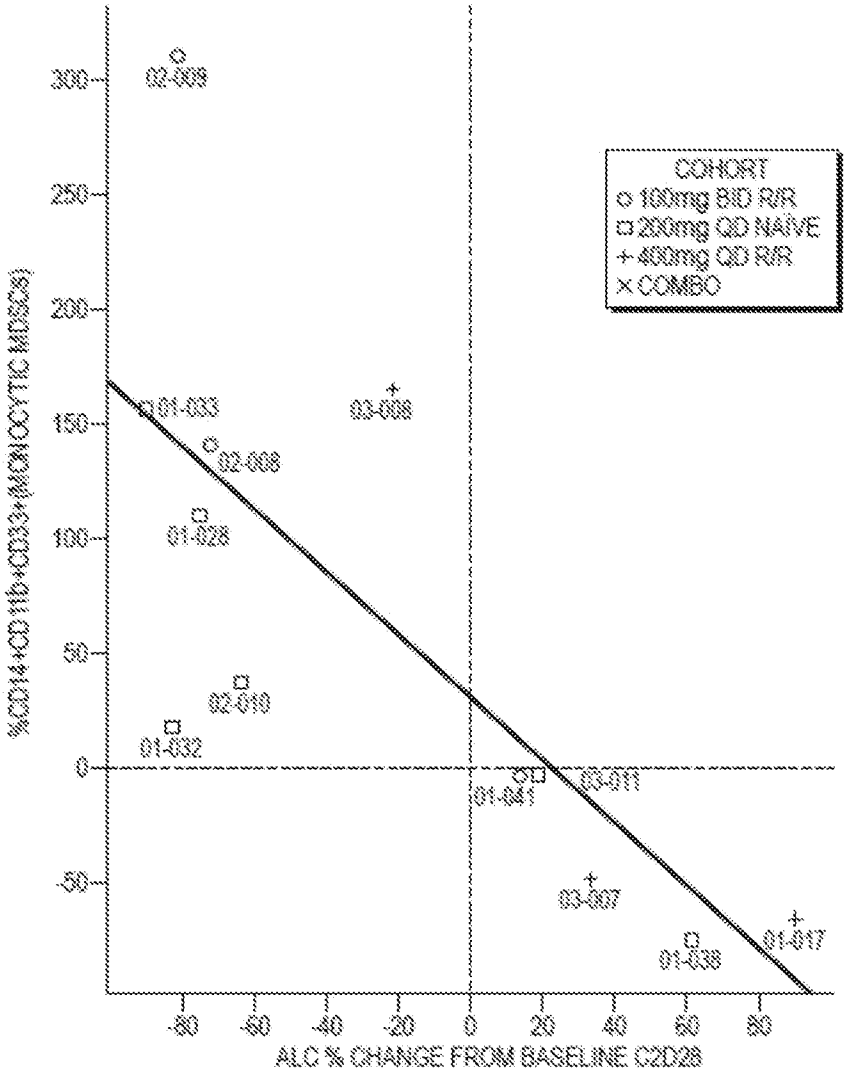

COHORT
100mg BID R/R
250mg QD NAIVE
400mg QD R/R
COMBO
%CD14+CD11b+CD33+(M/GRANULOCYTIC MDSCs)
ALC % CHANGE FROM BASELINE C2D28
300
250
200
150
100
50
0
-50
-80
-60
-40
-20
0
20
40
60
80
02-009
01-033
03-008
02-008
01-028
02-010
01-032
01-041
03-011
03-007
01-017
01-038

FIG. 53

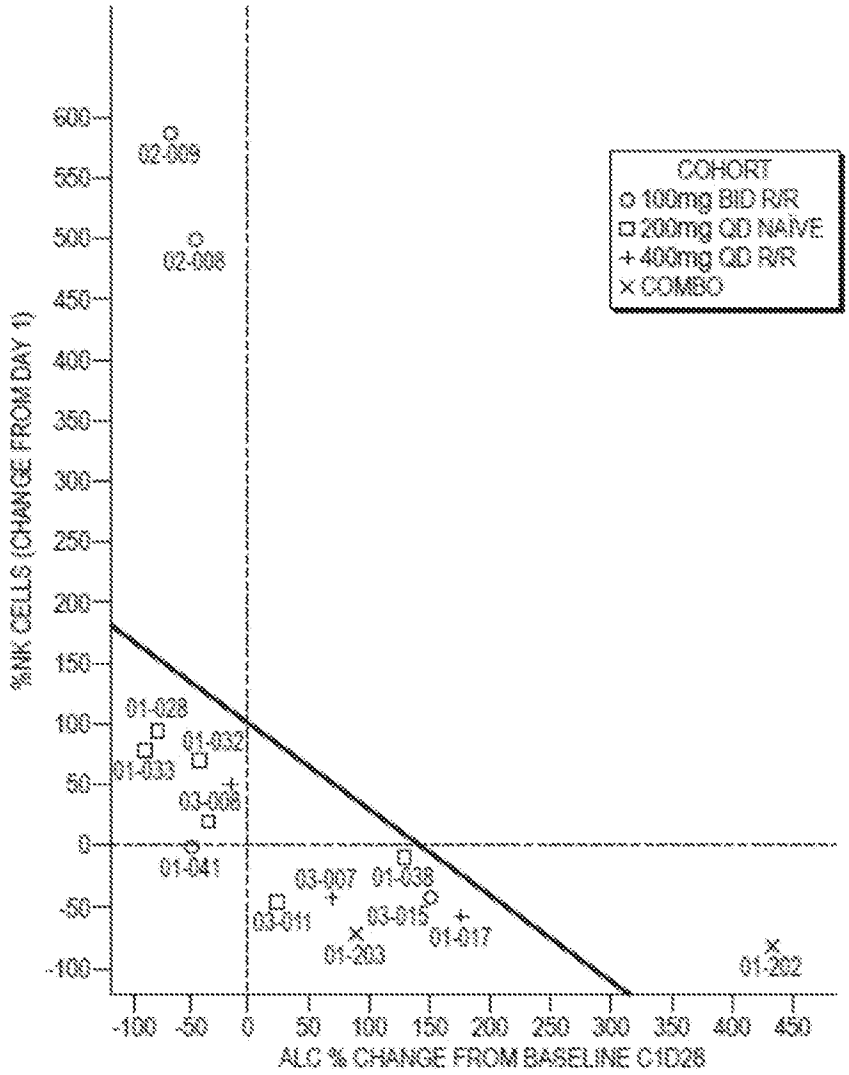

COHORT
100mg BID R/R
200mg QD NAIVE
400mg QD R/R
COMBO
%NK CELLS (CHANGE FROM DAY 1)
ALC % CHANGE FROM BASELINE C1D28
02-009
02-008
01-028
01-033
01-032
03-008
01-041
03-007
01-038
03-011
03-015
01-017
01-203
01-202

FIG. 54

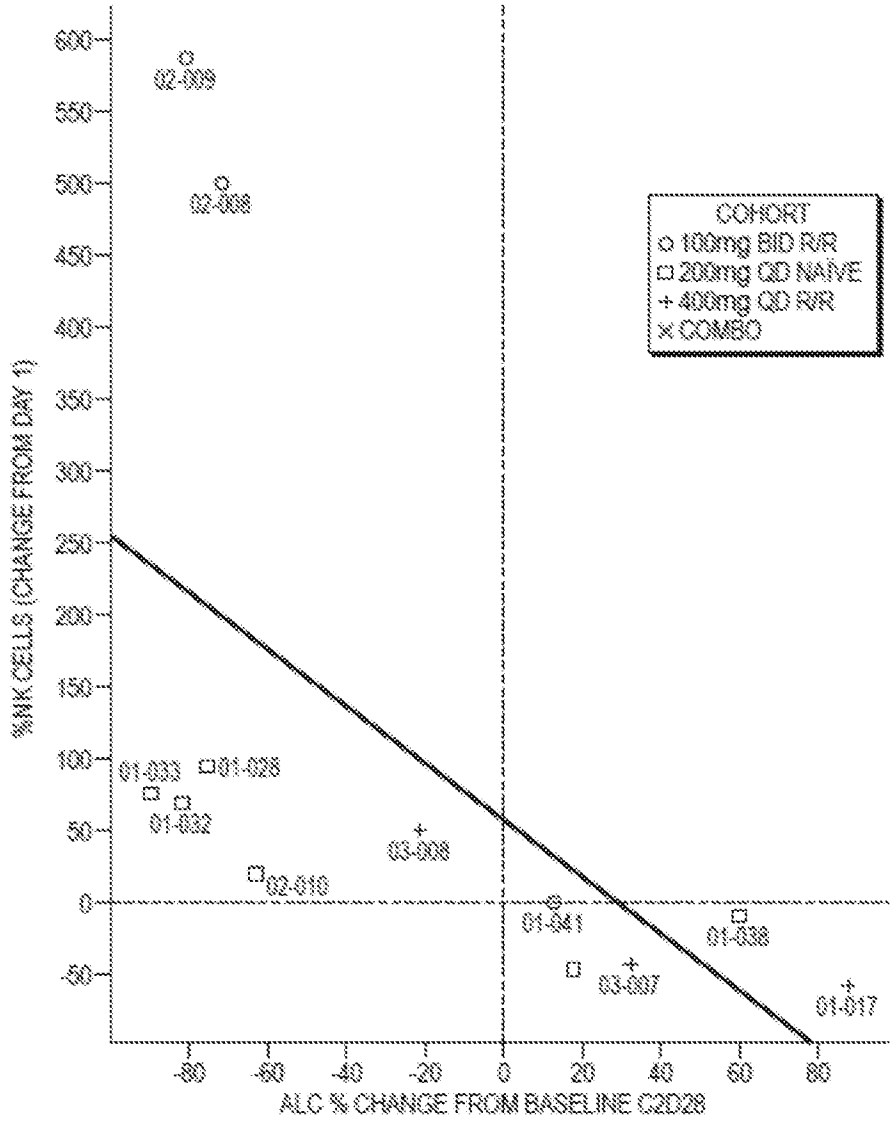

%NK CELLS (CHANGE FROM DAY 1)
ALC % CHANGE FROM BASELINE C2D28
COHORT
100mg BID R/R
200mg QD NAIVE
400mg QD R/R
COMBO
02-009
02-008
01-033
01-028
01-032
02-010
03-008
01-041
01-038
03-007
01-017

FIG. 55

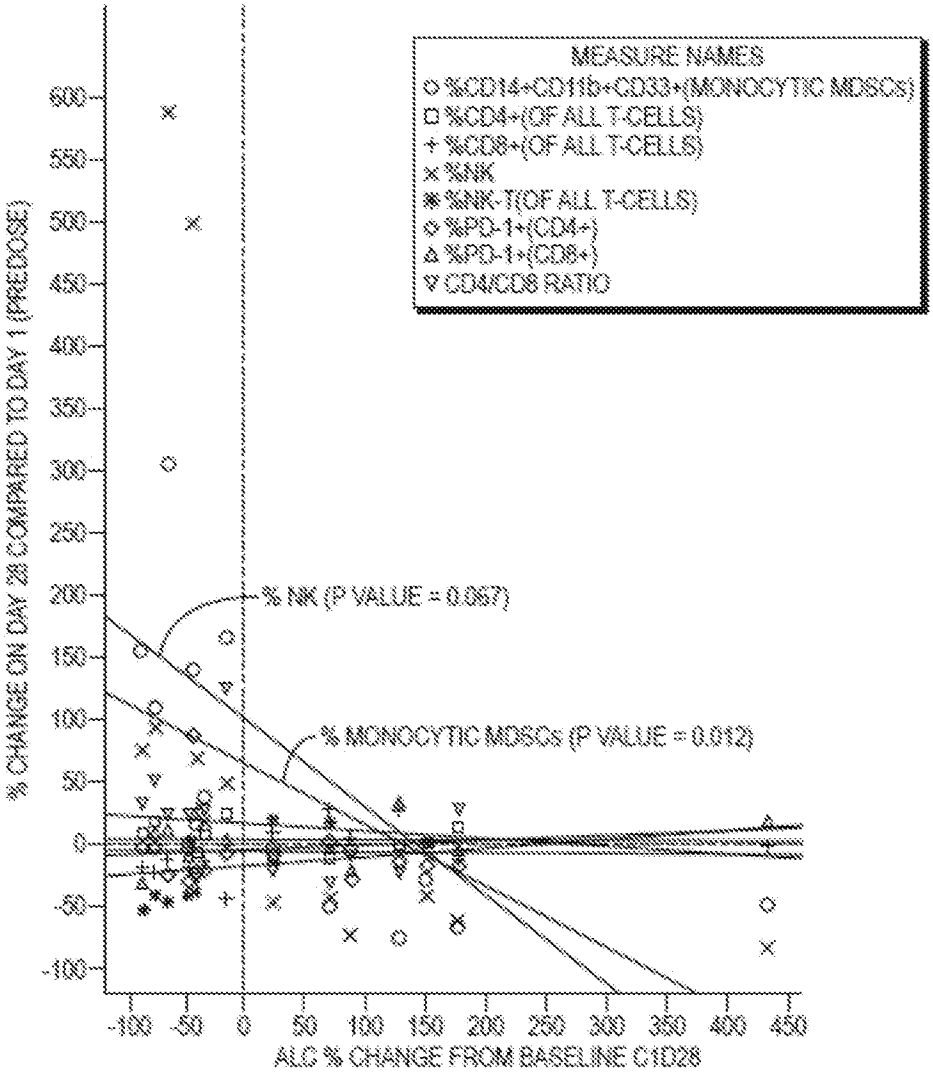

MEASURE NAMES
%CD14+CD11b+CD33+(MONOCYTIC MDSCs)
%CD4+(OF ALL T-CELLS)
%CD8+(OF ALL T-CELLS)
%NK
%NK-T(OF ALL T-CELLS)
%PD-1+(CD4+)
%PD-1+(CD8+)
CD4/CD8 RATIO
% NK (P VALUE = 0.057)
% MONOCYTIC MDSCs (P VALUE = 0.012)
% CHANGE ON DAY 28 COMPARED TO DAY 1 (PREDOSE)
ALC % CHANGE FROM BASELINE C1D28
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
-100
-100 -50 0 50 100 150 200 250 300 350 400 450

FIG. 56

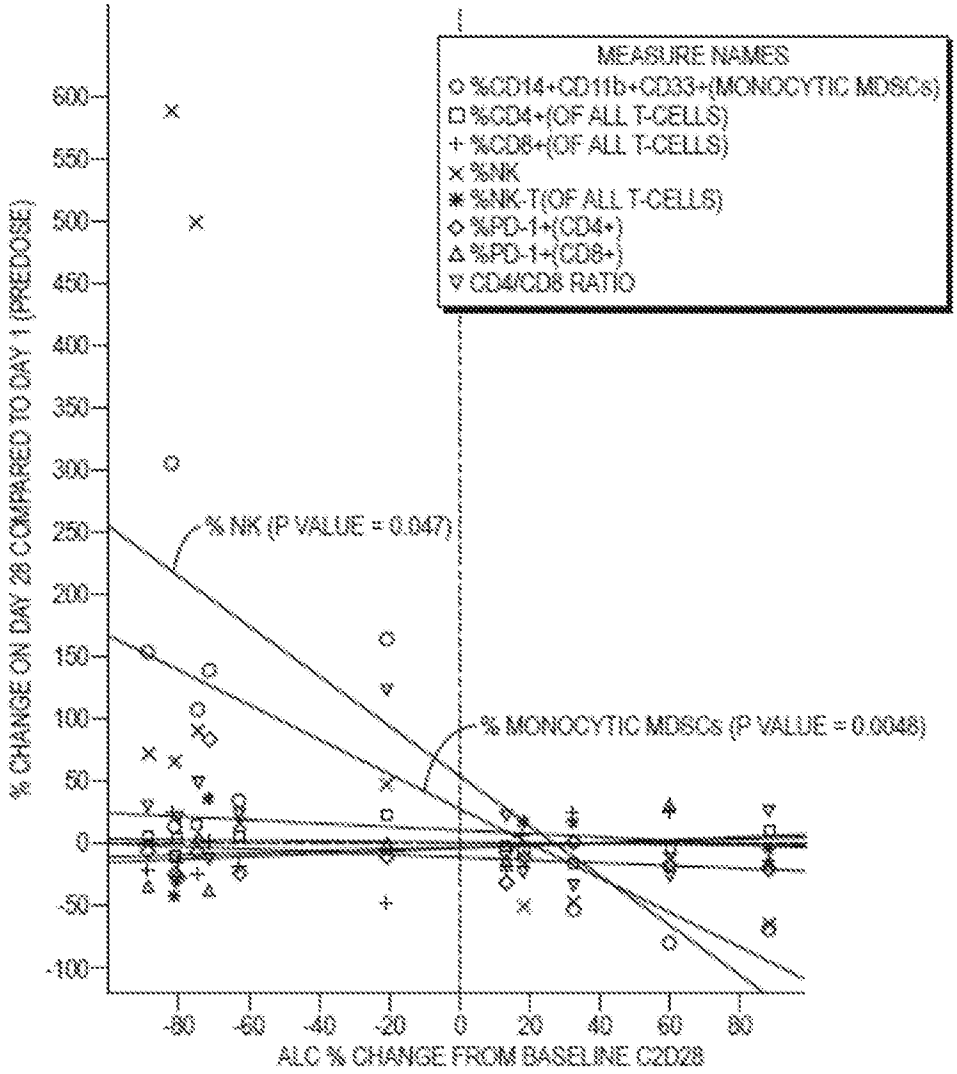

MEASURE NAMES
%CD14+CD11b+CD33+(MONOCYTIC MDSCs)
%CD4+(OF ALL T-CELLS)
%CD8+(OF ALL T-CELLS)
%NK
%NK-T(OF ALL T-CELLS)
%PD-1+(CD4+)
%PD-1+(CD8+)
CD4/CD8 RATIO
% NK (P VALUE = 0.047)
% MONOCYTIC MDSCs (P VALUE = 0.0048)
% CHANGE ON DAY 28 COMPARED TO DAY 1 (PREDOSE)
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
-100
-80
-60
-40
-20
0
20
40
60
80
ALC % CHANGE FROM BASELINE C2D28

FIG. 57

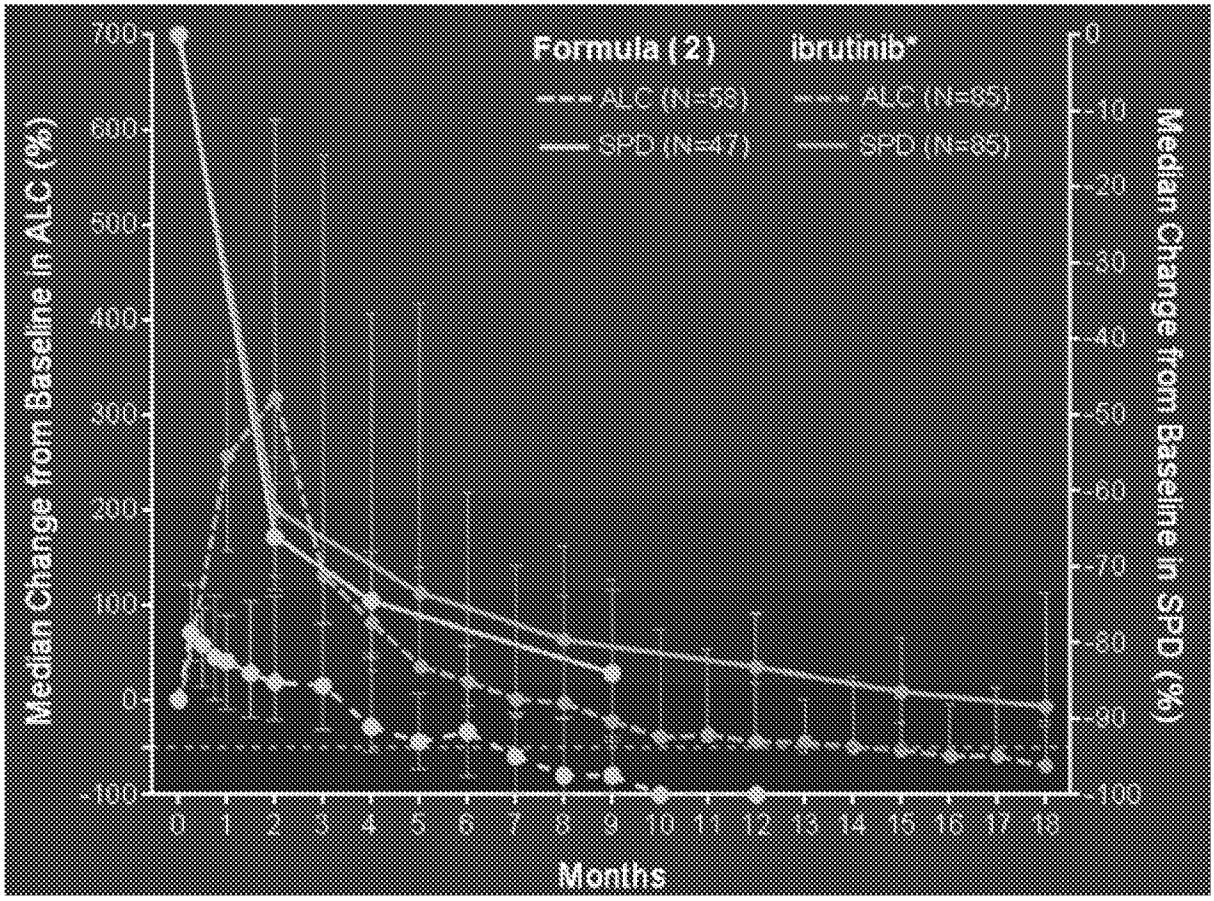

Formula (2)
ibrutinib*
ALC (N=58)
SPD (N=47)
ALC (N=85)
SPD (N=85)
Median Change from Baseline in ALC (%)
Median Change from Baseline in SPD (%)
Months
700
600
500
400
300
200
100
0
-100
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

FIG. 58

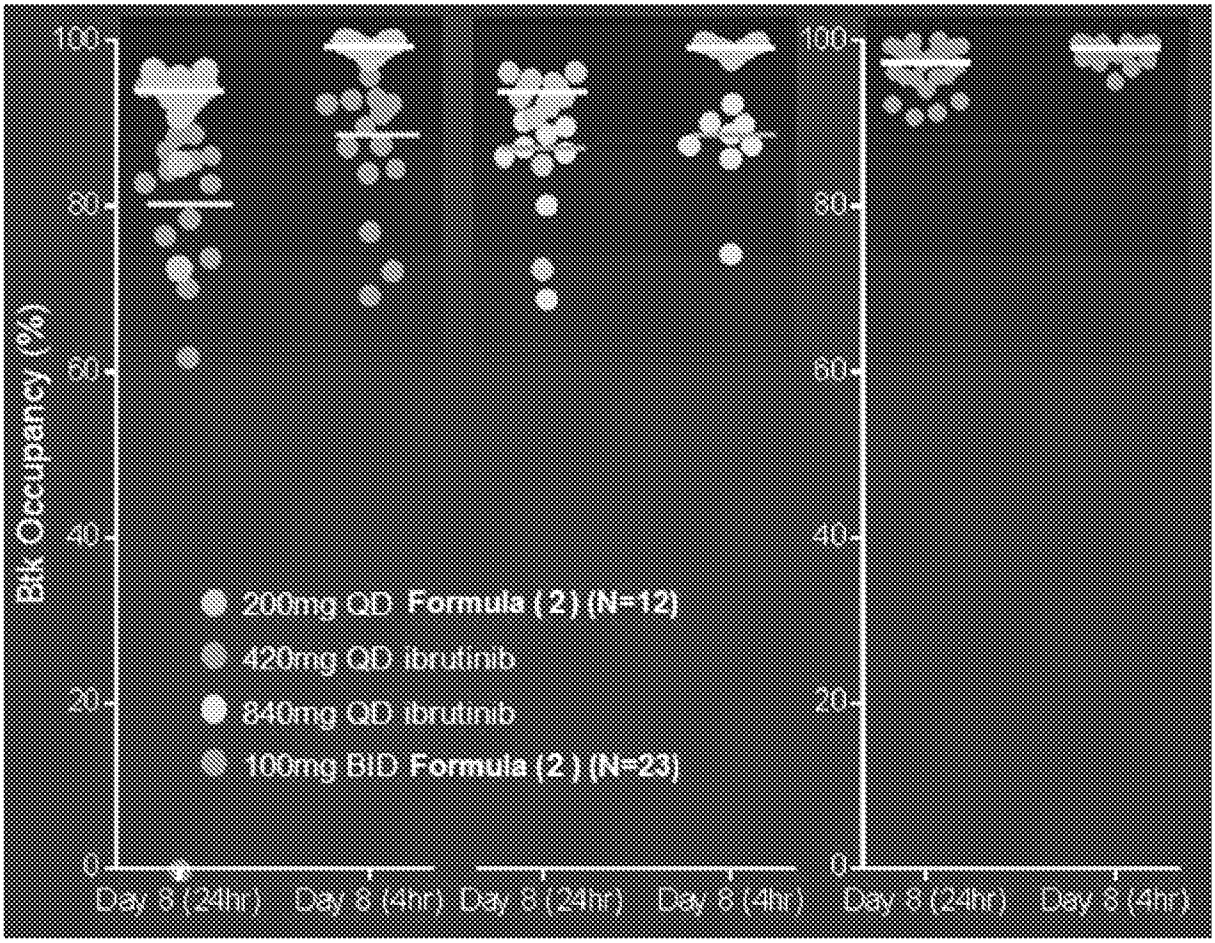
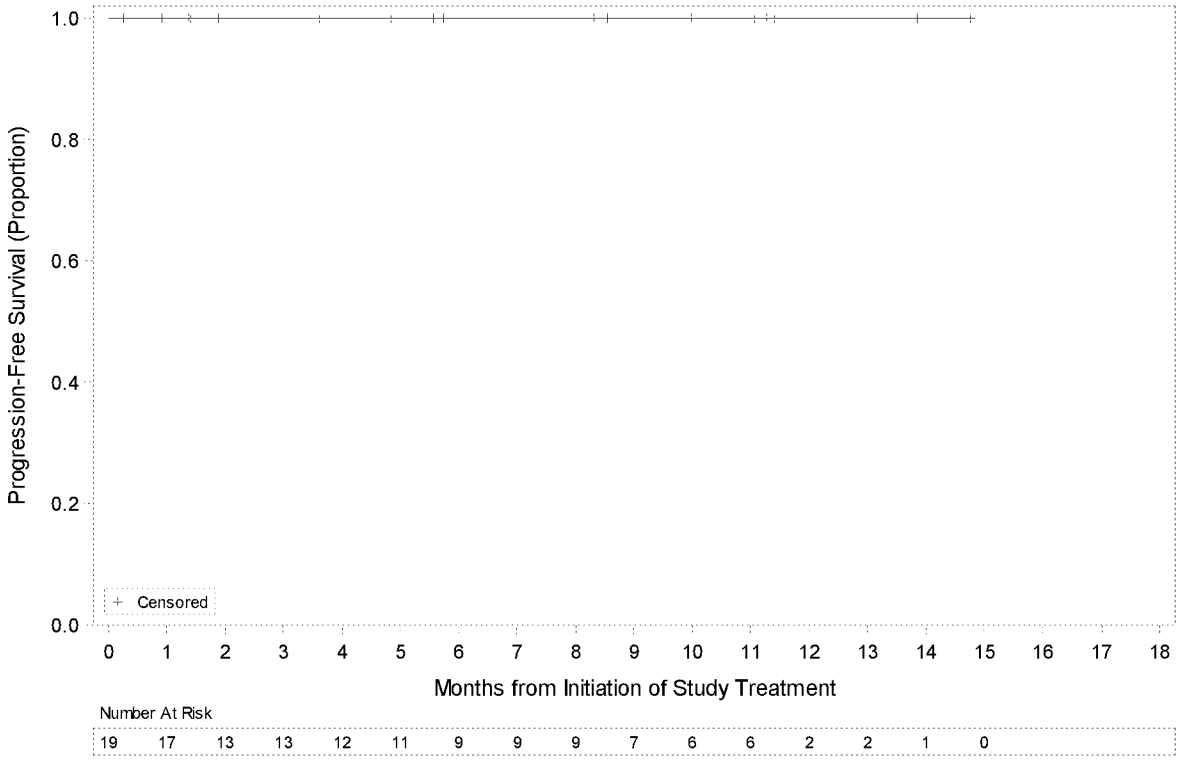

Btk Occupancy (%)
100
80
60
40
20
0
200mg QD Formula (2) (N=12)
420mg QD ibrutinib
840mg QD ibrutinib
100mg BID Formula (2) (N=23)
Day 8 (24hr)
Day 8 (4hr)
Day 8 (24hr)
Day 8 (4hr)
Day 8 (24hr)
Day 8 (4hr)

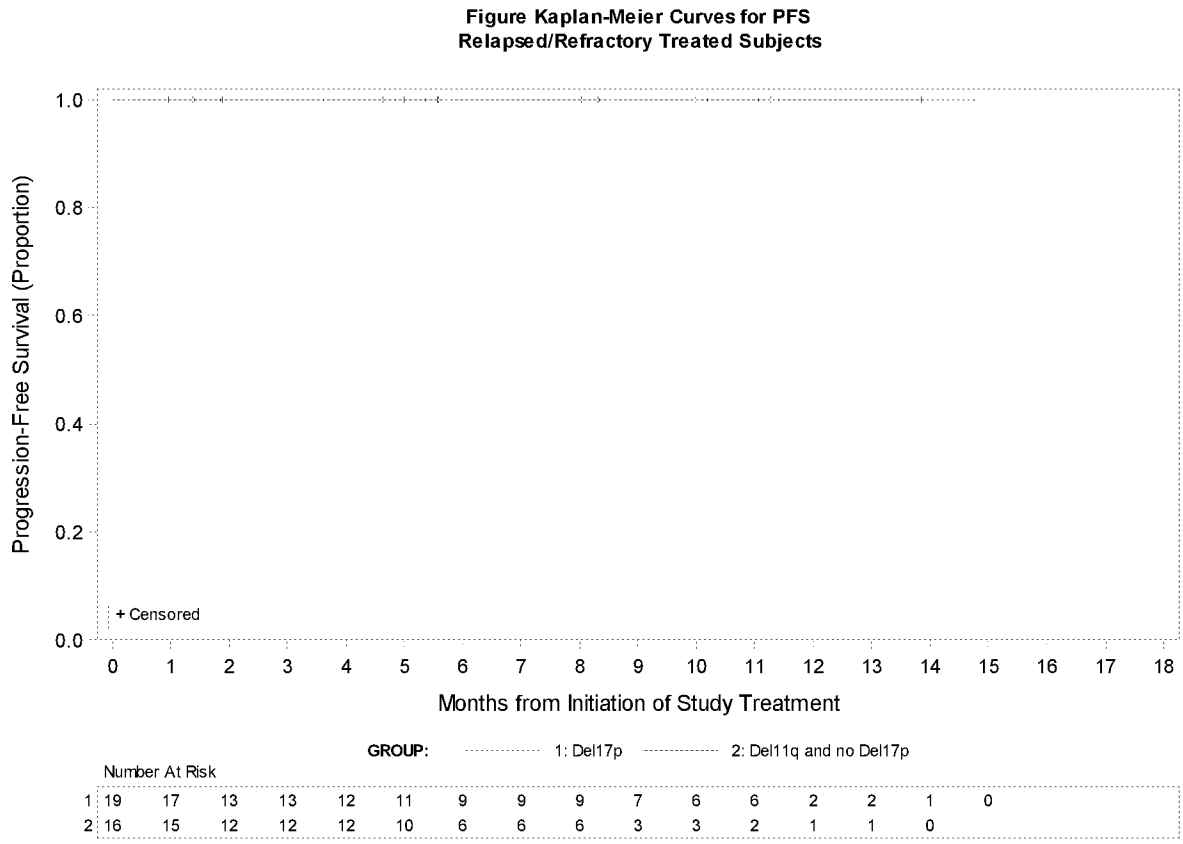
FIG. 59

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.

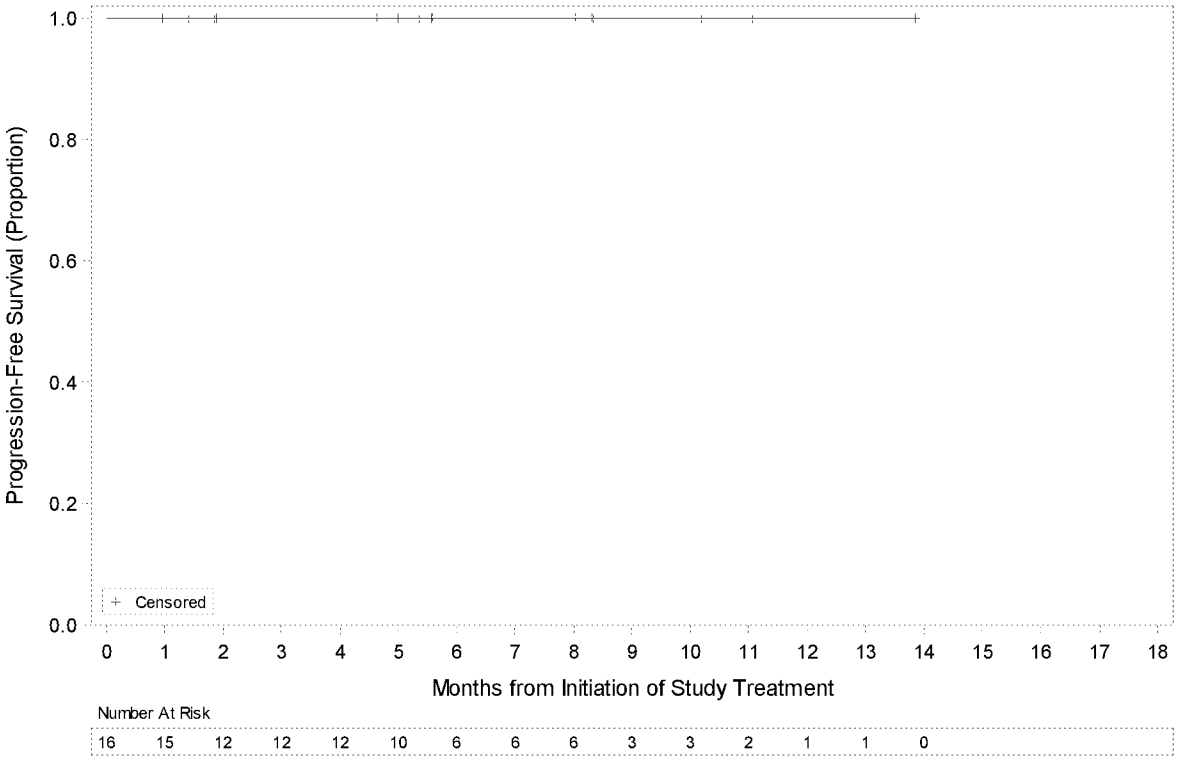
FIG. 60



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

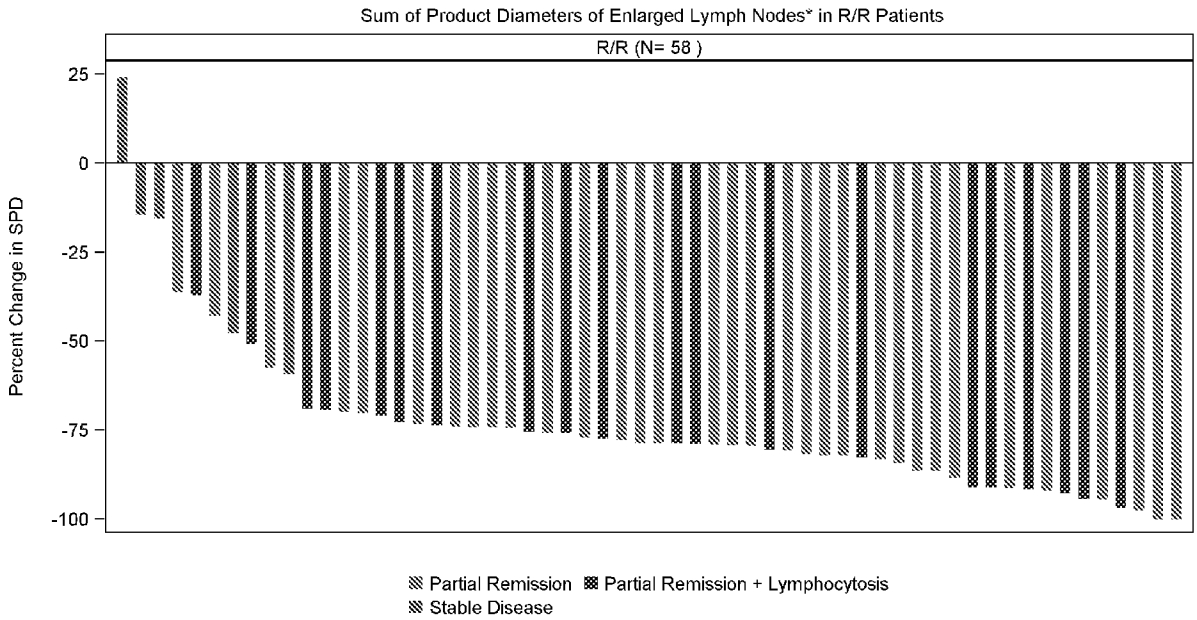
FIG. 61

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. 62



*Any node with a diameter > 1.5 cm.
N's are subjects with observed Lymphadenopathy and overall response data.
Subjects with overall response but no observed Lymphadenopathy, 01-025 = PR, 06-002 = PR, 06-003 = PR, 03-015 = PRL, 05-001 = PRL, 05-002 = PRL, 25-001 = PRL, 01-026 = SD, 01-035 = SD, 06-004 = SD

FIG. 63

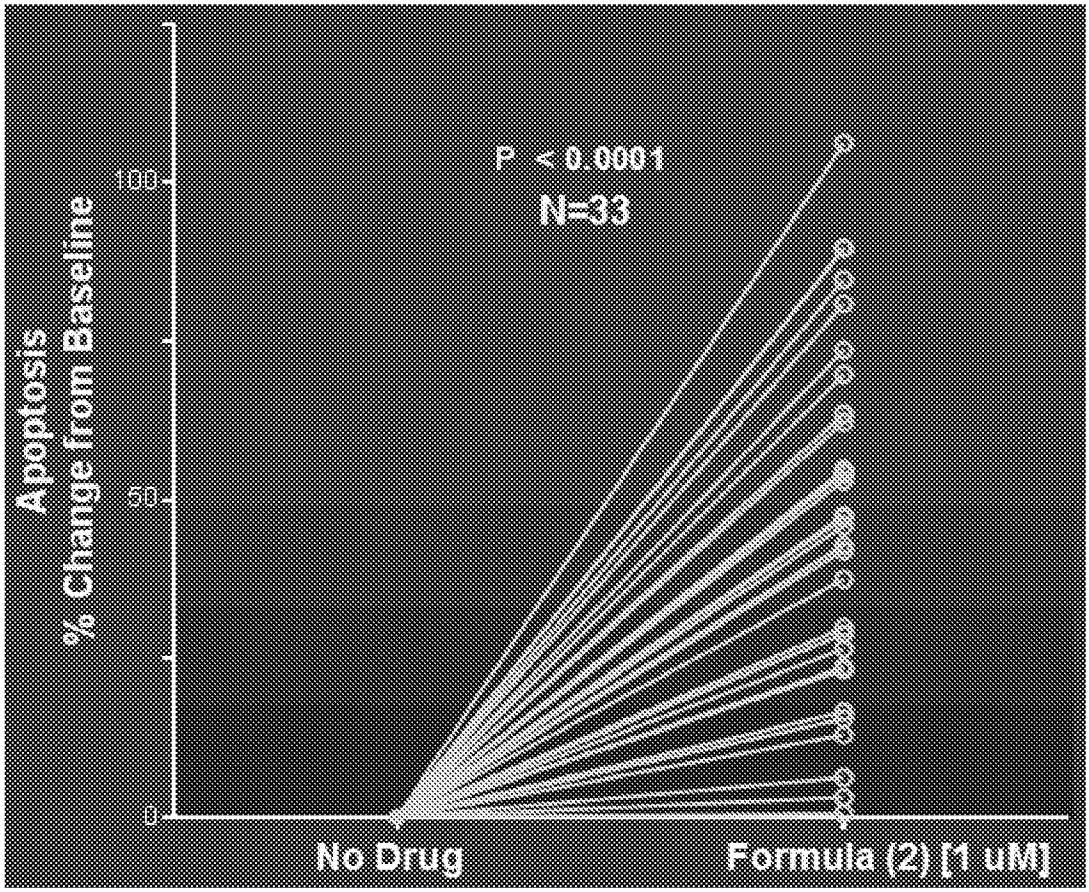

Apoptosis
% Change from Baseline
100
50
0
P < 0.0001
N=33
No Drug
Formula (2) [1 uM]

FIG. 64

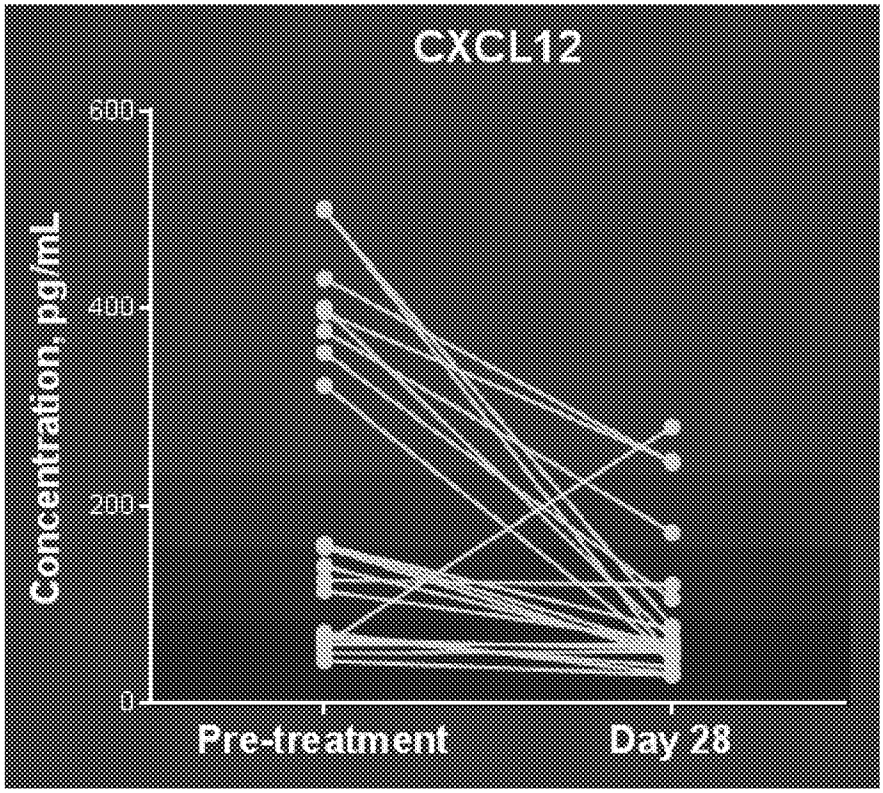

CXCL12
Concentration, pg/mL
600
400
200
0
Pre-treatment
Day 28

FIG. 65

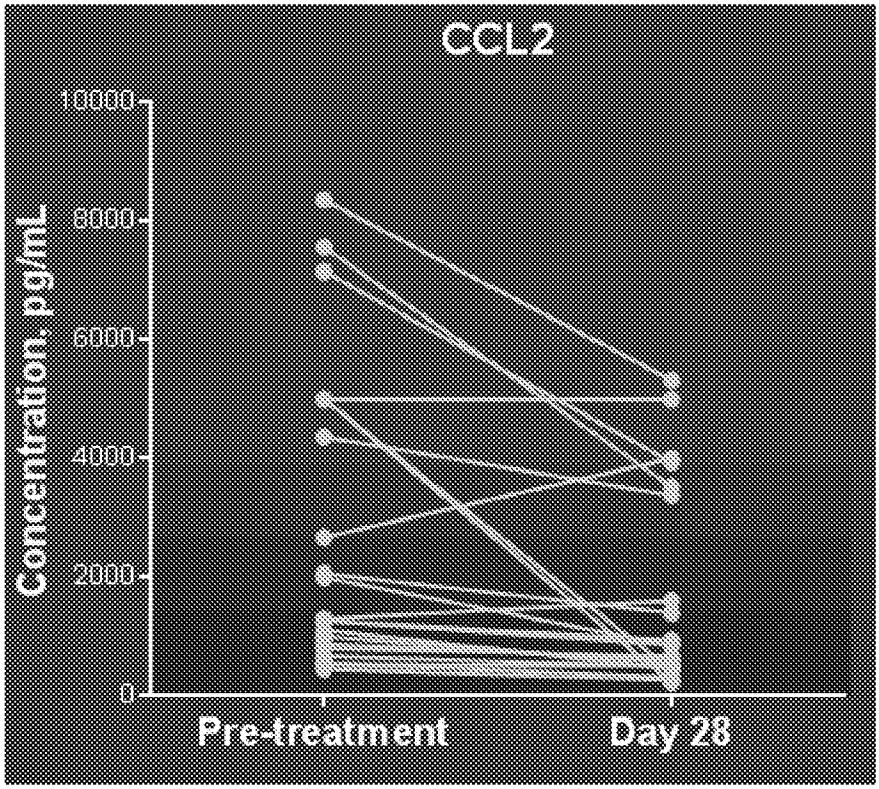

CCL2
Concentration, pg/mL
10000
8000
6000
4000
2000
0
Pre-treatment
Day 28

FIG. 66

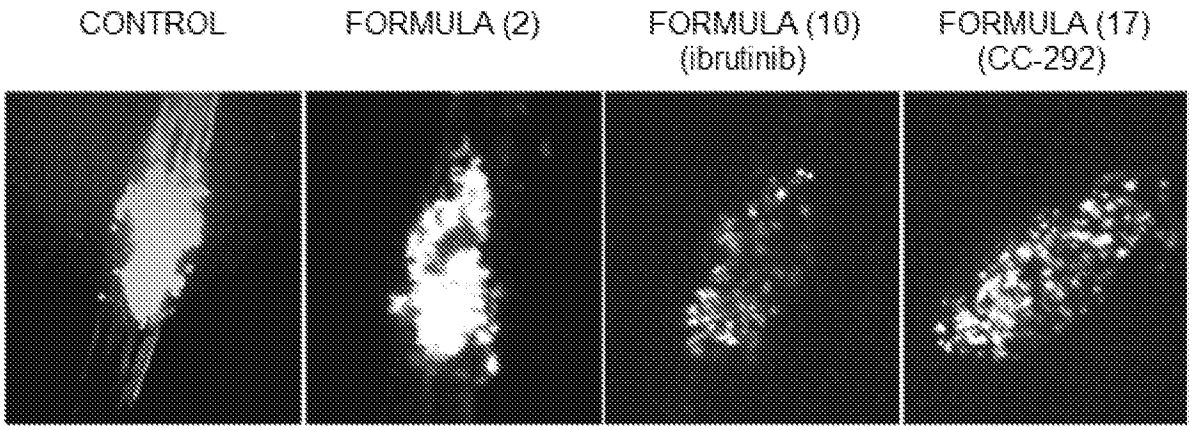


FIG. 67

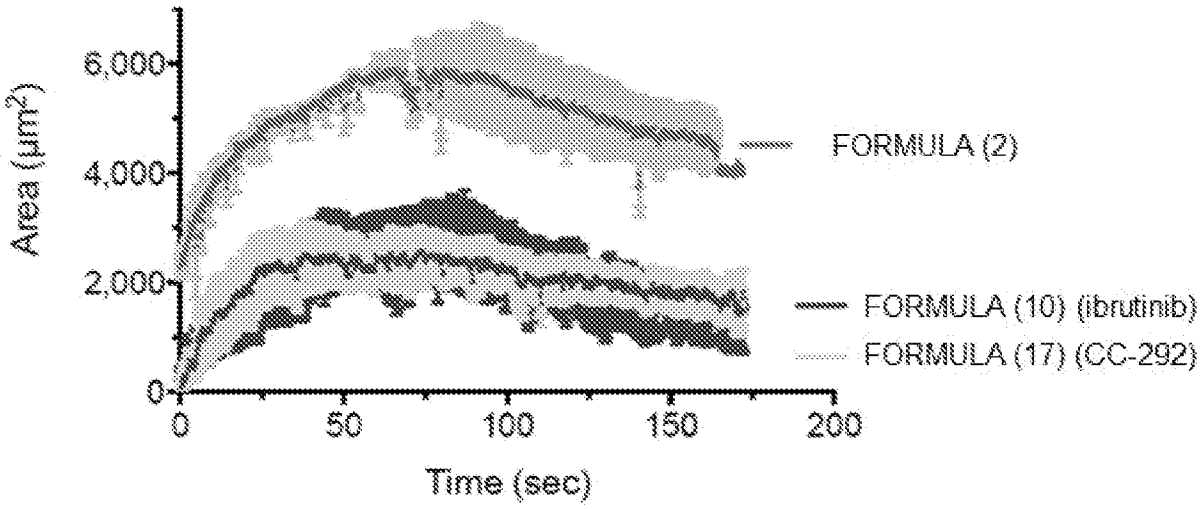

6,000
4,000
2,000
0
Area (μm²)
0
50
100
150
200
Time (sec)
FORMULA (2)
FORMULA (10) (ibrutinib)
FORMULA (17) (CC-292)

FIG. 68

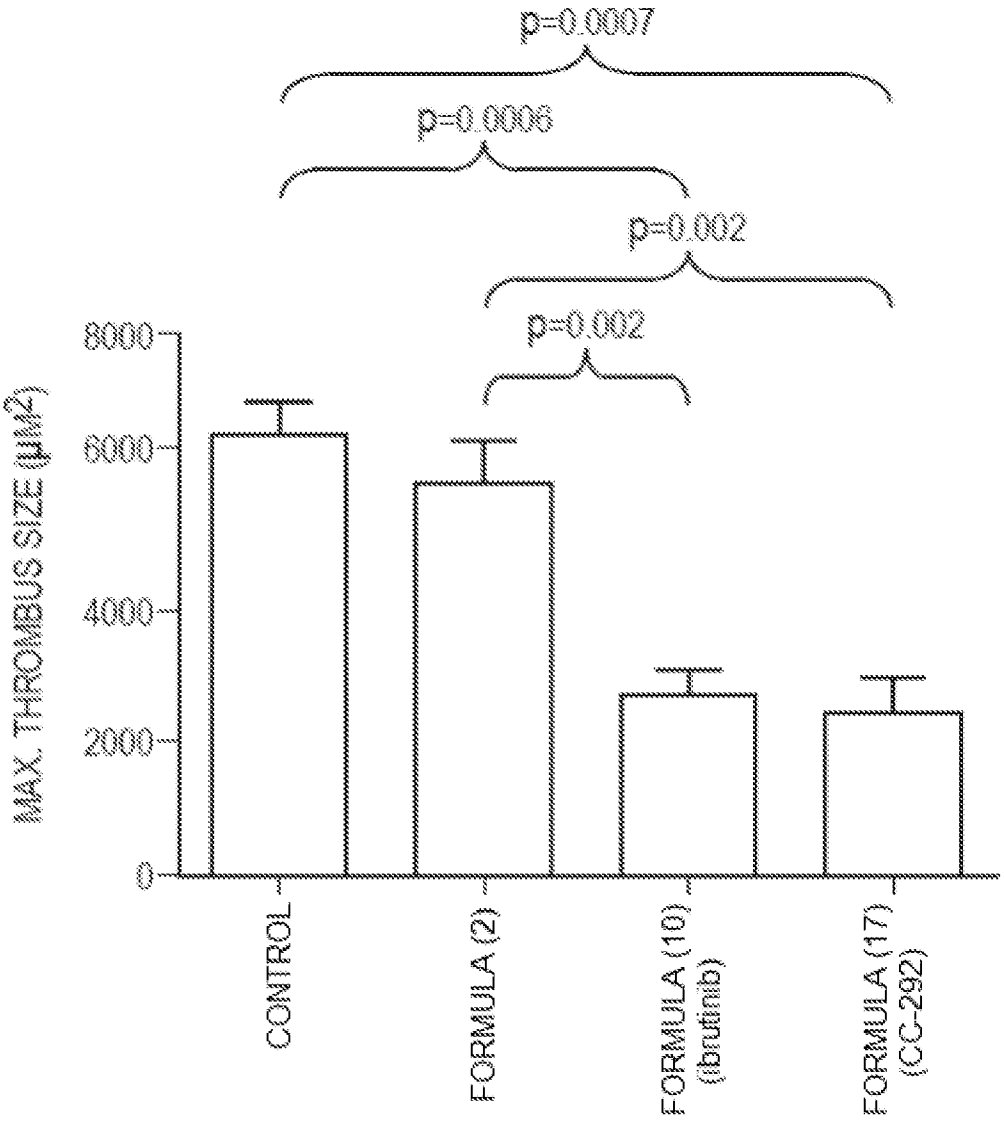

p=0.0007
p=0.0006
p=0.002
p=0.002
MAX. THROMBUS SIZE (µM2)
8000
6000
4000
2000
0
CONTROL
FORMULA (2)
FORMULA (10) (ibrutinib)
FORMULA (17) (CC-292)

FIG. 69

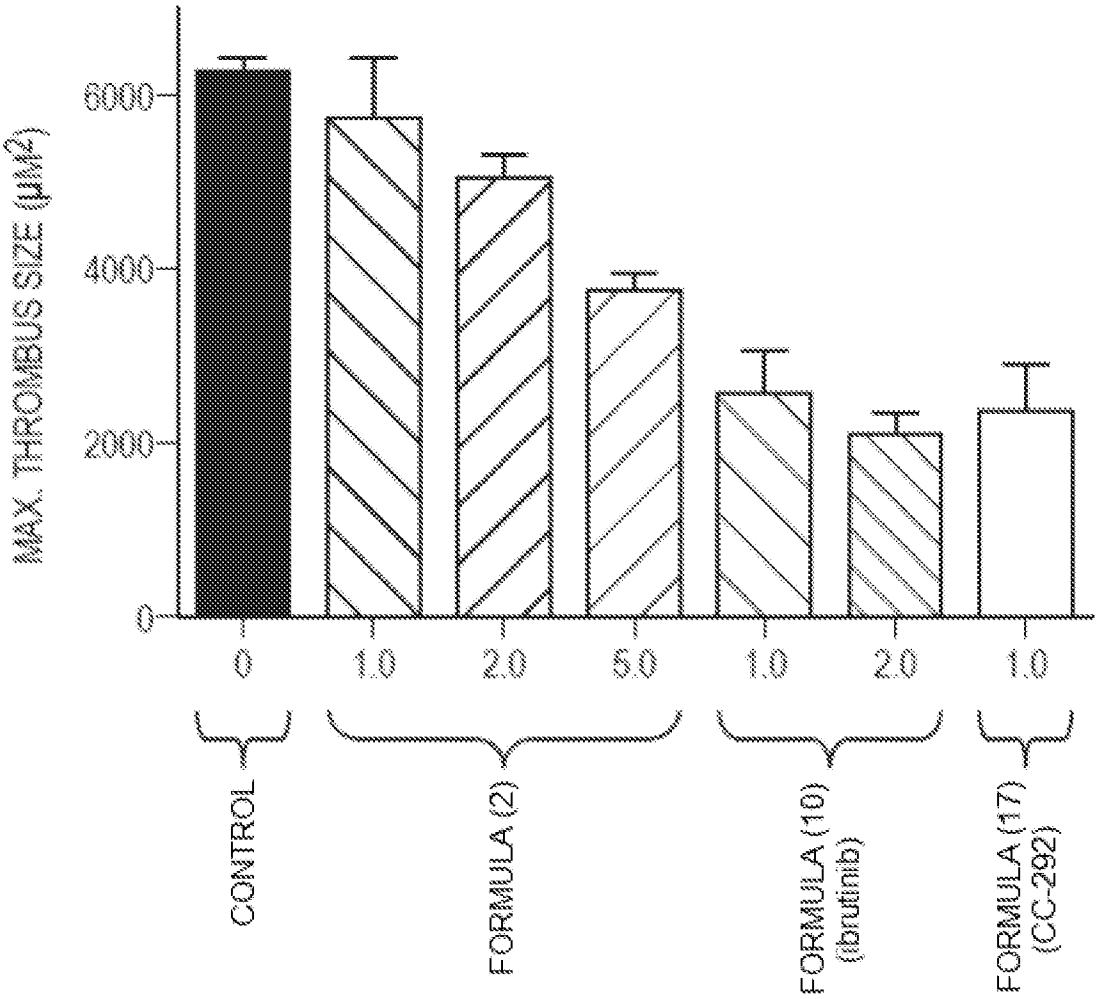

MAX. THROMBUS SIZE (μM²)
6000
4000
2000
0
0
1.0
2.0
5.0
1.0
2.0
1.0
CONTROL
FORMULA (2)
FORMULA (10) (ibrutinib)
FORMULA (17) (CC-292)

FIG. 70

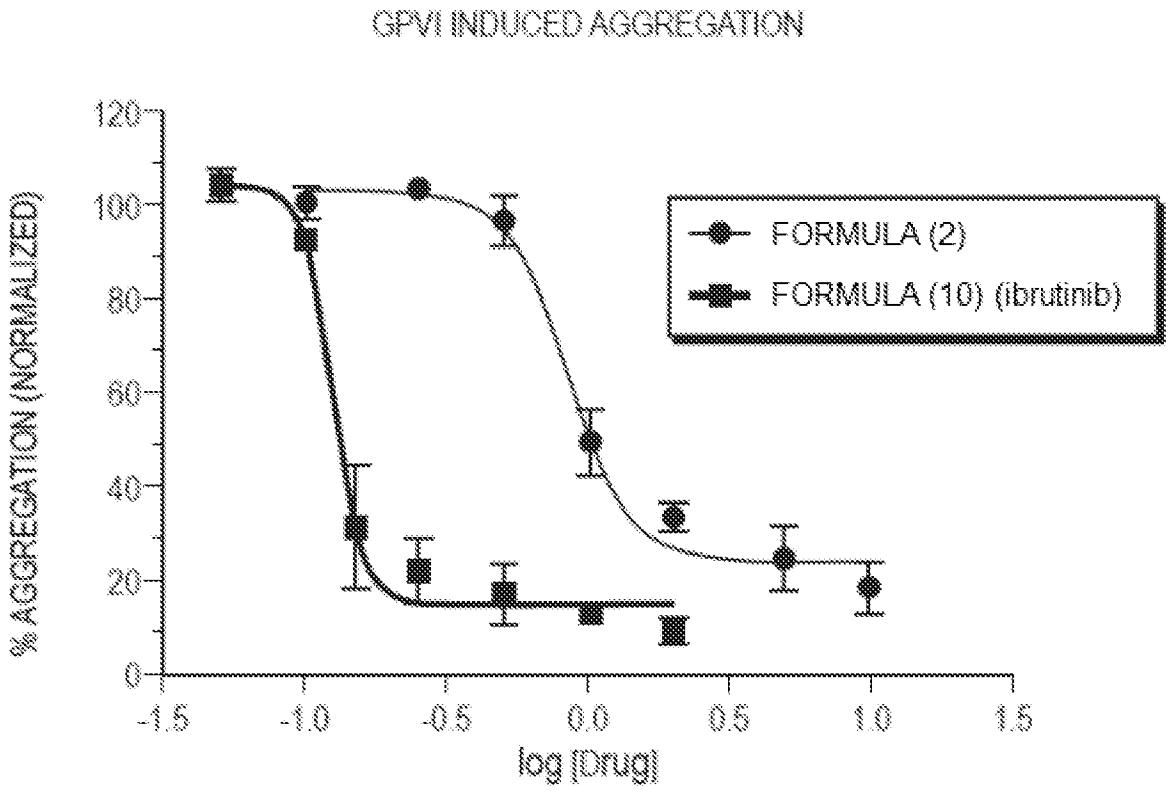

GPVI INDUCED AGGREGATION
% AGGREGATION (NORMALIZED)
120
100
80
60
40
20
0
-1.5
-1.0
-0.5
0.0
0.5
1.0
1.5
log [Drug]
FORMULA (2)
FORMULA (10) (ibrutinib)

FIG. 71

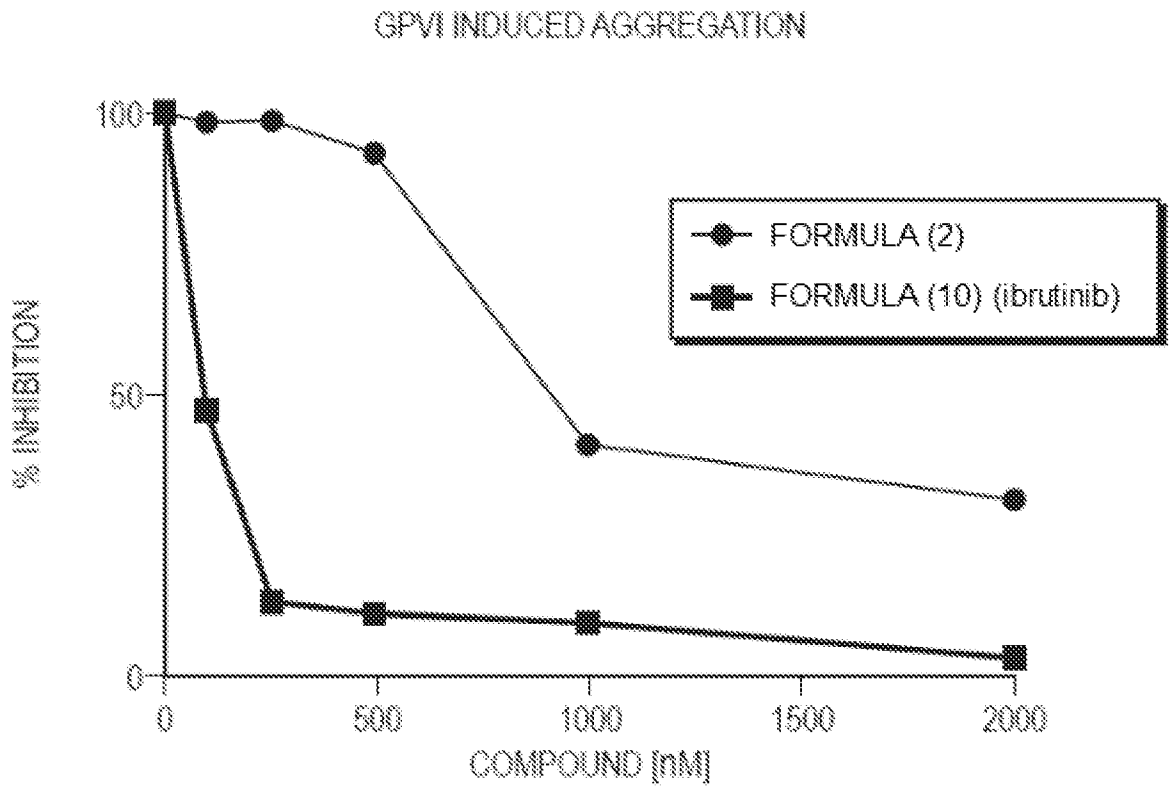

GPVI INDUCED AGGREGATION
% INHIBITION
100
50
0
0
500
1000
1500
2000
COMPOUND [nM]
FORMULA (2)
FORMULA (10) (ibrutinib)

FIG. 72

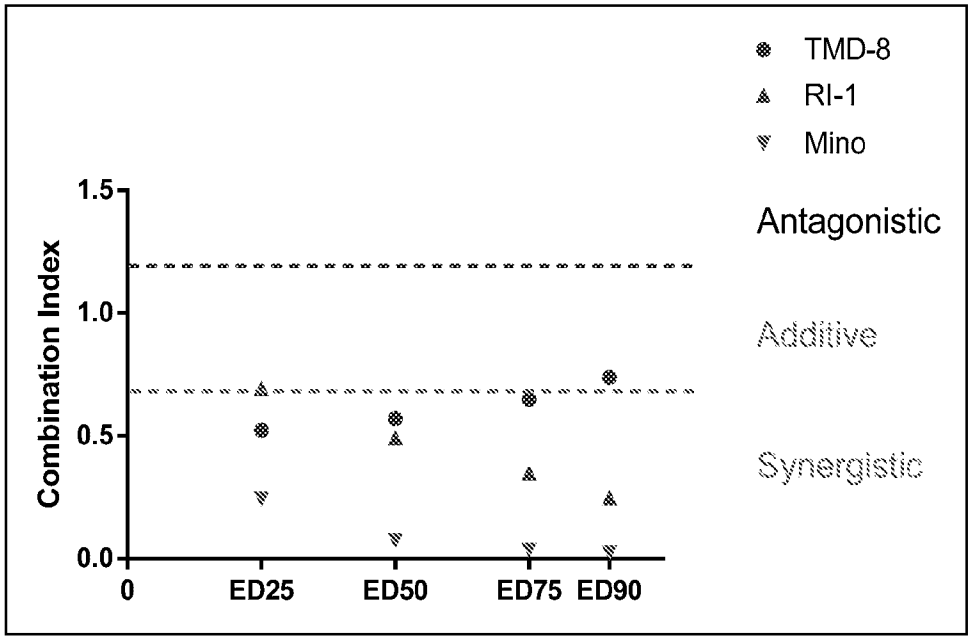

TMD-8
RI-1
Mino
Antagonistic
Additive
Synergistic
Combination Index
1.5
1.0
0.5
0.0
0
ED25
ED50
ED75
ED90

FIG. 73

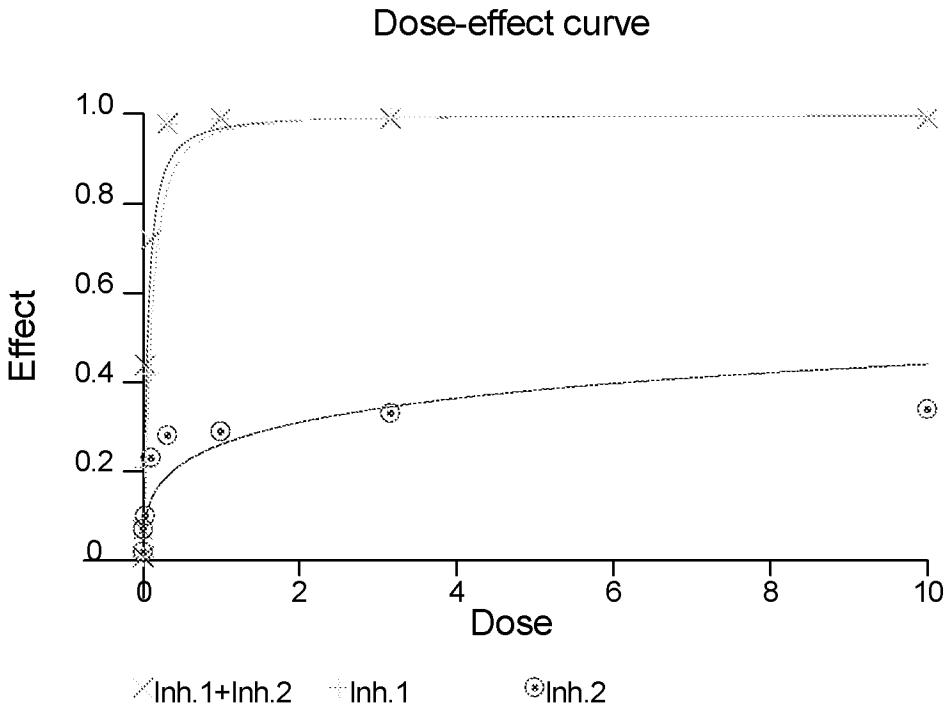

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.1+Inh.2
Inh.1
Inh.2

FIG. 74

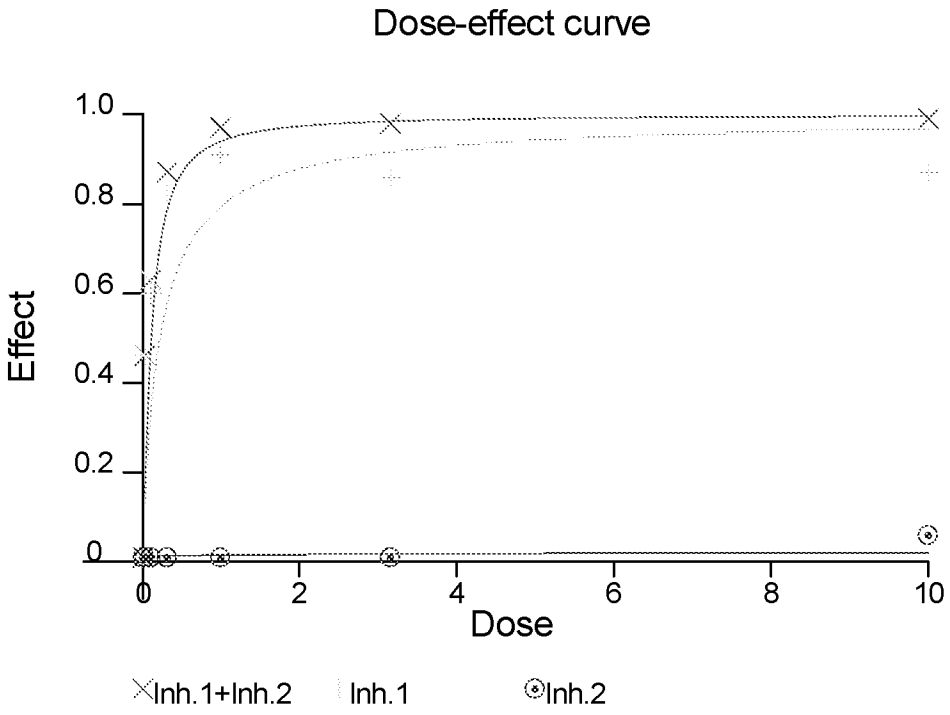

Dose-effect curve
1.0
0.8
0.6
0.4
0.2
0
Effect
0
2
4
6
8
10
Dose
Inh.1+Inh.2
Inh.1
Inh.2

FIG. 75

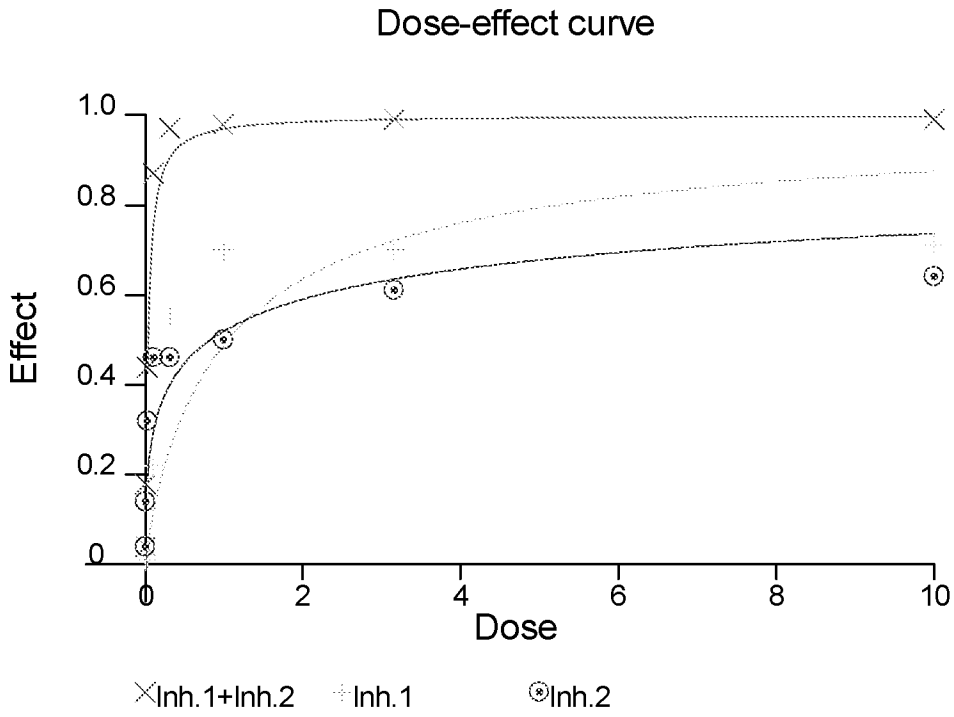

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Dose
Inh.1+Inh.2
Inh.1
Inh.2

FIG. 76

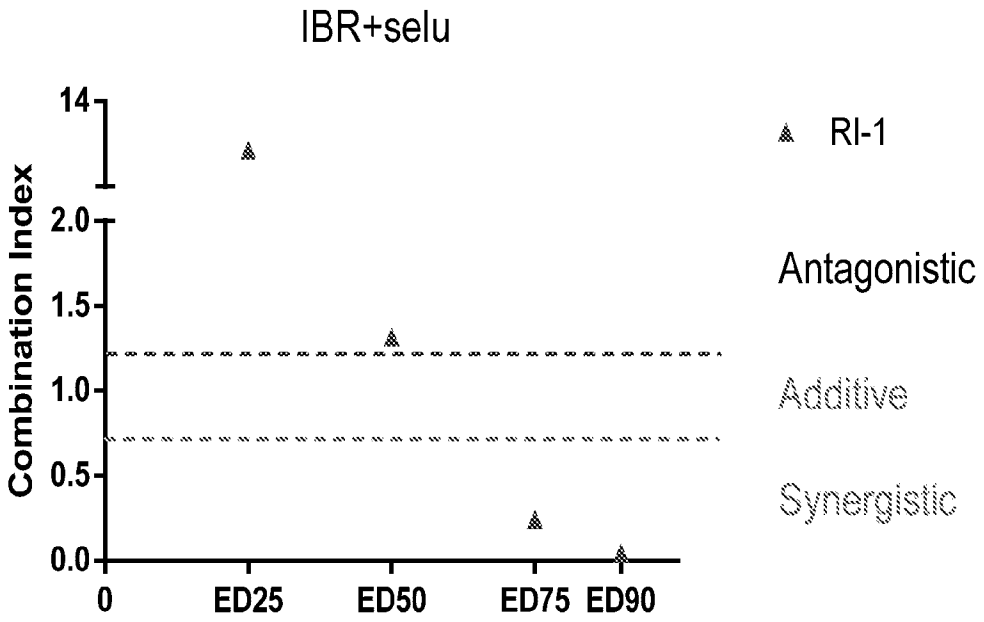

IBR+selu
Combination Index
14
2.0
1.5
1.0
0.5
0.0
0
ED25
ED50
ED75
ED90
RI-1
Antagonistic
Additive
Synergistic

FIG. 77

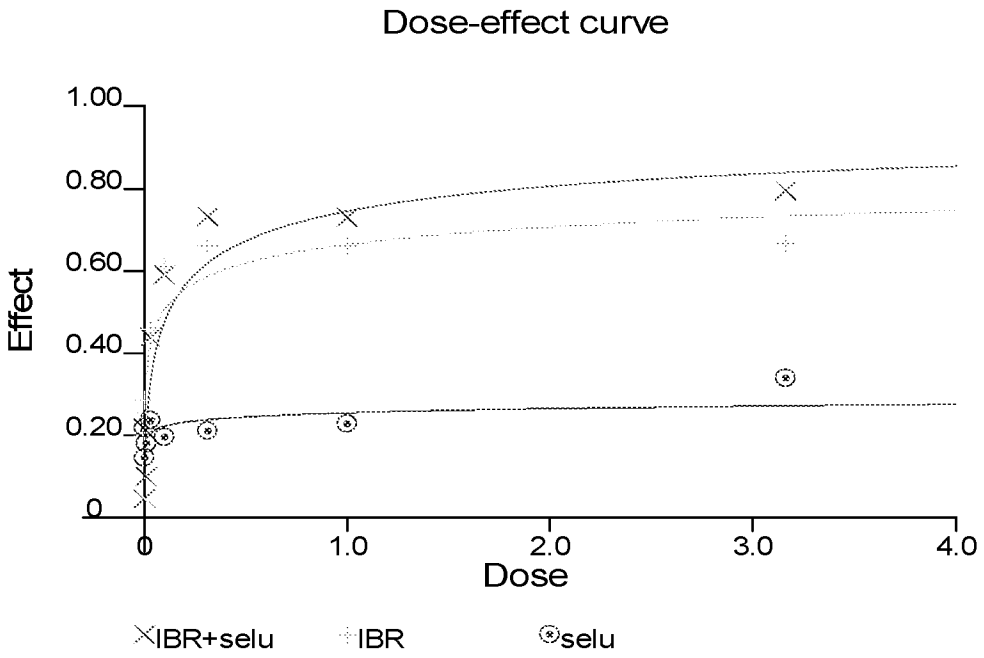

Dose-effect curve
1.00
0.80
0.60
0.40
0.20
0
Effect
0
1.0
2.0
3.0
4.0
Dose
IBR+selu
IBR
selu

FIG. 78

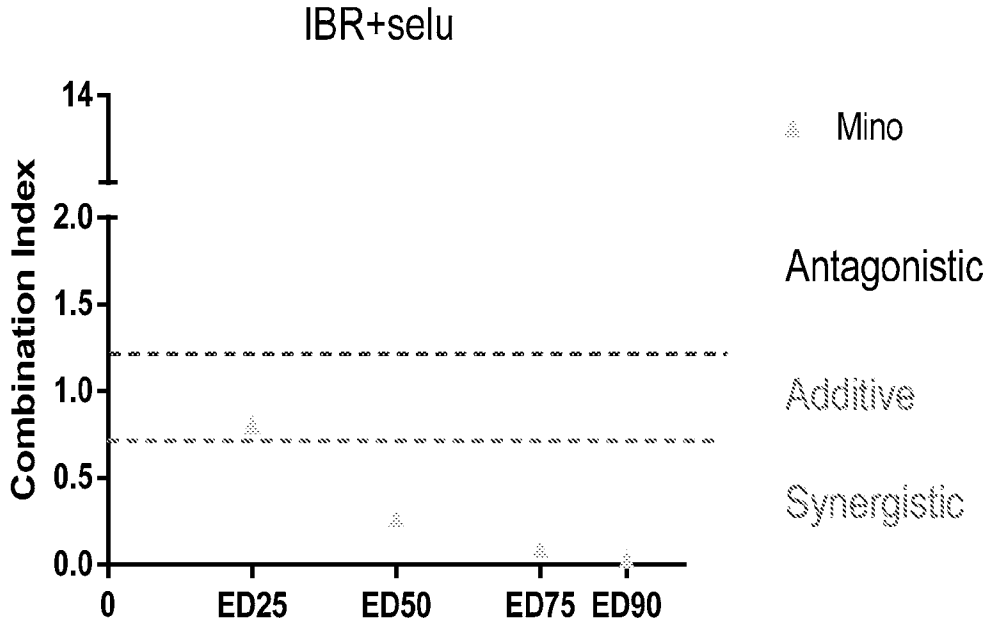

IBR+selu
Combination Index
14
2.0
1.5
1.0
0.5
0.0
0
ED25
ED50
ED75
ED90
Mino
Antagonistic
Additive
Synergistic

FIG. 79

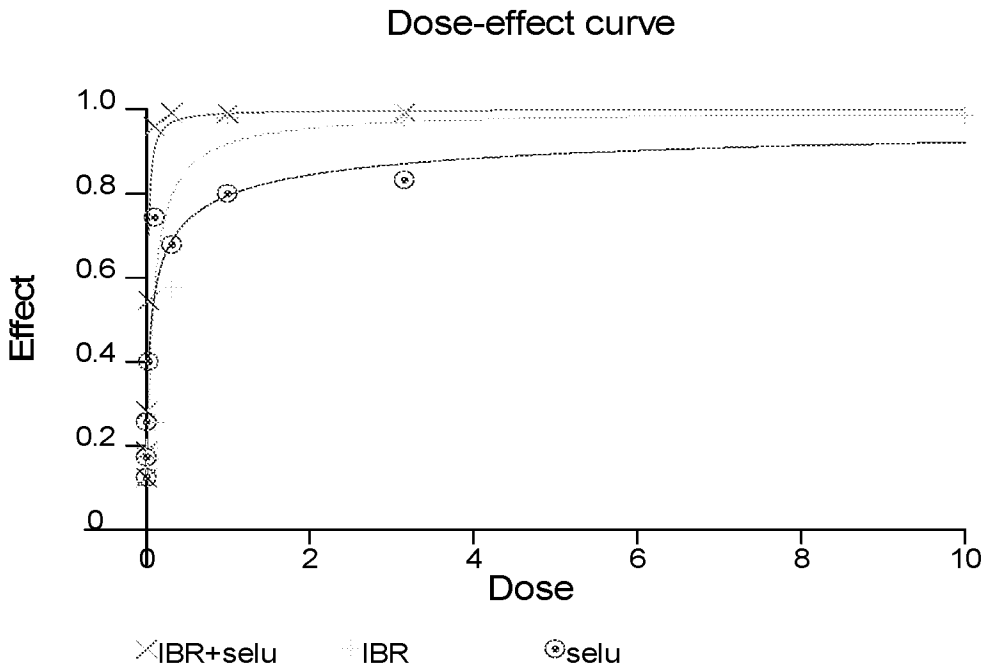

Dose-effect curve
1.0
0.8
0.6
0.4
0.2
0
Effect
0
2
4
6
8
10
Dose
IBR+selu
IBR
selu

FIG. 80

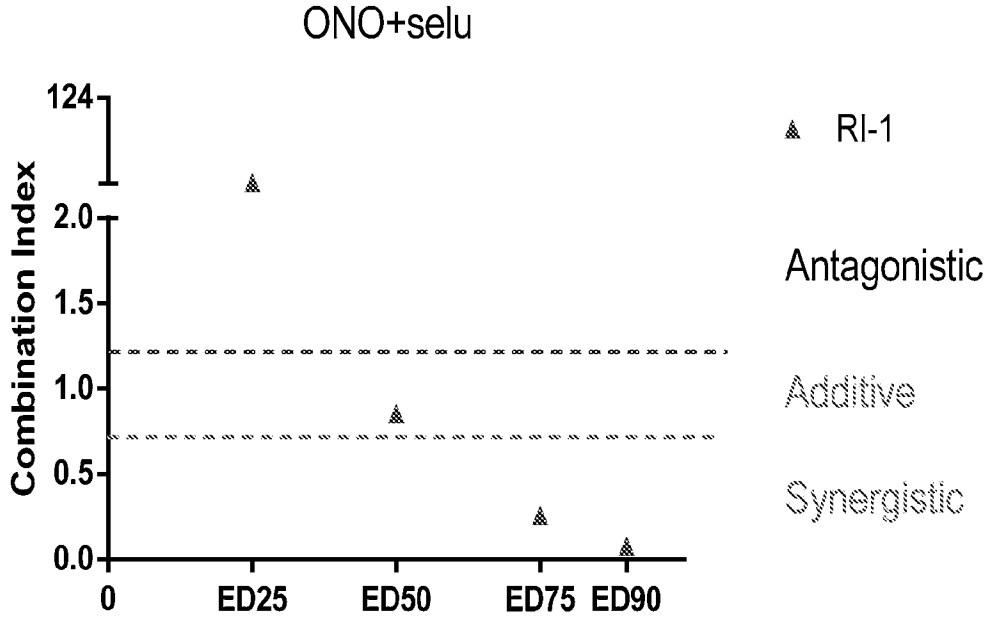

ONO+selu
Combination Index
124
2.0
1.5
1.0
0.5
0.0
0
ED25
ED50
ED75
ED90
RI-1
Antagonistic
Additive
Synergistic

FIG. 81

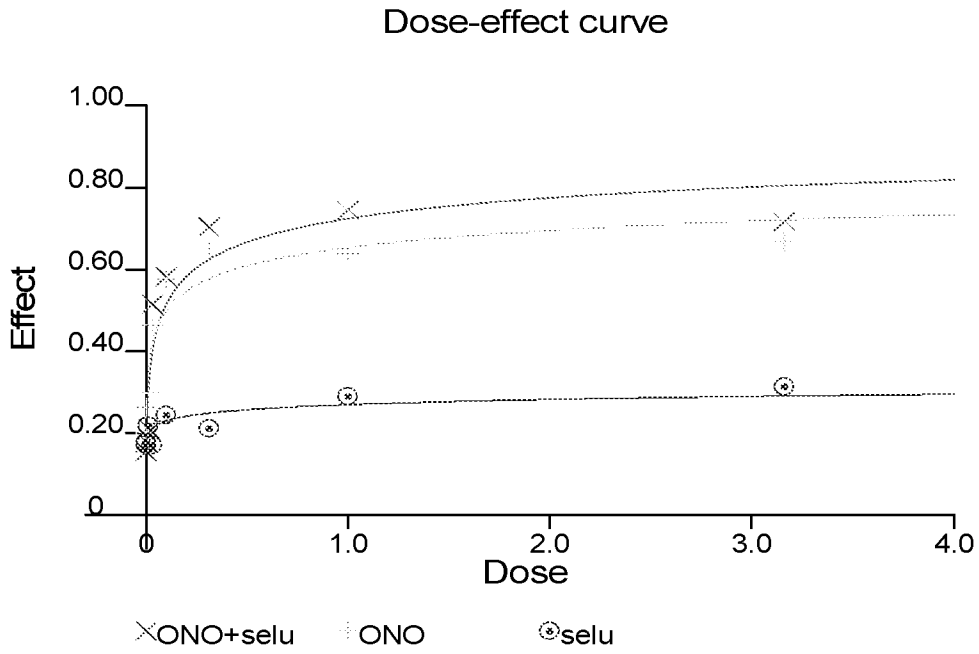

Dose-effect curve
1.00
0.80
0.60
0.40
0.20
0
Effect
0
1.0
2.0
3.0
4.0
Dose
ONO+selu
ONO
selu

FIG. 82

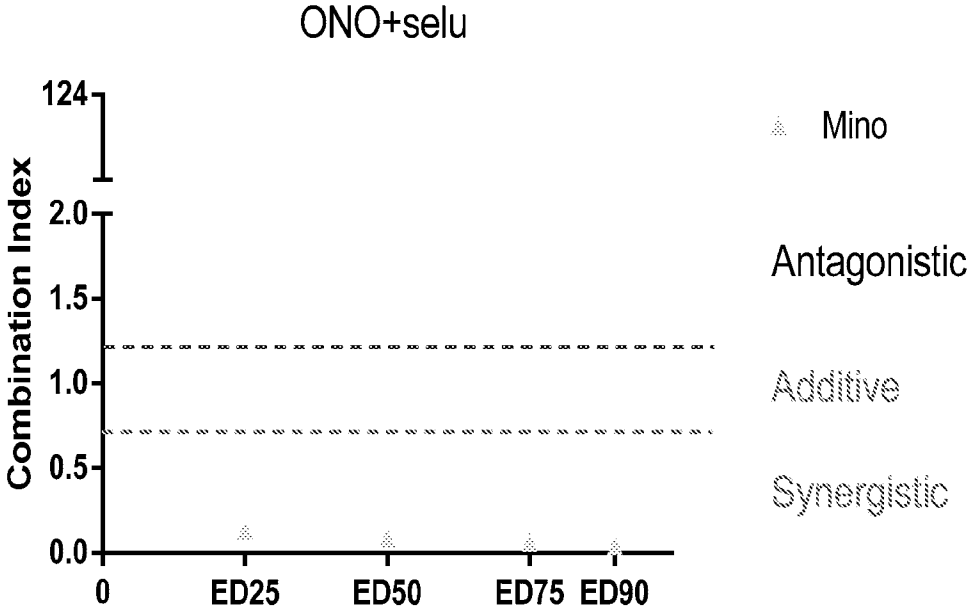

ONO+selu
Combination Index
124
2.0
1.5
1.0
0.5
0.0
0
ED25
ED50
ED75
ED90
Mino
Antagonistic
Additive
Synergistic

FIG. 83

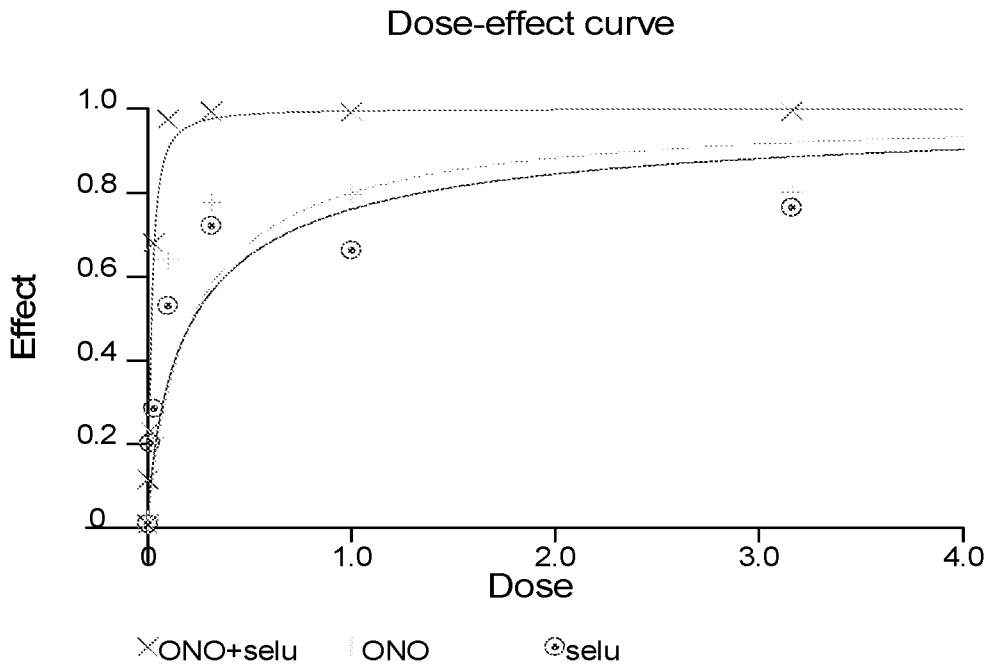

Dose-effect curve
Effect
1.0
0.8
0.6
0.4
0.2
0
0
1.0
2.0
3.0
4.0
Dose
ONO+selu
ONO
selu

FIG. 84

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2016/054988

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K45/06 A61K31/4184 A61K31/454 A61K31/4985 A61K31/519
A61P35/00 A61P35/02
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2013/010868 A1 (MSD OSS BV [NL]; BARF TJEERD A [NL]; JANS CHRISTIAAN GERARDUS JOHANNES) 24 January 2013 (2013-01-24) cited in the application p. 22, l. 15-20; examples 6, 134; claims 13, 14	1-5, 7-32, 34-71

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 November 2016	20/01/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Scheithe, Rupert

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Todd Covey: "ACP-196: a novel covalent Bruton's tyrosine kinase (Btk) inhibitor with improved selectivity and in vivo target coverage in chronic lymphocytic leukemia (CLL) patients", Cancer Research, 1 August 2015 (2015-08-01), page Abstract 2596, XP055315480, DOI: 10.1158/1538-7445.AM2015-2596 Retrieved from the Internet: URL:http://cancerres.aacrjournals.org/content/75/15_Supplement/2596 [retrieved on 2016-11-01] the whole document -----	1-5, 7-32, 34-71
Y	Kyle Crassini: "MEK1/2 Inhibition By MEK162 Is Effective Against Chronic Lymphocytic Leukaemia Cells Under Conditions That Mimic Stimulation of B-Cell Receptor-Mediated Signaling ¦ Blood Journal", Blood, 6 December 2014 (2014-12-06), page 3330, XP055315492, Retrieved from the Internet: URL:http://www.bloodjournal.org/content/124/21/3330?sso-checked=true [retrieved on 2016-11-01] the whole document -----	1-5, 7-32, 34-71
Y	J. JING ET AL: "Comprehensive Predictive Biomarker Analysis for MEK Inhibitor GSK1120212", MOLECULAR CANCER THERAPEUTICS, vol. 11, no. 3, 14 December 2011 (2011-12-14), pages 720-729, XP055066203, ISSN: 1535-7163, DOI: 10.1158/1535-7163.MCT-11-0505 abstract -----	1-5, 7-32, 34-71
Y	Eugenio Gaudio: "The MEK-inhibitor pimasertib is synergistic with PI3K-delta and BTK inhibitors in lymphoma models", Cancer Research, 1 August 2015 (2015-08-01), page Abstract 2676, XP055315257, DOI: 10.1158/1538-7445.AM2015-2676 Retrieved from the Internet: URL:http://cancerres.aacrjournals.org/content/75/15_Supplement/2676 [retrieved on 2016-10-31] the whole document -----	1-5, 7-32, 34-71

-/--

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2016/054988

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	N. JAIN ET AL: "Phase II Study of the Oral MEK Inhibitor Selumetinib in Advanced Acute Myelogenous Leukemia: A University of Chicago Phase II Consortium Trial", CLINICAL CANCER RESEARCH, vol. 20, no. 2, 31 October 2013 (2013-10-31), pages 490-498, XP055221318, US ISSN: 1078-0432, DOI: 10.1158/1078-0432.CCR-13-1311 the whole document -----	1-5, 7-32, 34-71

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2016/054988

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

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

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

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

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

see additional sheet

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

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

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

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

5, 20-28, 32, 47-55, 67(completely); 1-4, 7-19, 29-31, 34-46, 56-66 68-71(partially)

Remark on Protest

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

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

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 5, 20-28, 32, 47-55, 67(completely); 1-4, 7-19, 29-31, 34-46, 56-66, 68-71(partially)

A method of claims 1, 20, wherein the BTK inhibitor is selected from the group disclosed in claim 5.
A composition for use according to claims 29, 47, wherein the BTK inhibitor is selected from the group disclosed in claim 5.
A pharmaceutical composition according to claim 56, wherein the BTK inhibitor is selected from the group disclosed in claim 5.
A kit according to claim 58, wherein the BTK inhibitor is selected from the group disclosed in claim 5.
A MEK inhibitor in combination with a BTK inhibitor for use according to claim 60, wherein the BTK inhibitor is selected from the group disclosed in claim 5.
A combination according to claim 67.
Use according to claim 71, wherein the BTK inhibitor is selected from the group disclosed in claim 5.

---

2. claims: 1-4, 6-19, 29-31, 33-46, 56-66, 68-71(all partially)

A method of claim 1, wherein the BTK inhibitor is the first compound disclosed in claim 6.
A composition for use according to claim 29, wherein the BTK inhibitor is the first compound disclosed in claim 6.
A pharmaceutical composition according to claim 56, wherein the BTK inhibitor is the first compound disclosed in claim 6.
A kit according to claim 58, wherein the BTK inhibitor is the first compound disclosed in claim 6.
A MEK inhibitor in combination with a BTK inhibitor for use according to claim 60, wherein the BTK inhibitor is the first compound disclosed in claim 6.
Use according to claim 71, wherein the BTK inhibitor is the first compound disclosed in claim 6.

---

3. claims: 1-4, 6-19, 29-31, 33-46, 56-66, 68-71(all partially)

A method of claim 1, wherein the BTK inhibitor is the second compound disclosed in claim 6.
A composition for use according to claim 29, wherein the BTK inhibitor is the second compound disclosed in claim 6.
A pharmaceutical composition according to claim 56, wherein the BTK inhibitor is the second compound disclosed in claim 6.
A kit according to claim 58, wherein the BTK inhibitor is the second compound disclosed in claim 6.
A MEK inhibitor in combination with a BTK inhibitor for use according to claim 60, wherein the BTK inhibitor is the

second compound disclosed in claim 6.
Use according to claim 71, wherein the BTK inhibitor is the second compound disclosed in claim 6.

---

4. claims: 1-4, 6-19, 29-31, 33-46, 56-66, 68-71(all partially)

A method of claim 1, wherein the BTK inhibitor is the third compound disclosed in claim 6.
A composition for use according to claim 29, wherein the BTK inhibitor is the third compound disclosed in claim 6.
A pharmaceutical composition according to claim 56, wherein the BTK inhibitor is the third compound disclosed in claim 6.
A kit according to claim 58, wherein the BTK inhibitor is the third compound disclosed in claim 6.
A MEK inhibitor in combination with a BTK inhibitor for use according to claim 60, wherein the BTK inhibitor is the third compound disclosed in claim 6.
Use according to claim 71, wherein the BTK inhibitor is the third compound disclosed in claim 6.

---

5. claims: 1-4, 7-19, 29-31, 34-46, 56-66, 68-71(all partially)

A method of claim 1, wherein the BTK inhibitor is a BTK inhibitor not encompassed by the previous inventions.
A composition for use according to claim 29, wherein the BTK inhibitor is a BTK inhibitor not encompassed by the previous inventions.
A pharmaceutical composition according to claim 56, wherein the BTK inhibitor is a BTK inhibitor not encompassed by the previous inventions.
A kit according to claim 58, wherein the BTK inhibitor is a BTK inhibitor not encompassed by the previous inventions.
A MEK inhibitor in combination with a BTK inhibitor for use according to claim 60, wherein the BTK inhibitor is a BTK inhibitor not encompassed by the previous inventions.
Use according to claim 71, wherein the BTK inhibitor is a BTK inhibitor not encompassed by the previous inventions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2016/054988

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2013010868 A1	24-01-2013	AU 2012285987 A1	06-02-2014
		AU 2016203837 A1	30-06-2016
		CA 2841886 A1	24-01-2013
		CL 2014000130 A1	22-08-2014
		CN 103889987 A	25-06-2014
		CN 106243113 A	21-12-2016
		CO 6940411 A2	09-05-2014
		CR 20140030 A	03-06-2014
		DO P2014000008 A	30-04-2014
		EA 201490300 A1	30-05-2014
		EC SP14013217 A	31-03-2015
		EP 2734522 A1	28-05-2014
		JP 5826931 B2	02-12-2015
		JP 2014520870 A	25-08-2014
		JP 2016034968 A	17-03-2016
		KR 20140036324 A	25-03-2014
		KR 20160117642 A	10-10-2016
		MA 35348 B1	01-08-2014
		NZ 620085 A	27-05-2016
		PE 16812014 A1	14-11-2014
		SG 10201605913V A	29-09-2016
		US 2014155385 A1	05-06-2014
		US 2016151364 A1	02-06-2016
		US 2016159810 A1	09-06-2016
		WO 2013010868 A1	24-01-2013