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(54) Title: BTK INHIBITORS TO TREAT SOLID TUMORS THROUGH MODULATION OF THE TUMOR MICROENVIRONMENT

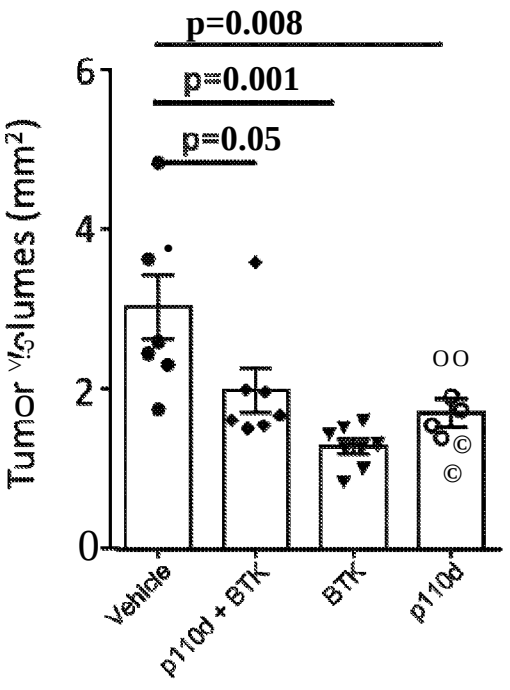


FIG. 1

(57) Abstract: In certain embodiments, the invention includes therapeutic methods of using a BTK inhibitor to treat solid tumor cancers by modulation of the tumor microenvironment, including 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.

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BTK INHIBITORS TO TREAT SOLID TUMORS
THE TUMOR MICROENVIRONMENT
BTK INHIBITORS TO TREAT SOLID TUMORS:
THE TUMOR MICROENVIRONMENT

## CROSS-REFERENCE TO RELATED APPLICATIONS

**[001]** This application claims the benefit of U.S. Provisional Application No. 62/035,818 filed on August 11, 2014; U.S. Provisional Application No. 62/088,069 filed on December 5, 2014; U.S. Provisional Application No. 62/115,539 filed on February 12, 2015; and U.S. Provisional Application No. 62/181,167 filed on June 17, 2015, all of which are herein incorporated by reference in their entireties.

## FIELD OF THE INVENTION

**[002]** In some embodiments, therapeutic uses of a Bruton's tyrosine kinase (BTK) inhibitor to treat solid tumors and other diseases through modulation of the tumor microenvironment are disclosed herein.

## BACKGROUND OF THE INVENTION

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

**[004]** BTK is expressed in numerous B cell lymphomas and leukemias. Other diseases with an important role for dysfunctional B cells are B cell malignancies, as described in Hendriks, *et al.*, *Nat. Rev. Cancer,* **2014,** *14,* 219-231. The reported role for BTK in the regulation of proliferation and apoptosis of B cells indicates the potential for BTK inhibitors in the treatment of B cell lymphomas. BTK inhibitors have thus been developed as potential therapies for many of these malignancies, as described in D'Cruz, *et al.*, *OncoTargets and Therapy* **2013,** *6,* 161-

176.

**[005]** 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. In addition, new research tools would also be useful to better understand the tumor microenvironment and signaling processes that occurs between solid tumor cells and the microenvironment.

## SUMMARY OF THE INVENTION

**[006]** In an embodiment, the invention provides a method of treating a hyperproliferative disease in a subject, comprising administering to a mammal in need thereof a therapeutically effective amount of a BTK inhibitor.

**[007]** In an embodiment, the invention provides a method of treating leukemia, lymphoma or a solid tumor cancer in a subject, comprising administering to a mammal in need thereof a therapeutically effective amount of a BTK inhibitor.

**[008]** In an embodiment, the invention provides a method of treating a solid tumor cancer in a human comprising administering a therapeutically effective dose of 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.

**[009]** In an embodiment, the invention provides a method of treating a solid tumor cancer in a

human comprising administering a therapeutically effective dose of a BTK inhibitor, wherein the dose is effective to cross the blood-brain barrier and/or 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.

**[0010]** In an embodiment, the invention provides a BTK inhibitor for use in the treatment of a hyperproliferative disease.

**[0011]** In an embodiment, the invention provides a BTK inhibitor for use in the treatment of a solid tumor cancer.

**[0012]** In an embodiment, the invention provides a BTK inhibitor for use in inhibition of 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.

**[0013]** In an embodiment, the invention provides a BTK inhibitor for use in the treatment of a solid tumor cancer wherein the BTK inhibitor inhibits 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.

**[0014]** In an embodiment, the invention provides use of a BTK inhibitor to inhibit signaling between a solid tumor cell 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.

**[0015]** In one embodiment, the invention comprises a composition comprising a solid tumor cell, a BTK inhibitor or a metabolite thereof, 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.

**[0016]** In one embodiment, the invention comprises a BTK inhibitor for use in the treatment of a disease, for example a solid tumor cancer, affecting the central nervous system and requiring transmission of the BTK inhibitor or a metabolite thereof across the blood-brain barrier.

**[0017]** In one embodiment, the invention comprises composition comprising a BTK inhibitor for use in the treatment of a disease, for example a solid tumor cancer, affecting the central nervous system and requiring transmission of the BTK inhibitor or a metabolite thereof across the blood-brain barrier.

**[0018]** In one embodiment, the invention comprises a BTK inhibitor for use in the treatment of a disease, for example a solid tumor cancer, affecting the central nervous system and wherein treatment requires transmission of the BTK inhibitor, or a metabolite thereof, across the blood-brain barrier, wherein the BTK inhibitor inhibits signaling between a solid tumor cell 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.

**[0019]** In one embodiment, the invention comprises a composition comprising a BTK inhibitor for use in the treatment of a disease, for example a solid tumor cancer, affecting the central nervous system and wherein treatment requires transmission of the BTK inhibitor, or a metabolite thereof, across the blood-brain barrier, wherein the BTK inhibitor inhibits signaling between a solid tumor cell 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.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0020]** 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.

**[0021]** FIG. 1 illustrates tumor growth suppression in an orthotopic pancreatic cancer model. Mice were dosed orally with 15 mg/kg of the BTK inhibitor of Formula (II), 15 mg/kg of a phosphoinositide 3-kinase ¡¡ (PI3K-¡¡) inhibitor (denoted “p110d”), or a combination of both

drugs. The statistical p-value (presumption against null hypothesis) is shown for each tested single agent and for the combination against the vehicle.

**[0022]** FIG. 2 illustrates the effects of oral dosing with 15 mg/kg of the BTK inhibitor of Formula (II), 15 mg/kg of a phosphoinositide 3-kinase ¡¡ (PI3K-¡¡) inhibitor (denoted “p110d”), or a combination of both inhibitors on myeloid tumor-associated macrophages (TAMs) in pancreatic tumor-bearing mice.

**[0023]** FIG. 3 illustrates the effects of oral dosing with 15 mg/kg of the BTK inhibitor of Formula (II), 15 mg/kg of a phosphoinositide 3-kinase ¡¡ (PI3K-¡¡) inhibitor (denoted “p110d”), or a combination of both inhibitors on myeloid-derived suppressor cells (MDSCs) in pancreatic tumor-bearing mice.

**[0024]** FIG. 4 illustrates the effects of oral dosing with 15 mg/kg of the BTK inhibitor of Formula (II), 15 mg/kg of a phosphoinositide 3-kinase ¡¡ (PI3K-¡¡) inhibitor, or a combination of both inhibitors on regulatory T cells (Tregs) in pancreatic tumor-bearing mice.

**[0025]** FIG. 5 illustrates the effects of vehicle on flux at two timepoints, as a control for comparison with FIG. 6, in the ID8 syngeneic orthotropic ovarian cancer model.

**[0026]** FIG. 6 illustrates the effects of the BTK inhibitor of Formula (II) on flux at two timepoints, for comparison with FIG. 5, in the ID8 syngeneic orthotropic ovarian cancer model.

**[0027]** FIG. 7 illustrates tumor response to treatment with the BTK inhibitor of Formula (II) correlates with a significant reduction in immunosuppressive tumor associated lymphocytes in tumor-bearing mice, in comparison to a control (vehicle).

**[0028]** FIG. 8 illustrates that treatment with the BTK inhibitor of Formula (II) impairs ID8 ovarian cancer growth in the syngeneic murine model in comparison to a control (vehicle).

**[0029]** FIG. 9 illustrates that treatment with the BTK inhibitor of Formula (II) induces a tumor response that correlates with a significant reduction in total B cells in tumor-bearing mice.

**[0030]** FIG. 10 illustrates that treatment with the BTK inhibitor of Formula (II) induces a tumor response that correlates with a significant reduction in B regulatory cells (Bregs) in tumor-bearing mice.

**[0031]** FIG. 11 illustrates that treatment with the BTK inhibitor of Formula (II) induces a

tumor response that correlates with a significant reduction in immunosuppressive tumor associated Tregs.

**[0032]** FIG. 12 illustrates that treatment with the BTK inhibitor of Formula (II) induces a tumor response that correlates with an increase in $CD8^+$ T cells.

**[0033]** FIG. 13 illustrates the effects on tumor volume of vehicle (measured in mm3) of the BTK inhibitor of Formula (II), a combination of the BTK inhibitor of Formula (II) and gemcitabine ("Gem"), and gemcitabine alone.

**[0034]** FIG. 14 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 (II), a combination of the BTK inhibitor of Formula (II) and gemcitabine ("Gem"), and gemcitabine alone.

**[0035]** FIG. 15 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 (II), a combination of the BTK inhibitor of Formula (II) and gemcitabine ("Gem"), and gemcitabine alone.

**[0036]** FIG. 16 illustrates the effects on the percentage of CD11b+, LY6Clow, 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 (II), a combination of the BTK inhibitor of Formula (II) and gemcitabine ("Gem"), and gemcitabine alone.

**[0037]** FIG. 17 illustrates the effects on the percentage of Gr1+ and LY6Chi, 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 (II), a combination of the BTK inhibitor of Formula (II) and gemcitabine ("Gem"), and gemcitabine alone.

**[0038]** FIG. 18 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).

**[0039]** FIG. 19 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.

**[0040]** FIG. 20 illustrates the effect of the tested BTK inhibitors on thrombus formation. The conditions used were N=4, 3 mice per drug; anti-clotting agents < 2000 μM2. In studies with ibrutinib, 48% MCL bleeding events were observed with 560 mg QD and 63% CLL bleeding events were observed with 420 mg QD, where bleeding event is defined as subdural hematoma, ecchymoses, GI bleeding, or hematuria.

**[0041]** FIG. 21 illustrates the effect of the concentration of the tested BTK inhibitors on thrombus formation.

**[0042]** FIG. 22 illustrates the results of GPVI platelet aggregation studies of Formula (II) (IC50 = 1.15 μM) and Formula (X) (ibrutinib, IC50 = 0.13 μM).

**[0043]** FIG. 23 illustrates the results of GPVI platelet aggregation studies of Formula (II) and Formula (X) (ibrutinib).

**[0044]** FIG. 24 illustrates the effects of treatment with single-active pharmaceutical ingredient Formula (II) on tumor volumes in the KPC pancreatic cancer model.

**[0045]** FIG. 25 illustrates the results of analysis of tumor tissues showing that immunosuppressive TAMs ($CD11b^+Ly6ClowF4/80^+Csf1r^+$) were significantly reduced with Formula (II) treatment in the KPC pancreatic cancer model.

**[0046]** FIG. 26 illustrates the results of analysis of tumor tissues showing that immunosuppressive MDSCs ($Gr1^+Ly6CHi$) were significantly reduced with Formula (II) treatment in the KPC pancreatic cancer model.

**[0047]** FIG. 27 illustrates the results of analysis of tumor tissues showing that immunosuppressive Tregs ($CD4^+CD25^+FoxP3^+$) were significantly reduced with Formula (II) treatment in the KPC pancreatic cancer model.

**[0048]** FIG. 28 illustrates that the decrease in immunosuppressive TAMs, MDSCs, and Tregs in the KPC pancreatic cancer model correlated with a significant increase in $CD8^+$ cells (FIG. 122).

**[0049]** FIG. 29 shows *in vitro* analysis of antibody-dependent NK cell–mediated INF-Ûrelease with BTK inhibitors. To evaluate NK cell function, purified NK cells were isolated from healthy

peripheral blood mononuclear cells and cultured with 0.1 or 1 μM of ibrutinib or 1 μM of Formula (II) for 4 hours together with rituximab-coated (10 μg/mL) lymphoma cells, DHL4, or trastuzumab-coated (10 μg/mL) HER2+ breast cancer cells, HER18, and supernatant was harvested and analyzed by enzyme-linked immunosorbent assay for interferon-Û(IFN-Û). All *in vitro* experiments were performed in triplicate. Labels are defined as follows: *p = 0.018, **p = 0.002, ***p = 0.001.

**[0050]** FIG. 30 shows *in vitro* analysis of antibody-dependent NK cell–mediated degranulation with BTK inhibitors. To evaluate NK cell function, purified NK cells were isolated from healthy peripheral blood mononuclear cells and cultured with 0.1 or 1 μM of ibrutinib or 1 μM of Formula (II) 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.

**[0051]** FIG. 31 shows that ibrutinib antagonizes antibody-dependent NK cell–mediated cytotoxicity using the Raji cell line. NK cell cytotoxicity as percent lysis of tumor cells was analyzed in chromium release assays with purified NK cells incubated with chromium-labeled Raji cells for 4 hours at variable rituximab concentrations at a constant effector:target ratio of 25:1 and ibrutinib (1 μM), Formula (II) (1 μM), or other ITK sparing BTK inhibitors CGI-1746, inhibA (1 μM) and BGB-3111 ("inhib B," 1 μM). All *in vitro* experiments were performed in triplicate. Labels are defined as follows: *p = 0.001.

**[0052]** FIG. 32 shows a summary of the results given in FIG. 31 at the highest concentration of rituximab ("Ab") (10 μg/mL).

**[0053]** FIG. 33 shows that ibrutinib antagonizes antibody-dependent NK cell–mediated cytotoxicity in primary CLL cells, as with Raji cells in FIG. 31.

**[0054]** FIG. 34 illustrates *in vivo* potency of Formula (II) (labeled "BTK inhibitor") and ibrutinib. Mice were gavaged at increasing drug concentration and sacrificed at one time point (3 h post-dose). BCR is stimulated with IgM and the expression of activation markers CD69 and CD86 are monitored by flow cytometry to determine $EC_{50}$'s. The results show that Formula (II) is more potent at inhibiting expression of activation makers than ibrutinib.

**[0055]** FIG. 35 illustrates *in vitro* potency in whole blood of Formula (II), ibrutinib and CC-292 in inhibition of signals through the B cell receptor.

**[0056]** FIG. 36 illustrates EGF receptor phosphorylation *in vitro* was also determined for Formula (II) and ibrutinib.

**[0057]** FIG. 37 illustrates the results of the clinical study of Formula (II) (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 (II) causes a much smaller relative increase and much faster decrease in absolute lymphocyte count (ALC) relative to the BTK inhibitor ibrutinib. The sum of the product of greatest diameters (SPD) also decreases more rapidly during treatment with the BTK inhibitor than with the BTK inhibitor ibrutinib.

**[0058]** FIG. 38 shows overall response data shown by SPD of enlarged lymph nodes in CLL patients as a function of dose of the BTK inhibitor of Formula (II).

**[0059]** FIG. 39 shows a comparison of progression-free survival (PFS) in CLL patients treated with the BTK inhibitor ibrutinib or the BTK inhibitor of Formula (II). The ibrutinib data is taken from Byrd, *et al.*, *N. Engl. J. Med.* **2013,** *369,* 32-42. CLL patients treated with Formula (II) for at least 8 days are included.

**[0060]** FIG. 40 shows a comparison of number of patients at risk in CLL patients treated with the BTK inhibitor ibrutinib or the BTK inhibitor of Formula (II). CLL patients treated with Formula (II) for at least 8 days are included.

**[0061]** FIG. 41 shows a comparison of progression-free survival (PFS) in CLL patients exhibiting the 17p deletion and treated with the BTK inhibitor ibrutinib or the BTK inhibitor of Formula (II). The ibrutinib data is taken from Byrd, *et al.*, *N. Engl. J. Med.* **2013,** *369,* 32-42.

**[0062]** FIG. 42 shows a comparison of number of patients at risk in CLL patients exhibiting the 17p deletion and treated with the BTK inhibitor ibrutinib or the BTK inhibitor of Formula (II). The ibrutinib data is taken from Byrd, *et al.*, *N. Engl. J. Med.* **2013,** *369,* 32-42. CLL patients treated with Formula (II) for at least 8 days are included.

**[0063]** FIG. 43 shows improved BTK target occupancy of Formula (II) at lower dosage versus ibrutinib in relapsed/refractory CLL patients.

**[0064]** FIG. 44 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.

**[0065]** FIG. 45 shows the % change in MDSC (monocytic) level over 28 days versus % ALC change at Cycle 2, day 28 (C2D28) with trendlines.

**[0066]** FIG. 46 shows the % change in natural killer (NK) cell level over 28 days versus % ALC change at Cycle 1, day 28 (C2D28) with trendlines.

**[0067]** FIG. 47 shows the % change in NK cell level over 28 days versus % ALC change at Cycle 2, day 28 (C2D28) with trendlines.

**[0068]** FIG. 48 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, $PD\text{-}1^+$ $CD4^+$ T cells, and $PD\text{-}1^+$ $CD8^+$ 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.

**[0069]** FIG. 49 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, $PD\text{-}1^+$ $CD4^+$ T cells, and $PD\text{-}1^+$ $CD8^+$ 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.

**[0070]** FIG. 50 shows an update of the data presented in FIG. 37.

**[0071]** FIG. 51 shows an update of the data presented in FIG. 43, and includes BID dosing results.

**[0072]** FIG. 52 illustrates PFS for patients with 17p deletion.

**[0073]** FIG. 53 illustrates PFS across relapsed/refractory patients with 11p deletion and with 17q deletion and no 11p deletion.

**[0074]** FIG. 54 illustrates PFS for patients with 11q deletion and no 17p deletion.

**[0075]** FIG. 55 illustrates updated SPD results from the clinical study of Formula (II) in relapsed/refractory CLL patients.

**[0076]** FIG. 56 illustrates that treatment of CLL patients with Formula (II) resulted in increased apoptotis.

**[0077]** FIG. 57 illustrates a decrease in CXCL12 levels observed in patients treated with Formula (II).

**[0078]** FIG. 58 illustrates a decrease in CCL2 levels observed in patients treated with Formula (II).

**[0079]** FIG. 59 illustrates BTK inhibitory effects on MDSCs.

**[0080]** FIG. 60 illustrates the dosing schema used with the KrasLA2 non-small cell lung cancer (NSCLC) model.

**[0081]** FIG. 61 illustrates tumor volume variation from baseline as assessed by microcomputerized tomography (microCT) in the KrasL2 NSCLC model.

**[0082]** FIG. 62 illustrates TAMs in the KrasL2 NSCLC model, and indicates that Formula (II) induces a tumor response that correlates with a significant reduction in immunosuppressive tumor associated TAMs.

**[0083]** FIG. 63 illustrates MDSCs in the KrasL2 NSCLC model, and indicates that Formula (II) induces a tumor response that correlates with a significant reduction in immunosuppressive tumor associated MDSCs.

**[0084]** FIG. 64 illustrates Tregs in the KrasL2 NSCLC model, and indicates that Formula (II) induces a tumor response that correlates with a significant reduction in immunosuppressive tumor associated Tregs.

**[0085]** FIG. 65 illustrates $CD8^+$ T cells in the KrasL2 NSCLC model.

**[0086]** FIG. 66 shows that Formula (II) has no adverse effect on T helper 17 (Th17) cells, which are a subset of T helper cells that produce interleukin 17 (IL-17), while ibrutinib strongly inhibits Th17 cells.

**[0087]** FIG. 67 shows that Formula (II) has no effect on regulatory T cell (Treg) development, while ibrutinib strongly increases Treg development.

**[0088]** FIG. 68 shows that Formula (II) has no effect on $CD8^+$ T cell viability, development, while ibrutinib strongly affects $CD8^+$ T cell viability at higher doses.

**[0089]** FIG. 69 illustrates the results of the cytotoxicity assay for $CD8^+$ T cell function. Formula (X) (ibrutinib) affects $CD8^+$ T cell function as measured by % cytotoxicity, while Formula (II) has no effect on $CD8^+$ T cell function as measured by % cytotoxicity relative to vehicle.

**[0090]** FIG. 70 illustrates the results of IFN-γ level measurements for $CD8^+$ T cell function. Formula (X) (ibrutinib) affects $CD8^+$ T cell function as measured by IFN-γ level, while Formula (II) has no effect on $CD8^+$ T cell function as measured by IFN-γ level relative to vehicle.

**[0091]** FIG. 71 shows the results of the brain penetration study, demonstrating the surprising result that Formula (II) crosses the blood-brain barrier.

**[0092]** FIG. 72 shows NK cell degranulation results. The percentage of $CD56^+/CD107a^+$ NK cells observed in whole blood after pretreatment for 1 hour with the BTK inhibitors and stimulation with MEC-1 cells opsonised with obinutuzumab at 1 μg/mL for 4 hours (n = 3) is shown.

**[0093]** FIG. 73 shows the effects of BTK inhibition on generalized NK cell mediated cytotoxicity.

## BRIEF DESCRIPTION OF THE SEQUENCE LISTING

**[0094]** SEQ ID NO:1 is the heavy chain amino acid sequence of the anti-CD20 monoclonal antibody rituximab.

**[0095]** SEQ ID NO:2 is the light chain amino acid sequence of the anti-CD20 monoclonal antibody rituximab.

**[0096]** SEQ ID NO:3 is the heavy chain amino acid sequence of the anti-CD20 monoclonal antibody obinutuzumab.

**[0097]** SEQ ID NO:4 is the light chain amino acid sequence of the anti-CD20 monoclonal antibody obinutuzumab.

**[0098]** SEQ ID NO:5 is the variable heavy chain amino acid sequence of the anti-CD20 monoclonal antibody ofatumumab.

**[0099]** SEQ ID NO:6 is the variable light chain amino acid sequence of the anti-CD20 monoclonal antibody ofatumumab.

**[00100]** SEQ ID NO:7 is the Fab fragment heavy chain amino acid sequence of the anti-CD20 monoclonal antibody ofatumumab.

**[00101]** SEQ ID NO:8 is the Fab fragment light chain amino acid sequence of the anti-CD20 monoclonal antibody ofatumumab.

**[00102]** SEQ ID NO:9 is the heavy chain amino acid sequence of the anti-CD20 monoclonal antibody veltuzumab.

**[00103]** SEQ ID NO:10 is the light chain amino acid sequence of the anti-CD20 monoclonal antibody veltuzumab.

**[00104]** SEQ ID NO:11 is the heavy chain amino acid sequence of the anti-CD20 monoclonal antibody tositumomab.

**[00105]** SEQ ID NO:12 is the light chain amino acid sequence of the anti-CD20 monoclonal antibody tositumomab.

**[00106]** SEQ ID NO:13 is the heavy chain amino acid sequence of the anti-CD20 monoclonal antibody ibritumomab.

**[00107]** SEQ ID NO:14 is the light chain amino acid sequence of the anti-CD20 monoclonal antibody ibritumomab.

## DETAILED DESCRIPTION OF THE INVENTION

**[00108]** 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.

**[00109]** 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.

**[00110]** The terms “co-administration,” “co-administering,” “administered in combination with,” and “administering in combination with” as used herein, encompass administration of two or more agents to a subject so that both agents 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 agents are present.

**[00111]** 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.

**[00112]** A “therapeutic effect” as that term is used herein, encompasses a therapeutic benefit and/or a prophylactic benefit as described above. 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.

**[00113]** The term “pharmaceutically acceptable salt” refers to salts derived from a variety of organic and inorganic counter ions known in the art. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluenesulfonic acid and salicylic acid. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese and aluminum. Organic

bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins. Specific examples include isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. In some embodiments, the pharmaceutically acceptable base addition salt is chosen from ammonium, potassium, sodium, calcium, and magnesium salts. The term "cocrystal" refers to a molecular complex derived from a number of cocrystal formers known in the art. Unlike a salt, a cocrystal typically does not involve hydrogen transfer between the cocrystal and the drug, and instead involves intermolecular interactions, such as hydrogen bonding, aromatic ring stacking, or dispersive forces, between the cocrystal former and the drug in the crystal structure.

**[00114]** "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. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions of the invention is contemplated. Supplementary active ingredients can also be incorporated into the described compositions.

**[00115]** "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, Design of Prodrugs, Elsevier, Amsterdam, 1985). 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.

**[00116]** The term "*in vivo*" refers to an event that takes place in a subject's body.

**[00117]** 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.

**[00118]** 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.

**[00119]** 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 from, for example, between 1% and 15% 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.

**[00120]** "Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to ten carbon atoms (*e.g.*, ($C_{1}$-$_{10}$)alkyl or $C_{1}$-$_{10}$ alkyl). Whenever it appears herein, a numerical range such as "1 to 10" refers to each integer in the given range - *e.g.*, "1 to 10 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 10 carbon atoms, although the definition is also intended to cover the occurrence of the term "alkyl" where no numerical range is specifically designated. Typical alkyl groups include, but are in no

way limited to, methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, sec-butyl isobutyl, 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 (iso-propyl), 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 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.

**[00121]** "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.

**[00122]** "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.

**[00123]** "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.

**[00124]** 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.

**[00125]** "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.

**[00126]** "Alkenyl-cycloalkyl" refers to an -(alkenyl)cycloalkyl radical where alkenyl and cyclo alkyl 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.

**[00127]** "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.

**[00128]** "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.

**[00129]** "Carboxaldehyde" refers to a -(C=O)H radical.

**[00130]** "Carboxyl" refers to a -(C=O)OH radical.

**[00131]** "Cyano" refers to a -CN radical.

**[00132]** "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, cycloseptyl, 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, $-OR^{a}$, $-SR^{a}$, $-OC(O)-R^{a}$, $-N(R^{a})_{2}$, $-C(O)R^{a}$, $-C(O)OR^{a}$, $-OC(O)N(R^{a})_{2}$, $-C(O)N(R^{a})_{2}$, $-N(R^{a})C(O)OR^{a}$, $-N(R^{a})C(O)R^{a}$, $-N(R^{a})C(O)N(R^{a})_{2}$, $N(R^{a})C(NR^{a})N(R^{a})_{2}$, $-N(R^{a})S(O)_{t}R^{a}$ (where t is 1 or 2), $-S(O)_{t}OR^{a}$ (where t is 1 or 2), $-S(O)_{t}N(R^{a})_{2}$ (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.

**[00133]** "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.

**[00134]** "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.

**[00135]** "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.

**[00136]** 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.

**[00137]** 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.

**[00138]** The term "alkoxycarbonyl" refers to a group of the formula (alkoxy)(C=O)- attached through the carbonyl carbon wherein the alkoxy group has the indicated number of carbon atoms. Thus a $(C_1-_6)$alkoxycarbonyl group is an alkoxy group having from 1 to 6 carbon atoms attached through its oxygen to a carbonyl linker. "Lower alkoxycarbonyl" refers to an alkoxycarbonyl group wherein the alkoxy group is a lower alkoxy group.

**[00139]** 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.

**[00140]** "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.

**[00141]** "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.

**[00142]** "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.

**[00143]** 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.

**[00144]** "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, 1999, which is incorporated herein by reference in its entirety.

**[00145]** "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.

**[00146]** "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.

**[00147]** "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.

**[00148]** "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.

**[00149]** "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.

**[00150]** "Heteroalkyl", "heteroalkenyl" and "heteroalkynyl" include optionally substituted alkyl, alkenyl and alkynyl radicals and which have one or more skeletal chain atoms selected from an atom other than carbon, e.g., oxygen, nitrogen, sulfur, phosphorus or combinations thereof. A numerical range may be given - *e.g.*, $C_1$-$C_4$ heteroalkyl which refers to the chain length in total, which in this example is 4 atoms long. A heteroalkyl group may be substituted with one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, nitro, oxo, thioxo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each $R^a$ is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

**[00151]** "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.

**[00152]** "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.

**[00153]** "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.

**[00154]** "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.

**[00155]** "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.

**[00156]** Substituted heteroaryl also includes ring systems substituted with one or more oxide (-O-) substituents, such as, for example, pyridinyl N-oxides.

**[00157]** “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.

**[00158]** "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.

**[00159]** "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.

**[00160]** "Nitro" refers to the $-NO_2$ radical.

**[00161]** "Oxa" refers to the -O- radical.

**[00162]** "Oxo" refers to the =O radical.

**[00163]** "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.

**[00164]** "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.

**[00165]** In some embodiments, the enantiomerically enriched composition has a higher potency with respect to therapeutic utility per unit mass than does the racemic mixture of that composition. Enantiomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred enantiomers can be prepared by asymmetric syntheses. See, for example, Jacques, *et al*., Enantiomers, Racemates and Resolutions, Wiley Interscience, New York, 1981; Eliel, Stereochemistry of Carbon Compounds, McGraw-Hill, NY, 1962; and Eliel and Wilen, Stereochemistry of Organic Compounds, Wiley-Interscience, New York, 1994.

**[00166]** 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.

**[00167]** "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.

**[00168]** "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.

**[00169]** 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.

**[00170]** "Protecting group" is intended to mean a group that selectively blocks one or more reactive sites in a multifunctional compound such that a chemical reaction can be carried out selectively on another unprotected reactive site and the group can then be readily removed after the selective reaction is complete. A variety of protecting groups are disclosed, for example, in T. H. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, Third Edition, John Wiley & Sons, New York (1999).

**[00171]** "Solvate" refers to a compound in physical association with one or more molecules of a pharmaceutically acceptable solvent.

**[00172]** "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.

**[00173]** "Sulfanyl" refers to groups that include -S-(optionally substituted alkyl), -S-(optionally substituted aryl), -S-(optionally substituted heteroaryl) and -S-(optionally substituted heterocycloalkyl).

**[00174]** "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).

**[00175]** "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).

**[00176]** "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.

**[00177]** "Sulfoxyl" refers to a -$S(=O)_2$OH radical.

**[00178]** "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.

**[00179]** 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.

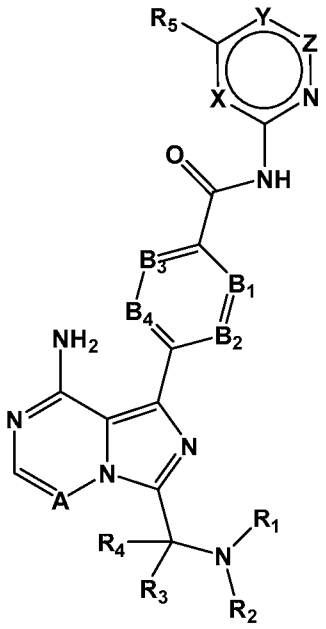
**[00180]** The term "microenvironment," as used herein, may refer to the tumor microenvironment as a whole or to an individual subset of cells within the microenvironment.

**[00181]** 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.

BTK Inhibitors

**[00182]** The BTK inhibitor may be any BTK inhibitor known in the art. In particular, it is one of the BTK inhibitors described in more detail in the following paragraphs. For avoidance of doubt, references herein to a BTK inhibitor may refer to a compound or a pharmaceutically acceptable salt, ester, solvate, hydrate, cocrystal, or prodrug thereof.

**[00183]** In an embodiment, the BTK inhibitor is a compound of Formula (I):



Formula (I)

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

X is CH, N, O or S;

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

Z is CH, N or bond;

A is CH or N;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

with the proviso that:

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

when one atom selected from X, Y is O or S, then Z is a bond and the other atom selected from

X, Y can not be O or S;

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

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

with the terms used having the following meanings:

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

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

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

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

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

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

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

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

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

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

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

being cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl;

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

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

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

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

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

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

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

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

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

$_4$)alkyl]amino group is dimethylamino;

halogen means fluorine, chlorine, bromine or iodine;

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

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

($C_{2-6}$)heterocycloalkenyl means a heterocycloalkenyl group having 2-6 carbon atoms, preferably 3-5 carbon atoms; and 1 heteroatom selected from N, O and/or S; preferred ($C_{2-}$ $_6$)heterocycloalkenyl groups are oxycyclohexenyl and azacyclohexenyl group.

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

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

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

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

**[00184]** In a preferred embodiment, the BTK inhibitor is a compound of Formula (I) 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.

**[00185]** In an embodiment of Formula (I), $B_1$ 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.

**[00186]** In an embodiment of Formula (I), the ring containing X, Y and Z is selected from the group consisting of pyridyl, pyrimidyl, pyridazyl, triazinyl, thiazolyl, oxazolyl and isoxazolyl.

**[00187]** In an embodiment of Formula (I), the ring containing X, Y and Z is selected from the group consisting of pyridyl, pyrimidyl and pyridazyl.

**[00188]** In an embodiment of Formula (I), the ring containing X, Y and Z is selected from the group consisting of pyridyl and pyrimidyl.

**[00189]** In an embodiment of Formula (I), the ring containing X, Y and Z is pyridyl.

**[00190]** In an embodiment of Formula (I), $R_5$ is selected from the group consisting of hydrogen, fluorine, methyl, methoxy and trifluoromethyl.

**[00191]** In an embodiment of Formula (I), $R_5$ is hydrogen.

**[00192]** In an embodiment of Formula (I), $R_2$ 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.

**[00193]** In an embodiment of Formula (I), $R_2$ and $R_3$ together form a heterocycloalkyl ring selected from the group consisting of azetidinyl, pyrrolidinyl and piperidinyl.

**[00194]** In an embodiment of Formula (I), $R_2$ and $R_3$ together form a pyrrolidinyl ring.

**[00195]** In an embodiment of Formula (I), $R_1$ 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.

**[00196]** In an embodiment of Formula (I), $R_1$ is independently selected from the group consisting of $R^{11}$(CO)- wherein $R^{11}$ is selected from ($C_{1-6}$)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.

**[00197]** In an embodiment of Formula (I), $B_1$, $B_2$, $B_3$ 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-$CH_3$.

**[00198]** In an embodiment of Formula (I), $B_1$, $B_2$, $B_3$ 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-$CH_3$.

**[00199]** In an embodiment of Formula (I), $B_1$, $B_2$, $B_3$ 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.

**[00200]** In an embodiment of Formula (I), $B_1$, $B_2$, $B_3$ 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.

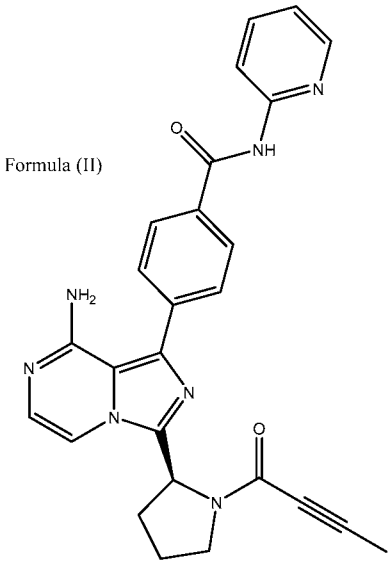
**[00201]** In an embodiment of Formula (I), $B_1$, $B_2$, $B_3$ and $B_4$ are CH; X, Y and Z are CH; $R_5$ is $CH_3$; A is CH; $R_2$ and $R_3$ together form a piperidinyl ring; $R_4$ is H; and $R_1$ is CO-propynyl.

**[00202]** In an embodiment of Formula (I), $B_1$, $B_2$, $B_3$ 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.

**[00203]** In an embodiment of Formula (I), $B_1$, $B_2$, $B_3$ 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.

**[00204]** In a preferred embodiment, the BTK inhibitor is a compound of Formula (II):

Formula (II)




or a pharmaceutically acceptable salt, ester, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of this compound is described in U.S. Patent Application Publication No. 2014/0155385 A1, the disclosure of which is incorporated herein by reference. The preparation of this compound is described at Example 6 of 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. The preparation of this compound and related structures are described in the Examples of 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.

**[00205]** (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide was made from (*S*)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1 ,5-*a*]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide and 2-butynoic acid as follows. To a solution of (*S*)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide (19.7 mg, 0.049 mmol), triethylamine (20 mg, 0.197 mmol, 0.027 mL) 2-butynoic acid (4.12 mg,

0.049 mmol) in dichloromethane (2 mL) was added HATU (18.75 mg, 0.049 mmol). The mixture was stirred for 30 min at room temperature. The mixture was washed with water dried over magnesium sulfate and concentrated in vacuo. The residue was purified by preparative HPLC. Fractions containing product were collected and reduced to dryness to afford the title compound (10.5 mg, 18.0%).

**[00206]** (*S*)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide was prepared from the following intermediary compounds.

**[00207]** (a). (3-Chloropyrazin-2-yl)methanamine hydrochloride was prepared as follows. To a solution of 3-chloropyrazine-2-carbonitrile (160 g, 1 .147 mol) in acetic acid (1.5 L) was added Raney Nickel (50% slurry in water, 70 g, 409 mmol). The resulting mixture was stirred under 4 bar hydrogen at room temperature overnight. Raney Nickel was removed by filtration over decalite and the filtrate was concentrated under reduced pressure and co-evaporated with toluene. The remaining brown solid was dissolved in ethyl acetate at 50°C and cooled on an ice-bath. 2M hydrogen chloride solution in diethyl ether (1 .14 L) was added in 30 min. The mixture was allowed to stir at room temperature over weekend. The crystals were collected by filtration, washed with diethyl ether and dried under reduced pressure at 40°C. The product brown solid obtained was dissolved in methanol at 60°C. The mixture was filtered and partially concentrated, cooled to room temperature and diethyl ether (1000 ml) was added. The mixture was allowed to stir at room temperature overnight. The solids formed were collected by filtration, washed with diethyl ether and dried under reduced pressure at 40°C to give 153.5 g of (3-chloropyrazin-2-yl)methanamine.hydrochloride as a brown solid (74.4 %, content 77 %).

**[00208]** (b). (*S*)-benzyl 2-((3-chloropyrazin-2-yl)methylcarbamoyl)pyrrolidine-1-carboxylate was prepared as follows. To a solution of (3-chloropyrazin-2-yl)methanamine HCI (9.57 g, 21.26 mmol, 40% wt) and Z-Pro-OH (5.3 g, 21.26 mmol) in dichloromethane (250 mL) was added triethylamine (11.85 mL, 85 mmol) and the reaction mixture was cooled to 0°C. After 15 min stirring at 0°C, HATU (8.49 g, 22.33 mmol) was added. The mixture was stirred for 1 hour at 0°C and then overnight at room temperature. The mixture was washed with 0.1 M HCI-solution, 5% NaHC03, water and brine, dried over sodium sulfate and concentrated in vacuo. The product was purified using silica gel chromatography (heptane/ethyl acetate = 1/4 v/v%) to

give 5 g of (S)-benzyl 2-((3-chloropyrazin-2-yl)methylcarbamoyl)pyrrolidine-1-carboxylate (62.7%).

**[00209]** (c). (*S*)-Benzyl 2-(8-chloroimidazo[1,5- *a*]pyrazin-3-yl)pyrrolidine-1-carboxylate was prepared as follows. (*S*)-Benzyl 2-((3-chloropyrazin-2-yl)methylcarbamoyl)pyrrolidine-1-carboxylate (20.94 mmol, 7.85 g) was dissolved in acetonitrile (75 ml), 1 ,3-dimethyl-2-imidazolidinone (62.8 mmol, 6.9 ml, 7.17 g) was added and the reaction mixture was cooled to 0°C before POCI3 (84 mmol, 7.81 ml, 12.84 g) was added drop wise while the temperature remained around 5°C. The reaction mixture was refluxed at 60-65°C overnight. The reaction mixture was poured carefully in ammonium hydroxide 25% in water (250 ml)/crushed ice (500 ml) to give a yellow suspension (pH -8-9) which was stirred for 15 min until no ice was present in the suspension. Ethyl acetate was added, layers were separated and the aqueous layer was extracted with ethyl acetate (3x). The organic layers were combined and washed with brine, dried over sodium sulfate, filtered and evaporated to give 7.5 g crude product. The crude product was purified using silica gel chromatography (heptane/ethyl acetate = 1/4 v/v%) to give 6.6 g of (S)-benzyl 2-(8- chloroimidazo[1 ,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (88%).

**[00210]** (d). (S)-Benzyl 2-(1-bromo-8-chloroimidazo[1 ,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate was prepared as follows. N-Bromosuccinimide (24.69 mmol, 4.4 g) was added to a stirred solution of (S)-benzyl 2-(8- chloroimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (24.94 mmol, 8.9 g) in DMF (145 mL). The reaction was stirred 3 h at rt. The mixture was poored (slowly) in a stirred mixture of water (145 mL), ethyl acetate (145 mL) and brine (145 mL). The mixture was then transferred into a separating funnel and extracted. The water layer was extracted with 2x145 mL ethyl acetate. The combined organic layers were washed with 3x300 mL water, 300 mL brine, dried over sodium sulfate, filtered and evaporated. The product was purified using silica gel chromatography (ethyl acetate/heptane = 3/1 v/v%) to give 8.95 g of (S)-benzyl 2-(1-bromo-8-chloroimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (82.3%).

**[00211]** (e). (*S*)-Benzyl 2-(8-amino-1-bromoimidazo[1 ,5-*a*]pyrazin-3-yl)pyrrolidine-1-carboxylate was prepared as follows. (S)-Benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (20.54 mmol, 8.95 g) was suspended in 2-propanol (113 ml) in a pressure vessel. 2-propanol (50 ml) was cooled to -78°C in a pre-weighed flask (with stopper and stirring bar) and ammonia gas (646 mmol, 11 g) was lead through for 15 minutes. The

resulting solution was added to the suspension in the pressure vessel. The vessel was closed and stirred at room temperature and a slight increase in pressure was observed. Then the suspension was heated to 110 °C which resulted in an increased pressure to 4.5 bar. The clear solution was stirred at 110 °C, 4.5 bar overnight. After 18h the pressure remained 4 bar. The reaction mixture was concentrated in vacuum, the residue was suspended in ethyl acetate and subsequent washed with water. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water, saturated sodium chloride solution, dried over sodium sulfate and concentrated to give 7.35 g of (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (86%).

**[00212]** (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide was prepared as follows.

**[00213]** (a). (S)-benzyl 2-(8-amino-1-(4-(pyridin-2-ylcarbamoyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate was prepared as follows. (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (0.237 mmol, 98.5 mg) and 4-(pyridin-2-yl-aminocarbonyl)benzeneboronic acid (0.260 mmol, 63.0 mg) were suspended in a mixture of 2N aqueous potassium carbonate solution (2.37 mmol, 1.18 mL) and dioxane (2.96 mL). Nitrogen was bubbled through the mixture, followed by the addition of 1,1'-bis(diphenylphosphino)ferrocene palladium (ii) chloride (0.059 mmol, 47.8 mg). The reaction mixture was heated for 20 minutes at 140°C in the microwave. Water was added to the reaction mixture, followed by an extraction with ethyl acetate (2x). The combined organic layer was washed with brine, dried over magnesium sulfate and evaporated. The product was purified using silicagel and dichloromethane/methanol = 9/1 v/v% as eluent to afford 97.1 mg of (S)-benzyl 2-(8-amino-1-(4-(pyridin-2-ylcarbamoyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (77%).

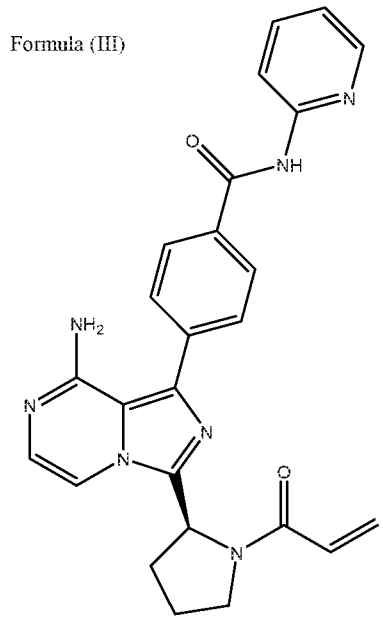
**[00214]** (b). (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-alpyrazin-1-yl)-N-(pyridin-2-yl)benzamide was prepared as follows. To (S)-benzyl 2-(8-amino-1-(4-(pyridin-2-ylcarbamoyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1- carboxylate (0.146 mmol, 78 mg) was added a 33% hydrobromic acid/acetic acid solution (1 1.26 mmol, 2 ml) and the mixture was left at room temperature for 1 hour. The mixture was diluted with water and extracted with dichloromethane. The aqueous phase was neutralized using 2N sodium hydroxide solution, and

then extracted with dichloromethane. The organic layer was dried over magnesium sulfate, filtered and evaporated to give 34 mg of (S)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide (58%).

**[00215]** 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.

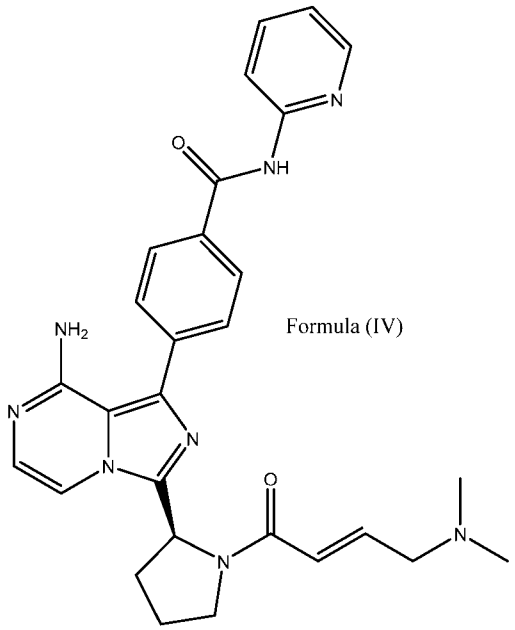
**[00216]** In a preferred embodiment, the BTK inhibitor is a compound of Formula (III):

Formula (III)




or a pharmaceutically acceptable salt, ester, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of this compound is described in U.S. Patent Application Publication No. 2014/0155385 A1, the disclosure of which is incorporated herein by reference.

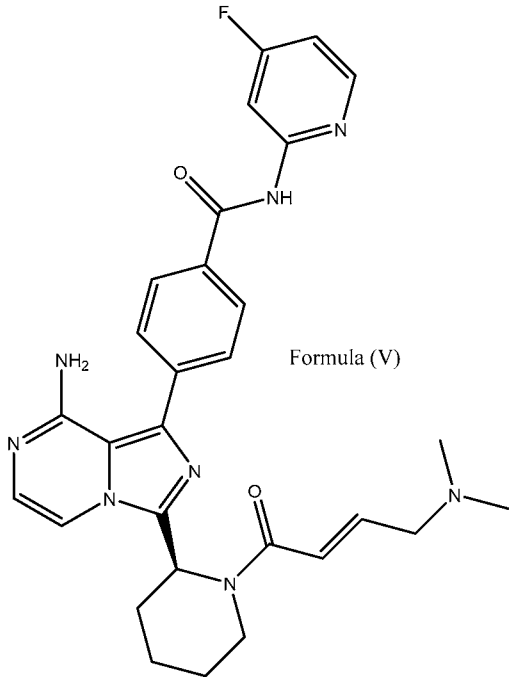
**[00217]** In a preferred embodiment, the BTK inhibitor is a compound of Formula (IV):



Formula (IV)

or a pharmaceutically acceptable salt, ester, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of this compound is described in U.S. Patent Application Publication No. 2014/0155385 A1, the disclosure of which is incorporated herein by reference.

**[00218]** In a preferred embodiment, the BTK inhibitor is a compound of Formula (V):

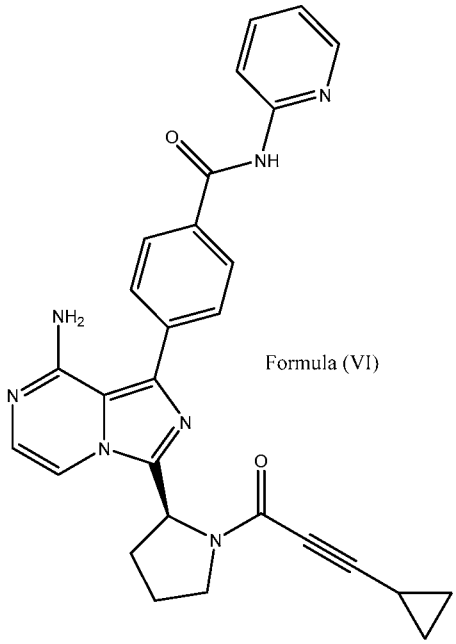


Formula (V)

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

preparation of this compound is described in U.S. Patent Application Publication No. 2014/0155385 A1, the disclosure of which is incorporated herein by reference.

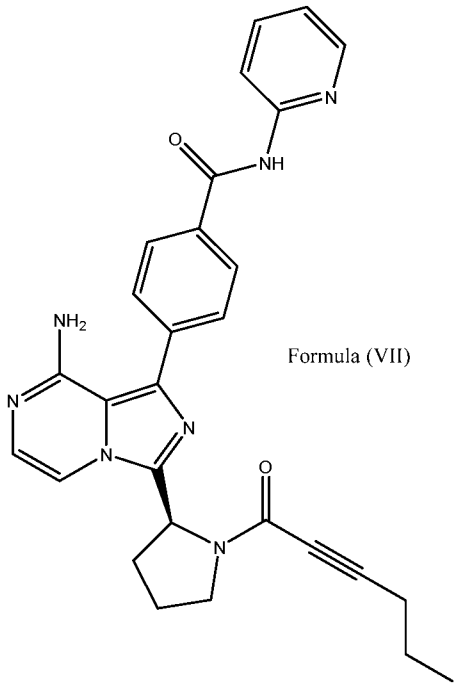
**[00219]** In a preferred embodiment, the BTK inhibitor is a compound of Formula (VI):



Formula (VI)

or a pharmaceutically acceptable salt, ester, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of this compound is described in U.S. Patent Application Publication No. 2014/0155385 A1, the disclosure of which is incorporated herein by reference.

**[00220]** In a preferred embodiment, the BTK inhibitor is a compound of Formula (VII):

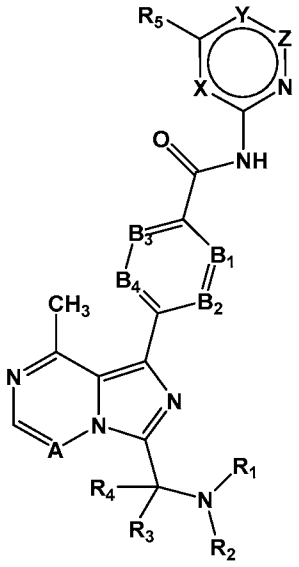


Formula (VII)

or a pharmaceutically acceptable salt, ester, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of this compound is described in U.S. Patent Application Publication No. 2014/0155385 A1, the disclosure of which is incorporated herein by reference.

**[00221]** In other embodiments, the BTK inhibitors include, but are not limited to, those compounds described in U.S. Patent Application Publication No. 2014/0155385 A1, the disclosures of each of which are specifically incorporated by reference herein.

**[00222]** In an embodiment, the BTK inhibitor is a compound of Formula (VIII):



Formula (VIII)

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

X is CH, N, O or S;

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

Z is CH, N or bond;

A is CH or N;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

with the proviso that

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

with the terms used having the following meanings:

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

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

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

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

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

($C_{2-3}$)alkenyl means an alkenyl group having 2-3 carbon atoms, such as ethenyl or 2- propenyl;

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

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

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

($C_{2-3}$)alkynyl means an alkynyl group having 2-3 carbon atoms, such as ethynyl or 2-propynyl;

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

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

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

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

preferred groups are piperidine, morpholine, pyrrolidine and piperazine; a most preferred ($C_{2-6}$)heterocycloalkyl is pyrrolidine; and the heterocycloalkyl group may be attached via a heteroatom if feasible;

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

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

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

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

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

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

halogen means fluorine, chlorine, bromine or iodine;

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

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

($C_{2-6}$)heterocycloalkenyl means a heterocycloalkenyl group having 2-6 carbon atoms, preferably

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

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

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

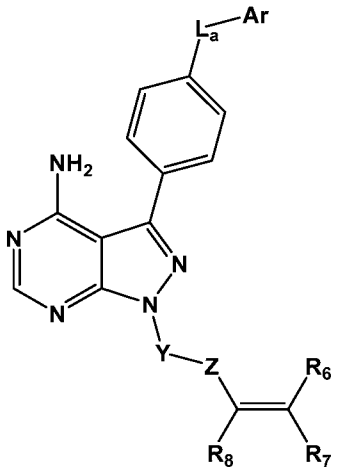
A circle in a ring of Formula (VIII) indicates that the ring is aromatic.

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

**[00223]** In a preferred embodiment, the invention relates to a compound according to Formula (VIII) wherein $B_1$ is $C(R_7)$; $B_2$ is $C(R_8)$; $B_3$ is $C(R_9)$ and $B_4$ is $C(R_{10})$.

**[00224]** In other embodiments, the BTK inhibitors include, but are not limited to, those compounds described in International Patent Application Publication No. WO 2013/010869, the disclosures of each of which are specifically incorporated by reference herein.

**[00225]** In an embodiment, the BTK inhibitor is a compound of Formula (IX):




Formula (IX)

or a pharmaceutically acceptable salt, ester, 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;

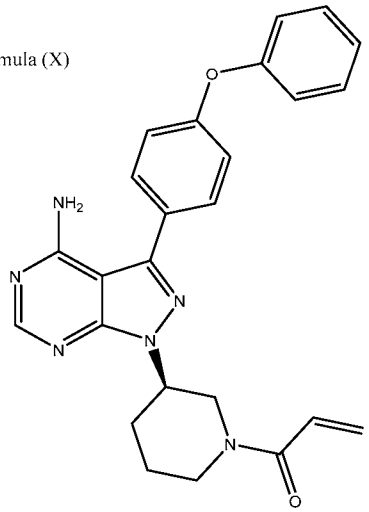
$R^7$ and $R^8$ are each independently H; or $R^7$ and $R^8$ taken together form a bond;

$R^6$ is H; and

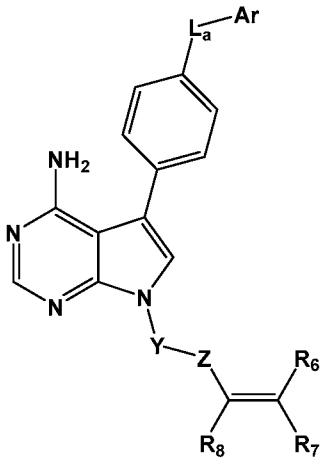
R is H or ($C_{1-6}$)alkyl.

**[00226]** In a preferred embodiment, the BTK inhibitor is ibrutinib, also known as PCI-32765, or a pharmaceutically acceptable salt, ester, solvate, hydrate, cocrystal, or prodrug thereof. In an exemplary 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, or a pharmaceutically acceptable salt, ester, solvate, hydrate, cocrystal, or prodrug thereof. In an 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, or a pharmaceutically acceptable salt, ester, solvate, hydrate, cocrystal, or prodrug thereof. In an 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, or a pharmaceutically acceptable salt, ester, solvate, hydrate, cocrystal, or prodrug thereof. In a preferred embodiment, the BTK inhibitor has the structure of Formula (X), or an enantiomer thereof, or a pharmaceutically acceptable salt, ester, solvate, hydrate, cocrystal, or prodrug thereof:

Formula (X)




**[00227]** In an embodiment, the BTK inhibitor is a compound of Formula (XI):




Formula (XI)

or a pharmaceutically acceptable salt, ester, 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;

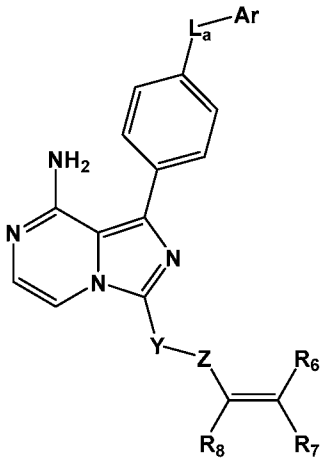
Z is C(=O), OC(=O), NRC(=O), C(=S), $S(=O)_x$, $OS(=O)_x$ or $NRS(=O)_x$, where x is 1 or 2;

$R^7$ 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.

**[00228]** In an embodiment, the BTK inhibitor is a compound of Formula (XII):




Formula (XII)

or a pharmaceutically acceptable salt, ester, 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;

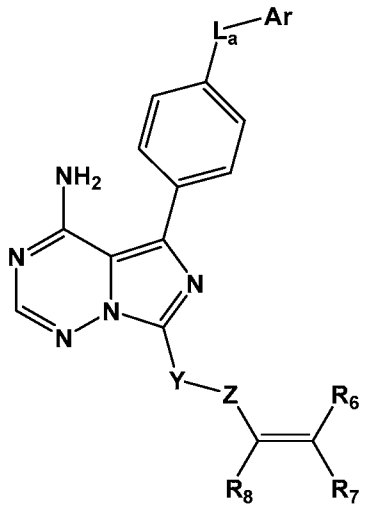
Z is C(=O), OC(=O), NRC(=O), C(=S), $S(=O)_x$, $OS(=O)_x$ or $NRS(=O)_x$, where x is 1 or 2;

$R^7$ 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.

**[00229]** In an embodiment, the BTK inhibitor is a compound of Formula (XIII):




Formula (XIII)

or a pharmaceutically acceptable salt, ester, 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;

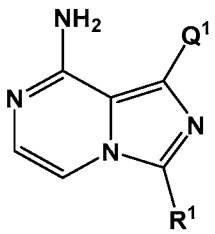
Z is C(=O), OC(=O), NRC(=O), C(=S), $S(=O)_x$, $OS(=O)_x$ or $NRS(=O)_x$, where x is 1 or 2;

$R^7$ 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.

**[00230]** 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 (XIV):




Formula (XIV)

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

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

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

$G^1$ and $G^{41}$ are each independently halo, oxo, $-CF_3$, $-OCF_3$, $-OR^2$, $-NR^2R^3(R^{3a})_{j1}$, $-C(O)R^2$, $-CO_2R^2$, $-CONR^2R^3$, $-NO_2$, -CN, $-S(O)_{j1}R^2$, $-SO_2NR^2R^3$, $NR^2(C=O)R^3$, $NR^2(C=O)OR^3$, $NR^2(C=O)NR^2R^3$, $NR^2S(O)_{j1}R^3$, $-(C=S)OR^2$, $-(C=O)SR^2$, $-NR^2(C=NR^3)NR^{2a}R^{3a}$, $-NR^2(C=NR^3)OR^{2a}$, $-NR^2(C=NR^3)SR^{3a}$, $-O(C=O)OR^2$, $-O(C=O)NR^2R^3$, $-O(C=O)SR^2$, $-S(C=O)OR^2$, $-S(C=O)NR^2R^3$, $(C_{0-10})$alkyl, $(C_2-_{10})$alkenyl, $(C_2-_{10})$alkynyl, $(C_1-_{10})$alkoxy$(C_1-_{10})$alkyl, $(C_1-_{10})$alkoxy$(C_2-_{10})$alkenyl, $(C_1-_{10})$alkoxy$(C_2-_{10})$alkynyl, $(C_1-_{10})$alkylthio$(C_1-_{10})$alkyl, $(C_1-_{10})$alkylthio$(C_2-_{10})$alkenyl, $(C_1-_{10})$alkylthio$(C_2-_{10})$alkynyl, cyclo$(C_3-_8)$alkyl, cyclo$(C_3-_8)$alkenyl, cyclo$(C_3-_8)$alkyl$(C_1-_{10})$alkyl, cyclo$(C_3-_8)$alkenyl$(C_1-_{10})$alkyl, cyclo$(C_3-_8)$alkyl$(C_2-_{10})$alkenyl, cyclo$(C_3-_8)$alkenyl$(C_2-_{10})$alkenyl, cyclo$(C_3-_8)$alkyl$(C_2-_{10})$alkynyl, cyclo$(C_3-_8)$alkenyl$(C_2-_{10})$alkynyl, heterocyclyl-$(C_{0-10})$alkyl, heterocyclyl-$(C_2-_{10})$alkenyl, or heterocyclyl-$(C_2-_{10})$alkynyl, any of which is optionally substituted with one or more independent halo, oxo, $-CF_3$, $-OCF_3$, $-OR^{222}$, $-NR^{222}R^{333}(R^{333}a)_{j1a}$, $-C(O)R^{222}$, $-CO_2R^{222}$, $-CONR^{222}R^{333}$, $-NO_2$, -CN, $-S(O)_{j1a}R^{222}$, $-SO_2NR^{222}R^{333}$, $NR^{222}(C=O)R^{333}$, $NR^{222}(C=O)OR^{333}$, $NR^{222}(C=O)NR^{222}R^{333}$, $NR^{222}S(O)_{j1a}R^{333}$, $-(C=S)OR^{222}$, $-(C=O)SR^{222}$, $-NR^{222}(C=NR^{333})NR^{222a}R^{333a}$, $-NR^{222}(C=NR^{333})OR^{222a}$, $-NR^{222}(C=NR^{333})SR^{333a}$, $-O(C=O)OR^{222}$, $-O(C=O)NR^{222}R^{333}$, $-O(C=O)SR^{222}$, $-S(C=O)OR^{222}$, or $-S(C=O)NR^{222}R^{333}$ substituents; or $-(X^1)_n-(Y^1)_m-R^4$; or aryl-$(C_{0-10})$alkyl, aryl-$(C_2-_{10})$alkenyl, or aryl-$(C_2-_{10})$alkynyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{222}$, $-NR^{222}R^{333}(R^{333a})_{j2a}$, $-C(O)R^{222}$, $-CO_2R^{222}$, $-CONR^{222}R^{333}$, $-NO_2$, -CN, $-S(O)_{j2a}R^{222}$, $-SO_2NR^{222}R^{333}$, $NR^{222}(C=O)R^{333}$, $NR^{222}(C=O)OR^{333}$, $NR^{222}(C=O)NR^{222}R^{333}$, $NR^{222}S(O)_{j2a}R^{333}$, $-(C=S)OR^{222}$, $-(C=O)SR^{222}$, $-NR^{222}(C=NR^{333})NR^{222a}R^{333a}$, $-NR^{222}(C=NR^{333})OR^{222a}$, $-NR^{222}(C=NR^{333})SR^{333a}$, $-O(C=O)OR^{222}$, $-O(C=O)NR^{222}R^{333}$, $-O(C=O)SR^{222}$, $-S(C=O)OR^{222}$, or $-S(C=O)NR^{222}R^{333}$ substituents; or hetaryl-$(C_{0-10})$alkyl, hetaryl-$(C_2-_{10})$alkenyl, or hetaryl-$(C_2-_{10})$alkynyl, any of which is optionally substituted with

one or more independent halo, -$CF_3$, -$OCF_3$, -$OR^{222}$, -$NR^{222}$, $R^{333}$ ($R^{333a}$)$_{j3a}$, -$C(O)R^{222}$, -$CO_2R^{222}$, -$CONR^{222}R^{333}$, -$NO_2$, -CN, -$S(O)_{j3a}R^{222}$, -$SO_2NR^{222}R^{333}$, $NR^{222}(C=O)R^{333}$, $NR^{222}(C=O)OR^{333}$, $NR^{222}(C=O)NR^{222}R^{333}$, $NR^{222}S(O)_{j3a}R^{333}$, -$(C=S)OR^{222}$, -$(C=O)SR^{222}$, -$NR^{222}(C=NR^{333})NR^{222}aR^{333}a$, -$NR^{222}(C=NR^{333})OR^{222a}$, -$NR^{222}(C=NR^{333})SR^{333}a$, -$O(C=O)OR^{222}$, -$O(C=O)NR^{222}R^{333}$, -$O(C=O)SR^{222}$, -$S(C=O)OR^{222}$, or -$S(C=O)NR^{222}R^{333}$ substituents;

$G^{11}$ is halo, oxo, -$CF_3$, -$OCF_3$, -$OR^{21}$, -$NR^{21}R^{31}(R^{3a1})_{j4}$, -$C(O)R^{21}$, -$CO_2R^{21}$, -$CONR^{21}R^{31}$, -$NO_2$, -CN, -$S(O)_{j4}R^{21}$, -$SO_2NR^{21}R^{31}$, $NR^{21}(C=O)R^{31}$, $NR^{21}(C=O)OR^{31}$, $NR^{21}(C=O)NR^{21}R^{31}$, $NR^{21}S(O)_{j4}R^{31}$, -$(C=S)OR^{21}$, -$(C=O)SR^{21}$, -$NR^{21}(C=NR^{31})NR^{2a1}R^{3a1}$, -$NR^{21}(C=NR^{31})OR^{2a1}$, -$NR^{21}(C=NR^{31})SR^{3a1}$, -$O(C=O)OR^{21}$, -$O(C=O)NR^{21}R^{31}$, -$O(C=O)SR^{21}$, -$S(C=O)OR^{21}$, -$S(C=O)NR^{21}R^{31}$, -$P(O)OR^{21}OR^{31}$, $(C_0$-$_{10})$alkyl, $(C_2$-$_{10})$alkenyl, $(C_2$-$_{10})$alkynyl, $(C_1$-$_{10})$alkoxy$(C_1$-$_{10})$alkyl, $(C_1$-$_{10})$alkoxy$(C_2$-$_{10})$alkenyl, $(C_1$-$_{10})$alkoxy$(C_2$-$_{10})$alkynyl, $(C_1$-$_{10})$alkylthio$(C_1$-$_{10})$alkyl, $(C_1$-$_{10})$alkylthio$(C_2$-$_{10})$alkenyl, $(C_1$-$_{10})$alkylthio$(C_2$-$_{10})$alkynyl, cyclo$(C_3$-$_8)$alkyl, cyclo$(C_3$-$_8)$alkenyl, cyclo$(C_3$-$_8)$alkyl$(C_1$-$_{10})$alkyl, cyclo$(C_3$-$_8)$alkenyl$(C_1$-$_{10})$ alkyl, cyclo$(C_3$-$_8)$alkyl$(C_2$-$_{10})$alkenyl, cyclo$(C_3$-$_8)$alkenyl$(C_2$-$_{10})$alkenyl, cyclo$(C_3$-$_8)$ alkyl$(C_2$-$_{10})$ alkynyl, cyclo$(C_3$-$_8)$alkenyl$(C_2$-$_{10})$alkynyl, heterocyclyl-$(C_0$-$_{10})$alkyl, heterocyclyl-$(C_2$-$_{10})$ alkenyl, or heterocyclyl-$(C_2$-$_{10})$alkynyl, any of which is optionally substituted with one or more independent halo, oxo, -$CF_3$, -$OCF_3$, -$OR^{2221}$, -$NR^{2221}R^{3331}$ ($R^{333a1}$)$_{j4a}$, -$C(O)R^{2221}$, -$CO_2R^{2221}$, -$CONR^{2221}R^{3331}$, -$NO_2$, -CN, -$S(O)_{j4a}R^{2221}$, -$SO_2NR^{2221}R^{3331}$, $NR^{2221}(C=O)R^{3331}$, $NR^{2221}(C=O)OR^{3331}$, $NR^{2221}(C=O)NR^{2221}R^{3331}$, $NR^{2221}S(O)_{j4a}R^{3331}$, -$(C=S)OR^{2221}$, -$(C=O)SR^{2221}$, -$NR^{2221}(C=NR^{3331})NR^{222a1}R^{333a1}$, -$NR^{2221}(C=NR^{3331})OR^{222a1}$, -$NR^{2221}(C=NR^{3331})SR^{333a1}$, -$O(C=O)OR^{2221}$, -$O(C=O)NR^{2221}R^{3331}$, -$O(C=O)SR^{2221}$, -$S(C=O)OR^{2221}$, -$P(O)OR^{2221}OR^{3331}$, or -$S(C=O)NR^{2221}R^{3331}$ substituents; or aryl-$(C_0$-$_{10})$alkyl, aryl-$(C_2$-$_{10})$alkenyl, or aryl-$(C_2$-$_{10})$alkynyl, any of which is optionally substituted with one or more independent halo, -$CF_3$, -$OCF_3$, -$OR^{2221}$, -$NR^{2221}R^{3331}$ ($R^{333a1}$)$_{j5a}$, -$C(O)R^{2221}$, -$CO_2R^{2221}$, -$CONR^{2221}R^{3331}$, -$NO_2$, -CN, -$S(O)_{j5a}R^{2221}$, -$SO_2NR^{2221}R^{3331}$, $NR^{2221}(C=O)R^{3331}$, $NR^{2221}(C=O)OR^{3331}$, $NR^{2221}(C=O)NR^{2221}R^{3331}$, $NR^{2221}S(O)_{j5a}R^{3331}$, -$(C=S)OR^{2221}$, -$(C=O)SR^{2221}$, -$NR^{2221}(C=NR^{3331})NR^{222a1}R^{333a1}$, -$NR^{2221}(C=NR^{3331})OR^{222a1}$, -$NR^{2221}(C=NR^{3331})SR^{333a1}$, -$O(C=O)OR^{2221}$, -$O(C=O)NR^{2221}R^{3331}$, -$O(C=O)SR^{2221}$, -$S(C=O)OR^{2221}$, -$P(O)OR^{2221}R^{3331}$, or -$S(C=O)NR^{2221}R^{3331}$ substituents; or hetaryl-$(C_0$-$_{10})$ alkyl, hetaryl-$(C_2$-$_{10})$alkenyl, or hetaryl-$(C_2$-$_{10})$alkynyl, any of which is optionally substituted

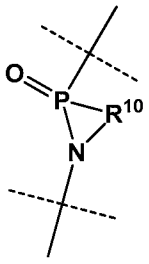
with one or more independent halo, -$CF_3$, -$OCF_3$, -$OR^{2221}$, -$NR^{2221}R^{3331}(R^{333a1})_{j6a}$, -$C(O)R^{2221}$, -$CO_2R^{2221}$, -$CONR^{2221}R^{3331}$, -$NO_2$, -CN, -$S(O)_{j6a}R^{2221}$, -$SO_2NR^{2221}R^{3331}$, $NR^{2221}(C=O)R^{3331}$, $NR^{2221}(C=O)OR^{3331}$, $NR^{2221}(C=O)NR^{2221}R^{3331}$, $NR^{2221}S(O)_{j6a}R^{3331}$, -$(C=S)OR^{2221}$, -$(C=O)SR^{2221}$, -$NR^{2221}(C=NR^{3331})NR^{222a1}R^{333a1}$, -$NR^{2221}(C=NR^{3331})OR^{222a1}$, -$NR^{2221}(C=NR^{3331})SR^{333a1}$, -$O(C=O)OR^{2221}$, -$O(C=O)NR^{2221}R^{3331}$, -$O(C=O)SR^{2221}$, -$S(C=O)OR^{2221}$, -$P(O)OR^{2221}OR^{3331}$, or -$S(C=O)NR^{2221}R^{3331}$ substituents; or $G^{11}$ is taken together with the carbon to which it is attached to form a double bond which is substituted with $R^5$ and $G^{111}$;

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

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

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

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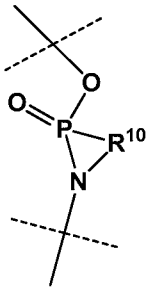
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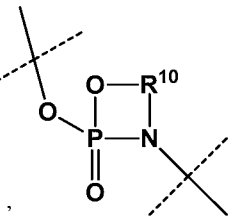
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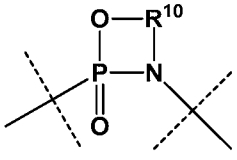
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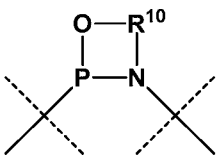
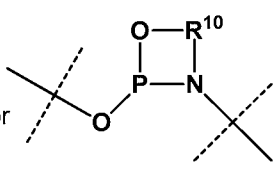

or

;

$R^{10}$, 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 $(C_0\text{-}_{10})$alkyl, $(C_2\text{-}_{10})$alkenyl, $(C_2\text{-}_{10})$alkynyl, $(C_1\text{-}_{10})$alkoxy$(C_1\text{-}_{10})$alkyl, $(C_1\text{-}_{10})$alkoxy$(C_2\text{-}_{10})$alkenyl, $(C_1\text{-}_{10})$alkoxy$(C_2\text{-}_{10})$alkynyl, $(C_1\text{-}_{10})$alkylthio$(C_1\text{-}_{10})$alkyl, $(C_1\text{-}_{10})$alkylthio$(C_2\text{-}_{10})$alkenyl, $(C_1\text{-}_{10})$alkylthio$(C_2\text{-}_{10})$alkynyl, cyclo$(C_3\text{-}_8)$alkyl, cyclo$(C_3\text{-}_8)$alkenyl, cyclo$(C_3\text{-}_8)$alkyl$(C_1\text{-}_{10})$alkyl, cyclo$(C_3\text{-}_8)$alkenyl$(C_1\text{-}_{10})$alkyl, cyclo$(C_3\text{-}_8)$alkyl$(C_2\text{-}_{10})$alkenyl, cyclo$(C_3\text{-}_8)$alkenyl$(C_2\text{-}_{10})$alkenyl, cyclo$(C_3\text{-}_8)$alkyl$(C_2\text{-}_{10})$alkynyl, cyclo$(C_3\text{-}_8)$alkenyl$(C_2\text{-}_{10})$alkynyl, heterocyclyl-$(C_0\text{-}_{10})$alkyl, heterocyclyl-$(C_2\text{-}_{10})$alkenyl, or heterocyclyl-$(C_2\text{-}_{10})$alkynyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{77}$, $-NR^{77}R^{87}$, $-C(O)R^{77}$, $-CO_2R^{77}$, $-CONR^{77}R^{87}$, $-NO_2$, -CN, $-S(O)_{j5a}R^{77}$, $-SO_2NR^{77}R^{87}$, $NR^{77}(C=O)R^{87}$, $NR^{77}(C=O)OR^{87}$, $NR^{77}(C=O)NR^{78}R^{87}$, $NR^{77}S(O)_{j5a}R^{87}$, $-(C=S)OR^{77}$, $-(C=O)SR^{77}$, $-NR^{77}(C=NR^{87})NR^{78}R^{88}$, $-NR^{77}(C=NR^{87})OR^{78}$, $-NR^{77}(C=NR^{87})SR^{78}$, $-O(C=O)OR^{77}$, $-O(C=O)NR^{77}R^{87}$, $-O(C=O)SR^{77}$, $-S(C=O)OR^{77}$, $-P(O)OR^{77}OR^{87}$, or $-S(C=O)NR^{77}R^{87}$ substituents; or aryl-$(C_0\text{-}_{10})$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, $-CF_3$, $-OCF_3$, $-OR^{77}$, $-NR^{77}R^{87}$, $-C(O)R^{77}$, $-CO_2R^{77}$, $-CONR^{77}R^{87}$, $-NO_2$, -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-$(C_0\text{-}_{10})$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, $-CF_3$, $-OCF_3$, $-OR^{77}$, $-NR^{77}R^{87}$, $-C(O)R^{77}$, $-CO_2R^{77}$, $-CONR^{77}R^{87}$, $-NO_2$, -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;

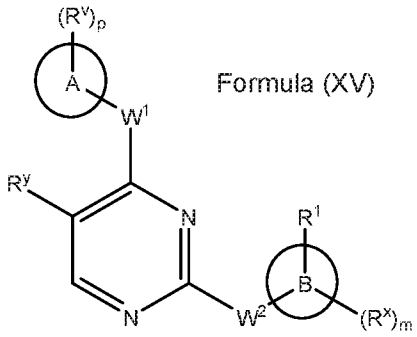
$R^{69}$ is equal to halo, $-OR^{78}$, -SH, $-NR^{78}R^{88}$, $-CO_2R^{78}$, $-CONR^{78}R^{88}$, $-NO_2$, -CN, $-S(O)_{j8}R^{78}$, $-SO_2NR^{78}R^{88}$, $(C_{0-10})$alkyl, $(C_{2-10})$alkenyl, $(C_{2-10})$alkynyl, $(C_{1-10})$alkoxy$(C_{1-10})$alkyl, $(C_{1-10})$alkoxy$(C_{2-10})$alkenyl, $(C_{1-10})$alkoxy$(C_{2-10})$alkynyl,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

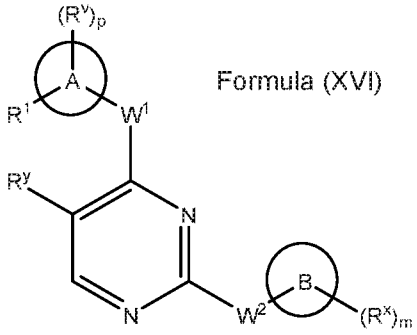
$R^{77}$, $R^{78}$, $R^{87}$, $R^{88}$, $R^{778}$, and $R^{888}$ are each independently $(C_{0-10})$alkyl, $(C_{2-10})$alkenyl, $(C_{2-10})$alkynyl, $(C_{1-10})$alkoxy$(C_{1-10})$alkyl, $(C_{1-10})$alkoxy$C_{2-10})$alkenyl, $(C_{1-10})$alkoxy$(C_{2-10})$alkynyl, $(C_{1-10})$alkylthio$(C_{1-10})$alkyl, $(C_{1-10})$alkylthio$(C_{2-10})$alkenyl, $(C_{1-10})$alkylthio$(C_{2-10})$alkynyl, cyclo$(C_{3-8})$alkyl, cyclo$(C_{3-8})$alkenyl, cyclo$(C_{3-8})$alkyl$(C_{1-10})$alkyl, cyclo$(C_{3-8})$alkenyl$(C_{1-10})$alkyl, cyclo$(C_{3-8})$alkyl$(C_{2-10})$alkenyl, cyclo$(C_{3-8})$alkenyl$(C_{2-10})$alkenyl, cyclo$(C_{3-8})$alkyl$(C_{2-10})$alkynyl, cyclo$(C_{3-8})$alkenyl$(C_{2-10})$alkynyl, heterocyclyl-$(C_{0-10})$alkyl, heterocyclyl-$(C_{2-10})$alkenyl, heterocyclyl-$(C_{2-10})$alkynyl, $(C_{1-10})$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.

**[00231]** 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 (XV) or Formula (XVI):




or a pharmaceutically acceptable salt, ester, 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.

**[00232]** In an embodiment, the BTK inhibitor is a compound of Formula (XV) or Formula (XVI), 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, 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 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, an optionally substituted 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an optionally substituted 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

$R^1$ is -L-Y, wherein:

L is a covalent bond or a bivalent $C_{1-8}$ saturated or unsaturated, straight or branched, hydrocarbon

chain, wherein one, two, or three methylene units of L are optionally and independently replaced by cyclopropylene, —NR—, —N(R)C(O)—, —C(O)N(R)—, —N(R)$SO_2$—, —$SO_2$N(R)—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —SO—, —$SO_2$—, —C(ő:S)—, —C(ő:NR)—, —Nő:N—, or —C(ő:$N_2$)—;

Y is hydrogen, $C_{1-6}$ aliphatic optionally substituted with oxo, halogen, or CN, or a 3-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein said ring is substituted with at 1-4 groups independently selected from -Q-Z, oxo, $NO_2$, halogen, CN, or $C_{1-6}$ aliphatic, wherein:

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

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

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

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

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

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

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

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

m and p are independently 0-4; and

$R^x$ and $R^v$ are independently selected from —R, halogen, —OR, —O($CH_2$)$_q$OR, —CN, —$NO_2$,

—$SO_2R$, —$SO_2N(R)_2$, —SOR, —C(O)R, —$CO_2R$, —$C(O)N(R)_2$, —NRC(O)R, —$NRC(O)NR_2$, —$NRSO_2R$, or —$N(R)_2$, wherein R is independently selected from the group consisting of hydrogen, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, and heterocycly; or:

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

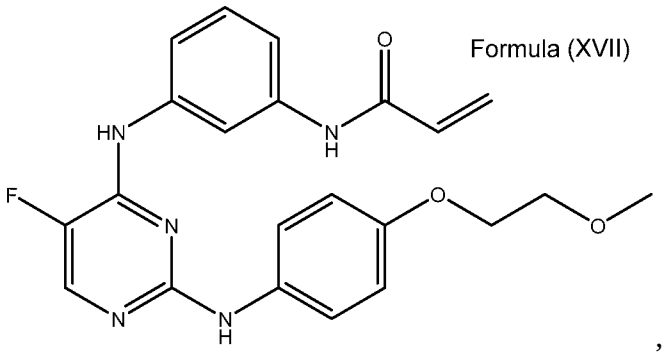
$R^v$ and $R^1$ when concurrently present on Ring A are taken together with their intervening atoms to form a 5-7 membered saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with a warhead group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

**[00233]** As defined generally above, 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, 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.

**[00234]** In some 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 some embodiments, Ring B is an optionally substituted phenyl group.

**[00235]** In certain embodiments, Ring A in Formula (XV) or Formula (XVI) is substituted as defined herein. In some embodiments, Ring A is substituted with one, two, or three groups independently selected from halogen, $R^{\circ}$, or —$(CH_2)_{0-4}OR^{\circ}$, or —$O(CH_2)_{0-4}R^{\circ}$, wherein each $R^{\circ}$ is independently selected from the group consisting of cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl. Exemplary substituents on Ring A include Br, I, Cl, methyl, —$CF_3$, —CŁCH, —$OCH_2$phenyl, —$OCH_2$(fluorophenyl), or —$OCH_2$pyridyl.

**[00236]** In a preferred embodiment, the BTK inhibitor is CC-292 (also known as AVL-292), or a pharmaceutically acceptable salt, ester, solvate, hydrate, cocrystal, or prodrug thereof, most preferably a hydrochloride salt or a besylate salt thereof. In a preferred embodiment, the BTK inhibitor is a compound of Formula (XVII):

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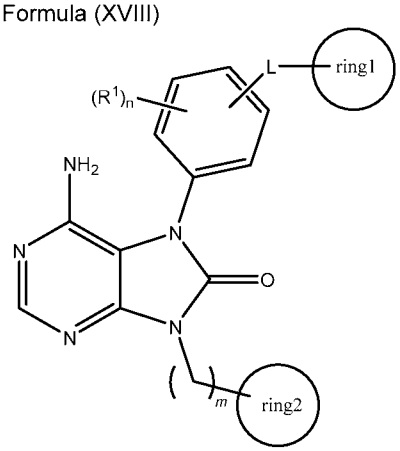
which is *N*-(3-((5-fluoro-2-((4-(2-methoxyethoxy)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide, or a pharmaceutically acceptable salt, ester, solvate, hydrate, cocrystal, or prodrug thereof, or in an preferred embodiment is a hydrochloride salt or a besylate salt thereof. The preparation of this compound is described in U.S. Patent Application Publication No. 2010/0029610 A1 at Example 20, the disclosure of which is incorporated by reference herein. The preparation of the besylate salt (*i.e.*, the benzenesulfonic acid 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.

**[00237]** 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, ester, solvate, hydrate, cocrystal, or prodrug thereof, or more preferably a hydrochloride salt or besylate 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. 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 of this compound is described in U.S. Patent Application Publication No. 2012/0077832 A1, the disclosure of which is incorporated by reference herein.

**[00238]** In an embodiment, the BTK inhibitor is a compound of Formula (XVIII):

Formula (XVIII)




or a pharmaceutically acceptable salt, ester, solvate, hydrate, 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;

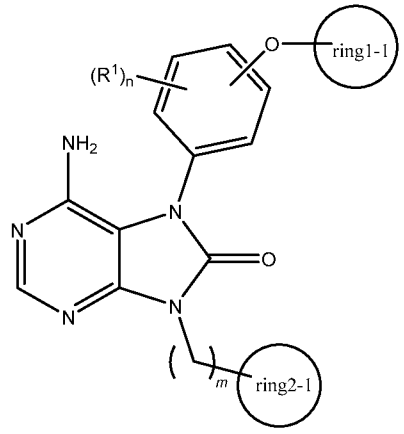
n represents an integer from 0 to 4;

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).

**[00239]** In an embodiment, the BTK inhibitor is a compound of Formula (XIX):

Formula (XIX)



or a pharmaceutically acceptable salt, ester, solvate, hydrate, 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;

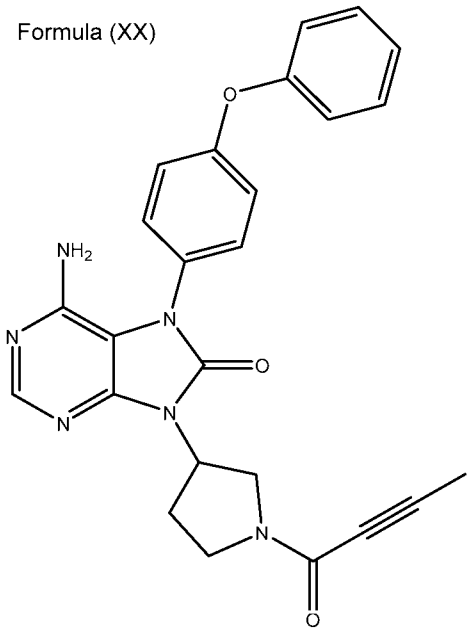
n represents an integer from 0 to 4;

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).

**[00240]** In a preferred embodiment, the BTK inhibitor is a compound of Formula (XX):

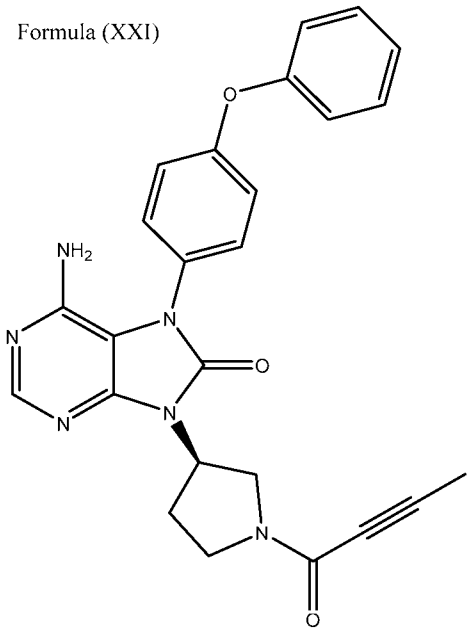
Formula (XX)



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

**[00241]** The *R*-enantiomer of Formula (XX) is also known as ONO-4059, and is given by Formula (XXI). In a preferred embodiment, the BTK inhibitor is a compound of Formula (XXI):

Formula (XXI)



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

**[00242]** 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 or a pharmaceutically acceptable salt, ester, solvate, hydrate, cocrystal, or prodrug thereof, preferably a hydrochloride salt thereof.

**[00243]** The preparation of Formula (XXI) is described in International Patent Application Publication No. WO 2013/081016 A1 and U.S. Patent Application Publication No. 2014/0330015 A1, the disclosure of each of which is incorporated by reference herein. In brief, the BTK inhibitor of Formula (XXI) can be prepared by the following procedure.

**[00244]** 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).

**[00245]** Step 2: The compound prepared in Step 1 (19 g) and tert-butyl (3R)-3-aminopyrrolidine-1-carboxylate (10.5 g) are dissolved in dioxane (58 mL). Triethylamine (8.1

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

**[00246]** 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).

**[00247]** 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).

**[00248]** 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).

**[00249]** 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).

**[00250]** Step 7: At room temperature 4 N HCl/dioxane (13 mL) is added to a methanol (13 mL) suspension of the compound prepared in Step 6 (1.3 g 2.76 mmol, 1.0 equivalent), and the mixture is stirred for 1 hour. The solvent is then distilled off to obtain (3R)-6-amino-9-pyrrolidin-3-yl-7-(4-phenoxyphenyl)-7,9-dihydro-8*H*-purin-8-one dihydrochloride (1.5 g).

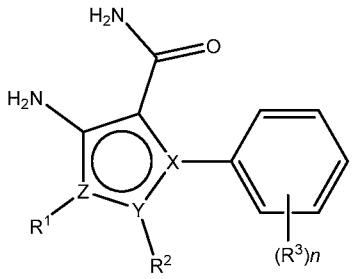
**[00251]** Step 8: After 2-butylnoic acid (34 mg), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC) (78 mg), 1-hydroxybenzotriazole (HOBt) (62 mg), and triethylamine (114 mL) are added to a solution of the compound prepared in Step 7 (100 mg) in dimethyl formamide (3 mL), the mixture is stirred at room temperature for 3 hours. Water is added to the reaction mixture and extraction with ethyl acetate is performed. The organic layer is washed with saturated sodium carbonate solution and saturated aqueous sodium chloride solution, then dried over anhydrous sodium sulfate, and the solvent is distilled off. The residue is purified by thin layer chromatography (dichloromethane:methanol:28% ammonia water=90:10:1) to obtain 6-amino-9-[(3*R*)-1-(2-butynoyl)-3-pyrrolidinyl]-7-(4-phenoxyphenyl)-7,9-dihydro-8H-purin-8-one (Formula (XXI)) (75 mg).

**[00252]** The hydrochloride salt of the compound of Formula (XXI) 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).

**[00253]** In an embodiment, the BTK inhibitor is a compound selected from the structures disclosed in International Patent Application Publication No. WO 2013/081016 A1 and U.S. Patent Application Publication No. US 2014/0330015 A1, the disclosure of each of which is incorporated by reference herein.

**[00254]** In an embodiment, the BTK inhibitor is a compound of Formula (XXII):

Formula (XXII)




or a pharmaceutically acceptable salt, ester, 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.

**[00255]** In some embodiments, the BTK inhibitor is one of the following particular embodiments of Formula (XXII):

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 $SO_2$R', 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.

**[00256]** In some embodiments, the BTK inhibitor is one of the following particular embodiments of Formula (XXII):

$R^1$ is piperidine or azaspiro[3.3]heptane, N-substituted with $R^4$, wherein $R^4$ is H, COR' or $SO_2$R', and R' is substituted or unsubstituted alkenyl, particularly substituted or unsubstituted ethenyl;

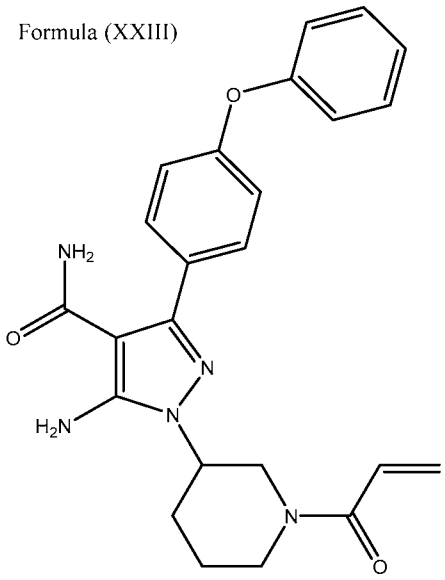
$R^3$ is –$OR^5$, $R^5$ is phenyl, and n is 1;

$R^1$ 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

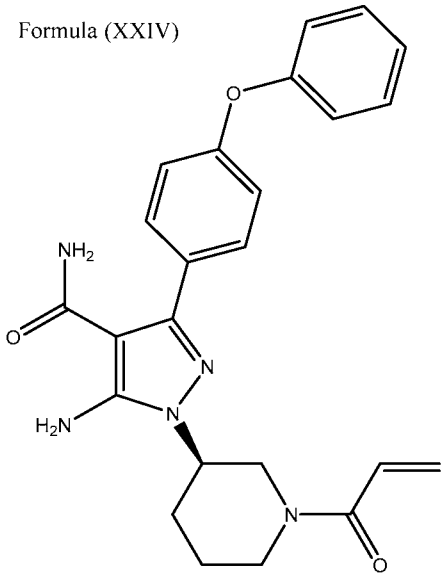
X--Y--Z is C--N--N and $R^2$ is absent; $R^1$ is piperidine, N-substituted with $R^4$; $R^3$ is –$OR^5$; n is 1; $R^4$ is COR', and R' is unsubstituted or substituted alkenyl, particularly ethenyl; and $R^5$ is substituted or unsubstituted aryl, particularly phenyl.

**[00257]** In a preferred embodiment, the BTK inhibitor is a compound selected from the group consisting of Formula (XXIII), Formula (XXIV), and Formula (XXV):

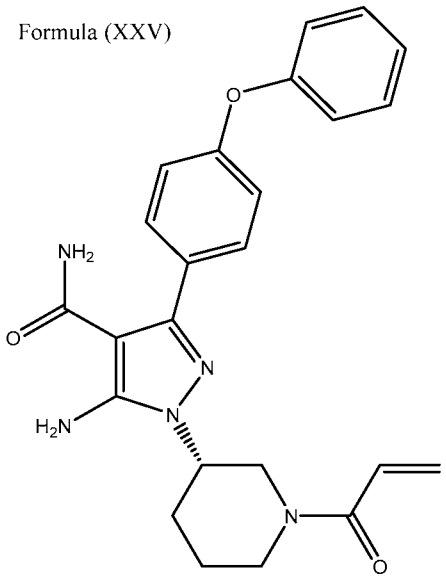
Formula (XXIII)



Formula (XXIV)



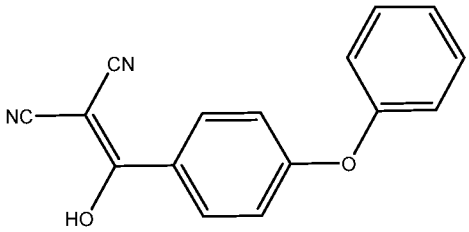
Formula (XXV)



or a pharmaceutically acceptable salt, ester, solvate, hydrate, cocrystal, or prodrug thereof. Formula (XXIV) 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 disclosures of which are incorporated by reference herein.

**[00258]** In brief, the BTK inhibitor of Formula (XXIII) can be prepared by the following procedure.

**[00259]** Step 1. Preparation of 2-(hydroxy(4-phenoxyphenyl)methylene)malononitrile:

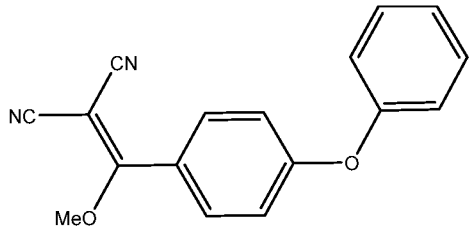


**[00260]** A solution of 4-phenoxybenzoic acid (300 g, 1.4 mol) in $SOCl_2$ (1.2 L) is stirred at 80° C under $N_2$ for 3 hours. The mixture is concentrated in vacuum to give the intermediate (315 g) which is used for next step without further purification.

**[00261]** To a solution of propanedinitrile (89.5 g, 1355 mmol) and DIEA (350 g, 2710 mmol) in THF (800 mL) is dropwise a solution of the intermediate (315 g) in toluene (800 mL) at 0-5° C. over 2 hours. The resultant mixture is allowed to warm to RT and stirred for 16 hours. The

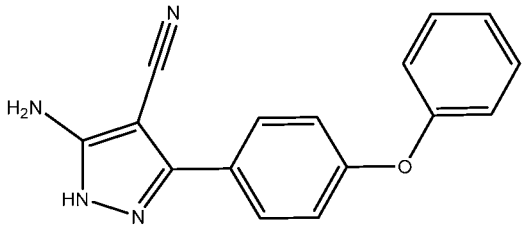
reaction is quenched with water (2.0 L) and extracted with of EA (2.0 L × 3). The combined organic layers are washed with 1000 mL of 3 N HCl aqueous solution, brine (2.0 L × 3), dried over $Na_2SO_4$ and concentrated to give the crude product (330 g, 93%).

**[00262]** Step 2. Preparation of 2-(Methoxy(4-phenoxyphenyl)methylene)malononitrile:



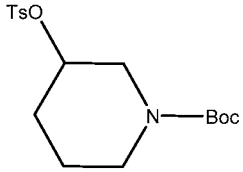

**[00263]** A solution of 2-(hydroxy(4-phenoxyphenyl)methylene)malononitrile (50 g, 190.8 mmol) in $CH(OMe_3)$ (500 mL) is heated to 75°C for 16 hours. Then the mixture is concentrated to a residue and washed with MeOH (50 mL) to give 25 g (47.5%) of 2-(methoxy(4-phenoxyphenyl)methylene)malononitrile as a yellow solid.

**[00264]** Step 3. Preparation of 5-amino-3-(4-phenoxyphenyl)-1*H*-pyrazole-4-carbonitrile:




**[00265]** 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.

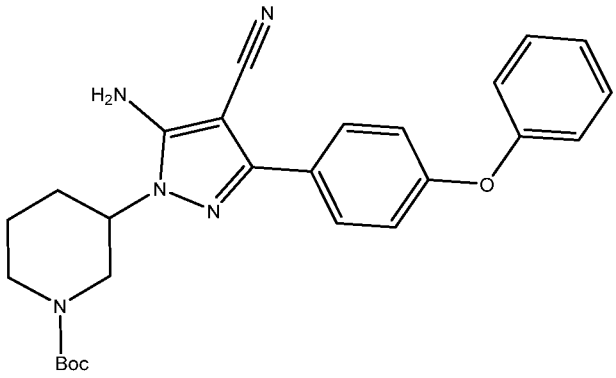
**[00266]** Step 4. Preparation of *tert*-butyl 3-(tosyloxy)piperidine-1-carboxylate:




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

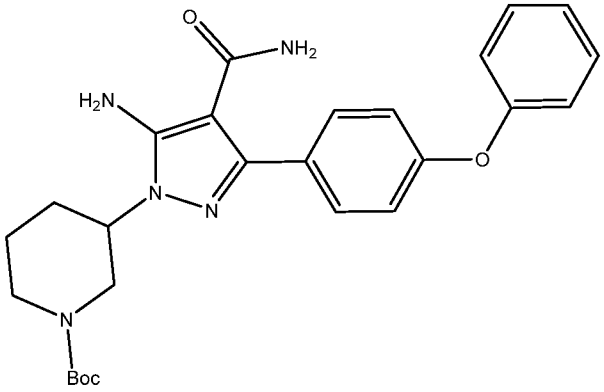
**[00267]** To a solution of *tert*-butyl 3-hydroxypiperidine-1-carboxylate (1.05 g, 5.0 mmol) in pyridine (8 mL) is added TsCl (1.425 g, 7.5 mmol). The mixture is stirred at RT under $N_2$ for two days. The mixture is concentrated and partitioned between 100 mL of EA and 100 mL of HCl (1 N) aqueous 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.

**[00268]** Step 5. Preparation of *tert*-butyl 3-(5-amino-4-cyano-3-(4-phenoxyphenyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate:



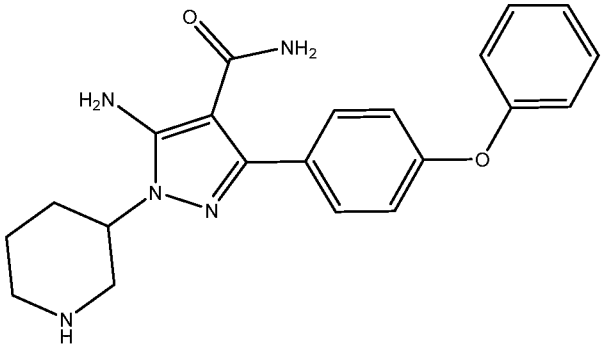

**[00269]** To a solution of *tert*-butyl 3-(tosyloxy)piperidine-1-carboxylate (355 mg, 1.0 mmol) and 5-amino-3-(4-phenoxyphenyl)-1*H*-pyrazole-4-carbonitrile (276 mg, 1.0 mmol) in 5 mL of DMF is added $Cs_2CO_3$ (650 mg, 2.0 mmol). A tosyloxy leaving group is employed in this reaction. The mixture is 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.

**[00270]** Step 6. Preparation of *tert*-butyl 3-(5-amino-4-carbamoyl-3-(4-phenoxyphenyl)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate:




**[00271]** To a solution of *tert*-butyl 3-(5-amino-4-cyano-3-(4-phenoxyphenyl)-1 *H*-pyrazol-1-yl)piperidine-1-carboxylate (100 mg, 0.22 mmol) in DMSO (2 mL) and ethanol (2 mL) was added the solution of NaOH (200 mg, 5 mmol) in water (1 mL) and $H_2O_2$ (1 mL). The mixture is stirred at 60° C for 15 min and concentrated to remove EtOH, after which 10 mL of water and 50 mL of ethyl acetate are added. The organic layer is separated from aqueous layer, washed with brine (30 mL × 3) and dried over $Na_2SO_4$. After concentration, 50 mg of residue is used directly in the next step, wherein 50 mg of residue is purified by pre-TLC (eluted with petroleum ether/ethyl actate = 1/1) to afford 12 mg (30%) of *tert*-butyl 3-(5-amino-4-carbamoyl-3-(4-phenoxyphenyl)-1 *H*-pyrazol-1-yl)piperidine-1-carboxylate as a white solid.

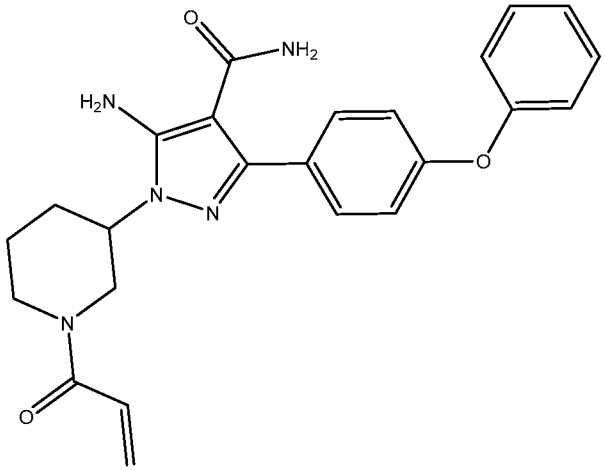
**[00272]** Step 7. Preparation of 5-amino-3-(4-phenoxyphenyl)-1-(piperidin-3-yl)-1 *H*-pyrazole-4-carboxamide:




**[00273]** 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.

**[00274]** Step 8. Preparation of 1-(1-acryloylpiperidin-3-yl)-5-amino-3-(4-phenoxyphenyl)-1*H*-pyrazole-4-carboxamide:




**[00275]** 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.

**[00276]** The enantiomers of Formula (XXIII) 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 (XXIV), or from (*R*)-*tert*-butyl 3-hydroxypiperidine-1-carboxylate using a similar procedure (step 4 to 8) for Formula (XXV). Under appropriate conditions recognized by one of ordinary skill in the art, a racemic mixture of Formula (XXIII) may be separated by chiral HPLC, the crystallization of

chiral salts, or other means described above to yield Formula (XXIV) and Formula (XXV) of high enantiomeric purity.

**[00277]** 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.

**[00278]** Other BTK inhibitors suitable for use in the described combination with a JAK-2 inhibitor or a PI3K inhibitor, the PI3K inhibitor being preferably selected from the group consisting of a PI3K-Ûinhibitor, a PI3K-¡¦ inhibitor, and a PI3K-Û¡¦ inhibitor, also include, but are not limited to, those described in, for example, International Patent Application Publication Nos. WO 2013/010868, WO 2012/158843, WO 2012/135944, WO 2012/135937, U.S. Patent Application Publication No. 2011/0177011, and U.S. Patent Nos. 8,501,751, 8,476,284, 8,008,309, 7,960,396, 7,825,118, 7,732,454, 7,514,444, 7,459,554, 7,405,295, and 7,393,848, the disclosures of each of which are incorporated herein by reference.

Pharmaceutical Compositions

**[00279]** In some embodiments, the invention provides pharmaceutical compositions for treating solid tumor cancers, lymphomas and leukemia, particularly a solid tumor cancer.

**[00280]** The pharmaceutical compositions are typically formulated to provide a therapeutically effective amount of a BTK inhibitor as the active ingredients, or a pharmaceutically acceptable salt, ester, prodrug, solvate, hydrate or derivative thereof. Where desired, the pharmaceutical compositions contain a pharmaceutically acceptable salt and/or coordination complex thereof, and one or more pharmaceutically acceptable excipients, carriers, including inert solid diluents and fillers, diluents, including sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers and adjuvants.

**[00281]** The pharmaceutical compositions are administered as a BTK inhibitor. Where desired, other agent(s) may be mixed into a preparation or both components may be formulated into separate preparations for use in combination separately or at the same time.

**[00282]** In some embodiments, the concentration of each of the BTK inhibitors provided in the pharmaceutical compositions of the invention is independently less than, for example, 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%,

11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002% or 0.0001% w/w, w/v or v/v, relative to the total mass or volume of the pharmaceutical composition.

**[00283]** In some embodiments, the concentration of each of the BTK inhibitors provided in the pharmaceutical compositions of the invention is independently greater than 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19.75%, 19.50%, 19.25% 19%, 18.75%, 18.50%, 18.25% 18%, 17.75%, 17.50%, 17.25% 17%, 16.75%, 16.50%, 16.25% 16%, 15.75%, 15.50%, 15.25% 15%, 14.75%, 14.50%, 14.25% 14%, 13.75%, 13.50%, 13.25% 13%, 12.75%, 12.50%, 12.25% 12%, 11.75%, 11.50%, 11.25% 11%, 10.75%, 10.50%, 10.25% 10%, 9.75%, 9.50%, 9.25% 9%, 8.75%, 8.50%, 8.25% 8%, 7.75%, 7.50%, 7.25% 7%, 6.75%, 6.50%, 6.25% 6%, 5.75%, 5.50%, 5.25% 5%, 4.75%, 4.50%, 4.25%, 4%, 3.75%, 3.50%, 3.25%, 3%, 2.75%, 2.50%, 2.25%, 2%, 1.75%, 1.50%, 125%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002% or 0.0001% w/w, w/v, or v/v, relative to the total mass or volume of the pharmaceutical composition.

**[00284]** In some embodiments, the concentration of each of the BTK inhibitors of the invention is independently in the range from approximately 0.0001% to approximately 50%, approximately 0.001% to approximately 40%, approximately 0.01% to approximately 30%, approximately 0.02% to approximately 29%, approximately 0.03% to approximately 28%, approximately 0.04% to approximately 27%, approximately 0.05% to approximately 26%, approximately 0.06% to approximately 25%, approximately 0.07% to approximately 24%, approximately 0.08% to approximately 23%, approximately 0.09% to approximately 22%, approximately 0.1% to approximately 21%, approximately 0.2% to approximately 20%, approximately 0.3% to approximately 19%, approximately 0.4% to approximately 18%, approximately 0.5% to approximately 17%, approximately 0.6% to approximately 16%, approximately 0.7% to approximately 15%, approximately 0.8% to approximately 14%, approximately 0.9% to approximately 12% or approximately 1% to approximately 10% w/w, w/v or v/v, relative to the total mass or volume of the pharmaceutical composition.

**[00285]** In some embodiments, the concentration of each of the BTK inhibitors of the invention is independently in the range from approximately 0.001% to approximately 10%, approximately 0.01% to approximately 5%, approximately 0.02% to approximately 4.5%, approximately 0.03% to approximately 4%, approximately 0.04% to approximately 3.5%, approximately 0.05% to approximately 3%, approximately 0.06% to approximately 2.5%, approximately 0.07% to approximately 2%, approximately 0.08% to approximately 1.5%, approximately 0.09% to approximately 1%, approximately 0.1% to approximately 0.9% w/w, w/v or v/v, relative to the total mass or volume of the pharmaceutical composition.

**[00286]** In some embodiments, the amount of each of the BTK inhibitors of the invention is independently equal to or less than 3.0 g, 2.5 g, 2.0 g, 1.5 g, 1.0 g, 0.95 g, 0.9 g, 0.85 g, 0.8 g, 0.75 g, 0.7 g, 0.65 g, 0.6 g, 0.55 g, 0.5 g, 0.45 g, 0.4 g, 0.35 g, 0.3 g, 0.25 g, 0.2 g, 0.15 g, 0.1 g, 0.09 g, 0.08 g, 0.07 g, 0.06 g, 0.05 g, 0.04 g, 0.03 g, 0.02 g, 0.01 g, 0.009 g, 0.008 g, 0.007 g, 0.006 g, 0.005 g, 0.004 g, 0.003 g, 0.002 g, 0.001 g, 0.0009 g, 0.0008 g, 0.0007 g, 0.0006 g, 0.0005 g, 0.0004 g, 0.0003 g, 0.0002 g or 0.0001 g.

**[00287]** In some embodiments, the amount of each of the BTK inhibitors of the invention is independently more than 0.0001 g, 0.0002 g, 0.0003 g, 0.0004 g, 0.0005 g, 0.0006 g, 0.0007 g, 0.0008 g, 0.0009 g, 0.001 g, 0.0015 g, 0.002 g, 0.0025 g, 0.003 g, 0.0035 g, 0.004 g, 0.0045 g, 0.005 g, 0.0055 g, 0.006 g, 0.0065 g, 0.007 g, 0.0075 g, 0.008 g, 0.0085 g, 0.009 g, 0.0095 g, 0.01 g, 0.015 g, 0.02 g, 0.025 g, 0.03 g, 0.035 g, 0.04 g, 0.045 g, 0.05 g, 0.055 g, 0.06 g, 0.065 g, 0.07 g, 0.075 g, 0.08 g, 0.085 g, 0.09 g, 0.095 g, 0.1 g, 0.15 g, 0.2 g, 0.25 g, 0.3 g, 0.35 g, 0.4 g, 0.45 g, 0.5 g, 0.55 g, 0.6 g, 0.65 g, 0.7 g, 0.75 g, 0.8 g, 0.85 g, 0.9 g, 0.95 g, 1 g, 1.5 g, 2 g, 2.5, or 3 g.

**[00288]** Each of the BTK inhibitors according to the invention is effective over a wide dosage range. For example, in the treatment of adult humans, dosages independently range from 0.01 to 1000 mg, from 0.5 to 100 mg, from 1 to 50 mg per day, and from 5 to 40 mg per day are examples of dosages that may be used. The exact dosage will depend upon the route of administration, the form in which the compound is administered, the gender and age of the subject to be treated, the body weight of the subject to be treated, and the preference and experience of the attending physician.

**[00289]** Described below are non-limiting pharmaceutical compositions and methods for

preparing the same.

Pharmaceutical Compositions for Oral Administration

**[00290]** In some embodiments, the invention provides a pharmaceutical composition for oral administration containing the BTK inhibitor, and a pharmaceutical excipient suitable for oral administration.

**[00291]** In some embodiments, the invention provides a solid pharmaceutical composition for oral administration containing: (i) an effective amount of a BTK inhibitor and (ii) a pharmaceutical excipient suitable for oral administration. In some embodiments, the composition further contains (iii) an effective amount of a further compound.

**[00292]** In some embodiments, the pharmaceutical composition may be a liquid pharmaceutical composition suitable for oral consumption. Pharmaceutical compositions of the invention suitable for oral administration can be presented as discrete dosage forms, such as capsules, sachets, or tablets, or liquids or aerosol sprays each containing a predetermined amount of an active ingredient as a powder or in granules, a solution, or a suspension in an aqueous or non-aqueous liquid, an oil-in-water emulsion, a water-in-oil liquid emulsion, powders for reconstitution, powders for oral consumptions, bottles (including powders or liquids in a bottle), orally dissolving films, lozenges, pastes, tubes, gums, and packs. Such dosage forms can be prepared by any of the methods of pharmacy, but all methods include the step of bringing the active ingredient(s) into association with the carrier, which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient(s) with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet can be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with an excipient such as, but not limited to, a binder, a lubricant, an inert diluent, and/or a surface active or dispersing agent. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

**[00293]** 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.

**[00294]** Each of the 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.

**[00295]** 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.

**[00296]** 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.

**[00297]** 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.

**[00298]** 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.

**[00299]** When aqueous suspensions and/or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents,

coloring matter or dyes and, if so desired, emulsifying and/or suspending agents, together with such diluents as water, ethanol, propylene glycol, glycerin and various combinations thereof.

**[00300]** 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.

**[00301]** 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.

**[00302]** 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.

**[00303]** 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.

**[00304]** 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.

**[00305]** 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.

**[00306]** 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.

**[00307]** 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.

**[00308]** 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.

**[00309]** 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.

**[00310]** 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, ڕ-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, ¡›-valerolactone and isomers thereof, ŭ-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.

**[00311]** 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.

**[00312]** 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.

**[00313]** 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.

**[00314]** 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.

**[00315]** 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

**[00316]** In some embodiments, the invention provides a pharmaceutical composition for injection containing the BTK inhibitors and a pharmaceutical excipient suitable for injection. Components and amounts of agents in the compositions are as described herein.

**[00317]** 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.

**[00318]** 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.

**[00319]** Sterile injectable solutions are prepared by incorporating the BTK inhibitors in the required amounts in the appropriate solvent with various other ingredients as enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the

case of sterile powders for the preparation of sterile injectable solutions, certain desirable methods of preparation are spray-drying, vacuum-drying and freeze-drying (lyophilization) techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. Other lyophilized or spray-dried antibody formulations known to those of skill in the art may also be employed with the present invention. Such formulations include those disclosed in U.S. Patent Nos. 5,908,826, 6,267,958, 7,682,609, 7,592,004, and 8,298,530, and U.S. Patent Application Publication No. 2010/0158925, the teachings of which are specifically incorporated by reference herein.

Pharmaceutical Compositions for Topical Delivery

**[00320]** In some embodiments, the invention provides a pharmaceutical composition for transdermal delivery containing the BTK inhibitors and a pharmaceutical excipient suitable for transdermal delivery.

**[00321]** 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.

**[00322]** 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.

**[00323]** Another formulation for use in the methods of the present invention employs

transdermal delivery devices (“patches”). Such transdermal patches may be used to provide continuous or discontinuous infusion of the BTK inhibitors in controlled amounts, either with or without another agent.

**[00324]** 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.

Other Pharmaceutical Compositions

**[00325]** Pharmaceutical compositions may also be prepared from compositions described herein and one or more pharmaceutically acceptable excipients suitable for sublingual, buccal, rectal, intraosseous, intraocular, intranasal, epidural, or intraspinal administration. Preparations for such pharmaceutical compositions are well-known in the art. See, *e.g.*, Anderson et al., *Handbook of Clinical Drug Data*, Tenth Edition, McGraw-Hill, 2002; and Pratt and Taylor, eds., *Principles of Drug Action*, Third Edition, Churchill Livingston, N.Y., 1990, each of which is incorporated by reference herein in its entirety.

**[00326]** Administration of the BTK inhibitors or pharmaceutical compositions 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.

**[00327]** 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.

**[00328]** The invention also provides kits. The kits include the 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 agent. In some embodiments, the BTK inhibitors and the agent are provided as separate compositions in separate containers within the kit. In some embodiments, the 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 some embodiments, be marketed directly to the consumer.

Dosages and Dosing Regimens

**[00329]** The amounts of BTK inhibitors administered will be dependent on the mammal being treated, the severity of the disorder or condition, the rate of administration, the disposition of the compounds and the discretion of the prescribing physician. However, an effective dosage is in the range of about 0.001 to about 100 mg per kg body weight per day, such as about 1 to about 35 mg/kg/day, in single or divided doses. For a 70 kg human, this would amount to about 0.05 to 7 g/day, such as about 0.05 to about 2.5 g/day. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect - *e.g.*, by dividing such larger doses into several small doses for administration throughout the day.

**[00330]** In some embodiments, the BTK inhibitor is administered in a single dose. Typically, such administration will be by injection, for example by intravenous injection, in order to introduce the agents quickly. However, other routes may be used as appropriate. A single dose of the BTK inhibitor may also be used for treatment of an acute condition.

**[00331]** In some embodiments, the BTK inhibitor is administered in multiple doses. Dosing may be about once, twice, three times, four times, five times, six times, or more than six times per day. Dosing may be about once a month, once every two weeks, once a week, or once every other day. In other embodiments, the BTK inhibitor is administered about once per day to about

6 times per day. In another embodiment the administration of the combination of the BTK inhibitor 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.

**[00332]** Administration of the agents of the invention may continue as long as necessary. In some embodiments, the BTK inhibitor is administered for more than 1, 2, 3, 4, 5, 6, 7, 14, or 28 days. In some embodiments, the BTK inhibitor is administered for less than 28, 14, 7, 6, 5, 4, 3, 2, or 1 day. In some embodiments, the BTK inhibitor is administered chronically on an ongoing basis - *e.g.*, for the treatment of chronic effects.

**[00333]** An effective amount of the BTK inhibitor 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 Cancers, Including Solid Tumor Cancers, and Other Diseases

**[00334]** In some embodiments, the invention relates to a method of treating a hyperproliferative disorder in a mammal that comprises administering to said mammal a therapeutically effective amount of a BTK inhibitor, or a pharmaceutically acceptable salt or ester, prodrug, solvate or hydrate of the BTK inhibitor. In an embodiment, the subject is a mammal. In an embodiment, the subject is a human. In an embodiment, the subject is a companion animal, such as a canine, feline, or equine.

**[00335]** In some embodiments, the invention relates to a method of treating, with a BTK inhibitor, a hyperproliferative disorder in a mammal selected from the group consisting of bladder cancer, 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, aquired 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 and 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, 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, or stage IV melanoma.

**[00336]** In some embodiments, the invention relates to a method of treating a solid tumor cancer which solid tumor cancer is selected from 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, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, colon cancer, and brain cancer

**[00337]** In some embodiments, the invention relates to a method of treating an inflammatory, immune, or autoimmune disorder in a mammal with a BTK inhibitor. In some embodiments, the invention also relates to a method of treating a disease with a BTK inhibitor, wherein the disease is selected from the group consisting of tumor angiogenesis, chronic inflammatory disease, rheumatoid arthritis, atherosclerosis, inflammatory bowel disease, skin diseases such as psoriasis, eczema, and scleroderma, diabetes, diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, glioma, melanoma, ulcerative colitis, atopic dermatitis, pouchitis, spondylarthritis, uveitis, Behcets disease, polymyalgia rheumatica, giant-cell arteritis, sarcoidosis, Kawasaki disease, juvenile idiopathic arthritis, hidratenitis suppurativa, Sjögren’s syndrome, psoriatic arthritis, juvenile rheumatoid arthritis, ankylosing spoldylitis, Crohn’s Disease, lupus, and lupus nephritis.

**[00338]** In some embodiments, the invention relates to a method of treating with a BTK inhibitor a hyperproliferative disorder, including but not limited to a cancer such as acute myeloid leukemia, thymus cancer, brain cancer, lung cancer, squamous cell cancer, skin cancer, eye cancer, retinoblastoma, intraocular melanoma, oral cavity and oropharyngeal cancer, bladder cancer, gastric cancer, stomach cancer, pancreatic cancer, bladder cancer, breast cancer, cervical, head cancer, neck cancer, renal cancer, kidney cancer, liver cancer, ovarian cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, and CNS, PNS, AIDS-related (*e.g.*, lymphoma and Kaposi's sarcoma) or viral-induced cancers. In some embodiments, said pharmaceutical composition is for the treatment of a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin (*e.g.*, psoriasis), restenosis, or prostate (*e.g.*, benign prostatic hypertrophy (BPH)).

**[00339]** In some embodiments, the invention relates to a method of treating with a BTK inhibitor a cancer, wherein the cancer is a B cell hematological malignancy selected from the group consisting of chronic lymphocytic leukemia (CLL), small lymphocytic leukemia (SLL), non-Hodgkin’s lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Hodgkin’s lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Burkitt’s lymphoma, Waldenström's macroglobulinemia (WM), Burkitt’s lymphoma, multiple myeloma, or myelofibrosis.

**[00340]** In some embodiments, the invention relates to a method of treating with a BTK inhibitor a hyperproliferative disorder selected from the group consisting of myeloproliferative proliferative neoplasm, chronic myelogenous leukemia, chronic neutrophilic leukemia, polycythemia vera, primary myelofibrosis, essential thrombocythemia, chronic eosinophilic leukemia, mastocytosis, and myelodysplastic syndrome.

**[00341]** In some embodiments, the invention relates to a method of treating with a BTK inhibitor a glioma, wherein the glioma is selected from the group consisting of fibrillary astrocytoma, anaplastic astrocytoma, pilocytic astrocytoma, astrocytoma, pleomorphic xanthoastrocytoma, subependymal giant cell astrocytoma, glioblastoma multiforme, oligodendroglioma, ependymoma, subependymoma, choroid plexus tumor, choroid plexus papilloma, choroid plexus carcinoma, oligoastrocytoma, gliomatosis cerebri, and gliosarcoma.

**[00342]** In some embodiments, the invention relates to a method of treating with a BTK

inhibitor a cancer, wherein the cancer is selected from primary central nervous system lymphoma, reticulum cell sarcoma, diffuse histiocytic lymphoma, and microglioma.

**[00343]** In some embodiments, the invention relates to a method of treating a solid tumor cancer with a composition including 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 some embodiments, the invention relates to a method of treating pancreatic cancer, breast cancer, ovarian cancer, melanoma, lung cancer, squamous cell carcinoma including head and neck cancer, and colorectal cancer using a 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.

**[00344]** 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 synergistic combination of a BTK inhibitor, or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof, 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 synergistic combination of a BTK inhibitor and gemcitabine, or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof, wherein the BTK inhibitor is a compound of Formula (II), 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 synergistic combination of a BTK inhibitor and gemcitabine, or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof, wherein the BTK inhibitor is a compound of Formula (I), or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof. Gemcitabine has the chemical names 2',2'-difluorodeoxycytidine or 4-amino-1-((2*R*,4*R*,5*R*)-3,3-difluoro-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)pyrimidin-2(1*H*)-

one, and is described, *e.g.*, in Cerqueira, *et al.*, *Chemistry Eur. J.* **2007,** *13(30),* 8507-15.

**[00345]** In some embodiments, the invention relates to a BTK inhibitor, for example a compound of Formula (I) and particularly a compound of Formula (II) to Formula (VII), or a pharmaceutically acceptable salt or ester, prodrug, solvate or hydrate thereof, for use in the treatment of a hyperproliferative disease. The invention also provides a composition comprising a BTK inhibitor, for example a compound of Formula (I) and particularly a compound of Formula (II) to Formula (VII), or a pharmaceutically acceptable salt or ester, prodrug, solvate or hydrate thereof, for use in the treatment of a hyperproliferative disease. The hyperproliferative disease may be selected from bladder cancer, 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, aquired 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 and 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, 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 and stage IV melanoma. The hyperproliferative disease, including but not limited to cancer, may be selected from acute myeloid leukemia, thymus cancer, brain cancer, lung cancer, squamous cell cancer, skin cancer, eye cancer, retinoblastoma, intraocular melanoma, oral cavity and oropharyngeal cancer, bladder cancer, gastric cancer, stomach cancer, pancreatic cancer, bladder cancer, breast cancer, cervical, head cancer, neck cancer, renal cancer, kidney cancer, liver cancer, ovarian

cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, and CNS, PNS, AIDS-related (*e.g.*, lymphoma and Kaposi's sarcoma) or viral-induced cancers. In some embodiments, said BTK inhibitor and/or composition is for the treatment of a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin (*e.g.*, psoriasis), restenosis, or prostate (*e.g.*, benign prostatic hypertrophy (BPH)).

**[00346]** In some embodiments, the invention relates to a BTK inhibitor, for example a compound of Formula (I) and particularly a compound of Formula (II) to Formula (VII), or a pharmaceutically acceptable salt or ester, prodrug, solvate or hydrate thereof, for use in the treatment of a glioma. In some embodiments, the invention relates to a BTK inhibitor, for example a compound of Formula (I) and particularly a compound of Formula (II) to Formula (VII), or a pharmaceutically acceptable salt or ester, prodrug, solvate or hydrate thereof, for use in the treatment of a glioma, wherein the glioma is selected from the group consisting of fibrillary astrocytoma, anaplastic astrocytoma, pilocytic astrocytoma, astrocytoma, pleomorphic xanthoastrocytoma, subependymal giant cell astrocytoma, glioblastoma multiforme, oligodendroglioma, ependymoma, subependymoma, choroid plexus tumor, choroid plexus papilloma, choroid plexus carcinoma, oligoastrocytoma, gliomatosis cerebri, and gliosarcoma.

**[00347]** In some embodiments, the invention relates to a BTK inhibitor, for example a compound of Formula (I) and particularly a compound of Formula (II) to Formula (VII), or a pharmaceutically acceptable salt or ester, prodrug, solvate or hydrate thereof, for use in the treatment of an inflammatory, immune, or autoimmune disorder. The invention also provides a composition comprising a BTK inhibitor, for example a compound of Formula (I) and particularly a compound of Formula (II) to Formula (VII), or a pharmaceutically acceptable salt or ester, prodrug, solvate or hydrate thereof, for use in the treatment of an inflammatory, immune, or autoimmune disorder. The inflammatory, immune, or autoimmune disorder may be 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, melanoma, ulcerative colitis, atopic dermatitis, pouchitis, spondylarthritis, uveitis, Behcets disease, polymyalgia rheumatica, giant-cell arteritis, sarcoidosis, Kawasaki disease, juvenile idiopathic arthritis, hidratenitis suppurativa, Sjögren’s syndrome, psoriatic arthritis, juvenile rheumatoid arthritis, ankylosing spoldylitis, Crohn’s

Disease, lupus, and lupus nephritis.

**[00348]** In some embodiments, the invention relates to a BTK inhibitor, for example a compound of Formula (I) and particularly a compound of Formula (II) to Formula (VII), or a pharmaceutically acceptable salt or ester, prodrug, solvate or hydrate of the BTK inhibitor, for use in the treatment of a solid tumor cancer. The invention also provides a composition comprising a BTK inhibitor, for example a compound of Formula (I) and particularly a compound of Formula (II) to Formula (VII), or a pharmaceutically acceptable salt or ester, prodrug, solvate or hydrate thereof, for use in the treatment of a solid tumor cancer, for example wherein the BTK inhibitor inhibits 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. The solid tumor cancer may be selected from pancreatic cancer, breast cancer, ovarian cancer, melanoma, lung cancer, squamous cell carcinoma including head and neck cancer, and colorectal cancer.

**[00349]** In some embodiments, the invention relates to a combination of a BTK inhibitor, for example a compound of Formula (I) and particularly a compound of Formula (II) to Formula (VII), or a pharmaceutically acceptable salt or ester, prodrug, solvate or hydrate thereof, and gemcitabine or a pharmaceutically acceptable salt or ester, prodrug, solvate or hydrate thereof, for use in the treatment of a solid tumor cancer. The invention also provides a combination comprising a BTK inhibitor, for example a compound of Formula (I) and particularly a compound of Formula (II) to Formula (VII), or a pharmaceutically acceptable salt or ester, prodrug, solvate or hydrate thereof, and gemcitabine or a pharmaceutically acceptable salt or ester, prodrug, solvate or hydrate thereof, for use in the treatment of a solid tumor cancer, for example wherein the BTK inhibitor inhibits 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. The solid tumor cancer may be selected from pancreatic cancer, breast cancer, ovarian cancer, melanoma, lung cancer, squamous cell carcinoma including head and neck cancer, and colorectal cancer.

**[00350]** Efficacy of the compounds and combinations of compounds described herein in

treating, preventing and/or managing the indicated diseases or disorders can be tested using various models known in the art. For example, models for determining efficacy of treatments for pancreatic cancer are described in Herreros-Villanueva, *et al.*, *World J. Gastroenterol.* **2012,** *18,* 1286-1294. Models for determining efficacy of treatments for breast cancer are described *e.g.* in Fantozzi, *Breast Cancer Res.* **2006,** *8,* 212. Models for determining efficacy of treatments for ovarian cancer are described 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 below in the examples.

**[00351]** Efficacy of the compounds and combinations of compounds described herein in treating, preventing and/or managing other indicated diseases or disorders described here can also be tested using various 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,* 315-334. Efficacy in treating, preventing and/or managing scleroderma can be assessed using a mouse model induced by repeated local injections of bleomycin described, for example, in Yamamoto, *et al.*, *J. Invest. Dermatol.* **1999,** *112,* 456-462. Efficacy in treating, preventing and/or managing dermatomyositis can be assessed using a myositis mouse model induced by immunization with rabbit myosin as described, for example, in Phyanagi, *et al.*, *Arthritis & Rheumatism,* **2009,** *60(10),* 3118-3127. Efficacy in treating, preventing and/or managing lupus can be assessed using various animal models described, for example, in Ghoreishi, *et al.*, *Lupus,* **2009,** *19,* 1029-1035; Ohl et al., *J. Biomed. & Biotechnol.*, Article ID 432595 (2011); Xia, *et al.*, *Rheumatology,* **2011,** *50,* 2187-2196; Pau et al., *PLoS ONE,* **2012,** *7(5),* e36761; Mustafa, *et al.*, *Toxicology,* **2011,** *90,* 156-168; Ichikawa et al., *Arthritis & Rheumatism,* **2012,** *62(2),* 493-503; Rankin, *et al.*, *J. Immunology,* **2012,** *188,* 1656-1667. Efficacy in treating, preventing and/or managing Sjögren's syndrome can be assessed using various mouse models described, for example, in Chiorini, *et al.*, *J. Autoimmunity,* **2009,** *33,* 190-196.

Methods of Treating Patients Sensitive to Bleeding Events

**[00352]** In some embodiments, the invention provides a method of treating a cancer in a human sensitive to bleeding events, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof. In a preferred embodiment, the invention provides a method of treating a cancer in a human sensitive to bleeding events, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is Formula (II), or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof. In some embodiments, the invention provides a method of treating a hyperproliferative disorder, such as a cancer or an inflammatory, immune, or autoimmune disease, in a human intolerant to ibrutinib using a BTK inhibitor, wherein the BTK inhibitor is Formula (II), or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof.

**[00353]** In an embodiment, the invention provides a method of treating a cancer in a human sensitive to bleeding events, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is Formula (II), or a pharmaceutically-acceptable

salt, cocrystal, hydrate, solvate, or prodrug thereof, further comprising the step of administering a therapeutically effective dose of an anticoagulent or antiplatelet active pharmaceutical ingredient. In some embodiments, the invention provides a method of treating a cancer in a human sensitive to bleeding events, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is Formula (II), and wherein the cancer is selected from the group consisting of bladder cancer, squamous cell carcinoma including head and neck cancer, pancreatic ductal adenocarcinoma (PDA), pancreatic cancer, colon carcinoma, mammary carcinoma, breast cancer, fibrosarcoma, mesothelioma, renal cell carcinoma, lung carcinoma, thyoma, prostate cancer, colorectal cancer, ovarian cancer, acute myeloid leukemia, thymus cancer, brain cancer, squamous cell cancer, skin cancer, eye cancer, retinoblastoma, melanoma, intraocular melanoma, oral cavity and oropharyngeal cancers, gastric cancer, stomach cancer, cervical cancer, head, neck, renal cancer, kidney cancer, liver cancer, ovarian cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, aquired 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.

**[00354]** In some embodiments, the invention provides a method of treating a cancer in a human sensitive to platelet-mediated thrombosis comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is Formula (II), or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof.

**[00355]** In some embodiments, the BTK inhibitor and the anticoagulent or the antiplatelet active pharmaceutical ingredient are administered sequentially. In some embodiments, the BTK inhibitor and the anticoagulent or the antiplatelet active pharmaceutical ingredient are administered concomittently. In some embodiments, the BTK inhibitor is administered before the anticoagulent or the antiplatelet active pharmaceutical ingredient. In some embodiments, the

BTK inhibitor is administered after the anticoagulent or the antiplatelet active pharmaceutical ingredient.

**[00356]** Selected anti-platelet and anticoagulent active pharmaceutical ingredients for use in the methods of the present invention include, but are not limited to, cyclooxygenase inhibitors (e.g., aspirin), adenosine diphosphate (ADP) receptor inhibitors (e.g., clopidogrel and ticlopidine), phosphodiesterase inhibitors (e.g., cilostazol), glycoprotein IIb/IIIa inhibitors (e.g., abciximab, eptifibatide, and tirofiban), adenosine reuptake inhibitors (e.g., dipyridamole), and acetylsalicylic acid (aspirin). In other embodiments, examples of anti-platelet active pharmaceutical ingredients for use in the methods of the present invention include anagrelide, aspirin/extended-release dipyridamole, cilostazol, clopidogrel, dipyridamole, prasugrel, ticagrelor, ticlopidine, vorapaxar, tirofiban HCl, eptifibatide, abciximab, argatroban, bivalirudin, dalteparin, desirudin, enoxaparin, fondaparinux, heparin, lepirudin, apixaban, dabigatran etexilate mesylate, rivaroxaban, and warfarin.

**[00357]** In an embodiment, the invention includes a method of treating a cancer, comprising the step of orally administering, to a human in need thereof, a Bruton's tyrosine kinase (BTK) inhibitor, wherein the BTK inhibitor is (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, further comprising the step of administering a therapeutically effective dose of an anticoagulant or antiplatelet active pharmaceutical ingredient, wherein the anticoagulant or antiplatelet active pharmaceutical ingredient is selected from the group consisting of acenocoumarol, anagrelide, anagrelide hydrochloride, abciximab, aloxiprin, antithrombin, apixaban, argatroban, aspirin, aspirin with extended-release dipyridamole, beraprost, betrixaban, bivalirudin, carbasalate calcium, cilostazol, clopidogrel, clopidogrel bisulfate, cloricromen, dabigatran etexilate, darexaban, dalteparin, dalteparin sodium, defibrotide, dicumarol, diphenadione, dipyridamole, ditazole, desirudin, edoxaban, enoxaparin, enoxaparin sodium, eptifibatide, fondaparinux, fondaparinux sodium, heparin, heparin sodium, heparin calcium, idraparinux, idraparinux sodium, iloprost, indobufen, lepirudin, low molecular weight heparin, melagatran, nadroparin, otamixaban, parnaparin, phenindione, phenprocoumon, prasugrel, picotamide, prostacyclin, ramatroban, reviparin, rivaroxaban, sulodexide, terutroban, terutroban sodium, ticagrelor, ticlopidine, ticlopidine hydrochloride, tinzaparin, tinzaparin sodium, tirofiban, tirofiban hydrochloride, treprostinil, treprostinil sodium, triflusal, vorapaxar,

warfarin, warfarin sodium, ximelagatran, salts thereof, solvates thereof, hydrates thereof, and combinations thereof.

**[00358]** In some embodiments, the invention provides a method of treating a cancer in a human with a history of thrombosis, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof. In some embodiments, the invention provides a method of treating a cancer in a human sensitive to platelet-mediated thrombosis, method of treating a cancer in a human with a history of thrombosis, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is a compound of Formula (II) or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof. In some embodiments, the invention provides a method of treating a cancer in a human sensitive to platelet-mediated thrombosis, method of treating a cancer in a human with a history of thrombosis, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is a compound of Formula (II) or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof.

**[00359]** In some embodiments, the BTK inhibitor and the anticoagulent or the antiplatelet agent are administered sequentially. In some embodiments, the BTK inhibitor and the anticoagulent or the antiplatelet agent are administered concomittently. In some embodiments, the BTK inhibitor is administered before the anticoagulent or the antiplatelet agent. In some embodiments, the BTK inhibitor is administered after the anticoagulent or the antiplatelet agent.

**[00360]** Preferred anti-platelet and anticoagulent agents for use in the methods of the present invention include, but are not limited to, cyclooxygenase inhibitors (e.g., aspirin), adenosine diphosphate (ADP) receptor inhibitors (e.g., clopidogrel and ticlopidine), phosphodiesterase inhibitors (e.g., cilostazol), glycoprotein IIb/IIIa inhibitors (e.g., abciximab, eptifibatide, and tirofiban), adenosine reuptake inhibitors (e.g., dipyridamole), and acetylsalicylic acid (aspirin). In other embodiments, examples of anti-platelet agents 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.

**[00361]** In some embodiments, the invention provides a method of treating a cancer in a human sensitive to platelet-mediated thrombosis, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof. In an embodiment, the invention provides a method of treating a cancer in a human sensitive to platelet-mediated thrombosis, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is Formula (II), or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof. In an embodiment, the invention provides a method of treating a cancer in a human sensitive to platelet-mediated thrombosis, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is Formula (II), or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof, further comprising the step of administering a therapeutically effective dose of an anticoagulent or antiplatelet agent. In an embodiment, the invention provides a method of treating a cancer in a human sensitive to platelet-mediated thrombosis, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is Formula (I), or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof. In an

embodiment, the invention provides a method of treating a cancer in a human sensitive to platelet-mediated thrombosis, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is Formula (I), or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof, further comprising the step of administering a therapeutically effective dose of an anticoagulent or antiplatelet agent.

**[00362]** In an embodiment, the invention provides a method of treating a cancer in a human sensitive to platelet-mediated thrombosis, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is Formula (II), or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof, further comprising the step of administering a therapeutically effective dose of an anticoagulent or antiplatelet agent, wherein the anticoagulent or antiplatelet agent is selected from the group consisting of clopidogrel, prasugrel, ticagrelor, ticlopidine, warfarin, acenocoumarol, dicumarol, phenprocoumon, heparain, low molecular weight heparin, fondaparinux, and idraparinux.

**[00363]** In an embodiment, the invention provides a method of treating a cancer in a human sensitive to platelet-mediated thrombosis, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is Formula (I), or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof, further comprising the step of administering a therapeutically effective dose of an anticoagulent or antiplatelet agent, wherein the anticoagulent or antiplatelet agent is selected from the group consisting of clopidogrel, prasugrel, ticagrelor, ticlopidine, warfarin, acenocoumarol, dicumarol, phenprocoumon, heparain, low molecular weight heparin, fondaparinux, and idraparinux.

**[00364]** In some embodiments, the invention provides a method of treating a cancer in a human sensitive to platelet-mediated thrombosis, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is Formula (II), and wherein the cancer is selected from the group consisting of bladder cancer, squamous cell carcinoma including head and neck cancer, pancreatic ductal adenocarcinoma (PDA), pancreatic cancer, colon carcinoma, mammary carcinoma, breast cancer, fibrosarcoma, mesothelioma, renal cell carcinoma, lung carcinoma, thyoma, prostate cancer, colorectal cancer, ovarian cancer, acute myeloid leukemia, thymus cancer, brain cancer, squamous cell cancer, skin cancer, eye cancer, retinoblastoma, melanoma, intraocular melanoma, oral cavity and oropharyngeal cancers, gastric

cancer, stomach cancer, cervical cancer, head, neck, renal cancer, kidney cancer, liver cancer, ovarian cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, aquired 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.

**[00365]** In some embodiments, the invention provides a method of treating a cancer in a human sensitive to platelet-mediated thrombosis, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is Formula (I), and wherein the cancer is selected from the group consisting of bladder cancer, squamous cell carcinoma including head and neck cancer, pancreatic ductal adenocarcinoma (PDA), pancreatic cancer, colon carcinoma, mammary carcinoma, breast cancer, fibrosarcoma, mesothelioma, renal cell carcinoma, lung carcinoma, thyoma, prostate cancer, colorectal cancer, ovarian cancer, acute myeloid leukemia, thymus cancer, brain cancer, squamous cell cancer, skin cancer, eye cancer, retinoblastoma, melanoma, intraocular melanoma, oral cavity and oropharyngeal cancers, gastric cancer, stomach cancer, cervical cancer, head, neck, renal cancer, kidney cancer, liver cancer, ovarian cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, aquired 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.

**[00366]** In an embodiment, the invention provides a combination of a BTK inhibitor and an anticoagulant or antiplatelet active pharmaceutical ingredient for the treatment of cancer in a human sensitive to bleeding events.

**[00367]** In an embodiment, the invention provides a combination of a BTK inhibitor and an anticoagulant or antiplatelet active pharmaceutical ingredient for the treatment of cancer in a human sensitive to platelet-mediated thrombosis.

**[00368]** In an embodiment, the invention provides a combination of a BTK inhibitor and an anticoagulant or antiplatelet active pharmaceutical ingredient for the treatment of cancer in a human with a history of thrombosis.

**[00369]** The BTK inhibitor is preferably a compound of formula (I), for example a compound of formula (II), or a pharmaceutically acceptable salt, cocrystal, hydrate, solvate or prodrug thereof. The BTK inhibitor is preferably (*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, cocrystal, hydrate, solvate or prodrug thereof.

**[00370]** In one embodiment of the combination, the cancer is selected from the group consisting of bladder cancer, squamous cell carcinoma including head and neck cancer, pancreatic ductal adenocarcinoma (PDA), pancreatic cancer, colon carcinoma, mammary carcinoma, breast cancer, fibrosarcoma, mesothelioma, renal cell carcinoma, lung carcinoma, thyoma, prostate cancer, colorectal cancer, ovarian cancer, acute myeloid leukemia, thymus cancer, brain cancer, squamous cell cancer, skin cancer, eye cancer, retinoblastoma, melanoma, intraocular melanoma, oral cavity and oropharyngeal cancers, gastric cancer, stomach cancer, cervical cancer, head, neck, renal cancer, kidney cancer, liver cancer, ovarian cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, aquired 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.

**[00371]** In some embodiments, the BTK inhibitor and the anticoagulent or the antiplatelet active pharmaceutical ingredient are administered sequentially. In some embodiments, the BTK inhibitor and the anticoagulent or the antiplatelet active pharmaceutical ingredient are administered concomittently. In some embodiments, the BTK inhibitor is administered before the anticoagulent or the antiplatelet active pharmaceutical ingredient. In some embodiments, the BTK inhibitor is administered after the anticoagulent or the antiplatelet active pharmaceutical ingredient.

**[00372]** Selected anti-platelet and anticoagulent active pharmaceutical ingredients for use in the present invention include, but are not limited to, cyclooxygenase inhibitors (e.g., aspirin), adenosine diphosphate (ADP) receptor inhibitors (e.g., clopidogrel and ticlopidine), phosphodiesterase inhibitors (e.g., cilostazol), glycoprotein IIb/IIIa inhibitors (e.g., abciximab, eptifibatide, and tirofiban), adenosine reuptake inhibitors (e.g., dipyridamole), and acetylsalicylic acid (aspirin). In other embodiments, examples of anti-platelet active pharmaceutical ingredients for use in the 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. The anticoagulant or antiplatelet active pharmaceutical ingredient may also be 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.

**[00373]** The anticoagulent or antiplatelet agent may also be selected from the group consisting of clopidogrel, prasugrel, ticagrelor, ticlopidine, warfarin, acenocoumarol, dicumarol, phenprocoumon, heparain, low molecular weight heparin, fondaparinux, and idraparinux.

Combinations of BTK Inhibitors with Anti-CD20 Antibodies

**[00374]** The BTK inhibitors of the present invention may also be safely co-administered with immunotherapeutic antibodies such as the anti-CD20 antibodies rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, and ibritumomab, and or antigen-binding fragments, derivatives, conjugates, variants, and radioisotope-labeled complexes thereof, which may be given alone or with conventional chemotherapeutic active pharmaceutical ingredients such as those described herein. The CD20 antigen (also called human B-lymphocyte-restricted differentiation antigen, Bp35, or B1) is found on the surface of normal "pre-B" and mature B lymphocytes, including malignant B lymphocytes. Nadler, *et al.*, *J. Clin. Invest.* **1981,** *67,* 134-40; Stashenko, *et al.*, *J. Immunol.* **1980,** *139,* 3260-85. The CD20 antigen is a glycosylated integral membrane protein with a molecular weight of approximately 35 kD. Tedder, *et al.*, *Proc. Natl. Acad. Sci. USA,* **1988,** *85,* 208-12. CD20 is also expressed on most B cell non-Hodgkin's lymphoma cells, but is not found on hematopoietic stem cells, pro-B cells, normal plasma cells, or other normal tissues. Anti-CD20 antibodies are currently used as therapies for many hematological malignancies, including indolent NHL, aggressive NHL, and CLL/SLL. Lim, *et. al., Haematologica* **2010,** *95,* 135-43; Beers, *et. al.*, *Sem. Hematol.* **2010,** *47,* 107-14; and Klein, *et al.*, *mAbs* **2013,** *5,* 22-33.

**[00375]** In an embodiment, the invention relates to 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 (II), 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 anti-CD20 antibody is selected from a chimeric antibody, a humanized antibody and a human antibody or an antigen-binding fragment, derivative, conjugate, variant or

radio-labelled complex thereof. In an embodiment, the invention relates to 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 (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and further comprising the step of administering an anti-CD20 antibody, wherein the anti-CD20 antibody is an anti-CD20 monoclonal antibody or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof, and wherein the anti-CD20 antibody specifically binds to human CD20 with a $K_D$ selected from the group consisting of $1\times10^{-7}$ M or less, $5\times10^{-8}$ M or less, $1\times10^{-8}$ M or less, and $5\times10^{-9}$ M or less. Anti-CD20 monoclonal antibodies are classified as Type I or Type II, as described in Klein, *et al.*, *mAbs* **2013,** *5,* 22-33. Type I anti-CD20 monoclonal antibodies are characterized by binding to the Class I epitope, localization of CD20 to lipid rafts, high complement-dependent cytotoxicity, full binding capacity, weak homotypic aggregation, and moderate cell death induction. Type II anti-CD20 monoclonal antibodies are characterized by binding to the Class I epitope, a lack of localization of CD20 to lipid rafts, low complement-dependent cytotoxicity, half binding capacity, homotypic aggregation, and strong cell death induction. Both Type I and Type II anti-CD20 monoclonal antibodies exhibit antibody-dependent cytotoxiticy (ADCC) and are thus useful with BTK inhibitors described herein. Type I anti-CD20 monoclonal antibodies include but are not limited to rituximab, ocrelizumab, and ofatumumab. Type II anti-CD20 monoclonal antibodies include but are not limited to obinutuzumab and tositumomab.

**[00376]** In an embodiment, the invention relates to 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 (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and further comprising the step of administering an anti-CD20 antibody, wherein the anti-CD20 antibody is a monoclonal antibody or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof. In an embodiment, the invention relates to a method of treating a hematological malignancy or a solid tumor cancer in a human comprising the step of administering to said human a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and further comprising the step of administering an anti-CD20 antibody, wherein the anti-CD20 antibody is an anti-CD20 monoclonal antibody or an antigen-binding fragment,

derivative, conjugate, variant, or radioisotope-labeled complex thereof, and wherein the anti-CD20 antibody specifically binds to human CD20 with a $K_D$ selected from the group consisting of $1\times10^{-7}$ M or less, $5\times10^{-8}$ M or less, $1\times10^{-8}$ M or less, and $5\times10^{-9}$ M or less.

**[00377]** In an embodiment, the invention relates to 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 (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and further comprising the step of administering an Type I anti-CD20 antibody, or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof. In an embodiment, the invention relates to a method of treating a hematological malignancy or a solid tumor cancer in a human comprising the step of administering to said human a BTK inhibitor of Formula (II), 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.

**[00378]** In some embodiments, the BTK inhibitor of the present invention and the anti-CD20 monoclonal antibody are administered sequentially. In some embodiments, the BTK inhibitors of the present invention and the anti-CD20 monoclonal antibody are administered concomitantly. In some embodiments, a BTK inhibitor of the present invention is administered before the anti-CD20 monoclonal antibody. In some embodiments, a BTK inhibitors of the present invention is administered after the anticoagulant or the antiplatelet active pharmaceutical ingredient. In some embodiments, a BTK inhibitor of the present invention and the anti-CD20 monoclonal antibody are administered over the same time period, and the BTK inhibitor administration continues after the anti-CD20 monoclonal antibody administration is completed.

**[00379]** 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 one or more drug regulatory authority 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.

**[00380]** 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 one or more drug regulatory authority 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-Û1 heavy chain (222-219')-disulfide with humanized mouse monoclonal obinutuzumab κ light chain dimer (228-228":231-231")-bisdisulfide antibody.

**[00381]** 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 one or more drug regulatory authority 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 Û1 heavy chain (225-214')-disulfide with human monoclonal ofatumumab-CD20 κ light chain, dimer (231-231":234-234")-bisdisulfide antibody.

**[00382]** 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 one or more drug regulatory authority 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 Ǔ1 heavy chain (224-213')-disulfide with humanized mouse monoclonal hA20 @light chain (230-230":233-233")-bisdisulfide dimer

**[00383]** 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 one or more drug regulatory authority 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.

**[00384]** 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 one or more drug regulatory authority 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.

**[00385]** In an embodiment, an anti-CD20 antibody selected from the group consisting of obinutuzumab, ofatumumab, veltuzumab, tositumomab, and ibritumomab, and or antigen-binding fragments, derivatives, conjugates, variants, and radioisotope-labeled complexes thereof, is administered to a subject by infusion in a dose selected from the group consisting of about 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 monthly. In an embodiment, the anti-CD20 antibody is administered at a lower initial dose, which is escalated when administered at subsequent intervals admininstered monthly. For example, the first infusion can deliver 300 mg of anti-CD20 antibody, and subsequent weekly doses could deliver 2,000 mg of anti-CD20 antibody for eight weeks, followed by monthly doses of 2,000 mg of anti-CD20 antibody. During any of the foregoing embodiments, the BTK inhibitors of the present invention may be administered daily, twice daily, or at different intervals as described above, at the dosages described above.

**[00386]** In an embodiment, the invention provides a kit comprising a composition comprising a BTK inhibitor of the present invention and a composition comprising an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, and ibritumomab, or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof, for use in the treatment of CLL or SLL, hematological malignancies, B cell malignanciesor, 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.

**[00387]** The anti-CD20 antibody sequences referenced in the foregoing are summarized in Table 1.

TABLE 1. Anti-CD20 antibody amino acid sequences.

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

| Identifier | Sequence (One-Letter Amino Acid Symbols) | |
|---|---|---|
| chain | SSGLYSLSSV VTVPSSSLGT QTYICNVNHK PSNTKVDKKV EP | 222 |
| SEQ ID NO:8 ofatumumab Fab fragment light chain | EIVLTQSPAT LSLSPGERAT LSCRASQSVS SYLAWYQQKP GQAPRLLIYD ASNRATGIPA<br>RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ RSNWPITFGQ GTRLEIKRTV AAPSVFIFPP<br>SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT<br>LSKADYEKHK VYACEVTHQG LSSPVTKSFN R | 60<br>120<br>180<br>211 |
| SEQ ID NO:9 veltuzumab heavy chain | QVQLQQSGAE VKKPGSSVKV SCKASGYTFT SYNMHWVKQA PGQGLEWIGA IYPGMGDTSY<br>NQKFKGKATL TADESTNTAY MELSSLRSED TAFYYCARST YYGGDWYFDV WGQGTTVTVS<br>SASTKGPSVF PLAPSSKSTS GGTAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPAVLQS<br>SGLYSLSSVV TVPSSSLGTQ TYICNVNHKP SNTKVDKRVE PKSCDKTHTC PPCPAPELLG<br>GPSVFLFPPK PKDTLMISRT PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN AKTKPREEQY<br>NSTYRVVSVL TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP QVYTLPPSRE<br>EMTKNQVSLT CLVKGFYPSD IAVEWESNGQ PENNYKTTPP VLDSDGSFFL YSKLTVDKSR<br>WQQGNVFSCS VMHEALHNHY TQKSLSLSPG K | 60<br>120<br>180<br>240<br>300<br>360<br>420<br>451 |
| SEQ ID NO:10 veltuzumab light chain | DIQLTQSPSS LSASVGDRVT MTCRASSSVS YIHWFQQKPG KAPKPWIYAT SNLASGVPVR<br>FSGSGSGTDY TFTISSLQPE DIATYYCQQW TSNPPTFGGG TKLEIKRTVA APSVFIFPPS<br>DEQLKSGTAS VVCLLNNFYP REAKVQWKVD NALQSGNSQE SVTEQDSKDS TYSLSSTLTL<br>SKADYEKHKV YACEVTHQGL SSPVTKSFNR GEC | 60<br>120<br>180<br>213 |
| SEQ ID NO:11 tositumomab heavy chain | QAYLQQSGAE LVRPGASVKM SCKASGYTFT SYNMHWVKQT PRQGLEWIGA IYPGNGDTSY<br>NQKFKGKATL TVDKSSSTAY MQLSSLTSED SAVYFCARVV YYSNSYWYFD VWGTGTTVTV<br>SGPSVFPLAP SSKSTSGGTA ALGCLVKDYF PEPVTVSWNS GALTSGVHTF PAVLQSSGLY<br>SLSSVVTVPS SSLGTQTYIC NVNHKPSNTK VDKKAEPKSC DKTHTCPPCP APELLGGPSV<br>FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQYNSTY<br>RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK GQPREPQVYT LPPSRDELTK<br>NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS DGSFFLYSKL TVDKSRWQQG<br>NVFSCSVMHE ALHNHYTQKS LSLSPGK | 60<br>120<br>180<br>240<br>300<br>360<br>420<br>447 |
| SEQ ID NO:12 tositumomab light chain | QIVLSQSPAI LSASPGEKVT MTCRASSSVS YMHWYQQKPG SSPKPWIYAP SNLASGVPAR<br>FSGSGSGTSY SLTISRVEAE DAATYYCQQW SFNPPTFGAG TKLELKRTVA APSVFIFPPS<br>DEQLKSGTAS VVCLLNNFYP REAKVQWKVD NALQSGNSQE SVTEQDSKDS TYSLSSTLTL<br>SKADYEKHKV YACEVTHQGL SSPVTKSFNR | 60<br>120<br>180<br>210 |
| SEQ ID NO:13 ibritumomab heavy chain | QAYLQQSGAE LVRPGASVKM SCKASGYTFT SYNMHWVKQT PRQGLEWIGA IYPGNGDTSY<br>NQKFKGKATL TVDKSSSTAY MQLSSLTSED SAVYFCARVV YYSNSYWYFD VWGTGTTVTV<br>SAPSVYPLAP VCGDTTGSSV TLGCLVKGYF PEPVTLTWNS GSLSSGVHTF PAVLQSDLYT<br>LSSSVTVTSS TWPSQSITCN VAHPASSTKV DKKIEPRGPT IKPCPPCKCP APNLLGGPSV<br>FIFPPKIKDV LMISLSPIVT CVVVDVSEDD PDVQISWFVN NVEVHTAQTQ THREDYNSTL<br>RVVSALPIQH QDWMSGKEFK CKVNNKDLPA PIERTISKPK GSVRAPQVYV LPPPEEEMTK<br>KQVTLTCMVT DFMPEDIYVE WTNNGKTELN YKNTEPVLDS DGSYFMYSKL RVEKKNWVER<br>NSYSCSVVHE GLHNHHTTKS FSR | 60<br>120<br>180<br>240<br>300<br>360<br>420<br>443 |
| SEQ ID NO:14 ibritumomab light chain | QIVLSQSPAI LSASPGEKVT MTCRASSSVS YMHWYQQKPG SSPKPWIYAP SNLASGVPAR<br>FSGSGSGTSY SLTISRVEAE DAATYYCQQW SFNPPTFGAG TKLELKRADA APTVFIFPPS<br>DEQLKSGTAS VVCLLNNFYP REAKVQWKVD NALQSGNSQE SVTEQDSKDS TYSLSSTLTL<br>SKADYEKHKV YACEVTHQGL SSPVTKSFN | 60<br>120<br>180<br>209 |

Combinations of BTK Inhibitors with Chemotherapeutic Active Pharmaceutical Ingredients

**[00388]** The BTK inhibitors may also be safely and synergistically co-administered with chemotherapeutic active pharmaceutical ingredients such as gemcitabine and albumin-bound paclitaxel (nab-paclitaxel). In an embodiment, the invention relates to a method of treating a hematological malignancy or a solid tumor cancer in a human comprising the step of administering to said human a BTK inhibitor, and further comprising the step of administering a therapeutically-effective amount of gemcitabine, or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In an embodiment, the invention relates to a method of treating a hematological malignancy or a solid tumor cancer in a human comprising the step of administering to said human a BTK inhibitor of Formula (II), or a pharmaceutically

acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and further comprising the step of administering a therapeutically-effective amount of gemcitabine, or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate, or hydrate thereof. In an embodiment, the solid tumor cancer in any of the foregoing embodiments is pancreatic cancer. In an embodiment, the invention relates to a composition for use in treating a hematological malignancy or a solid tumor cancer in a human comprising a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt, ester, prodrug, cocrystal, solvate or hydrate thereof, and gemcitabine or gemcitabine hydrochloride.

**[00389]** In an embodiment, the invention relates to 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 further comprising the step of administering a therapeutically-effective amount of nab-paclitaxel. In an embodiment, the invention relates to a method of treating a hematological malignancy or a solid tumor cancer in a human comprising the step of administering to said human a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and further comprising the step of administering a therapeutically-effective amount of nab-paclitaxel. In an embodiment, the solid tumor cancer in any of the foregoing embodiments is pancreatic cancer.

**[00390]** In an embodiment, the invention provides a synergistic combination of a BTK inhibitor of Formula (II) and gemcitabine for the treatment of a hyperproliferative disorder.

**[00391]** In an embodiment, the invention provides a synergistic combination of a BTK inhibitor of Formula (II) and gemcitabine for the treatment of a cancer.

**[00392]** In an embodiment, the invention provides a synergistic combination of a BTK inhibitor of Formula (II) and gemcitabine for the treatment of a cancer, wherein the cancer is selected from the group consisting of ovarian cancer, breast cancer, non-small cell lung cancer, and pancreatic cancer. In an embodiment, the invention provides a synergistic combination of a BTK inhibitor of Formula (II), nab-paclitaxel, and gemcitabine for the treatment of a cancer, wherein the cancer is selected from the group consisting of ovarian cancer, breast cancer, non-small cell lung cancer, and pancreatic cancer.

**[00393]** In an embodiment, the invention provides a synergistic combination of a BTK inhibitor of Formula (II) and gemcitabine for the treatment of a cancer, comprising an amount of the BTK

inhibitor selected from the group consisting of 5 mg, 10 mg, 12.5 mg, 15 mg, 20 mg, 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 375 mg, 400 mg, 425 mg, 450 mg, 475 mg, or 500 mg, and comprising an amount of gemcitabine or gemcitabine hydrochloride selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, 1800 mg, 1900 mg, and 2000 mg. In an embodiment, the combination of the BTK inhibitor and gemcitabine is administered orally. In an embodiment, the combination of the BTK inhibitor and gemcitabine is administered intravenously. In an embodiment, the combination of the BTK inhibitor and gemcitabine is administered such that the BTK is administered orally BID and the gemcitabine is administered at a dose of 1000 mg/m$^2$ over 30 minutes once a week over the course of a cycle.

**[00394]** 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 BTK inhibitor, and a combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). 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.

**[00395]** 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 BTK inhibitor, and a combination of fludarabine, cyclophosphamide, and rituximab (FCR). FCR chemotherapy has been shown to improve survival in patients with cancer, as described in Hallek, *et al.*, *Lancet.* **2010,** *376*, 1164-1174.

## EXAMPLES

**[00396]** 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 – BTK Inhibitory Effects on Solid Tumor Microenvironment in an Orthotopic

Pancreatic Cancer Model

**[00397]** An orthotopic pancreatic cancer model was used to investigate the therapeutic efficacy of the BTK inhibitor of Formula (II) athrough treatment of the solid tumor microenvironment. Mice were dosed orally with 15 mg/kg of Formula (II), 15 mg/kg of a phosphoinositide 3-kinase ¡ (PI3K-¡) inhibitor (also referred to as "p110d"), or a combination of 15 mg/kg of both drugs.

**[00398]** Cell line 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, $1\times10^{6}$ cells were injected in C57BL/6 mice. Throughout the experiment, animals were provided with food and water ad libitum and subjected to a 12-h dark/light cycle. Animal studies were performed in accordance with the U.S. Public Health Service "Guidelines for the Care and Use of Laboratory Animals" (IACUC). After euthanization, pancreatic tumors were dissected out, weighed and single cell suspensions were prepared for flow cytometry analysis.

**[00399]** Results of the experiments are shown in FIG. 1, which illustrates tumor growth suppression in the orthotopic pancreatic cancer model. The statistical p-value (presumption against null hypothesis) is shown for the BTK inhibitor of Formula (II), a PI3K-¡ inhibitor (denoted "p110d"), and a combination of the two agents in comparison to the vehicle. The results show that all three treatments, including the single agent BTK inhibitor, provide statistically significant reductions in tumor volume in the pancreatic cancer model.

**[00400]** Additional results of the experiments relating to treatment of the tumor microenvironment are shown in FIG. 2 to FIG.4. FIG. 2 shows the effects of oral dosing with 15 mg/kg of the BTK inhibitor of Formula (II), 15 mg/kg of a phosphoinositide 3-kinase ¡ (PI3K-¡) inhibitor, or a combination of both drugs on myeloid tumor-associated macrophages (TAMs) in pancreatic tumor-bearing mice. FIG. 3 illustrates the effects of oral dosing with 15 mg/kg of the BTK inhibitor of Formula (II), 15 mg/kg of a phosphoinositide 3-kinase ¡ (PI3K-¡) inhibitor, or a combination of both inhibitors on myeloid-derived suppressor cells (MDSCs) in pancreatic tumor-bearing mice. FIG. 4 illustrates the effects of oral dosing with 15 mg/kg of the BTK inhibitor of Formula (II), 15 mg/kg of a phosphoinositide 3-kinase ¡ (PI3K-¡) inhibitor, or a combination of both inhibitors on regulatory T cells (Tregs) in pancreatic tumor-bearing mice. The results shown in FIG. 2 to FIG. 4 demonstrate that of the BTK inhibitor of Formula (II) and

the combination of the BTK inhibitor of Formula (II) and a phosphoinositide 3-kinase ¡¡ (PI3K-¡¡) inhibitor reduce immunosuppressive tumor associated myeloid cells and Tregs in pancreatic tumor-bearing mice. Overall, BTK inhibition with Formula (II) or a combination of Formula (II) and a phosphoinositide 3-kinase ¡¡ (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 immunospressive Tregs, demonstrating a strong effect of the BTK inhibitor on the tumor microenvironment.

Example 2 – BTK Inhibitory Effects on Solid Tumor Microenvironment in an Ovarian Cancer Model

**[00401]** The ID8 syngeneic orthotropic ovarian cancer murine model was used to investigate the therapeutic efficacy of the BTK inhibitor of Formula (II) through treatment of the solid tumor microenvironment. Human ovarian cancer models, including the ID8 syngeneic orthotropic ovarian cancer model and other animal models, are described in Fong and Kakar, *J. Ovarian Res.* **2009,** *2*, 12; Greenaway, *et al.*, *Gynecol. Oncol.* **2008,** *108,* 385-94; Urzua et al., *Tumour Biol.* **2005,** *26,* 236-44; Janat-Amsbury, *et al.*, *Anticancer Res.* **2006,** *26,* 3223-28; Janat-Amsbury, *et al.*, *Anticancer Res.* **2006,** *26,* 2785-89. Animals were treated with vehicle or Formula (II), 15 mg/kg/BID given orally. The results of the study are shown in FIG. 5, FIG. 6, FIG. 7, FIG. 8, FIG. 9, FIG. 10, FIG. 11, and FIG. 12.

**[00402]** FIG. 5 and FIG. 6 demonstrate that the BTK inhibitor of Formula (II) impairs ID8 ovarian cancer growth in the ID8 syngeneic murine model. FIG. 7 shows that tumor response to treatment with the BTK inhibitor of Formula (II) correlates with a significant reduction in immunosuppressive tumor-associated lymphocytes in tumor-bearing mice. FIG. 8 shows treatment with the BTK inhibitor of Formula (II) impairs ID8 ovarian cancer growth (through reduction in tumor volume) in the syngeneic murine model. FIG. 9 and FIG. 10 show that the tumor response induced by treatment with the BTK inhibitor of Formula (II) correlates with a significant reduction in immunosuppressive B cells in tumor-bearing mice. FIG. 11 and FIG. 12 show that the tumor response induced by treatment with the BTK inhibitor of Formula (II) correlates with a significant reduction in immunosuppressive tumor associated Tregs and an increase in $CD8^+$ T cells.

**[00403]** The results shown in FIG. 5 to FIG. 12 illustrate the surprising efficacy of the BTK inhibitor of Formula (II) in modulating tumor microenvironment in a model predictive of

efficacy as a treatment for ovarian cancer in humans.

Example 3 – BTK Inhibitory Effects on Solid Tumor Microenvironment Through Modulation of Tumor-Infiltrating MDSCs and TAMs

**[00404]** 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 (II) 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 (II), 15 mg/kg/BID given orally; (3) gemcitabine 15 mg/kg intravenous (IV) administered every 4 days for 3 injections; or (4) Formula (II), 15 mg/kg/BID given orally with together with gemcitabine, 15 mg/kg IV administered every 4 days for 3 injections.

**[00405]** 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 37C 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.

**[00406]** In FIG. 13, the reduction in tumor size upon treatment is shown. Formula (II) is observed to show efficacy alone, and a strong synergistic effect between Formula (II) and gemcitabine is also observed. The effects on particular cell subsets are shown in the flow cytometry data presented in FIG. 14, FIG. 15, FIG. 16, and FIG. 17.

**[00407]** The results shown in FIG. 13 to FIG. 17 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 (II).

Example 4 – Effects of BTK Inhibitors on Thrombosis

**[00408]** 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 approximately half of patients treated with ibrutinib (IMBRUVICA package insert and prescribing information, revised July 2014, U.S. Food and Drug Administration).

**[00409]** 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 (XVII) (CC-292), and Formula (X) (PCI-32765, ibrutinib), in clinical development. Importantly, early stage clinical trials have found ibrutinib to be particularly active in chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL), suggesting that this class of inhibitors may play a significant role in various types of cancers (Aalipour and Advani, *Br. J. Haematol.* **2013,** *163,* 436-43). However, their effects are not limited to leukemia or lymphomas as platelets also rely on the Tec kinases family members BTK and Tec for signal transduction in response to various thrombogenic stimuli (Oda, et al., *Blood* **2000**, *95(5),* 1663-70; Atkinson, et al. *Blood* **2003**, *102(10),* 3592-99). In fact, both Tec and BTK play an important role in the regulation of phospholipase CΫ2 (PLCΫ2) 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 ļtIIbὐ3 integrin and PI3K activity (Laffargue, et al., *FEBS Lett.* **1999,** *443(1),* 66-70). It has also been implicated in GPIbļt-dependent thrombus stability at sites of vascular injury (Liu, et al., *Blood* **2006**, *108(8),* 2596-603). Thus, BTK and Tec are involved in several processes important in supporting the formation of a stable hemostatic plug, which is critical for preventing significant blood loss in response to vascular injury. Hence, the effects of the BTK inhibitor of Formula (II) and ibrutinib were evaluated on human platelet-mediated thrombosis by utilizing the *in vivo* human thrombus

formation in the VWF HA1 mice model described in Chen, et al. *Nat. Biotechnol.* **2008,** *26(1),* 114-19.

**[00410]** Administration of anesthesia, insertion of venous and arterial catheters, fluorescent labeling and administration of human platelets (5 x $10^8$/ml), and surgical preparation of the cremaster muscle in mice have been previously described (Chen, et al. *Nat Biotechnol.* **2008,** *26(1),* 114-19). Injury to the vessel wall of arterioles (~40–65 mm diameter) was performed using a pulsed nitrogen dye laser (440 nm, Photonic Instruments) applied through a 20× water-immersion Olympus objective (LUMPlanFl, 0.5 numerical aperature (NA)) of a Zeiss Axiotech vario microscope. Human platelet and wall interactions were visualized by fluorescence microscopy using a system equipped with a Yokogawa CSU-22 spinning disk confocal scanner, iXON EM camera, and 488 nm and 561 nm laser lines to detect BCECF-labeled and rhodamine-labeled platelets, respectively (Revolution XD, Andor Technology). The extent of thrombus formation was assessed for 2 minutes after injury and the area ($\mu m^2$) of coverage determined (Image IQ, Andor Technology). For the Formula (II), Formula (XVII) (CC-292), and Formula (X) (ibrutinib) inhibition studies, the BTK inhibitors were were added to purified human platelets for 30 minutes before administration.

**[00411]** The *in vivo* throbus effects of the BTK inhibitors, Formula (II), Formula (XVII) (CC-292), and Formula (X) (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. 18, 19, and 20. Similarly, Formula (II) (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 (X) (ibrutinib), 2600 ± 246

$mm^2$ (mean ± s.e.m.), resulting in a reduction in maximal thrombus size by approximately 61% compared with control ($P > 0.001$) (FIG. 18 and 20). Similar results were obtained with platelets pretreated with 500 nM of Formula (II) 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 (XVII) (CC-292) were similar to that for Formula (X) (ibrutinib), as shown in FIG. 18, 19, and 20. The effect of the BTK inhibitor concentration is shown in FIG. 21. These results demonstrate the surprising advantage of the BTK inhibitor of Formula (II), which does not interfere with thrombus formation, while the BTK inhibitors of Formula (XVII) (CC-292) and Formula (X) (ibrutinib) interfere with thrombus formation.

**[00412]** 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 (II), Formula (XVII) (CC-292), and Formula (X) (ibrutinib) on thrombus formation. These results show that Formula (II) had no significant effect on human platelet-mediated thrombus formation while Formula (X) (ibrutinib) was able to limit this process, resulting in a reduction in maximal thrombus size by 61% compared with control. Formula (XVII) (CC-292) showed an effect similar to Formula (X) (ibrutinib). These results, which show reduced thrombus formation for ibrutinib at physiologically relevant concentrations, may provide some mechanistic background for the Grade $\geq 3$ bleeding events (eg, subdural hematoma, gastrointestinal bleeding, hematuria and postprocedural hemorrhage) that have been reported in $\leq$ 6% of patients treated with Formula (X) (ibrutinib).

**[00413]** GPVI platelet aggregation was measured for Formula (II) and Formula (X) (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. 22.

**[00414]** In FIG. 23, 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.

**[00415]** The results depicted in FIG. 22 and FIG. 23 indicate that the BTK inhibitor of Formula (X) (ibrutinib) significantly inhibits GPVI platelet aggregation, while the BTK inhibitor of Formula (II) does not, further illustrating the surprising benefits of the latter compound.

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

**[00416]** Given the potential for BTK inhibition to affect TAMs and MDSCs, single-active pharmaceutical ingredient Formula (II) 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 (II), 15 mg/kg BID given orally (N=6).

**[00417]** As shown in FIG. 24, treatment with single-active pharmaceutical ingredient Formula (II) 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 (II), 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 (II), survival at day 14 was 6/6 animals, and at day 28 was 5/6 animals.

**[00418]** 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 (II) treatment (FIG. 25, FIG. 26, and FIG. 27). As expected, the decrease in these immunosuppressive cell subsets correlated with a significant increase in $CD8^+$ cells (FIG. 28).

Example 6 – Effects of BTK Inhibitors on Antibody-Dependent NK Cell Mediated Cytotoxicity

**[00419]** 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.

**[00420]** In this example, the effects of Formula (II) and ibrutinib on NK cell function were evaluated in primary NK cells from healthy volunteers and CLL patients. The activation of NK cells co-cultured with antibody-coated target cells was strongly inhibited by ibrutinib. The secretion of IFN-Ûwas 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 (II) treatment at 1 μM, a clinically relevant concentration, did not inhibit IFN-Ûor 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 (II) 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 (II) provides an unexpected benefit in the treatment of CLL.

**[00421]** 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.

**[00422]** Ibrutinib (PCI-32765, IMBRUVICA), is a first-in-class therapeutic BTK inhibitor. This orally delivered, small-molecule drug is being developed by Pharmacyclics, Inc. for the therapy of B-cell malignancies. As described above, in patients with heavily pretreated indolent non-Hodgkin lymphoma (iNHL), mantle cell lymphoma (MCL), and CLL, ibrutinib showed substantial antitumor activity, inducing durable regressions of lymphadenopathy and splenomegaly in the majority of patients. Advani, *et al., J. Clin. Oncol.* **2013,** *31,* 88-94; Byrd, *et al., N. Engl. J. Med.* **2013**, *369,* 32-42; Wang, *et al., N. Engl. J. Med.* **2013,** *369,* 507-16; O'Brien, *et al., Blood* **2012,** *119,* 1182-89. The pattern of changes in CLL was notable. Inhibition of BTK with ibrutinib caused rapid and substantial mobilization of malignant CLL cells from tissues sites into the peripheral blood, as described in J. A. Woyach, *et al., Blood* **2014,** *123,* 1810-17; this effect was consistent with decreased adherence of CLL to protective stromal cells. Ponader, *et al., Blood* **2012,** *119,* 1182-89; de Rooij, *et al., Blood* **2012**, *119,* 2590-94. Ibrutinib has been generally well tolerated. At dose levels associated with total BTK occupancy, not dose-limiting toxicities were identified and subjects found the drug tolerable over periods extending to >2.5 years.

**[00423]** Given the homology between BTK and interleukin-2 inducible tyrosine kinase (ITK), it has been recently confirmed that ibrutinib irreversibly binds ITK. Dubovsky, *et al., Blood* **2013,** *122,* 2539-2549. ITK expression in Fc receptor (FcR)-stimulated NK cells leads to increased calcium mobilization, granule release, and cytotoxicity. Khurana, *et al., J. Immunol.* **2007,** *178,* 3575-3582. As rituximab is a backbone of lymphoma therapy, with mechanisms of action including ADCC, as well as direct induction of apoptosis and complement-dependent cytotoxicity and FcR stimulation is requisite for ADCC, we investigated if ibrutinib or Formula

(II) (lacking ITK inhibition) influenced rituximab's anti-lymphoma activity *in vitro* by assessing NK cell IFN-Ûsecretion, degranulation by CD107a mobilization, and cytotoxicity by chromium release using $CD20^+$ cell lines and autologous patient samples with chronic lymphocytic leukemia (CLL).

**[00424]** Formula (II) is a more selective inhibitor than ibrutinib, as shown previously. Formula (II) is not a potent inhibitor of Itk kinase in contrast to ibrutinib (see Table 2). Itk kinase is required for FcR-stimulated NK cell function including calcium mobilization, granule release, and overall ADCC. As anti-CD20 antibodies like rituximab are standard of care drugs, often as part of combination regimens, for the treatment of CD20+ B-cell malignancies, the potential of ibrutinib or Formula (II) to antagonize ADCC was evaluated *in vitro.* We hypothesized that Btk inhibitor, Formula (II) 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.

**[00425]** 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 ºC 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.

**[00426]** 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 (II), 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 ºC. Triplicate cultures were performed on NK cells from donors. After incubation, supernatants were harvested, centrifuged briefly, and then analyzed for interferon-Û using an enzyme-linked immunosorbent assay (ELISA).

**[00427]** 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.

**[00428]** ADCC assays were performed as follows. Briefly, target cells (Raji or primary CLL) were labeled by incubation at 37 ºC 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 ºC 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.

**[00429]** Ibrutinib inhibited rituximab-induced NK cell cytokine secretion in a dose-dependent manner (0.1 and 1 μM) (FIG. 29: 48% $p = 0.018$; 72% $p = 0.002$, respectively). At 1 μM, Formula (II) did not significantly inhibit cytokine secretion (FIG. 29: 3.5%). Similarly, Formula (II) had no inhibitory effect on rituximab-stimulated NK cell degranulation (< 2%) while

ibrutinib reduced degranulation by ~50% (p = 0.24, FIG. 30). Formula (II) had no inhibitory effect while ibrutinib prevented trastuzumab-stimulated NK cell cytokine release and degranulation by ~92% and ~84% at 1μM, respectively (FIG. 29 and FIG. 30: ***p = 0.004, **p = 0.002).

**[00430]** In Raji cell samples, *ex vivo* NK cell activity against autologous tumor cells was not inhibited by addition of Formula (II) at 1 μM, and increased cell lysis was observed with increasing concentrations of rituximab at a constant E:T ratio (FIG. 31). In contrast, addition of 1 μM ibrutinib completely inhibited ADCC, with less than 10% cell lysis at any rituximab concentration and no increase in cell lysis in the presence of rituximab, compared with cultures without rituximab. The difference between Formula (II) and ibrutinib was highly significant in this assay (p = 0.001). A plot highlighting the differences between Formula (II) and ibrutinib at 10 μM is shown in FIG. 32. In primary CLL samples, *ex vivo* NK cell activity against autologous tumor cells was not inhibited by addition of Formula (II) at 1 μM, and increased cell lysis was observed with increasing concentrations of rituximab at a constant E:T ratio (FIG. 33).

**[00431]** In ADCC assays using healthy donor NK cells, antibody-dependent lysis of rituximab-coated Raji cells was not inhibited by addition of 1 μM Formula (II) (FIG. 33). 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.

**[00432]** 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 (II), is superior to ibrutinib. Clinical investigation is needed to determine the impact of this finding on patients receiving rituximab, as these results provide support for the unexpected property of Formula (II) as a better active pharmaceutical ingredient than ibrutinib to use in combination with antibodies that have ADCC as a mechanism of action.

Example 7 – Preclinical Characteristics of BTK Inhibitors

**[00433]** The BTK inhibitor ibrutinib ((1-[(3*R*)-3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidin-1-yl]prop-2-en-1-one) is a first-generation BTK inhibitor. In clinical testing as a monotherapy in subjects with hematologic malignancies, ibrutinib was generally well tolerated at dose levels through 840 mg (the highest dose tested). Advani, *et al.*, *J. Clin. Oncol.* **2013,** *31,* 88-94; Byrd, *et al.*, *N. Engl. J. Med.* **2013**, *369,* 32-42; Wang, *et al.*, *N. Engl. J. Med.* **2013,** *369,* 507-16. No maximum tolerated dose (MTD) was apparent within the tested dose range. Furthermore, subjects typically found the drug tolerable over periods extending to > 2 years. No subject had tumor lysis syndrome. No overt pattern of myelosuppression was associated with ibrutinib treatment. No drug-related reductions in circulating $CD4^+$ T cells or serum immunoglobulins were noted. Adverse events with an apparent relationship to study drug included diarrhea and rash.

**[00434]** 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.

**[00435]** 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.

**[00436]** The preclinical selectivity and potency characteristics of the second-generation BTK inhibitor of Formula (II) were compared to the first-generation BTK inhibitor 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 (II) | Ibrutinib (Formula (X)) |
|---|---|---|
| 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 |

**[00437]** 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 (II) shows much greater selectivity for BTK compared to other kinases than ibrutinib.

**[00438]** A comparison of the *in vivo* potency results for the BTK inhibitors of Formula (II) and ibrutinib is shown in FIG. 34. CD86 and CD69 are cell surface proteins that are BCR activation markers. To obtain the *in vivo* potency results, mice were gavaged at increasing drug concentration and sacrificed at one time point (3 h post-dose). BCR was stimulated with IgM and the expression of activation marker CD69 and CD86 are monitored by flow cytometry and to determine $EC_{50}$ values.

**[00439]** *In vitro* and *in vivo* safety pharmacology studies with Formula (II) 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 (II) shows significant activity only against the A3 adenosine receptor; follow-up dose-response experiments indicated a $IC_{50}$ of 2.7 μM, suggesting a low clinical risk of off-target effects. Formula (II) 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 (II) 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 (II) inhibited hERG channel activity by 25% at 10 μM, suggesting a low clinical risk that Formula (II) would induce clinical QT prolongation as predicted by this assay. Formula (II) 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 (II) 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 (II) is unlikely to cause serious off-target effects or adverse effects on critical organ systems.

**[00440]** The drug-drug interaction potential of Formula (II) was also evaluated. *In vitro* experiments evaluating loss of parent drug as catalyzed by CYPs indicated that Formula (II) is metabolized by CYP3A4. *In vitro* metabolism studies using mouse, rat, dog, rabbit, monkey, and human hepatocytes incubated with $^{14}$C-labeled Formula (II) 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 (II) binds to glutathione but does not deplete glutathione *in vitro.* Nonclinical CYP interaction studies data indicate that Formula (II) is very unlikely to cause clinical drug-drug interactions through alteration of the metabolism of drugs that are substrates for CYP enzymes.

**[00441]** The *in vitro* potency in whole blood of Formula (II), ibrutinib and CC-292 in inhibiting signals through the B cell receptor was also assessed. Blood from four healthy donors was incubated for 2 hours with the compounds shown over a concentration range, and then stimulated with anti-human IgD [10 μg/mL] for 18 hours. The mean fluorescent intensity (MFI) of CD69 (and CD86, data not shown) on gated CD19+ B cells was measured by flow cytometry. MFI values were normalized so that 100% represents CD69 level in stimulated cells without inhibitor, while 0% represents the unstimulated/no drug condition. The results are shown in FIG. 35. 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 (II), ibrutinib, and CC-292, respectively.

**[00442]** The EGF receptor phosphorylation *in vitro* was also determined for Formula (II) and ibrutinib. Epidermoid carcinoma A431 cells were incubated for 2h with a dose titration of Formula (II) or ibrutinib, before stimulation with EGF (100 ng/mL) for 5 minutes 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. 36. EGF-induced p-EGFR inhibition was determined to be 7% at 10 μM for Formula (II), 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 8 – Clinical Study of a BTK Inhibitor in Leukemia/Lymphoma and Effects on Bone Marrow and Lymphoid Microenvironments

**[00443]** 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 (II), 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 (II) in treating subjects with chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL).

**[00444]** 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 (II). 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 (II) 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 (II) nonclinical safety pharmacology and toxicology studies support the safety of testing Formula (II) in subjects with B cell malignancies.

**[00445]** The primary objectives of the clinical study are as follows: (1) establish the safety and the MTD of orally administered Formula (II) in subjects with CLL/SLL; (2) determine pharmacokinetics (PK) of orally administered Formula (II) 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.

**[00446]** The secondary objective of the clinical study is to evaluate tumor responses in patients treated with Formula (II).

**[00447]** 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)

**[00448]** 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 (II) 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.

**[00449]** Treatment with Formula (II) 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.

**[00450]** 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.

**[00451]** 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.

**[00452]** 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.

**[00453]** The schedule of assessments is as follows, with all days stated in the following meaning the given day or +/- 2 days from the given day. A physical examination, including vital signs and weight, are performed at screening, during cycle 1 at 1, 8, 15, 22, and 28 days, during cycle 2 at 15 and 28 days, during cycles 3 to 24 at 28 days, and at follow up (after the last dose). The screening physical examination includes, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. Symptom-directed physical exams are done thereafter. Vital signs (blood pressure, pulse, respiratory rate, and temperature) are assessed after the subject has rested in the sitting position. Eastern Cooperative Oncology Group (ECOG) status is assessed at screening, during cycle 1 at 1, 8, 15, 22, and 28 days, during cycle 2 at 15 and 28 days, during cycles 3 to 24 at 28 days, and at follow up, using the published ECOG performance status indications described in Oken, *et al.*, *Am. J. Clin. Oncol.* **1982,** *5,* 649-655. ECG testing is performed at screening, during cycle 1 at 1, 2, 8, 15, 22, and 28 days, during cycle 2 at 15 and 28 days, during cycles 3 to 24 at 28 days, and at follow up. The 12-lead ECG test will be done in triplicate (≥ 1 minute apart) at screening. The calculated QTc average of the 3 ECGs must be <480 ms for eligibility. On cycle 1, day 1 and cycle 1, day 8, single ECGs are done predose and at 1, 2, 4, and 6 h postdose. The single ECG on Cycle 1 Day 2 is done predose. On cycle 1, day 15, day 22, and day 28, a single ECG is done 2 hours post-dose. Starting with cycle 2, a single ECG is done per visit. Subjects should be in supine position and resting for at least 10 minutes before study-related ECGs. Two consecutive machine-read QTc > 500 ms or > 60 ms above baseline require central ECG review. Hematology, including complete blood count with differential and platelet and reticulocyte counts, is 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.

**[00454]** 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<br>ANC >1.5 x $10^9$/L[b]<br>Platelets > 100 x $10^9$/L[b]<br>Hemoglobin > 11.0 g/dL (untransfused)[b] | Normocellular<br><30% lymphocytes<br>No B-lymphoid nodules | Normal (e.g., no lymph nodes >1.5 cm) |
| CRi | Lymphocytes < 4 x $10^9$/L<br>Persistent anemia, thrombocytopenia, or neutropenia related to drug toxicity | Hypocellular<br><30% lymphocytes | Normal (*e.g.*, no lymph nodes >1.5 cm) |
| PR | Lymphocytes ≥ 50% decrease from baseline<br>ANC > 1.5 x $10^9$/L<br>or<br>Platelets > 100 x $10^9$/L or 50% improvement over baseline[b]<br>or<br>Hemoglobin > 11.0 g/dL<br>or<br>50% improvement over baseline (untransfused)[b] | Not assessed | ≥50% reduction in lymphadenopathy[c] and/or in spleen or liver enlargement |

a. Computed tomography (CT) scan of abdomen, pelvis, and chest is required for this evaluation
b. Without need for exogenous growth factors
c. In the sum products of ≤ 6 lymph nodes or in the largest diameter of the enlarged lymph node(s) detected before therapy and no increase in any lymph node or new enlarged lymph nodes

**[00455]** 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<br>(b) Variably FDG-avid or PET negative; regression to normal size on CT | Not palpable, nodules disappeared | If infiltrate present at screening, infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohisto-chemistry should be negative |
| PR | Regression of measurable disease and no new sites | ≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes<br>(a) FDG-avid or PET positive prior to therapy; ≥ 1 PET positive at previously involved site<br>(b) Variably FDG-avid or PET negative; regression on CT | ≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen | Irrelevant if positive prior to therapy; cell type should be specified |
| SD | Failure to attain CR/PR or progressive disease | (a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease, and no new sites on CT or PET<br>(b) Variably FDG avid or PET negative; no change in size of previous lesions on CT | | |

**[00456]** The PK parameters of the study are as follows. The plasma PK of Formula (II) and a metabolite is characterized using noncompartmental analysis. The following PK parameters are calculated, whenever possible, from plasma concentrations of Formula (II):

$AUC_{(0-t)}$ : 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 $\lambda z$ is the apparent terminal elimination rate constant,

$C_{max}$ : Maximum observed plasma concentration,

$T_{max}$ : Time of the maximum plasma concentration (obtained without interpolation),

$t_{½}$: Terminal elimination half-life (whenever possible),

$\lambda z$: Terminal elimination rate constant (whenever possible),

Cl/F: Oral clearance.

**[00457]** The PD parameters of the study are as follows. The occupancy of BTK by Formula (II) are measured in peripheral blood mononuclear cells (PBMCs) with the aid of a biotin-tagged Formula (II) analogue probe. The effect of Formula (II) on biologic markers of B cell function will also be evaluated.

**[00458]** 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.

**[00459]** 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.

**[00460]** 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.

**[00461]** 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.

**[00462]** 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.

**[00463]** 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).

**[00464]** 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 (II), 100 mg QD for 28 days. Cohort 2 (N = 6) consists of Formula (II), 175 mg QD for 28 days. Cohort 3 (N = 6) consists of Formula (II), 250 mg QD for 28 days. Cohort 4 (N = 6) consists of Formula (II), 350 mg QD for 28 days. Cohort 5 (N = 6) consists of Formula (II), 450 mg QD for 28 days. Cohort 6 (N = 6) consists of

Formula (II), 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 (II) may be continued for greater than 28 days until disease progression or an unacceptable drug-related toxicity occurs.

**[00465]** 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).

**[00466]** The dosage form and strength of Formula (II) used in the clinical study is a hard gelatin capsules prepared using standard pharmaceutical grade excipients (microcrystalline cellulose) and containing 25 mg of Formula (II) 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).

**[00467]** 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) |

**[00468]** The results of the clinical study in relapsed/refractory CLL patients are summarized in Table 6.

TABLE 6. Activity of Formula (II) 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)** |

**[00469]** FIG. 37 shows the median % change in ALC and SPD from baseline in the clinical study of Formula (II), 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 (II) 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 (II) 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. 38, and in all cases shows significant responses.

**[00470]** A Kaplan-Meier curve showing PFS from the clinical CLL study of Formula (II) is shown in FIG. 39. 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. 40. Both FIG. 39 and FIG. 40 show the results for Formula (II) in comparison to the results reported for ibrutinib in Byrd, *et al.*, *N. Engl. J. Med.* **2013,** *369,* 32-42. An improvement in survival and a reduction in risk are observed in CLL patients treated with Formula (II) in comparison to patients treated with ibrutinib.

**[00471]** Based on the data and comparisons shown in FIG. 37 to FIG. 40, the CLL study with Formula (II) showed that the efficacy of Formula (II) was surprisingly superior to that of ibrutinib.

**[00472]** 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. 41, the PFS is shown for Formula (II) 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. 42, the number of patients at risk with the 17p deletion is compared. To date, no 17p patients have progressed on Formula (II).

**[00473]** 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 (II) 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) |

**[00474]** The clinical study of Formula (II) 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 (II).

**[00475]** BTK target occupany was measured for relapsed/refractory CLL patients with the results shown in FIG. 43. For 200 mg QD dosing of the BTK inhibitor of Formula (II), approximately 94% - 99% BTK occupancy was observed, with superior 24 hour coverage and less inter-patient variability also observed. For 420 mg and 840 mg QD of the BTK inhibitor ibrutinib, 80% - 90% BTK occupancy was observed, with more inter-patient variability and capped occupancy. These results indicate that the BTK inhibitor of Formula (II) achieves superior BTK occupancy in CLL patients than ibrutinib.

**[00476]** The effects of Formula (II) on cell subset percentages were also evaluated using flow cytometry analysis of peripheral blood, with the results shown in FIG. 44, FIG. 45, FIG. 46, FIG. 47, FIG. 48, and FIG. 49. PBMC samples from CLL patient samples drawn prior to (predose) and after 28 days of dosing with Formula (II) 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. 44 and FIG. 45, 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 (II) mobilizes MDSCs and thus affects the CLL tumor microenvironment in marrow and lymph nodes, which is an unexpected indication of superior efficacy. In FIG. 46 and FIG. 47, 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. 44 to FIG. 47 are observed in multiple cohorts, at doses including 100 mg BID, 200 mg QD, and 400 mg QD. In FIG. 48 and FIG. 49, 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.

**[00477]** These results suggest that after Formula (II) 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.

**[00478]** Updated clinical results from the CLL study are shown in FIG. 50 to FIG. 55. FIG. 50 shows an update of the data presented in FIG. 37. FIG. 51 shows an update of the data presented in FIG. 43, and includes BID dosing results. Formula (II) 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 (II) 100 mg BID dosing resulted in 97% - 99% BTK occupancy,

complete BTK coverage, and less inter-patient variability. The PFS for patients with 11p deletions and 17q deletions are illustrated in FIG. 52, FIG. 53, and FIG. 54. Updated SPD results are illustrated in FIG. 55.

**[00479]** Treatment of CLL patients with Formula (II) also resulted in increased apoptotis, as illustrated in FIG. 56. 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 (II) 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 (II), as shown in FIG. 57 and FIG. 58, respectively.

**[00480]** Overall, Formula (II) shows superior efficacy to first generation BTK inhibitors such as ibrutinib, or to monotherapy with PI3K-ĳ inhibitors such as idelalisib. Formula (II) 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-ĳ inhibitors, treatment with Formula (II) does not affect NK cell function. Finally, treatment with Formula (II) leads to a CLL tumor microenvironmental effect by excluding MDSC cells from the marrow and lymph nodes and reducing their number.

Example 9 – Clinical Study of a BTK Inhibitor in Leukemia/Lymphoma in Combination with Obinutuzumab (GA-101)

**[00481]** The primary objectives of the study are (1) to determine the overall response rate (ORR) at 12 months with the combination of Formula (II) and obinutuzumab in patients with relapsed or refractory CLL, (2) to determine the ORR at 12 months with the combination of Formula (II) and obinutuzumab in patients with treatment-naive CLL, and (3) to establish the safety and feasibility of the combination of Formula (II) and obinutuzumab.

**[00482]** The secondary objectives of this study are: (1) to determine the complete response (CR) rate and MRD-negative CR rate in previously untreated and relapsed and refractory CLL with this regimen; (2) to determine the progression-free survival (PFS), time to next treatment (TTNT), and overall survival (OS) with this regimen, (3) to perform baseline analysis of patients enrolled on this trial including fluorescence in situ hybridization (FISH), stimulated karyotype, Zap-70 methylation, and $IgV_H$ mutational status and describe relationships between these

biomarkers and ORR or PFS for patients treated with this regimen; (4) to determine pharmacokinetics (PK) of orally administered Formula (II); (5) to measure pharmacodynamic (PD) parameters including drug occupancy of BTK, change in miR and gene expression on day 8 and 29 of therapy of Formula (II); (6) to determine the influence of Formula (II) on NK cell and T cell function *in vivo*; (7) to assess for serial development of resistance by baseline and longitudinal assessment of mutations of BTK and PLCG2 at regular follow up intervals and by examining diagnosis to relapse samples by whole exome sequencing; (8) to determine the influence of Formula (II) on emotional distress and quality of life in CLL patients; and (9) to determine trajectory of psychological and behavioral responses to Formula (II) and covariation with response to therapy.

**[00483]** CLL is the most prevalent form of adult leukemia and has a variable clinical course, where many patients do not require treatment for years and have survival equal to age matched controls. Other patients, however, exhibit aggressive disease and have a poor prognosis despite appropriate therapy. Byrd, *et al.*, Chronic lymphocytic leukemia. *Hematology Am. Soc. Hematol. Educ. Program.* **2004,** 163-183. While patients with early disease have not been shown to have a survival advantage with early treatment, most patients will eventually require therapy for their disease with the onset of symptoms or cytopenias, and despite the relatively long life expectancy for early stage disease, CLL remains an incurable disease. Patients diagnosed with or progressing to advanced disease have a mean survival of 18 months to 3 years. Unfortunately these patients with advanced disease are also more refractory to conventional therapy.

**[00484]** The treatment of CLL has progressed significantly over the previous decades. While alkylator therapy was used in the past, randomized trials have demonstrated a higher response rate and longer progression free survival (PFS) with fludarabine and subsequently with fludarabine-and cyclophosphamide-based combinations. O'Brien, *et al.,* Advances in the biology and treatment of B-cell chronic lymphocytic leukemia. *Blood* **1995,** *85,* 307-18; Rai, *et al.,* Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic leukemia. N. Engl. J. Med. 2000, 343, 1750-57;Johnson, *et al.*, Multicentre prospective randomised trial of fludarabine versus cyclophosphamide, doxorubicin, and prednisone (CAP) for treatment of advanced-stage chronic lymphocytic leukaemia. The French Cooperative Group on CLL. *Lancet* **1996,** *347,* 1432-38; Leporrier, *et al.,* Randomized comparison of fludarabine, CAP, and ChOP

in 938 previously untreated stage B and C chronic lymphocytic leukemia patients. *Blood* **2001,** 98, 2319-25; Catovsky, *et al.*, Assessment of fludarabine plus cyclophosphamide for patients with chronic lymphocytic leukaemia (the LRF CLL4 Trial): A randomised controlled trial. *Lancet* **2007,** *370*, 230-239; Eichhorst, *et al.*, Fludarabine plus cyclophosphamide versus fludarabine alone in first-line therapy of younger patients with chronic lymphocytic leukemia. *Blood* **2006,** *107*, 885-91. At the same time, the chimeric anti-CD20 monoclonal antibody rituximab was introduced for the treatment of CLL. At high doses or with dose intensive treatment, single agent rituximab has shown efficacy; however complete responses and extended remissions are very rare. O'Brien, *et al.* Rituximab dose-escalation trial in chronic lymphocytic leukemia. *J. Clin. Oncol.* **2001,** *19*, 2165-70; Byrd, *et al.*, Rituximab using a thrice weekly dosing schedule in B-cell chronic lymphocytic leukemia and small lymphocytic lymphoma demonstrates clinical activity and acceptable toxicity. *Clin. Oncol.* **2001,** *19*, 2153-64. The efficacy of rituximab has been improved by combining it with traditional cytotoxic agents such as fludarabine or fludarabine and cyclophosphamide, which have produced high CR rates and extended progression free survival (PFS) compared to historical controls. Indeed, a large randomized clinical trial reported by the German CLL study group has shown a benefit of the addition of antibody therapy with rituximab to fludarabine and cyclophosphamide in the prolongation of PFS and OS in patients with untreated CLL. Hallek, *et al.*, Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet* **2010,** 376, 1164-74. This encouraging progress in therapy and our understanding of the disease has resulted in significantly improved response rates and PFS. However, significant improvements in overall survival (OS) and ultimately cure, remain elusive goals.

**[00485]** While fludarabine based chemoimmunotherapy is standard for younger patients, the therapy for older patients is less well defined. In the large Phase 2 and 3 trials outlined previously, median ages were typically in the early-60s, while the average age of patients diagnosed with CLL is 72, which calls into question whether these results are generalizable to the entire CLL population. In fact, the one randomized Phase 3 trial investigating primary CLL therapy in older patients demonstrated that in patients >65 years old, fludarabine is not superior to chlorambucil. Eichhorst, *et al.*, First-line therapy with fludarabine compared with chlorambucil does not result in a major benefit for elderly patients with advanced chronic

lymphocytic leukemia. *Blood* **2009,** *114,* 3382-91. This finding was corroborated by a large retrospective study of front-line trials performed by the Alliance for Clinical Trials in Oncology, which demonstrated again that fludarabine is not superior to chlorambucil in older patients, but also showed that the addition of rituximab to chemotherapy was beneficial regardless of age. Woyach, *et al.*, Impact of age on outcomes after initial therapy with chemotherapy and different chemoimmunotherapy regimens in patients with chronic lymphocytic leukemia: Results of sequential cancer and leukemia group B studies. *J. Clin. Oncol.* **2013,** *31,* 440-7. Two studies have evaluated the combination of rituximab with chlorambucil, showing that this combination is safe and moderately effective. Hillmen, *et al.,* rituximab plus chlorambucil in patients with CD20-positive B-cell chronic lymphocytic leukemia (CLL): Final response analysis of an open-label Phase II Study, ASH Annual Meeting Abstracts, *Blood* **2010,** *116,* 697; Foa, *et al.,* A Phase II study of chlorambucil plus rituximab followed by maintenance versus observation in elderly patients with previously untreated chronic lymphocytic leukemia: Results of the first interim analysis, ASH Annual Meeting Abstracts, *Blood* **2010,** *116*, 2462.

**[00486]** Recently, the type II glycoengineered CD20 monoclonal antibody obinutuzumab was introduced. In a Phase 1 trial of previously treated CLL as monotherapy, this antibody has a 62% response rate including 1 MRD-negative complete response, suggesting that alone this antibody may be more active in CLL than rituximab. Morschhauser, *et al.,* Phase I study of R05072759 (GA101) in relapsed/refractory chronic lymphocytic leukemia, ASH Annual Meeting Abstracts. *Blood*, **2009,** *114*, 884. The German CLL Study Group (GCLLSG) recently completed a Phase 3 trial of rituximab and chlorambucil or obinutuzumab and chlorambucil vs chlorambucil alone in patients with untreated CLL and significant comorbidities. In this population, obinutuzumab and chlorambucil (but not rituximab and chlorambucil) improved OS over chlorambucil alone (hazard ratio 0.41, p=0.002), and obinutuzumab and chlorambucil improved PFS over rituximab and chlorambucil (median PFS 26.7 months vs 14.9 months, p<0.001). Goede, *et al.*, Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions, *N. Engl. J. Med.* **2014,** *370,* 1101-10. On the basis of these favorable data, the combination of obinutuzumab and chlorambucil is FDA approved as frontline therapy for CLL patients.

**[00487]** Many older patients are also treated with the combination of bendamustine plus rituximab (BR). Although BR has not been compared directly with chlorambucil and rituximab,

results of a recent Phase 2 trial show an ORR of 88% with a median event free survival of 33.9 months and 90.5% OS at 27 months. Fischer, *et al.,* Bendamustine in combination with rituximab for previously untreated patients with chronic lymphocytic leukemia: A multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. *J. Clin. Oncol.* **2012,** *30,* 3209-16. These results held for patients > 70 years old, and compare favorably with results published for chlorambucil and rituximab. While results with this regimen appear to be improved over historical controls, outcomes are not as good as those observed in younger patients with chemoimmunotherapy. Therefore, the optimal therapy for older patients remains an unmet need in clinical trials.

**[00488]** Additionally, most patients eventually relapse with their disease and are frequently refractory to existing agents. Patients who relapse after combined chemoimmunotherapy have a poor outcome with subsequent standard therapies. While options for these patients include alemtuzumab, bendamustine, high dose corticosteroids, ofatumumab, and combination based approaches, none of these therapies produces durable remissions that exceed that observed with first line chemoimmunotherapy. Keating, *et al.,* Therapeutic role of alemtuzumab (Campath-1H) in patients who have failed fludarabine: results of a large international study. *Blood* **2002,** *99,* 3554-61; Bergmann, *et al.,* Efficacy of bendamustine in patients with relapsed or refractory chronic lymphocytic leukemia: results of a phase I/II study of the German CLL Study Group. *Haematologica* **2005,** *90,* 1357-64; Thornton PD, Matutes E, Bosanquet AG, et al. High dose methylprednisolone can induce remissions in CLL patients with p53 abnormalities. *Ann. Hematology* **2003,** *82,* 759-65; Coiffier, *et al.,* Safety and efficacy of ofatumumab, a fully human monoclonal anti-CD20 antibody, in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: A phase 1-2 study. *Blood* **2008,** *111,* 1094-1100; Tsimberidou, *et al.,* Phase I-II study of oxaliplatin, fludarabine, cytarabine, and rituximab combination therapy in patients with Richter's syndrome or fludarabine-refractory chronic lymphocytic leukemia. *J. Clin. Oncol.* **2008,** *26,* 196-203. Several of these therapies including alemtuzumab and high dose steroids are also associated with significant toxicities and sustained immunosuppression. Lozanski G, Heerema NA, Flinn 1W, et al. Alemtuzumab is an effective therapy for chronic lymphocytic leukemia with p53 mutations and deletions. *Blood* **2004,** *103,* 3278-81; Osuji, *et al.,* The efficacy of alemtuzumab for refractory chronic lymphocytic leukemia in relation to cytogenetic abnormalities of p53. *Haematologica* **2005,** 90, 1435-36; Thornton, *et al.,* High dose

methyl prednisolone in refractory chronic lymphocytic leukaemia. *Leuk. Lymphoma* **1999,** *34,* 167-70; Bowen, *et al*. Methylprednisolone-rituximab is an effective salvage therapy for patients with relapsed chronic lymphocytic leukemia including those with unfavorable cytogenetic features. *Leuk Lymphoma* **2007,** *48,* 2412-17; Castro, *et al.*, Rituximab in combination with high-dose methylprednisolone for the treatment of fludarabine refractory high-risk chronic lymphocytic leukemia. *Leukemia* **2008,** *22,* 2048-53.

**[00489]** In an ongoing Phase lb/2 study, the BTK inhibitor ibrutinib has shown activity in patients with relapsed or refractory CLL. In patients with relapsed or refractory CLL and measurable lymphadenopathy, the rate of lymph node shrinkage >50% is 89%. With a median follow-up of 4 months, ORR was 48% due to asymptomatic lymphocytosis, and with longer follow-up of 26 months in patients receiving the 420 mg dose, has improved to 71%, with an additional 20% of patients achieving a partial response with lymphocytosis (PR-L). Byrd, *et al.*, Activity and tolerability of the Bruton's tyrosine kinase (Btk) inhibitor PCI-32765 in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): Interim results of a phase Ib/II study. *J. Clin. Oncol.* ASCO Annual Meeting Abstracts, **2011,** *29,* Abstract 6508; Byrd, *et al*. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. *N. Engl. J. Med.* **2013,** *369,* 32-42. This lymphocytosis is likely related to B cell release from lymph node, spleen and marrow microenvironment due to disruption of homing signals or chemoattractants that are relevant to usual lymphocyte circulation dynamics. Lymphocytosis with ibrutinib is seen within 1-2 weeks of starting therapy, reaches plateau within the first 2-3 cycles, and has resolved over time in virtually all patients. The duration of lymphocytosis does not appear to be related to the depth of eventual response nor to response duration. Woyach, *et al.*, Prolonged lymphocytosis during ibrutinib therapy is associated with distinct molecular characteristics and does not indicate a suboptimal response to therapy. *Blood* **2014,** *123,* 1810-7. Response to ibrutinib occurs independently of high-risk genomic features including $IgV_H$ mutational status and del(17p13.1). Responses to this drug have been durable as well, with an estimated 26 month PFS of 76% and OS of 83% for these relapsed and refractory patients. This study also included a cohort of 31 previously untreated patients. With 16.6 months of follow-up, ORR is 71%, with an additional 10% of patients having persistent lymphocytosis; estimated 22 month PFS is 96%. This agent is currently in Phase 3 trials in treatment-naïve disease and is currently FDA approved for the treatment of relapsed CLL. These data with ibrutinib support the potential benefits of

selective BTK inhibition in CLL. However, while highly potent in inhibiting BTK, ibrutinib has also shown in vitro activity against other kinases (*e.g.*, epidermal growth factor receptor), which may be the cause of ibrutinib-related diarrhea and rash. Honigberg, *et al.,* The Bruton tyrosine kinase inhibitor PCI-32765 blocks B-cell activation and is efficacious in models of autoimmune disease and B-cell malignancy. *Proc. Natl. Acad. Sci. USA* **2010,** *107,* 13075-13080. In addition, it is a substrate for both cytochrome P450 (CYP) enzymes 3A4/5, which increases the possibility of drug-drug interactions. Finally, the inhibition of ITK that is seen with ibrutinib has the potential to abrogate NK cell ADCC, which makes combination with monoclonal antibodies less effective. Kohrt, *et al.,* Ibrutinib antagonizes rituximab-dependent NK cell-mediated cytotoxicity. *Blood* **2014,** *123,* 1957-60. These liabilities support the development of alternative BTK inhibitors for use in the therapy of lymphoid cancers.

**[00490]** In this Phase 1B study, two cohorts (relapsed/refractory and treatment-naïve) will be evaluated with slightly staggered enrollment. First, 6 subjects with R/R CLL will be enrolled into Cohort 1. Once the safety has been evaluated, the R/R cohort will be expanded to 26 subjects and enrollment of 6 treatment-naïve subjects can begin in Cohort 2. Once safety is established for Cohort 2, then the cohort will be expanded to 19 subjects.

**[00491]** Formula (II) will be administered starting cycle 1 day 1 and will be administered twice daily (100 mg BID) until disease progression. Obinutuzumab will be given in the standard dosing fashion starting on cycle 2 day 1. On cycle 2 day 1, patients will receive 100 mg IV. On cycle 2 day 2, patients will receive 900 mg. On cycle 2 days 8 and 15, patients will receive 1000 mg IV. On cycles 3-7, patients will receive 1000 mg on day 1 of each cycle. For patients treated at dose level -1, 100 mg will be given on Day 1 and 650 mg on Day 2 of Cycle 2. On cycle 2 day 8 and 15, patients will receive 750 mg IV and during cycles 3-7, patients will receive 750 mg on Day 1 of each cycle. It is acceptable for cycles to begin < a 24-hour (1 business day) window before and after the protocol-defined date for Day 1 of a new cycle.

**[00492]** The inclusion criteria for patient eligibility are as follows: (1) Patients with a diagnosis of intermediate or high risk CLL (or variant immunophenotype), SLL, or B-PLL by IWCLL 2008 criteria" who have: (a) COHORT 1: Previously received at least one therapy for their disease; (b) COHORT 2: Previously untreated disease and > 65 years old OR under 65 years old and refuse or are ineligible for chemoimmunotherapy; (2) Patients on Cohort 1 may have

received previous ibrutinib (or another BTK inhibitor) as long as discontinuation was for a reason other than "on-treatment" disease progression; (3) All patients must satisfy one of the following criteria for active disease requiring therapy: (a) Evidence of marrow failure as manifested by the development or worsening of anemia or thrombocytopenia (not attributable to autoimmune hemolytic anemia or thrombocytopenia); (b) Massive (> 6 cm below the costal margin), progressive or symptomatic splenomegaly; (c) Massive nodes (> 10 cm) or progressive or symptomatic lymphadenopathy; (d) Constitutional symptoms, which include any of the following: Unintentional weight loss of 10% or more within 6 months, Significant fatigue limiting activity, Fevers > 100.5 degrees F for 2 weeks or more without evidence of infection, Night sweats > 1 month without evidence of infection; (4) Measurable nodal disease by computed tomography (CT). Measurable nodal disease is defined as > 1 lymph node > 1.5 cm in the longest diameter in a site; (5) Patients with a history of Richter's syndrome are eligible if they now have evidence of CLL only, with < 10% large cells in the bone marrow; (6) Subjects must have adequate organ function, defined as creatinine < 2.5 times the upper limit of normal (ULN), ALT and AST < 3.0 x ULN, and bilirubin < 2.5 × ULN; (7) Platelets > $50 \times 10^9$/L. In subjects with CLL involvement of the marrow, > $30 \times 10^9$/L; (8) ANC > 750/$mm^3$ In subjects with CLL involvement of the marrow, ANC > 500/$mm^3$; (9) Subject must have an ECOG performance status < 2; (10) Subject must not have secondary cancers that result in a life expectancy of < 2 years or that would confound assessment of toxicity in this study; (11) Subjects must be > 18 years of age; (12) Subject must provide written informed consent. A signed copy of the consent form will be retained in the patient's chart; (13) Subject must be able to receive outpatient treatment and follow-up at the treating institution; (14) Subject must have completed all CLL therapies > 4 weeks prior to first study dose. Palliative steroids are allowed, but must be at a dose equivalent of < 20 mg prednisone daily for at least 1 week prior to treatment initiation; (15) Subjects capable of reproduction and male subjects who have partners capable of reproduction must agree to use an effective contraceptive method during the course of the study and for 2 months following the completion of their last treatment. Females of childbearing potential must have a negative E-hCG pregnancy test result within 3 days of first study dose. Female patients who are surgically sterilized or who are > 45 years old and have not experienced menses for > 2 years may have ther3-hCG pregnancy test waived; (16) Subjects must be able to swallow whole capsules.

**[00493]** The exclusion criteria for patient eligibility are as follows: (1) For cohort 1, previous therapy for CLL. Treatment of autoimmune complications of CLL with steroids or rituximab is allowed, however, CD20 must have returned on 10% of the CLL cells if rituximab was recently administered. Palliative steroids are acceptable at doses < 20 mg prednisone equivalent daily; (2) Any life-threatening illness, medical condition, or organ dysfunction which, in the investigator's opinion, could compromise the patients" safety, interfere with the absorption or metabolism of Formula (II), or put the study outcomes at undue risk; (3) Female subjects who are pregnant or breastfeeding; (4) Subjects with active cardiovascular disease not medically controlled or those who have had myocardial infarction in the past 6 months, or QTc > 480 ms; (5) Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel or gastric bypass, ulcerative colitis, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction; (6) Grade 2 toxicity (other than alopecia) continuing from prior anticancer therapy including radiation; (7) Major surgery within 4 weeks before first dose of study drug; (8) History of a bleeding diathesis (*e.g.*, hemophilia, von Willebrand disease); (9) Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenia purpura; (10) History of stroke or intracranial hemorrhage within 6 months before the first dose of study drug; (11) Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) within 28 days of first dose of study drug; (12) Requires treatment with long-acting proton pump inhibitors (*e.g.*, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole); (13) Subjects with active infections requiring IV antibiotic/antiviral therapy are not eligible for entry onto the study until resolution of the infection. Patients on prophylactic antibiotics or antivirals are acceptable; (14) Subjects with history of or ongoing drug-induced pneumonitis; (15) Subjects with human immunodeficiency virus (HIV) or active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV) or any uncontrolled active systemic infection; (16) Subjects who are known to have Hepatitis B infection or who are hepatitis B core antibody or surface antigen positive. Patients receiving prophylactic WIG may have false positive hepatitis serologies. Patients who are on WIG who have positive hepatitis serologies must have a negative hepatitis B DNA to be eligible; (17) Subjects with substance abuse or other medical or psychiatric conditions that, in the opinion of the investigator, would confound study interpretation or affect the patient's ability to tolerate or complete the study; (18) Subjects cannot concurrently participate in another therapeutic clinical

trial; (19) Subjects who have received a live virus vaccination within 1 month of starting study drug.

**[00494]** In this study, Formula (II) is administered 100 mg BID, with the second dose 11-13 hours after the first. Obinutuzumab is administered by IV infusion as an absolute (flat) dose. Obinutuzumab is administered in a single day, with the exception of the first administration when patients receive their first dose of obinutuzumab over two consecutive days (split dose) in Cycle 2: 100 mg on Day 1 and 900 mg on Day 2. For patients treated at dose level -1 (750 mg obinutuzumab), - 100 mg will be given on Day 1 and 650 mg on Day 2. On days when both Formula (II) and obinutuzumab are given, the order of study treatment administration will be Formula (II) followed at least 1 hour later by obinutuzumab. The full dosing schedule is given in Table 8.

TABLE 8. Dosing of obinutuzumab during 6 treatment cycles each of 28 days duration.

<table>
<tr><th colspan="2">Day of Treatment Cycle</th><th>Dose of Obinutuzumab</th><th>Rate of Infusion<br>(In the absence of infusion reactions/ hypersensitivity during previous infusions)</th></tr>
<tr><td rowspan="4">Cycle 2<br>(loading doses)</td><td>Day 1</td><td>100 mg</td><td>Administer at 25 mg/hr over 4 hours. Do not increase the infusion rate.</td></tr>
<tr><td>Day 2</td><td>900 mg</td><td>Administer at 50 mg/hr.<br>The rate of the infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.</td></tr>
<tr><td>Day 8</td><td>1000 mg</td><td rowspan="3">Infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.</td></tr>
<tr><td>Day 15</td><td>1000 mg</td></tr>
<tr><td>Cycles 3-7</td><td>Day 1</td><td>1000 mg</td></tr>
</table>

**[00495]** Anti-CD20 antibodies have a known safety profile, which include infusion related reactions (IRR). Anti-CD20 antibodies, and in particular obinutuzumab, can cause severe and life threatening infusion reactions. Sequelae of the infusion reactions include patient discontinuations from antibody treatment leading to suboptimal efficacy or increased medical resource utilization, such as hospitalization for hypotension or prolonged antibody infusion time.

In the initial study of obinutuzumab in relapsed/refractory CLL patients (Cartron, *et al., Blood* **2014**, *124*, 2196), all patients (n=13) in the Phase 1 portion experienced IRRs (15% Grade 3, no Grade 4, and 100% patients experienced all grade AE), with hypotension and pyrexia the most common symptoms. In the Phase 2 portion of the study, 95% of patients developed IRR, with 60% of cases developing symptoms of hypotension; of those, 25% were Grade 3 reactions. In the pivotal trial of obinutuzumab and chlorambucil in previously untreated patients, 69% developed infusion related reactions, of which 21% were grade 3-4.

**[00496]** The results of the Phase 1b study described in this example for Formula (II) in combination with obinutuzumab for patients with relapsed/refractory or untreated CLL/SLL/PLL are as follows. 6 patients have been treated in the study to date with the combination of Formula (II) and obinutuzumab. Patients are first treated with a month run-in of Formula (II) alone, then on cycle 2, day 1, patients are given obinutuzumab. To date, 41 doses of obinutuzumab have been administered to 6 patients. Lymphocyte counts immediately prior to treatment with obinutuzumab have ranged from 8 to 213 $\times 10^9$/L. No cases of serious or Grade 3-4 IRR's have been reported. Only 2 patients have had obinutuzumab temporarily held for chills and arthralgias/sluured, respectively, and were able to complete the planned infusion. An additional 3 patients had adverse events within 24 hours of the infusion, all grade 1 (terms: flushing, palpitations in one patient, rash, and restlessness and headache). Consequently, there has been a substantial decrease in serious or Grade 3-4 IRR"s with the one month lead-in of Formula (II), which could potentially lead to higher efficacy for the combination as well as better tolerability, leading to a decrease in medical resource utilization.

Example 10 – BTK Inhibitory Effects on MDSCs in the Solid Tumor Microenvironment

**[00497]** 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 (II). Complete BTK occupancy is observed for both the granulocytic and monocytic MDSC compartment on Day 8 at 4 hours post dose (N=5). The results are shown in FIG. 59.

Example 11 – BTK Inhibitory Effects on Solid Tumor Microenvironment in a Non-small Cell Lung Cancer (NSCLC) Model

**[00498]** A genetic tumor model of NSCLC (KrasLA2) was studied as a model for lung cancer using the treatment schema shown in FIG. 60. 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 (II) showed a significant decrease in tumor volumes versus vehicle (FIG. 61) and fewer overall tumors with dosing of 15 mg/kg. The effects on TAMs (FIG. 62), MDSCs (FIG. 63), Tregs (FIG. 64), and CD8+ cells (FIG. 65) were consistent with suppression of the solid tumor microenviroment as demonstrated previously.

Example 12 – Effects of BTK Inhibition on T Cells

**[00499]** An assay was performed to assess the effects of BTK inhibition using Formula (II) on T cells. Enriched $CD4^+$ T cells are plated on 24-well culture dishes that have been precoated 2 hr with 250 µL anti-TCRù (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-ù, 5 µg/mL IL-4, 5 µg/mL IFN-Ûand Treg; 0.5 ng/mL TGF-ù, 5 µg/mL IL-4, 5 µg/mL IFN-Û) and are supplemented with IL2 as a growth factor.

**[00500]** The results are shown in FIG. 66 and FIG. 67, and further illustrate the surprising properties of Formula (II) in comparison to ibrutinib. Because of the lack of activity of Formula (II) on Itk and Txk, no adverse effects on Th17 and Treg development was observed. Since ibrutinib inhibits both Itk and Txk, a profound inhibition of Th17 cells and an increase in Treg development is observed, which is comparable to the murine Itk/Txk double knock-out cells which were used as a control.

**[00501]** The effects of ibrutinib in comparison to Formula (II) on $CD8^+$ T cell viability was 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. 68, indicate that higher concentrations of ibrutinib have a strong, negative effect on $CD8^+$ T cell viability that is not observed with Formula (II) at any concentration.

**[00502]** $CD8^+$ T cells have at least two primary effector functions: (1) produce large amounts of IFN-Ɣ (which activates macrophages), and (2) cytolytic activity. A cytotoxic T cell (CTL) assay was performed to compare the BTK inhibitors of Formula (II) and Formula (X) (ibrutinib). Effectors were prepared by generating CTL by culturing MHC mismatched splenocytes for 4 days with (500 nM) and without Formula (II) or Formula (X) (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. 69, the results show that Formula (X) (ibrutinib) affects $CD8^+$ T cell function as measured by % cytotoxicity. Formula (II), 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-Ɣ levels, as shown in FIG. 70, where Formula (X) (ibrutinib) again results in a significant loss of function relative to Formula (II) and vehicle.

Example 13 – Blood-Brain Barrier Penentration of BTK Inhibitors in Rats

**[00503]** P-glycoprotein substrates may have relatively low brain exposure, due to activity of efflux pumps including P-glycoprotein at the blood-brain barrier (BBB). In a biodistribution study using radiolabeled Formula (II), low relative concentrations (3% to 4% of plasma concentrations) were observed in the brain. Preliminary brain PK experiments were performed to evaluate the potential for Formula (II) to cross the blood brain barrier, with results illustrated in FIG. 71. Four Sprague-Dawley rats per group were treated by oral gavage with 5 or 30 mg/kg/day Formula (II) and tissues were collected at 30 minutes after dosing – the approximate time of $C_{max}$ – on Days 1, 3 and 5. Two vehicle treated rats were sacrificed on each sampling day for comparison. Cerebral spinal fluid (CSF) was collected; and the brains were flushed with heparinized saline prior to collection and snap frozen for analysis of Formula (II). Bioanalytical methods specific to CSF and brain tissue were used to measure Formula (II) concentrations in these matrices. Results (FIG. 71) showed low but detectable levels of Formula (II) in the brain and CSF samples. Penetration of Formula (II) into the brain was surprising because of the efflux ratio observed with in vitro studies in Caco-2 cells. However, the ratio of Formula (II) in the flushed brains, compared with matched plasma concentrations, showed that brain extracts had ~3-4% of the observed plasma concentrations, consistent with the results from the biodistribution study. The ratios observed in clean CSF samples from rats treated with 5 and 30 mg/kg/day were between 1-2% of the plasma levels. The results indicate that Formula (II) can penetrate the

BBB, and because of the covalent binding of Formula (II) and low BTK resynthesis rates, high levels of BTK occupancy in tumor cells in the brain (such as infiltrating lymphocyties and microglia) as well as in cells of the solid tumor microenvironment in order to treat cancers such as gliomas and primary central nervous system lymphoma (Schideman, *et al., J. Neurosci. Res.* **2006,** *83(8),* 1471-84).

Example 14 – Effects of BTK Inhibition on Antibody-Dependent NK Cell Mediated Cytotoxicity Using Obinutuzumab

**[00504]** It has been shown above that ibrutinib undesirably antagonizes rituximab ADCC effects mediated by NK cells, and that Formula (II) 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. 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 (II).

**[00505]** 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 (II) 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 (II) and a second sample of ibrutinib, were provided to the investigators. Degranulation in whole blood was performed as follows. CLL targets (MEC-1 cells) were expanded in RPMI 1640 medium (Life Technologies, Inc.) with 10% fetal bovine serum (FBS). Exponentially growing cells were used. On the day of the experiment, 8 mL of blood was drawn from a normal volunteer into a test tube containing desirudin to obtain a final concentration of 50 μg/mL. A white blood cell (WBC) count of whole blood was performed. MEC-1 cells were re-suspended at the concentration of WBC in whole blood (*e.g.*, if $6 \times 10^6$ WBC/mL was measured, MEC-1 cells were re-suspended at $6 \times 10^6$ cells/mL, to allow for a final WBC:MEC-1 cell ratio of 1:1). The ibrutinib control and two blinded BTK inhibitors were diluted in X-VIVO 15 serum-free hematopoietic cell medium (Lonza Group, Ltd.) to concentrations of 200 μM, 20 μM and 2 μM. 170 μL aliquots of unmanipulated whole blood were incubated with 10 μL BTK inhibitors or X-VIVO 15 medium for one hour into a plate. Cetuximab and obinutuzumab (GA-101) were diluted in X-VIVO 15 medium to a concentration of 20 μg/mL. Equal volumes of MEC-1 cells

and antibodies were incubated for 5 minutes. After incubation, 20 μL of MEC-1 cells and antibodies was added to whole blood and the BTK inhibitors/X-VIVO 15 medium (for a final volume of 200 μL). The samples were placed in a 5% $CO_2$ incubator for 4 hours at 37 °C. The experimental conditions thus achieved a WBC:MEC-1 cell ratio of 1:1, with final concentrations of the BTK inhibitors in the assay of 10 μM, 1 μM and 0.1 μM and final concentrations of the antibodies of 1 μg/mL.

**[00506]** 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 ($CD56^+$).

**[00507]** The NK cell degranulation results are summarized in FIG. 72 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 (II) 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 (II) in treatment of human B cell malignancies and other diseases.

Example 15 – Effects of BTK Inhibition on Generalized NK Cell Mediated Cytotoxicity

**[00508]** An assay was performed to assess the effects of BTK inhibition using Formula (II) on generalized NK killing (non-ADCC killing). The targets (K562 cells) do not express MHC class I, so they do not inactivate NK cells. Target cells were grown to mid-log phase, and $5\times10^5$ cells were labeled in 100 μL of assay medium (IMDM with 10% FCS and penicillin/streptomycin) with 100 μCi of $^{51}Cr$ for 1 hour at 37 °C. Cells were washed twice and resuspended in assay

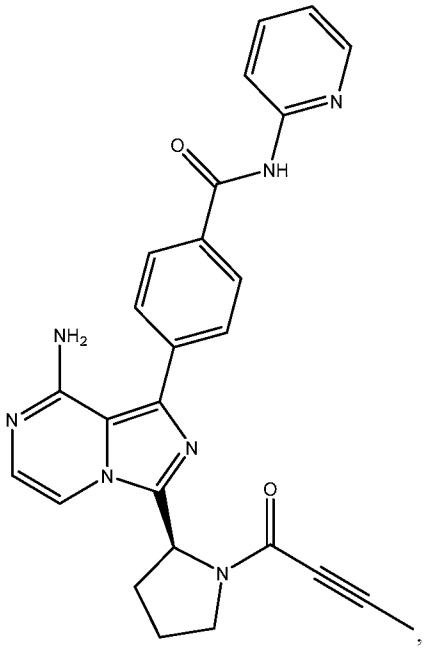
medium. A total of 5000 target cells/well was used in the assay. Effector cells were resuspended in assay medium, distributed on a V-bottom 96-well plate, and mixed with labeled target cells at 40:1 E:T ratios. Maximum release was determined by incubating target cells in 1% Triton X-100. For spontaneous release, targets were incubated without effectors in assay medium alone. After a 1 minute centrifugation at 1000 rpm, plates were incubated for 4 and 16 hours at 37 °C. Supernatant was harvested and $^{51}$Cr release was measured in a gamma counter. Percentage of specific release was calculated as (experimental release-spontaneous release)/(maximum release-spontaneous release) × 100. The results are shown in FIG. 73.

# CLAIMS

We claim:

1. A method of treating a cancer in a human, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the dose is effective to inhibit signaling between a cell of the solid tumor cancer 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.

2. The method of Claim 1, wherein the BTK inhibitor is selected from the group consisting of:



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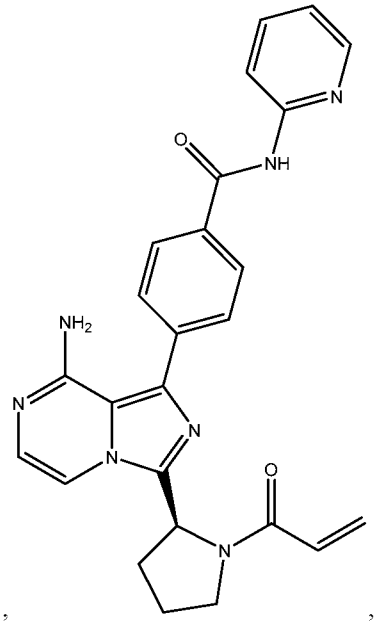

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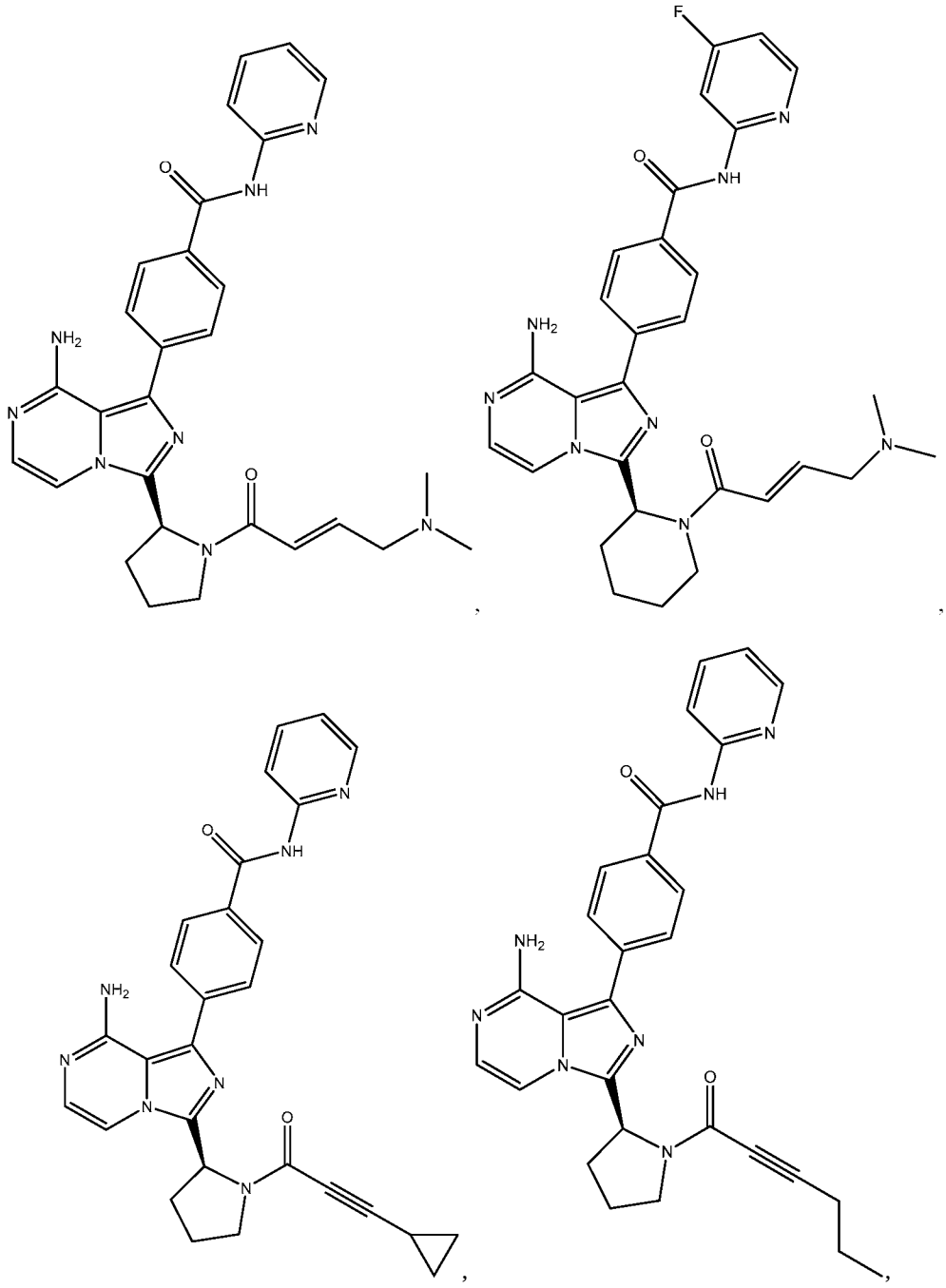
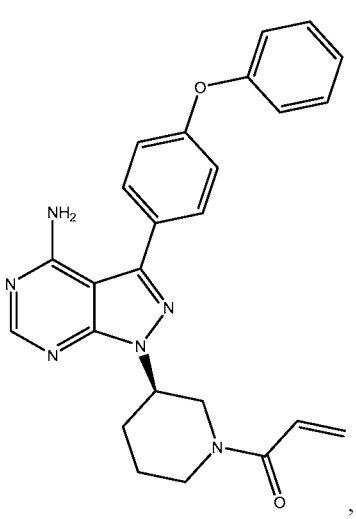
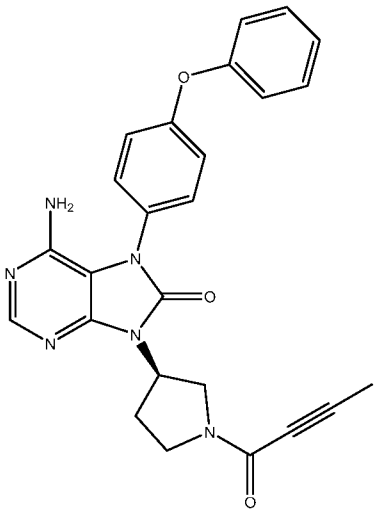
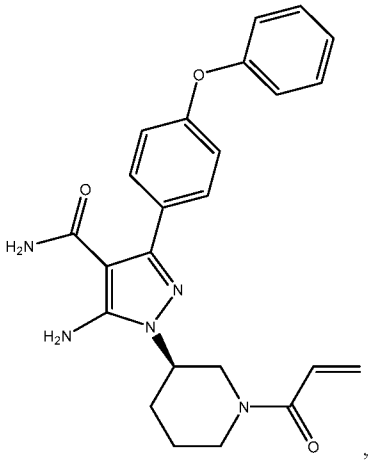


and a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof.

3. The method of Claim 2, further comprising the step of administering a therapeutically effective dose of an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof.

4. The method of Claim 1, wherein the BTK inhibitor is selected from the group consisting of:

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

5. The method of any one of Claims 1 to 4, wherein the cancer is a B cell hematological malignancy selected from the group consisting of chronic lymphocytic leukemia (CLL), small lymphocytic leukemia (SLL), non-Hodgkin's lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Hodgkin's lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Burkitt's lymphoma, Waldenström's macroglobulinemia (WM), Burkitt's lymphoma, multiple myeloma, or myelofibrosis.

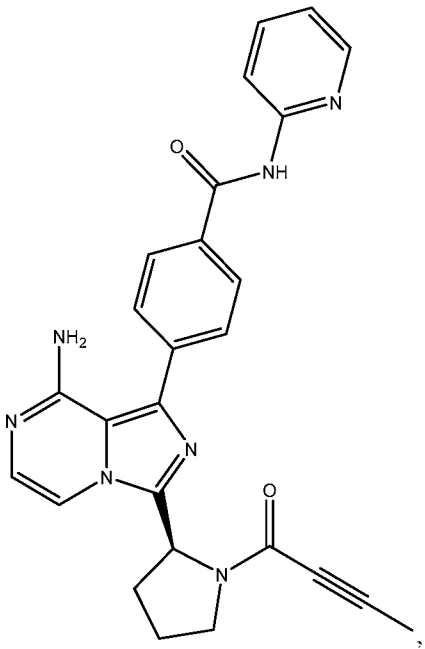
6. The method of any one of Claims 1 to 4, wherein the cancer is a solid tumor cancer selected from the group consisting of bladder cancer, non-small cell lung cancer, cervical cancer, anal cancer, pancreatic cancer, squamous cell carcinoma including head and neck cancer, renal cell carcinoma, melanoma, ovarian cancer, small cell lung cancer, glioblastoma, glioma, gastrointestinal stromal tumor, breast cancer, lung cancer, colorectal cancer, thyroid cancer, bone sarcoma, stomach cancer, oral cavity cancer, oropharyngeal cancer, gastric cancer, kidney cancer, liver cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, colon cancer, primary central nervous system lymphoma, and brain cancer.

7. The method of Claim 6, further comprising the step of administering a therapeutically effective dose of gemcitabine.

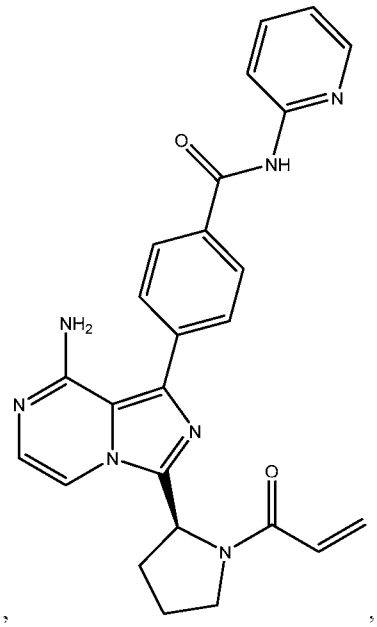
8. The method of Claim 6, further comprising the step of administering a therapeutically effective dose of albumin-bound paclitaxel.

9. The method of any one of Claims 6 to 8, wherein the therapeutically effective dose is effective to increase immune system recognition and rejection of the solid tumor by the human.

10. A method of treating a cancer in a human sensitive to bleeding events comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is selected from the group consisting of:



,



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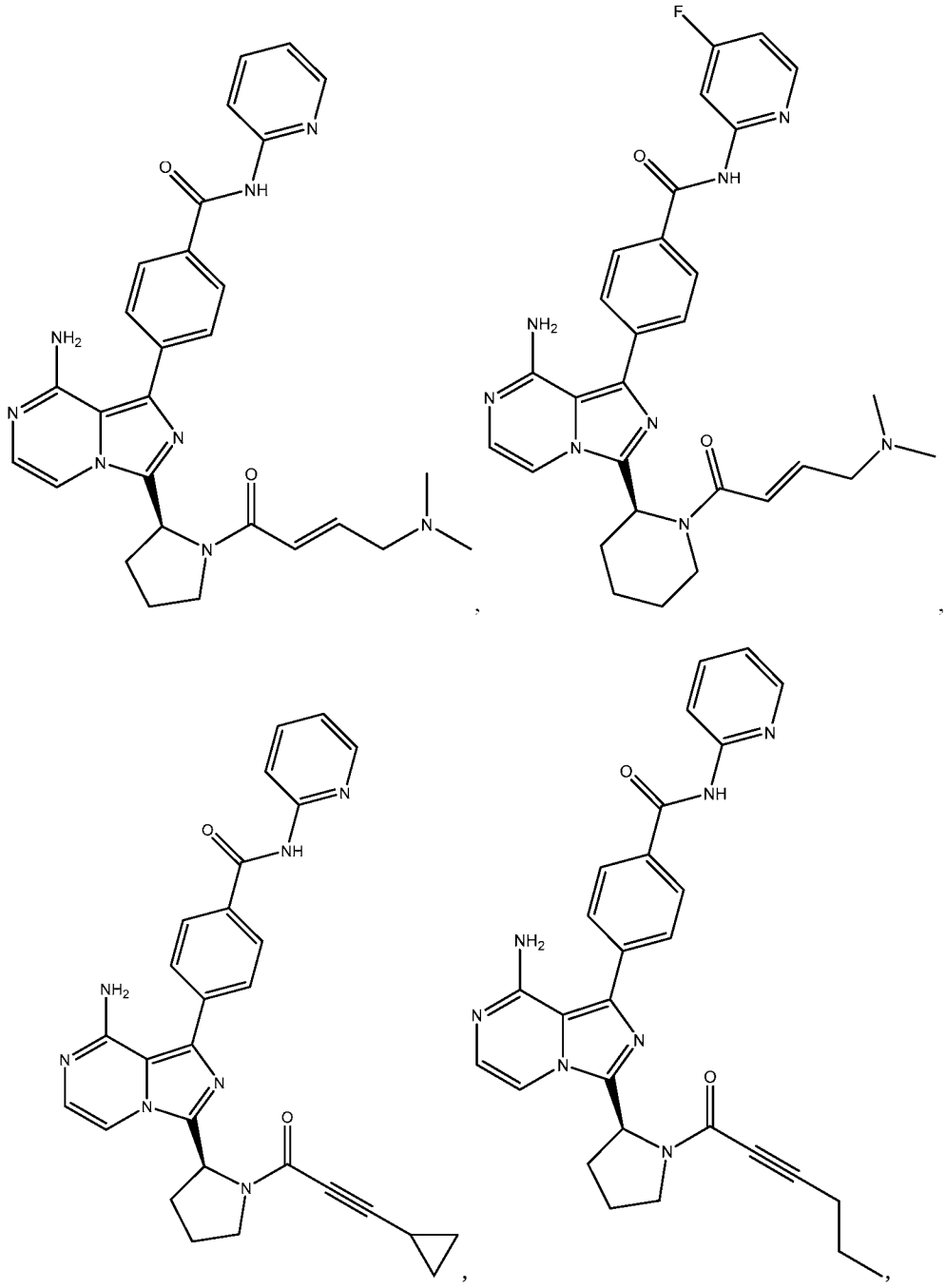


and a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof.

11. The method of Claim 10, wherein the bleeding event is selected from the group consisting of subdural hematoma, gastrointestinal bleeding, hematuria, post-procedural hemorrhage, bruising, and petechiae.

12. The method of any one of Claims 10 or 11, further comprising the step of administering a

therapeutically effective dose of an anticoagulant or antiplatelet active pharmaceutical ingredient.

13. The method of Claim 12, 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.

14. The method of any one of Claims 10 to 13, wherein the cancer is selected from the group consisting of bladder cancer, squamous cell carcinoma including head and neck cancer, pancreatic ductal adenocarcinoma (PDA), pancreatic cancer, colon carcinoma, mammary carcinoma, breast cancer, fibrosarcoma, mesothelioma, renal cell carcinoma, lung carcinoma, thyoma, prostate cancer, colorectal cancer, ovarian cancer, acute myeloid leukemia, thymus cancer, brain cancer, squamous cell cancer, skin cancer, eye cancer, retinoblastoma, melanoma, intraocular melanoma, oral cavity and oropharyngeal cancers, gastric cancer, stomach cancer, cervical cancer, head, neck, renal cancer, kidney cancer, liver cancer, ovarian cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, aquired immune deficiency syndrome (AIDS)-related cancers (e.g., lymphoma and Kaposi's sarcoma), viral-induced cancer, glioblastoma, glioma, esophogeal tumors, hematological neoplasms, non-small-cell lung cancer, chronic myelocytic leukemia, diffuse large B-cell lymphoma, esophagus tumor, follicle center lymphoma, head and neck tumor, hepatitis C virus infection, hepatocellular carcinoma, Hodgkin’s disease, metastatic colon cancer, multiple myeloma, non-Hodgkin’s lymphoma, indolent non-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, primary central nervous system lymphoma, and Burkitt's lymphoma.

15. A BTK inhibitor for use in the inhibition of signaling between the solid tumor cells and at least one component of a 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

16. A BTK inhibitor according to Claim 15 for use in the treatment of a hyperproliferative disease, for example cancer.

17. A BTK inhibitor according to Claim 16 for use in the treatment of a cancer selected from a B cell hematological malignancy selected from the hematological malignancy is selected from the group consisting of chronic lymphocytic leukemia (CLL), small lymphocytic leukemia (SLL), non-Hodgkin's lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Hodgkin's lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Burkitt's lymphoma, Waldenström's macroglobulinemia (WM), Burkitt's lymphoma, multiple myeloma, or myelofibrosis.

18. A BTK inhibitor according to Claim 16, wherein the hyperproliferative disease is a 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 and neck cancer, renal cancer, kidney cancer, liver cancer, ovarian cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, aquired immune deficiency syndrome (AIDS)-related cancers (e.g., lymphoma and Kaposi's sarcoma), viral-induced cancer, glioblastoma, glioma, esophogeal tumors, hematological neoplasms, non-small-cell lung cancer, chronic myelocytic leukemia, diffuse large B-cell lymphoma, esophagus tumor, follicle center lymphoma, head and neck tumor, hepatitis C virus infection, hepatocellular carcinoma, Hodgkin's disease, metastatic

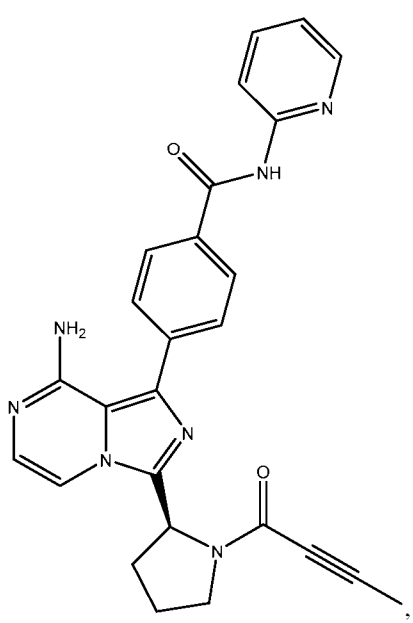
colon cancer, multiple myeloma, non-Hodgkin's lymphoma, indolent non-Hogkin's lymphoma, ovary tumor, pancreas tumor, renal cell carcinoma, small-cell lung cancer, stage IV melanoma, chronic lymphocytic leukemia, B-cell acute lymphoblastic leukemia (ALL), mature B-cell ALL, follicular lymphoma, mantle cell lymphoma, primary central nervous system lymphoma, and Burkitt's lymphoma.

19. A BTK inhibitor according to Claim 16, wherein the cancer is a solid tumor cancer.

20. A BTK inhibitor according to Claim 19, wherein the cancer is a solid tumor cancer, and wherein the solid tumor cancer is selected from the group consisting of bladder cancer, non-small cell lung cancer, cervical cancer, anal cancer, pancreatic cancer, squamous cell carcinoma including head and neck cancer, renal cell carcinoma, melanoma, ovarian cancer, small cell lung cancer, glioblastoma, glioma, gastrointestinal stromal tumor, breast cancer, lung cancer, colorectal cancer, thyroid cancer, bone sarcoma, stomach cancer, oral cavity cancer, oropharyngeal cancer, gastric cancer, kidney cancer, liver cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, colon cancer, primary central nervous system lymphoma, and brain cancer.

21. A BTK inhibitor according to any one of Claims 19 to 20, wherein the solid tumor cancer affects the central nervous system and wherein treatment requires transmission of the BTK inhibitor, or a metabolite thereof, across the blood-brain barrier.

22. A BTK inhibitor according to any one of Claims 15 to 21, wherein the BTK inhibitor is selected from the group consisting of:



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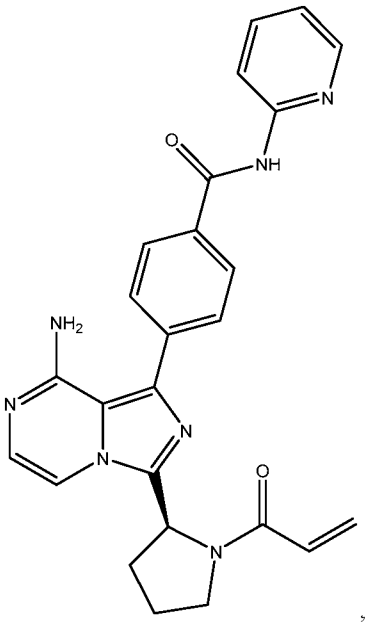

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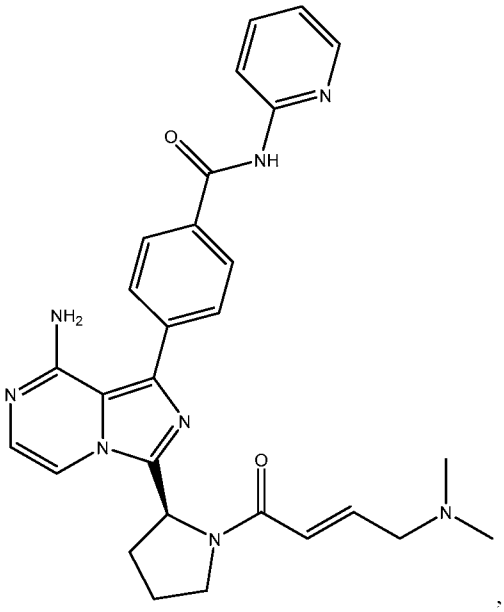

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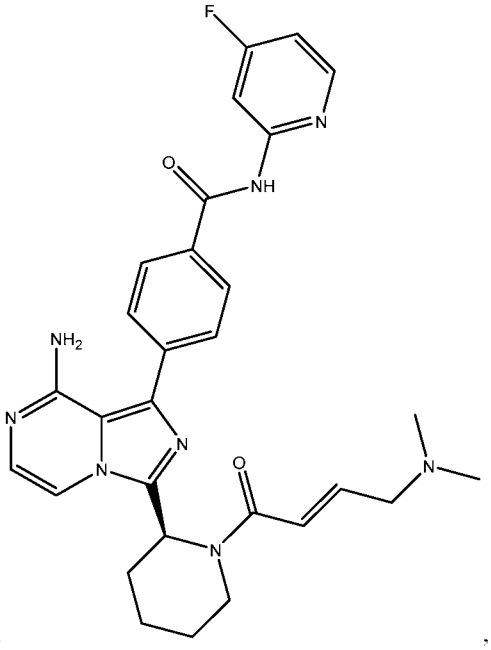

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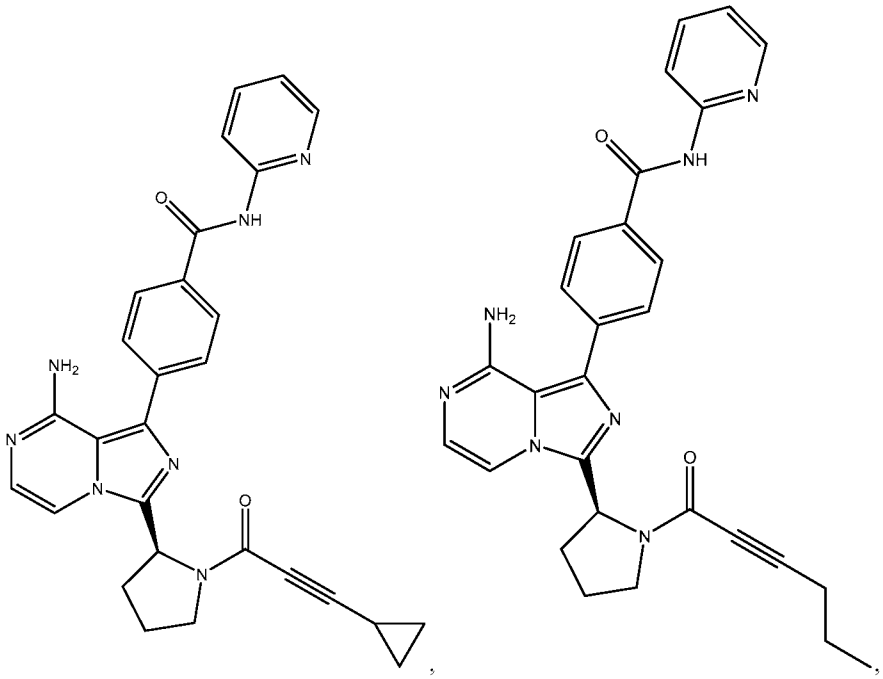
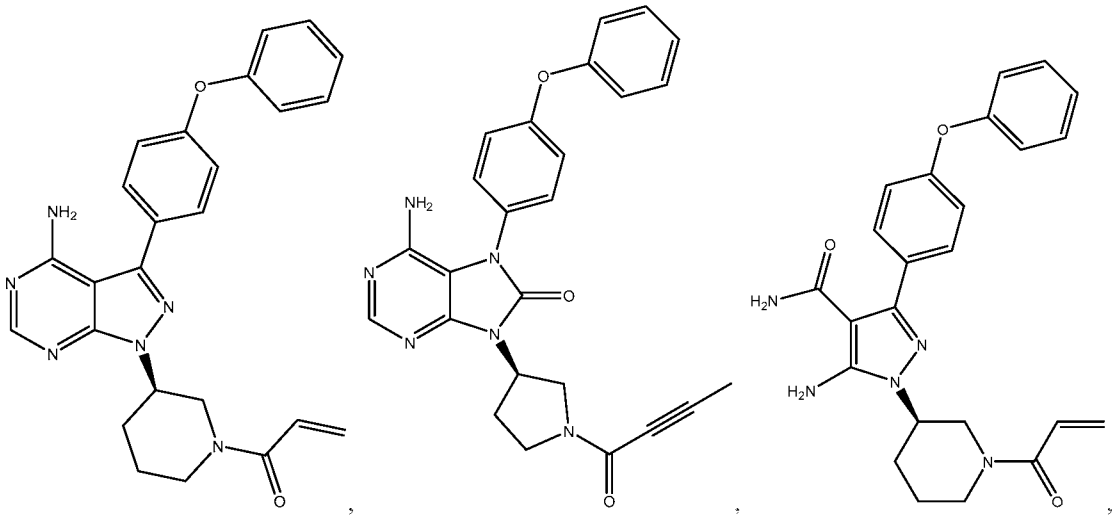


and a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof.

23. A BTK inhibitor according to any one of Claims 15 to 21, wherein the BTK inhibitor is selected from the group consisting of:



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

24. A BTK inhibitor according to any one of Claims 15 to 23, for use in combination with 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.

25. A BTK inhibitor according to any one of Claims 15 to 23, for use in combination with gemcitabine.

26. A BTK inhibitor according to any one of Claims 15 to 23, for use in combination with albumin-bound paclitaxel.

27. A BTK inhibitor according to any one of Claims 15 to 26, wherein the BTK inhibitor is in a dose effective to increase immune system recognition and rejection of the solid tumor by a human.

28. A BTK inhibitor according to any one of Claims 15 to 27 for use in the treatment of a cancer in a human sensitive to a bleeding event.

29. A BTK inhibitor according to Claim 28, wherein the bleeding event is selected from the group consisting of subdural hematoma, gastrointestinal bleeding, hematuria, post-procedural hemorrhage, bruising, and petechiae.

30. A BTK inhibitor according to Claim 28 or Claim 29 for use in combination with an anticoagulant or antiplatelet active pharmaceutical ingredient.

31. A BTK inhibitor according to Claim 30 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.

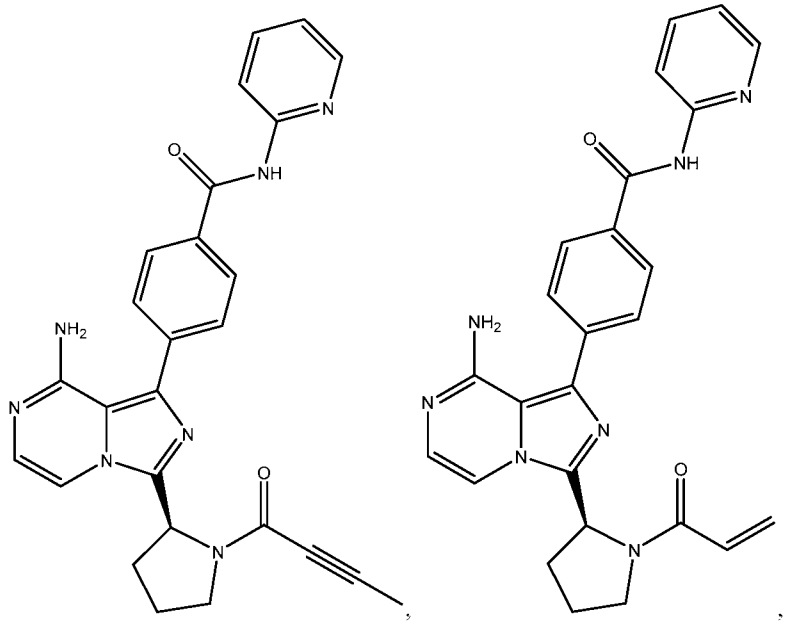
32. A composition comprising a BTK inhibitor as defined in any one of Claims 15 to 31 in

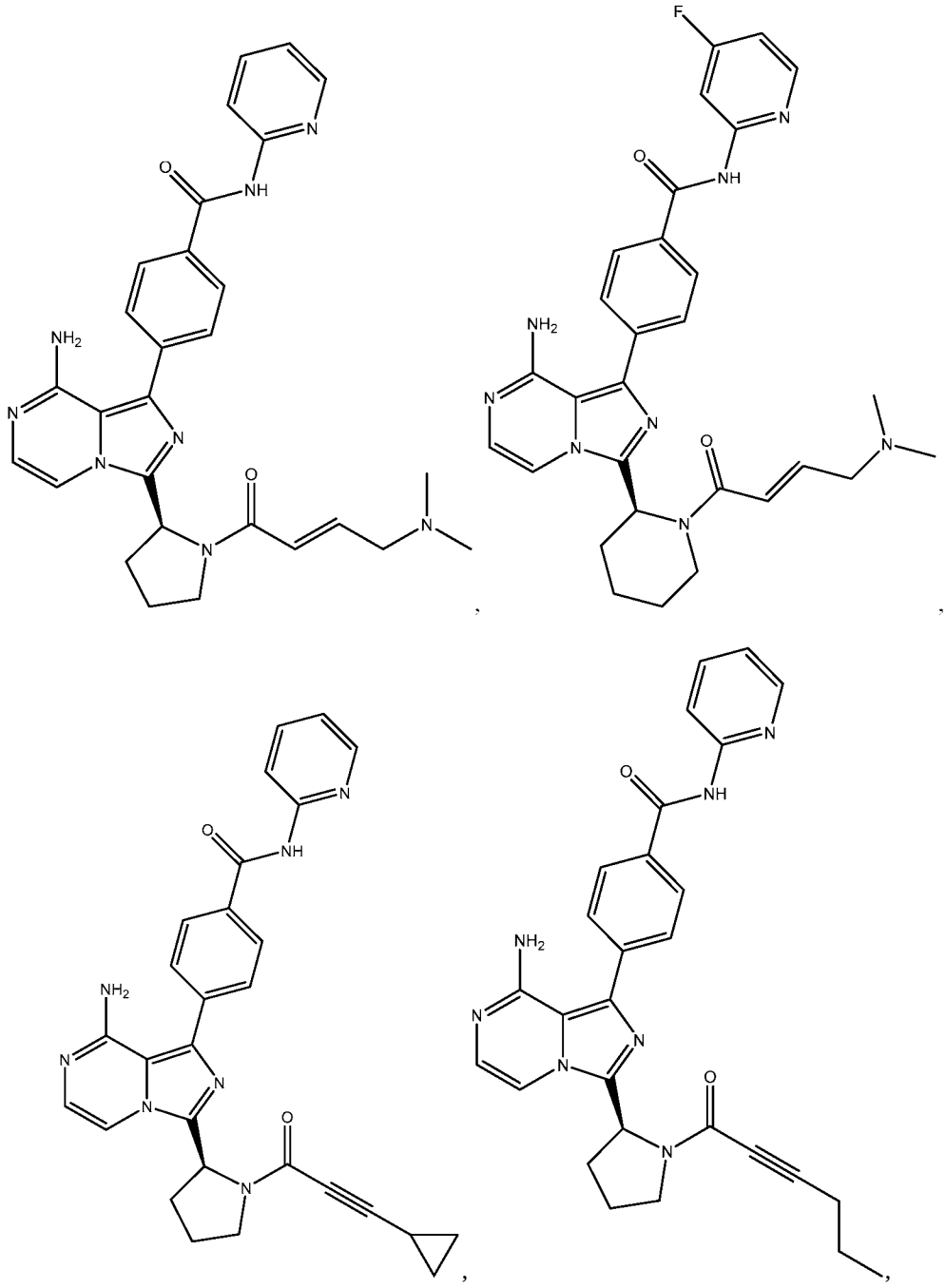
association with one or more pharmaceutically acceptable excipient, carrier, filler and/or diluent.

33. Use of a BTK inhibitor as defined in any one of Claims 15 to 32 to inhibit signaling between a solid tumor cell 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.

34. A composition comprising a solid tumor cell, a BTK inhibitor as defined in any one of Claims 15 to 33 or a metabolite thereof, 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.

35. A composition comprising a BTK inhibitor, wherein the BTK inhibitor is:





and a pharmaceutically-acceptable salt, cocrystal, solvate, or hydrate thereof, and gemcitabine, or a pharmaceutically-acceptable salt, cocrystal, solvate, or hydrate thereof.

36. The composition of Claim 35, comprising an amount of the BTK inhibitor selected from the group consisting of 5 mg, 10 mg, 12.5 mg, 15 mg, 20 mg, 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 375 mg, 400

mg, 425 mg, 450 mg, 475 mg, or 500 mg.

37. The composition of any of Claims 35 to 36, comprising an amount of gemcitabine selected from the group consisting of 25 mg, 50 mg, 75 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, 1800 mg, 1900 mg, and 2000 mg.

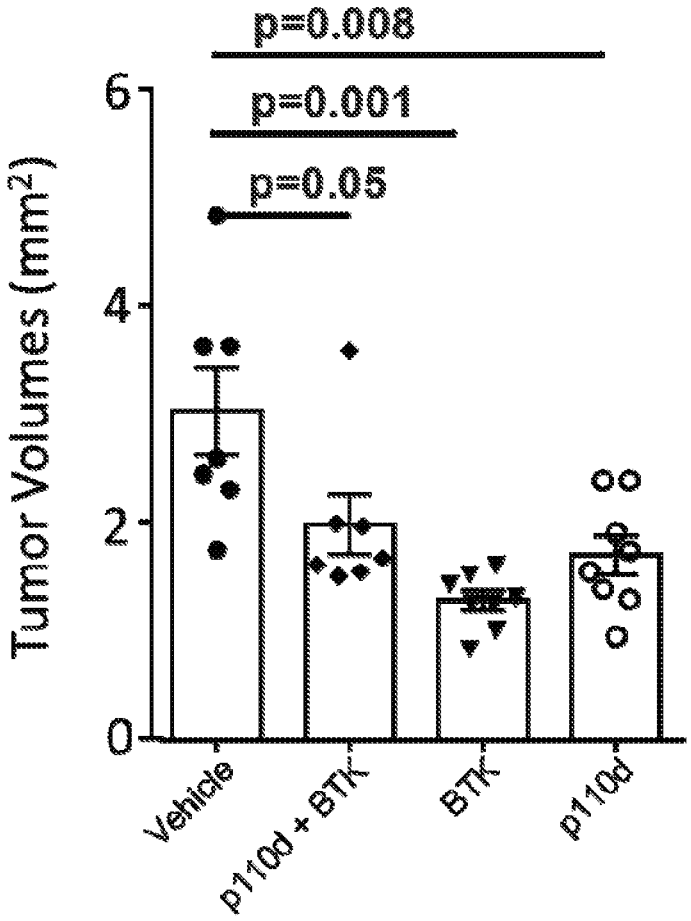

p=0.008
p=0.001
p=0.05
Tumor Volumes (mm2)
6
4
2
0
Vehicle
p110d + BTK-
BTK-
p110d

FIG. 1

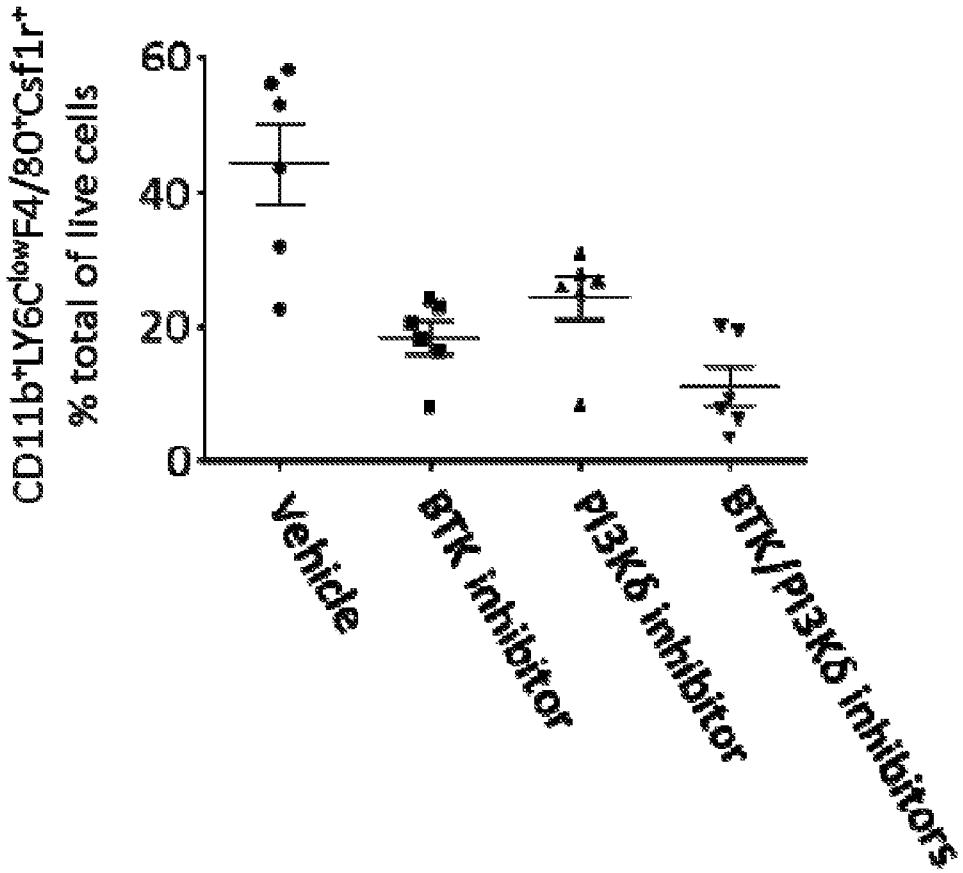

CD11b+LY6Clow F4/80+Csf1r+
% total of live cells
60
40
20
0
vehicle
BTK inhibitor
PI3Kδ inhibitor
BTK/PI3Kδ inhibitors

FIG. 2

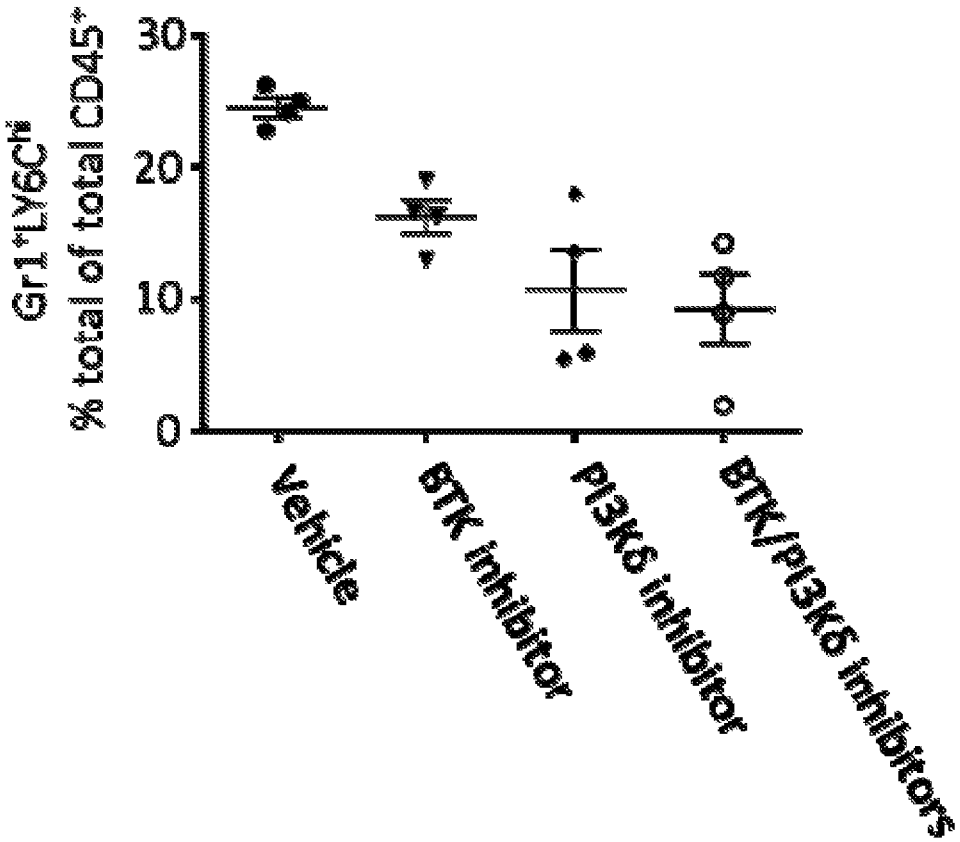

Gr1+LY6Chi
% total of total CD45+
30
20
10
0
Vehicle
BTK inhibitor
PI3Kδ inhibitor
BTK/PI3Kδ inhibitors

FIG. 3

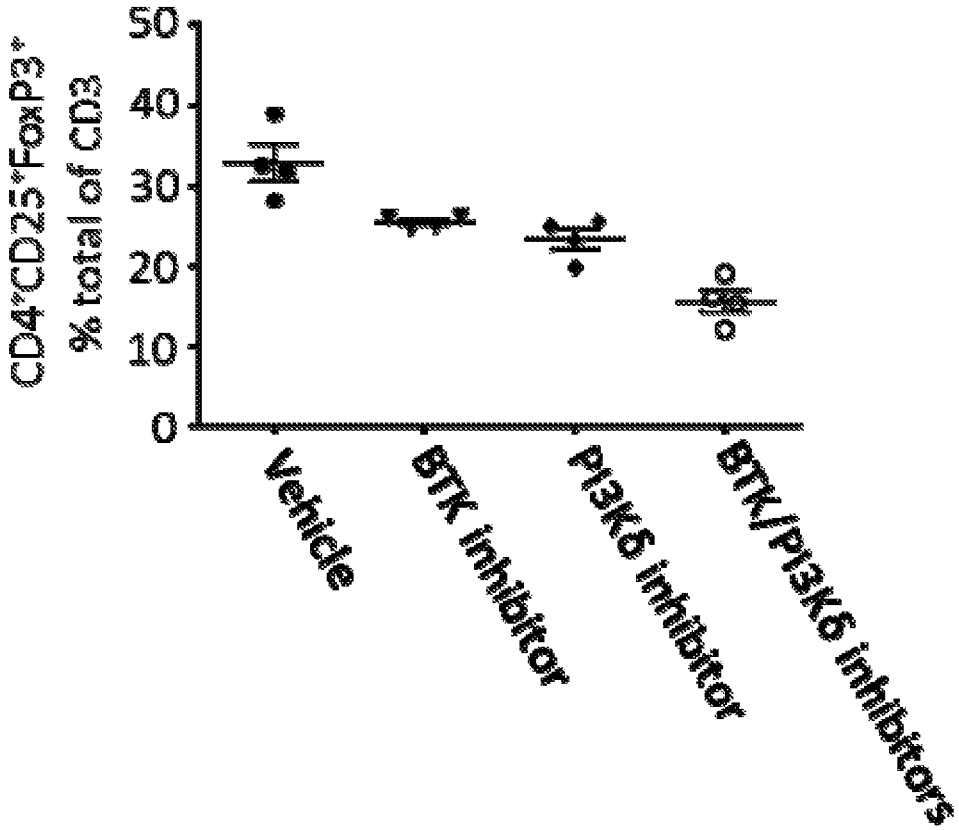

CD4+CD25+FoxP3+
% total of CD3
50
40
30
20
10
0
Vehicle
BTK inhibitor
PI3K6 inhibitor
BTK/PI3K6 inhibitors

FIG. 4

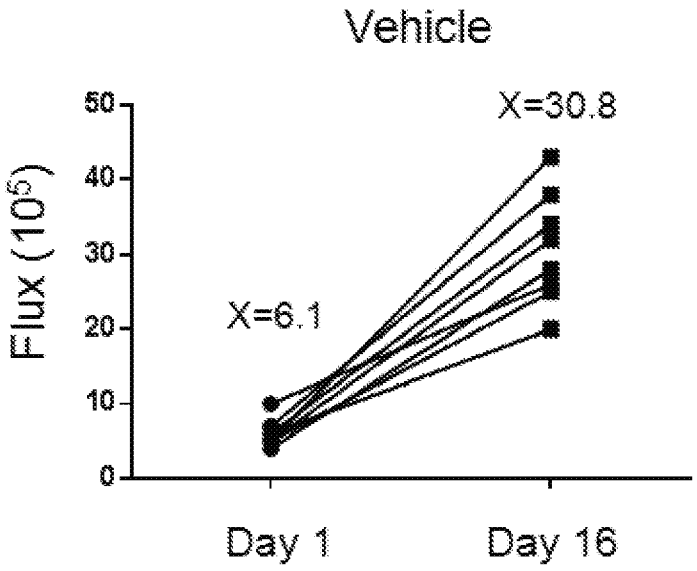



FIG. 5

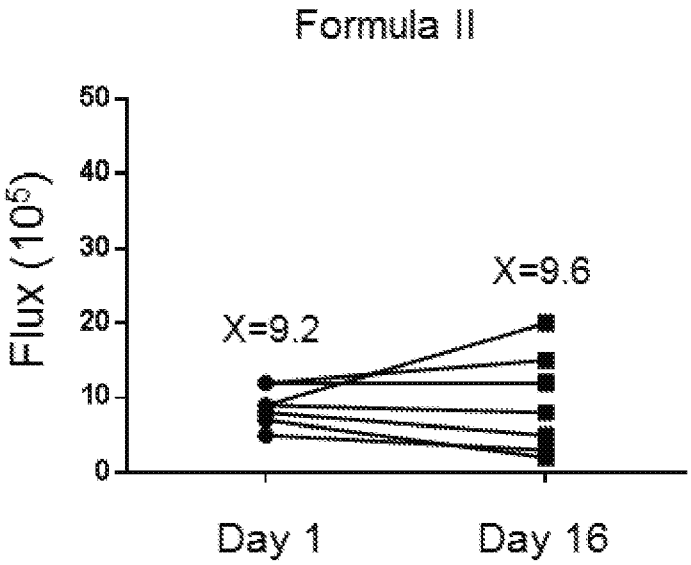



FIG. 6

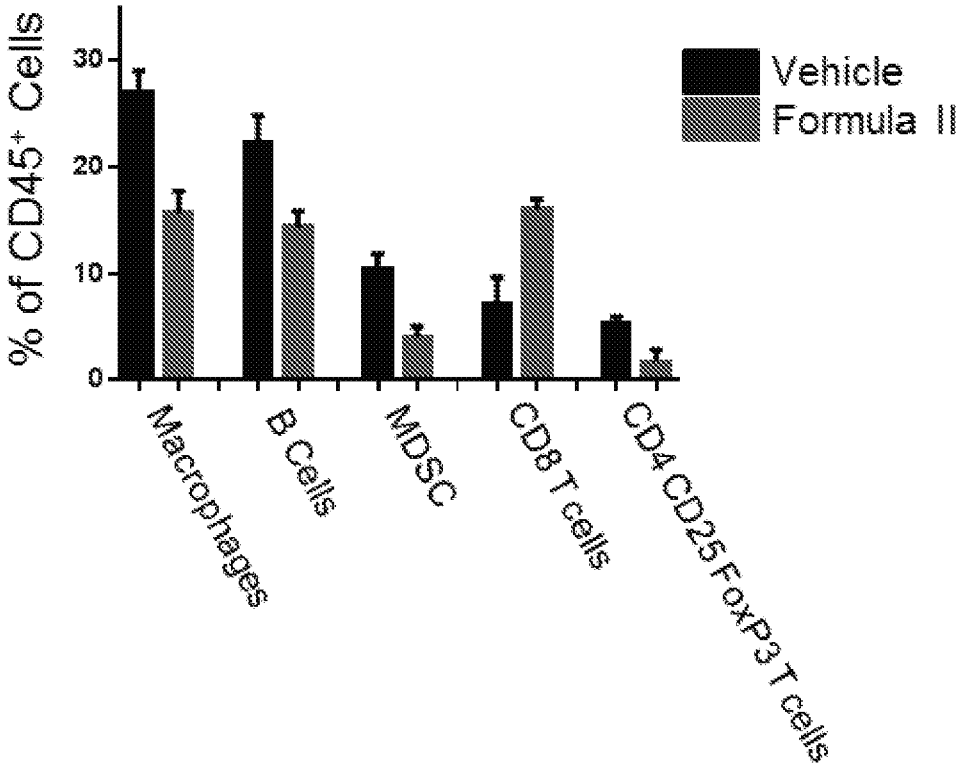

% of CD45+ Cells
30
20
10
0
Vehicle
Formula II
Macrophages
B Cells
MDSC
CD8 T cells
CD4 CD25 FoxP3 T cells

FIG. 7

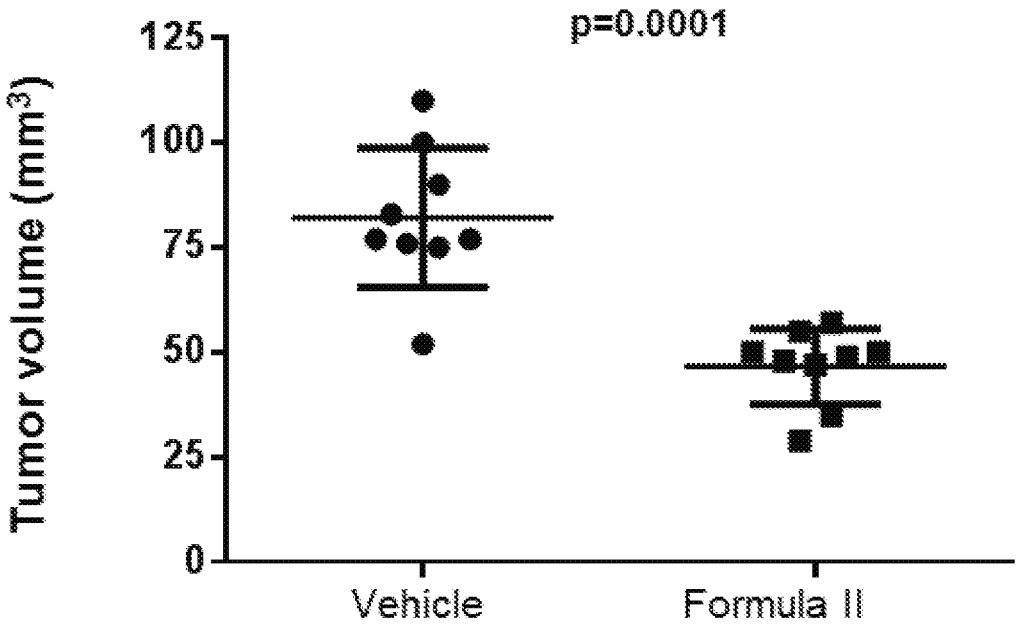



FIG. 8

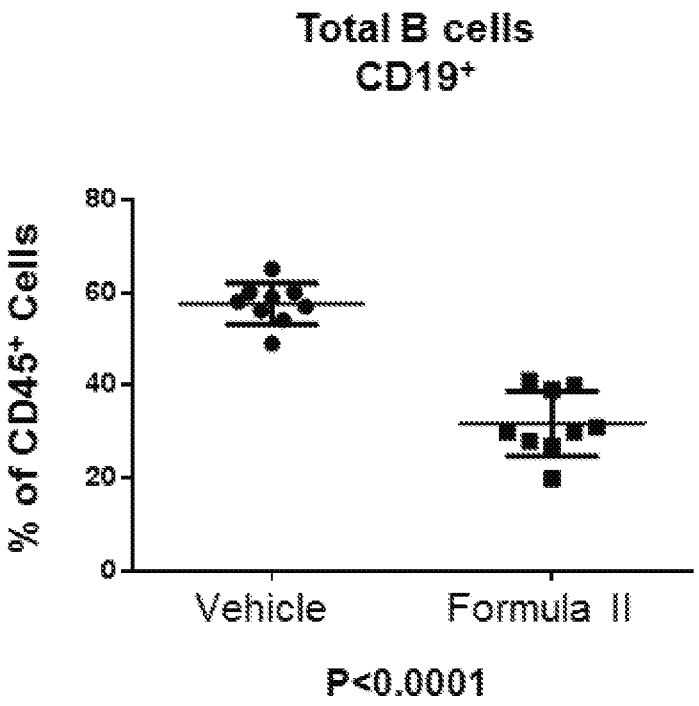

Total B cells
CD19+
% of CD45+ Cells
80
60
40
20
0
Vehicle
Formula II
P<0.0001

FIG. 9

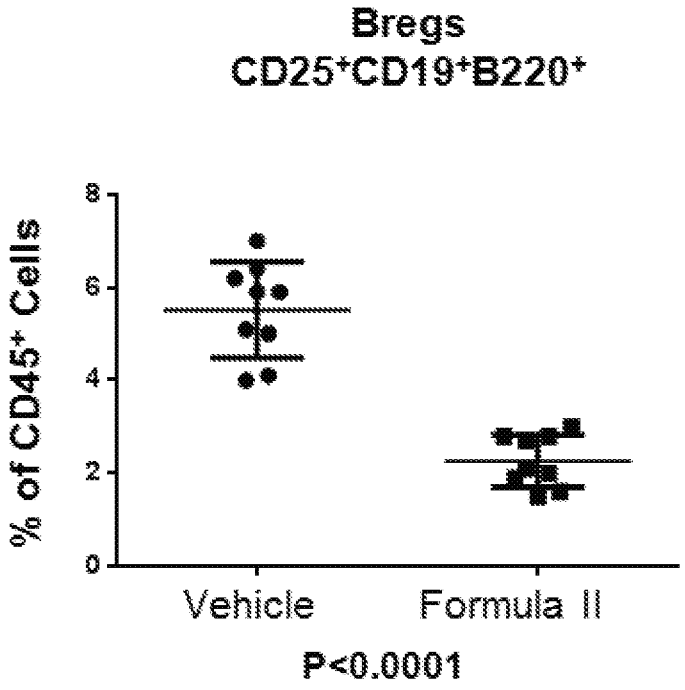

Bregs
CD25+CD19+B220+
% of CD45+ Cells
8
6
4
2
0
Vehicle
Formula II
P<0.0001

FIG. 10

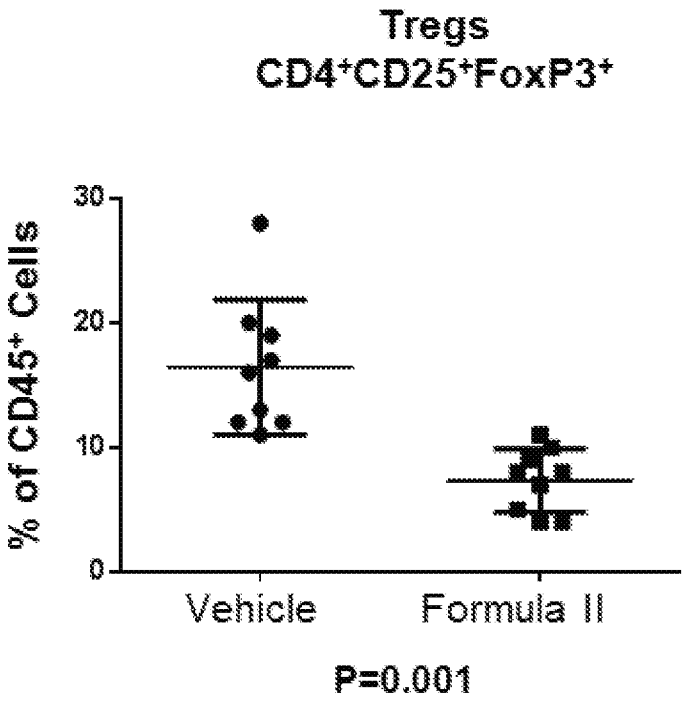

Tregs
CD4+CD25+FoxP3+
% of CD45+ Cells
30
20
10
0
Vehicle
Formula II
P=0.001

FIG. 11

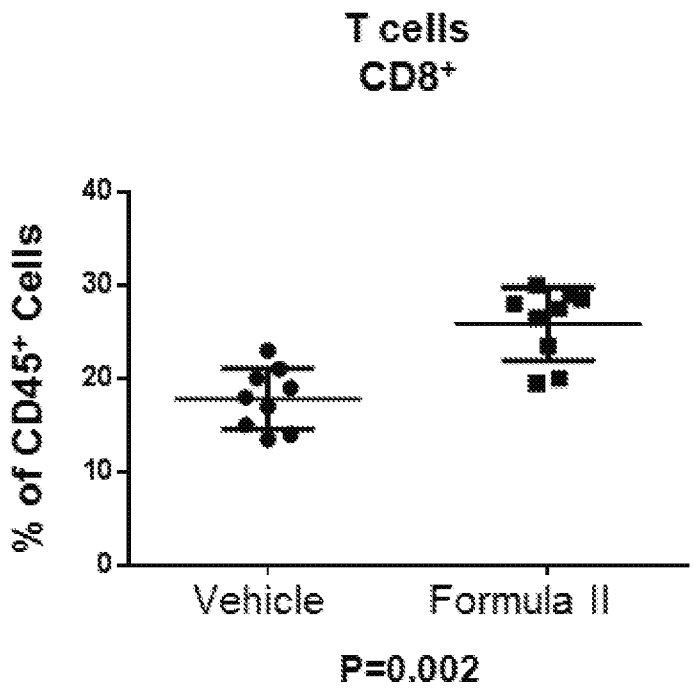

T cells
CD8+
% of CD45+ Cells
40
30
20
10
0
Vehicle
Formula II
P=0.002

FIG. 12

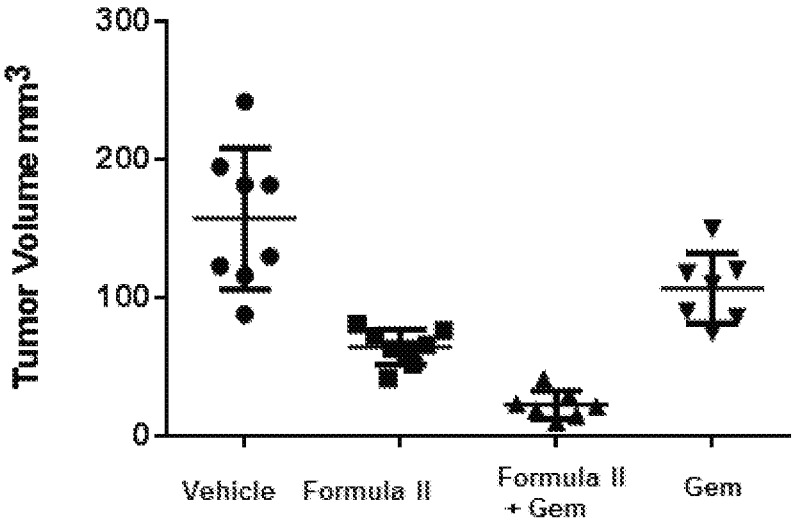

Tumor Volume mm3
300
200
100
0
Vehicle
Formula II
Formula II + Gem
Gem

FIG. 13

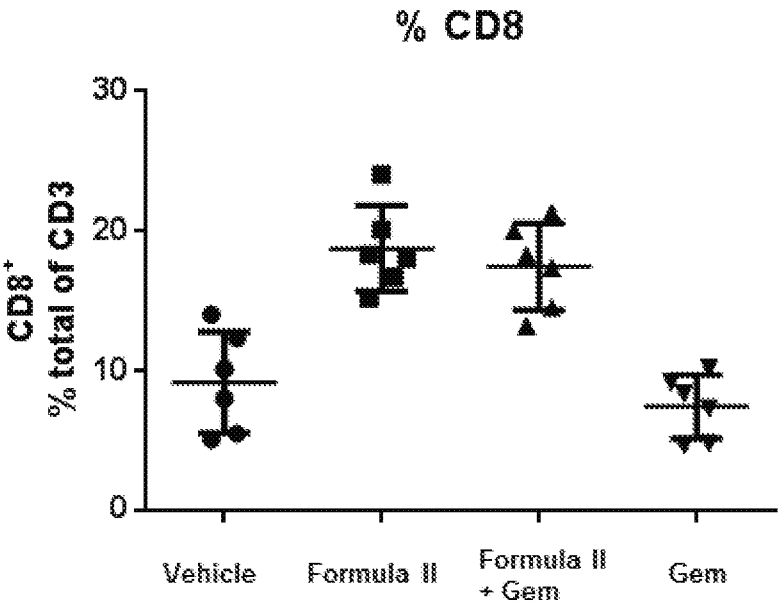

% CD8
CD8+ % total of CD3
30
20
10
0
Vehicle
Formula II
Formula II + Gem
Gem

FIG. 14

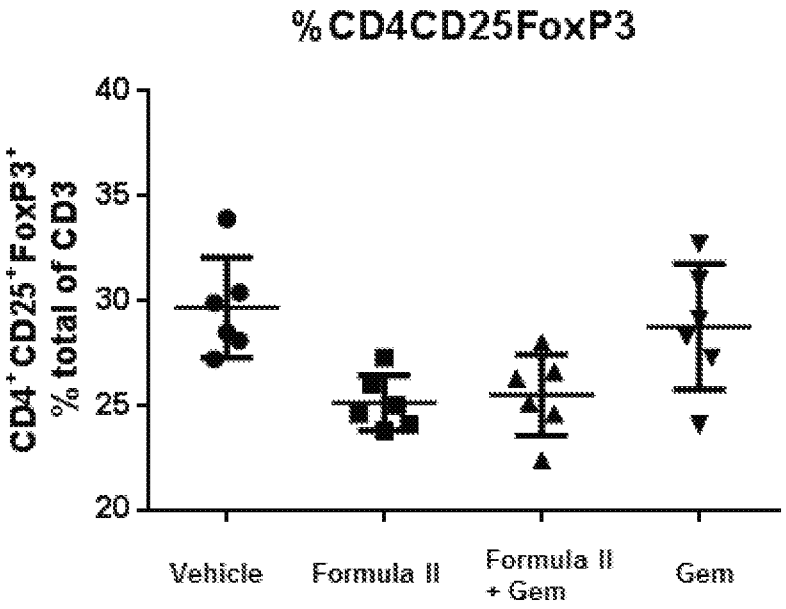

%CD4CD25FoxP3
CD4+CD25+FoxP3+
% total of CD3
40
35
30
25
20
Vehicle
Formula II
Formula II
+ Gem
Gem

FIG. 15

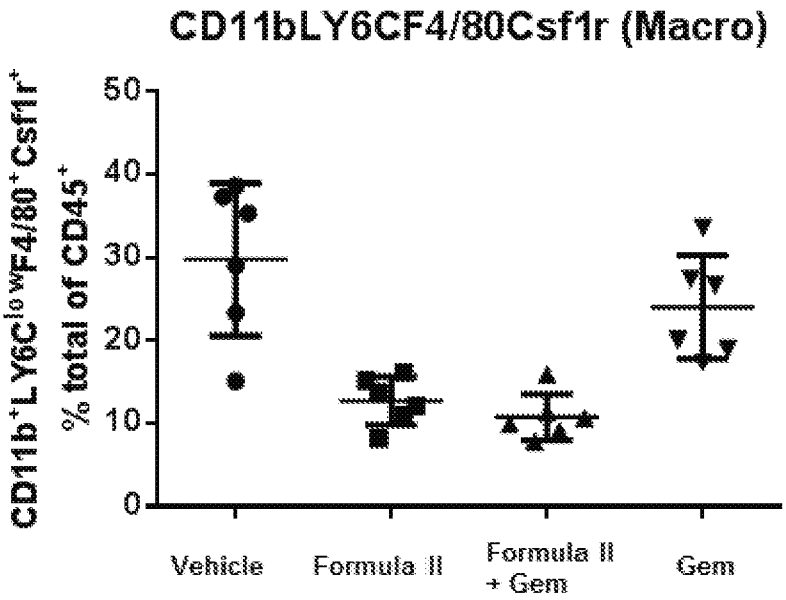

CD11bLY6CF4/80Csf1r (Macro)
CD11b+LY6Clo wF4/80+Csf1r+
% total of CD45+
50
40
30
20
10
0
Vehicle
Formula II
Formula II + Gem
Gem

FIG. 16

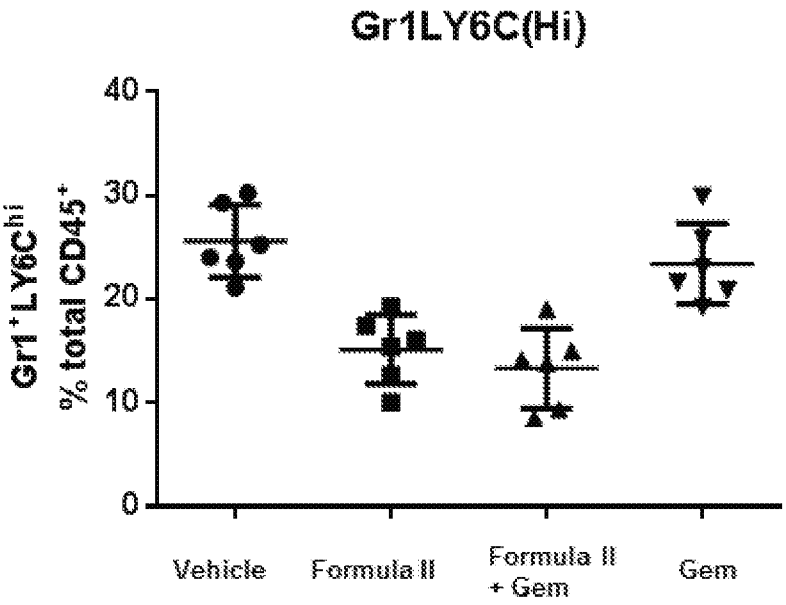

Gr1LY6C(Hi)
Gr1+LY6Chi
% total CD45+
40
30
20
10
0
Vehicle
Formula II
Formula II
+ Gem
Gem

FIG. 17

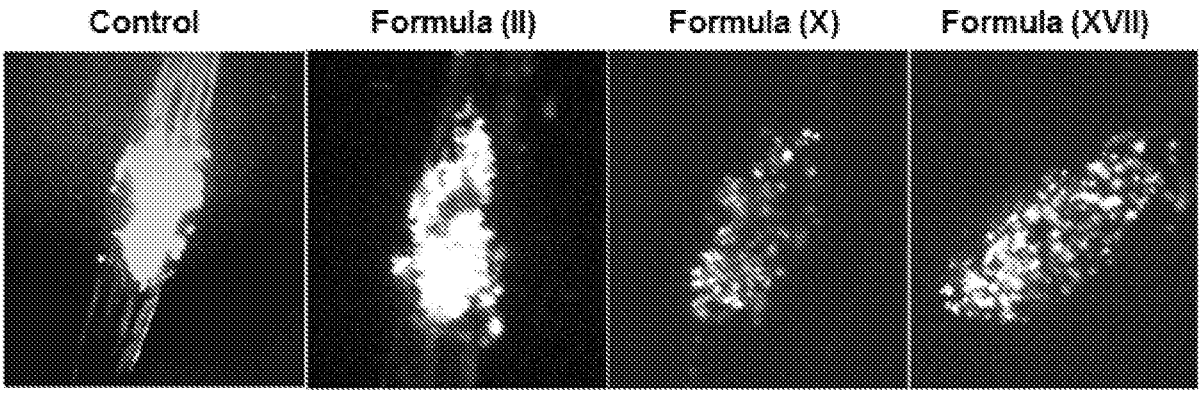



FIG. 18

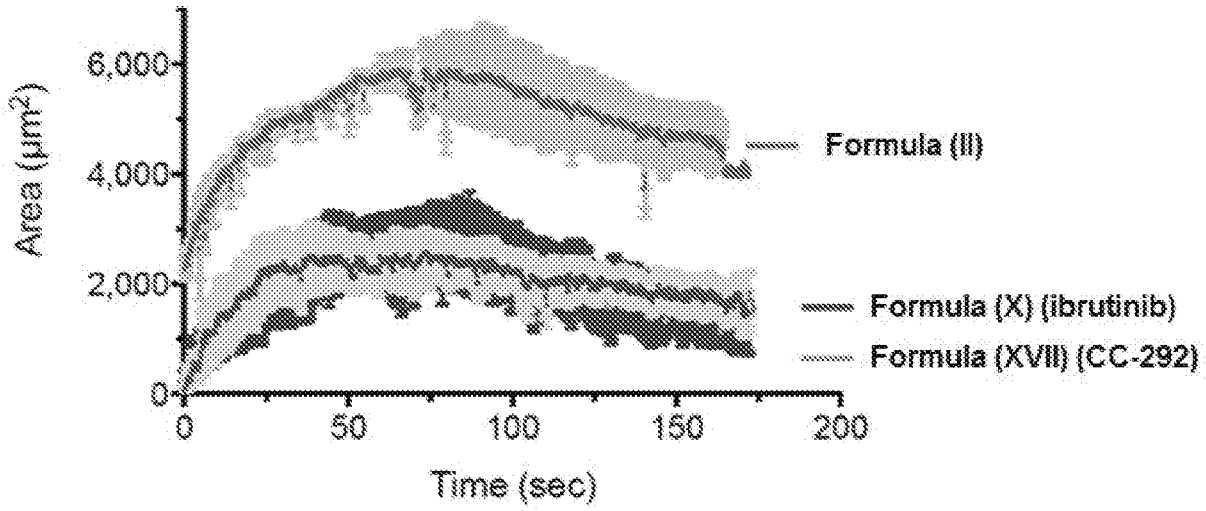

6,000
4,000
2,000
0
Area (µm²)
0
50
100
150
200
Time (sec)
Formula (II)
Formula (X) (ibrutinib)
Formula (XVII) (CC-292)

FIG. 19

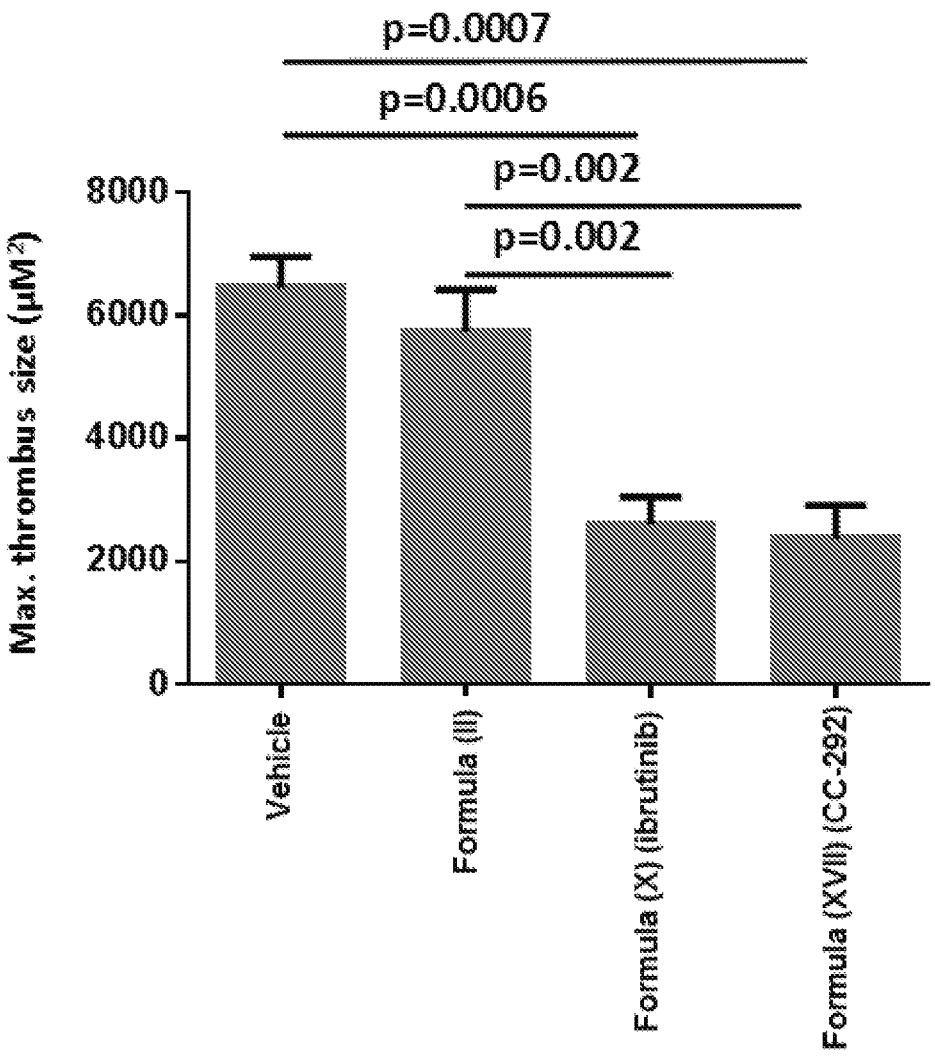

p=0.0007
p=0.0006
p=0.002
p=0.002
8000
6000
4000
2000
0
Max. thrombus size (μM²)
Vehicle
Formula (III)
Formula (X) (ibrutinib)
Formula (XVII) (CC-292)

FIG. 20

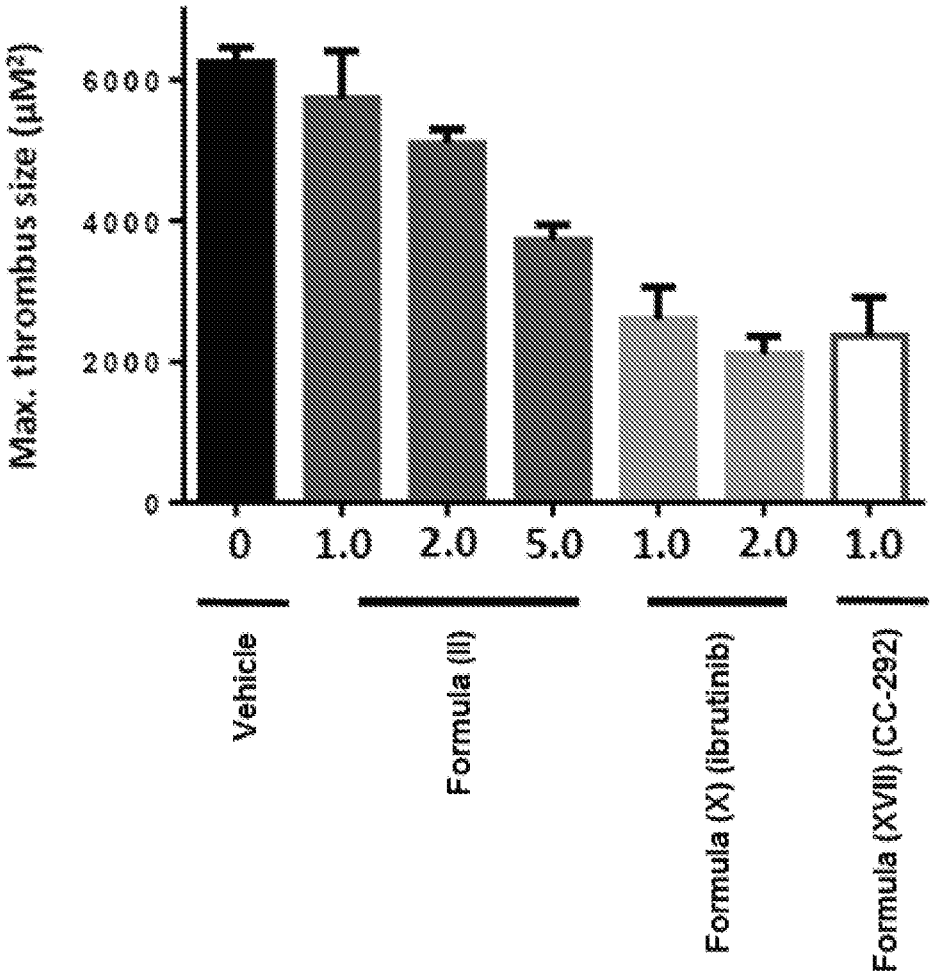

Max. thrombus size (μM²)
6000
4000
2000
0
0
1.0
2.0
5.0
1.0
2.0
1.0
Vehicle
Formula (II)
Formula (X) (ibrutinib)
Formula (XVII) (CC-292)

FIG. 21

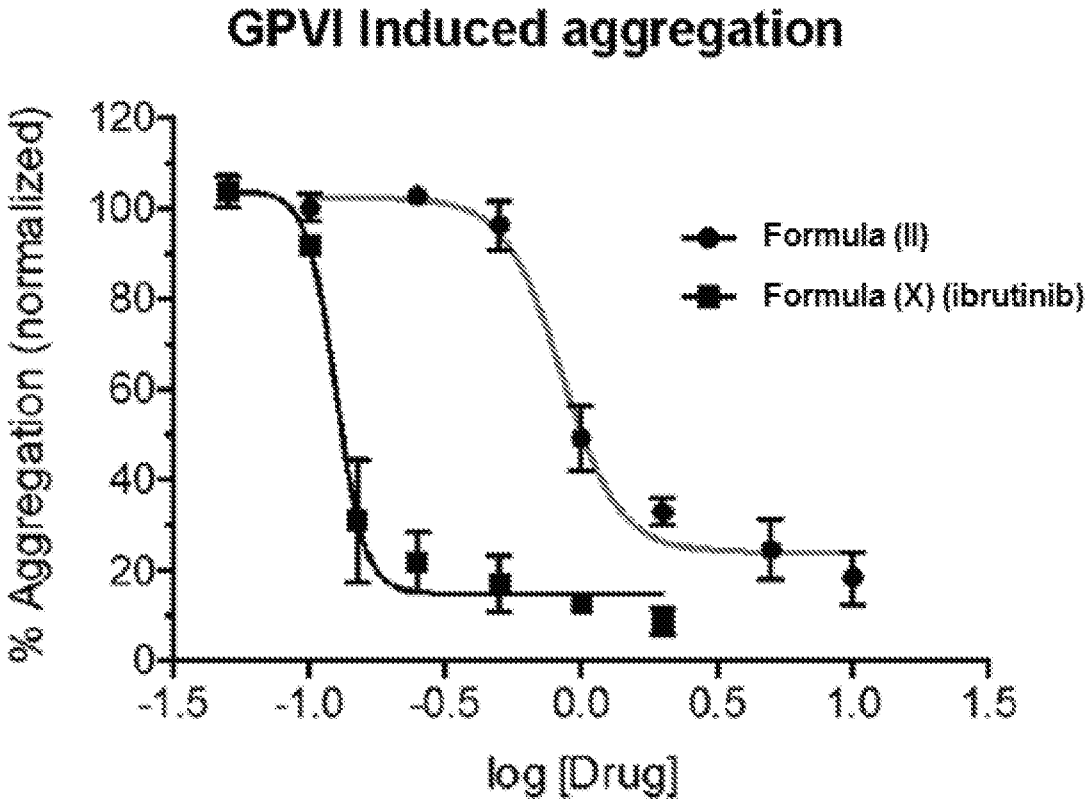

GPVI Induced aggregation
% Aggregation (normalized)
120
100
80
60
40
20
0
-1.5
-1.0
-0.5
0.0
0.5
1.0
1.5
log [Drug]
Formula (II)
Formula (X) (ibrutinib)

FIG. 22

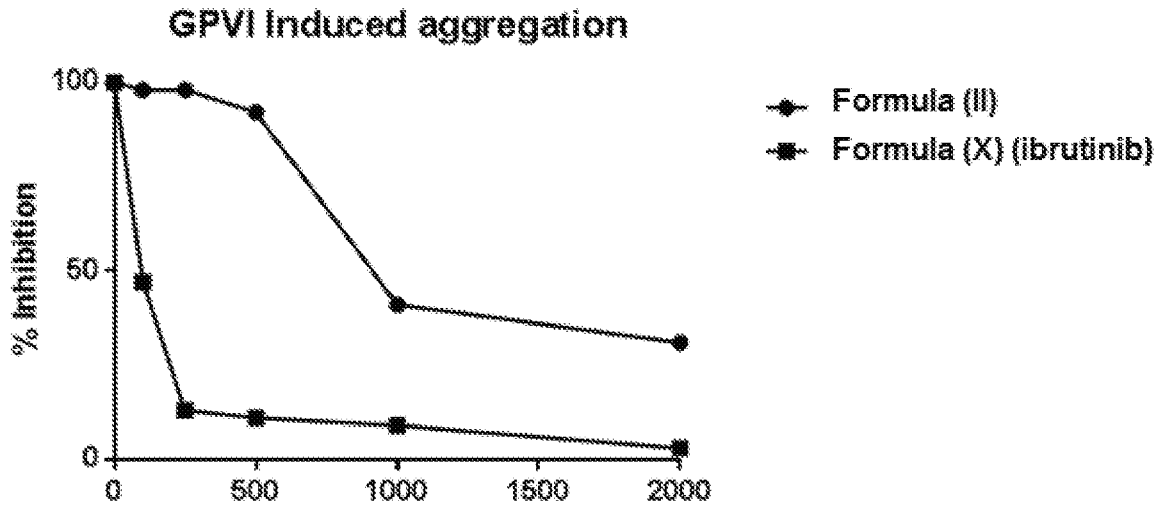

GPVI Induced aggregation
% Inhibition
100
50
0
0
500
1000
1500
2000
Formula (II)
Formula (X) (ibrutinib)

FIG. 23

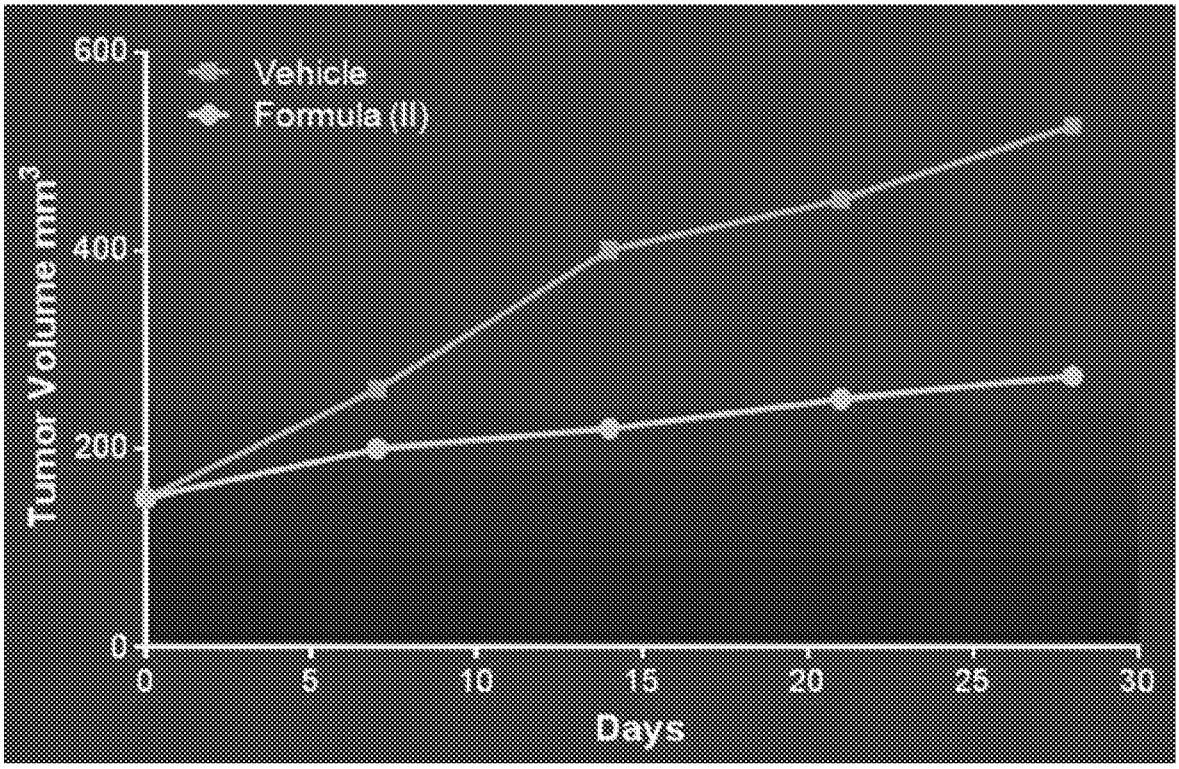

600
400
200
0
Tumor Volume mm3
Vehicle
Formula (II)
0
5
10
15
20
25
30
Days

FIG. 24

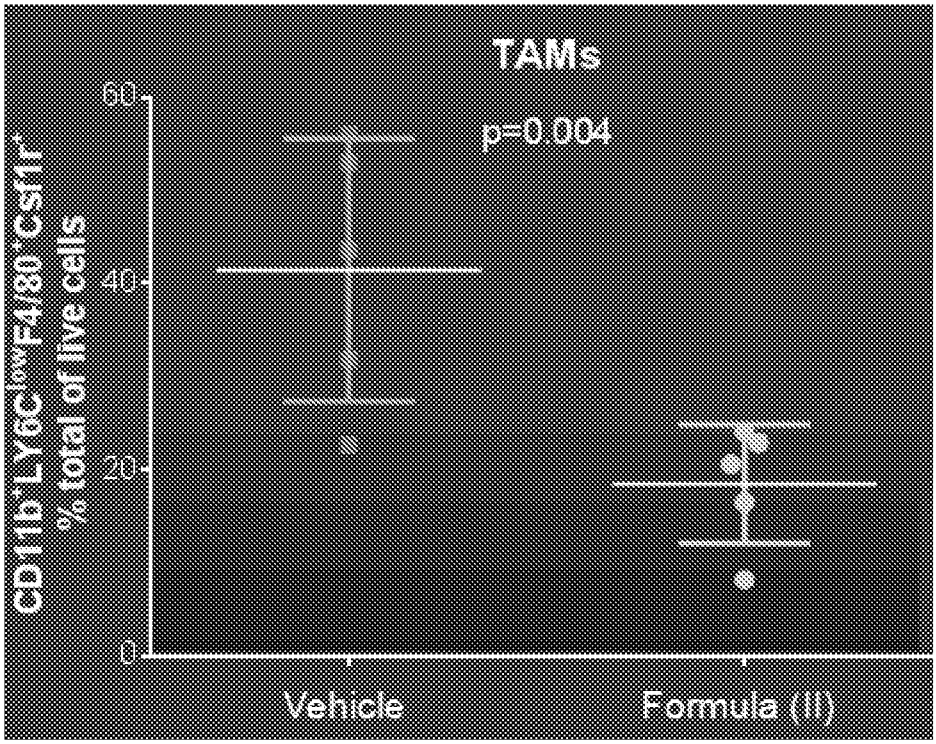

TAMs
p=0.004
CD11b+Ly6Clow F4/80+Csf1r+
% total of live cells
60
40
20
0
Vehicle
Formula (II)

FIG. 25

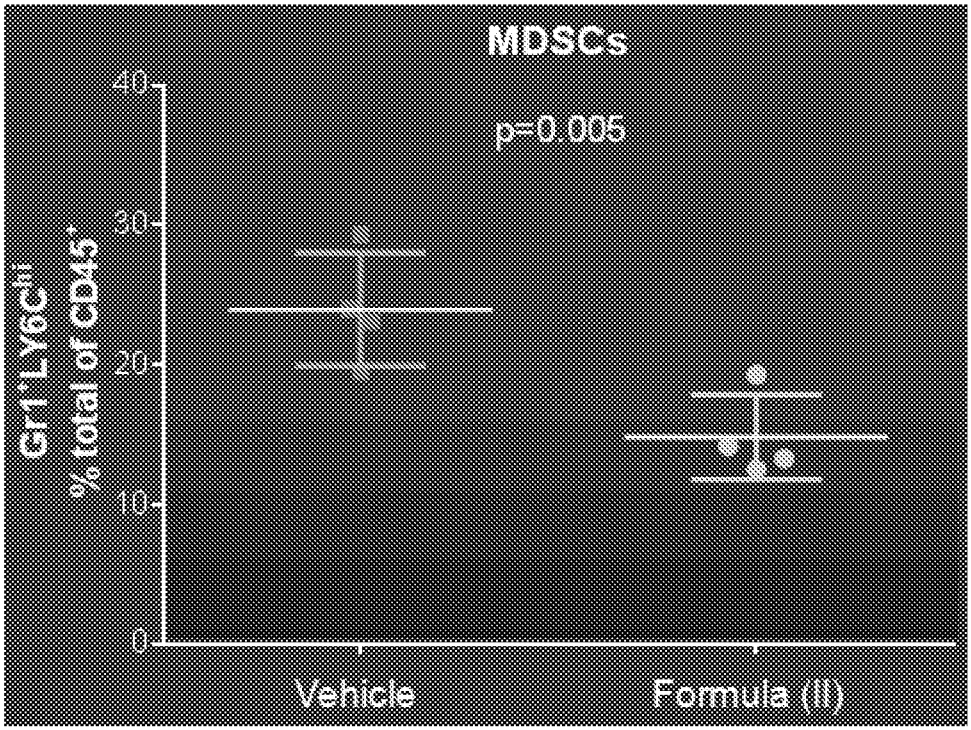

MDSCs
p=0.005
Gr1+LY6C++
% total of CD45+
40
30
20
10
0
Vehicle
Formula (II)

FIG. 26

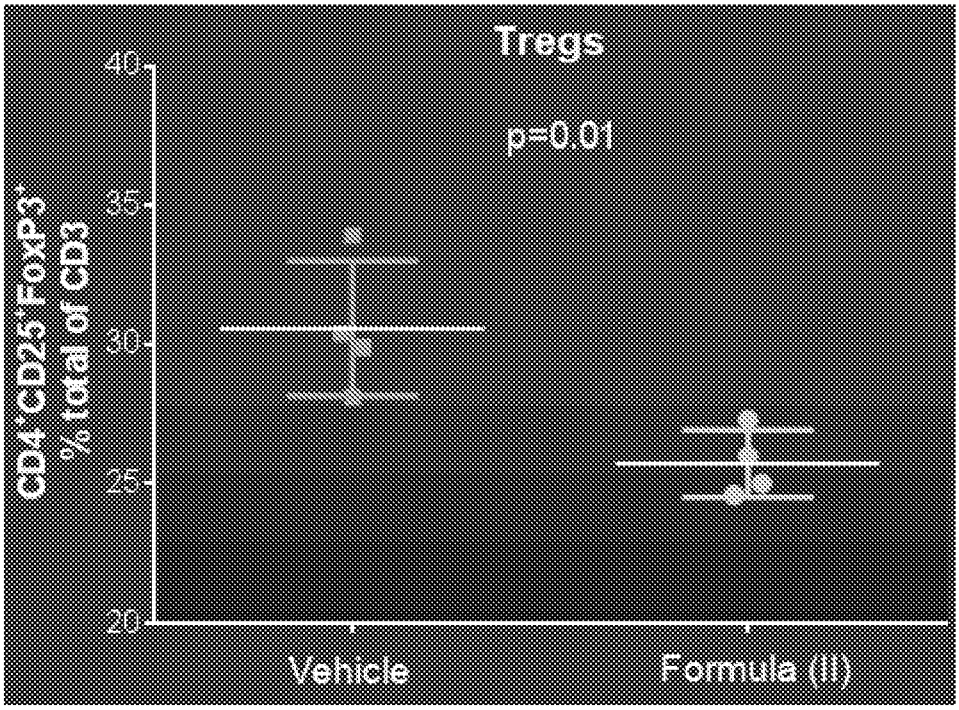

Tregs
p=0.01
CD4+CD25+FoxP3+
% total of CD3
40
35
30
25
20
Vehicle
Formula (II)

FIG. 27

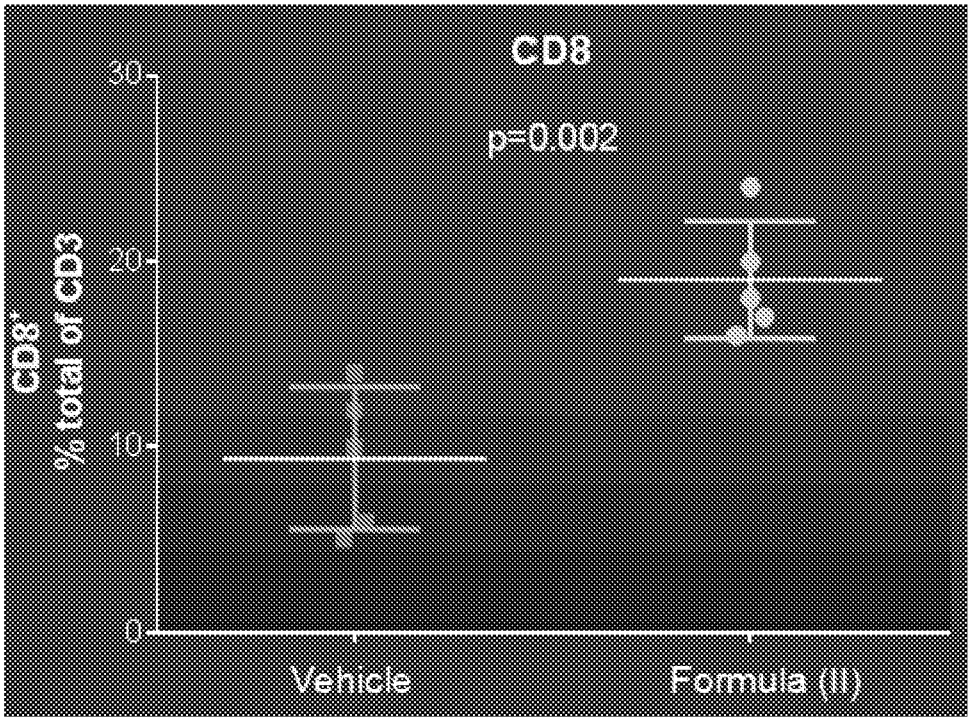



FIG. 28

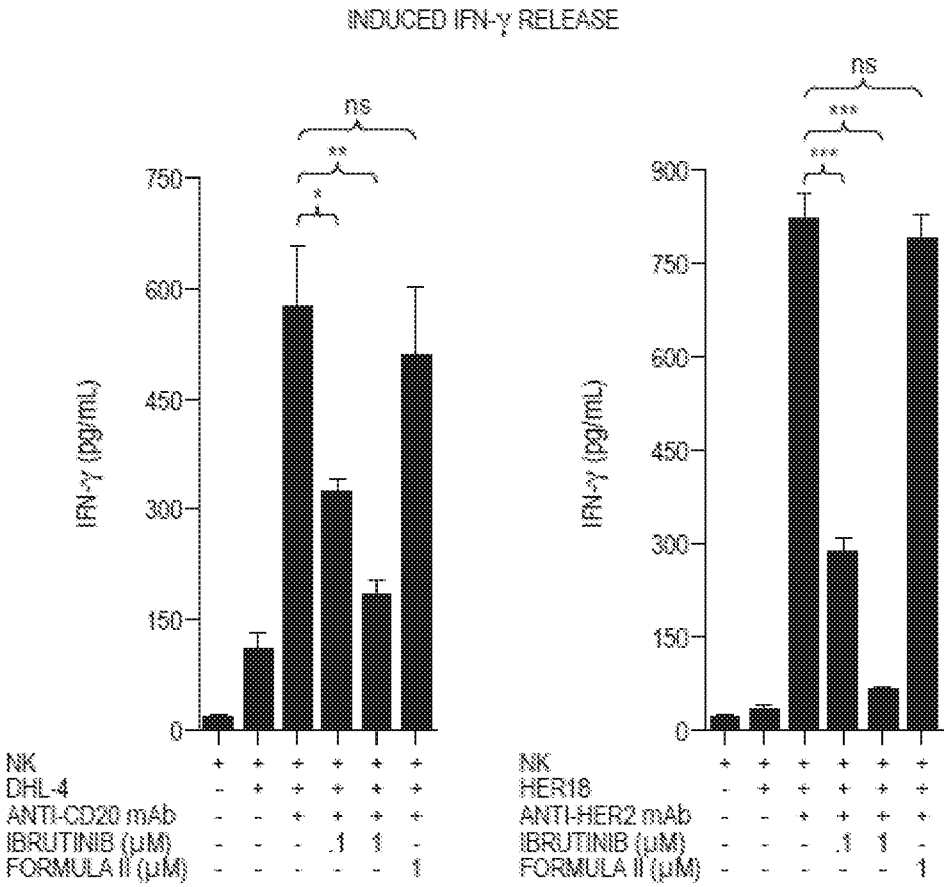

INDUCED IFN-γ RELEASE
IFN-γ (pg/mL)
750
600
450
300
150
0
ns
**
*
NK + + + + + +
DHL-4 - + + + + +
ANTI-CD20 mAb - - + + + +
IBRUTINIB (μM) - - - .1 1 -
FORMULA II (μM) - - - - - 1
IFN-γ (pg/mL)
900
750
600
450
300
150
0
ns
***
***
NK + + + + + +
HER18 - + + + + +
ANTI-HER2 mAb - - + + + +
IBRUTINIB (μM) - - - .1 1 -
FORMULA II (μM) - - - - - 1

FIG. 29

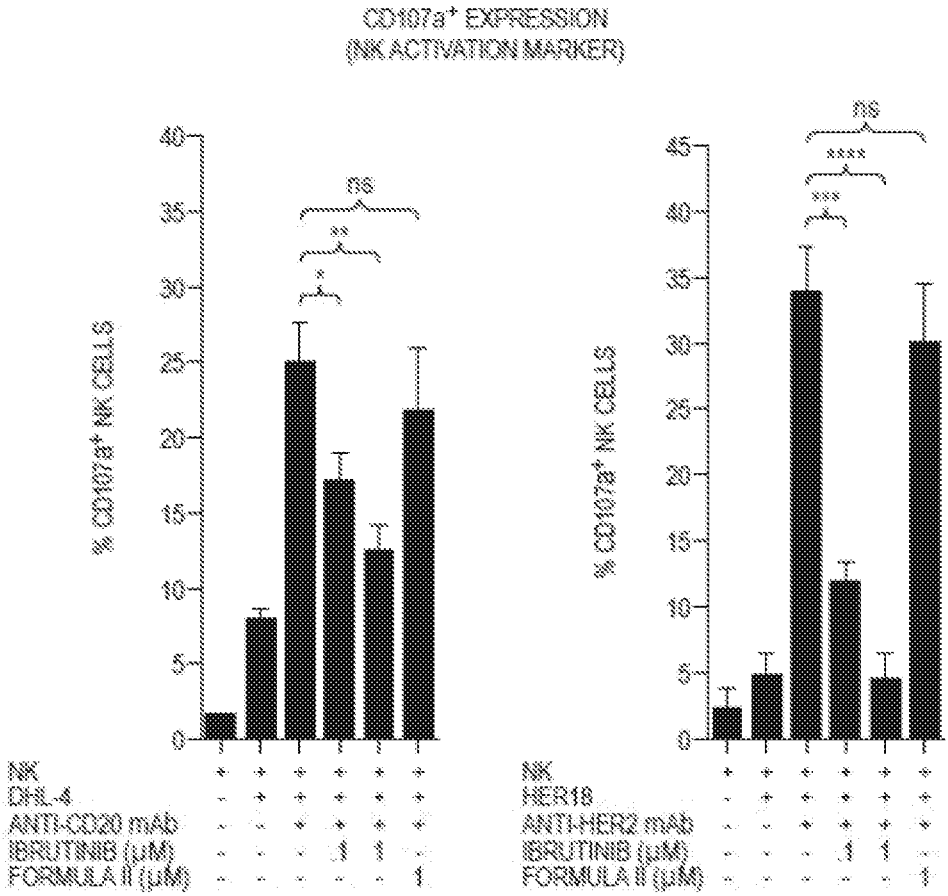

CD107a+ EXPRESSION
(NK ACTIVATION MARKER)
% CD107a+ NK CELLS
ns
*
**
****
NK
DHL-4
ANTI-CD20 mAb
IBRUTINIB (μM)
FORMULA II (μM)
HER18
ANTI-HER2 mAb

FIG. 30

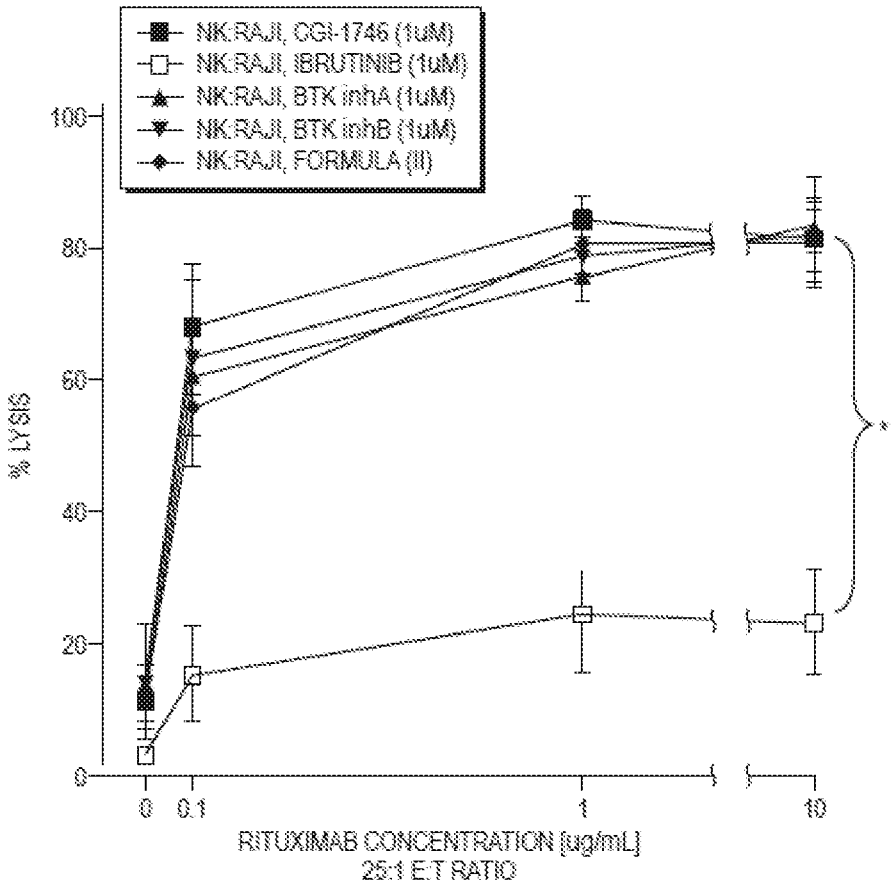

NK:RAJI, CGI-1746 (1uM)
NK:RAJI, IBRUTINIB (1uM)
NK:RAJI, BTK inhA (1uM)
NK:RAJI, BTK inhB (1uM)
NK:RAJI, FORMULA (II)
% LYSIS
100
80
60
40
20
0
0
0.1
1
10
*
RITUXIMAB CONCENTRATION [ug/mL]
25:1 E:T RATIO

FIG. 31

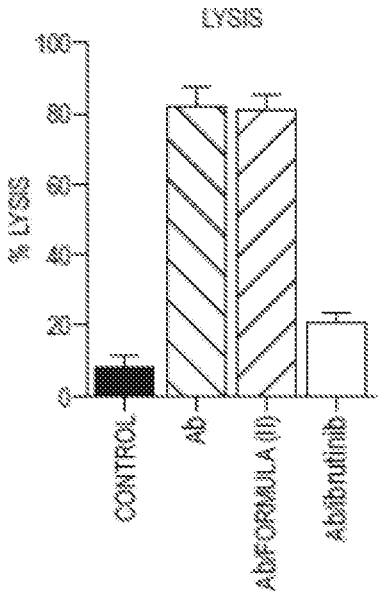

LYSIS
% LYSIS
100
80
60
40
20
0
CONTROL
Ab
ABFORMULA (II)
Abitrutinib

FIG. 32

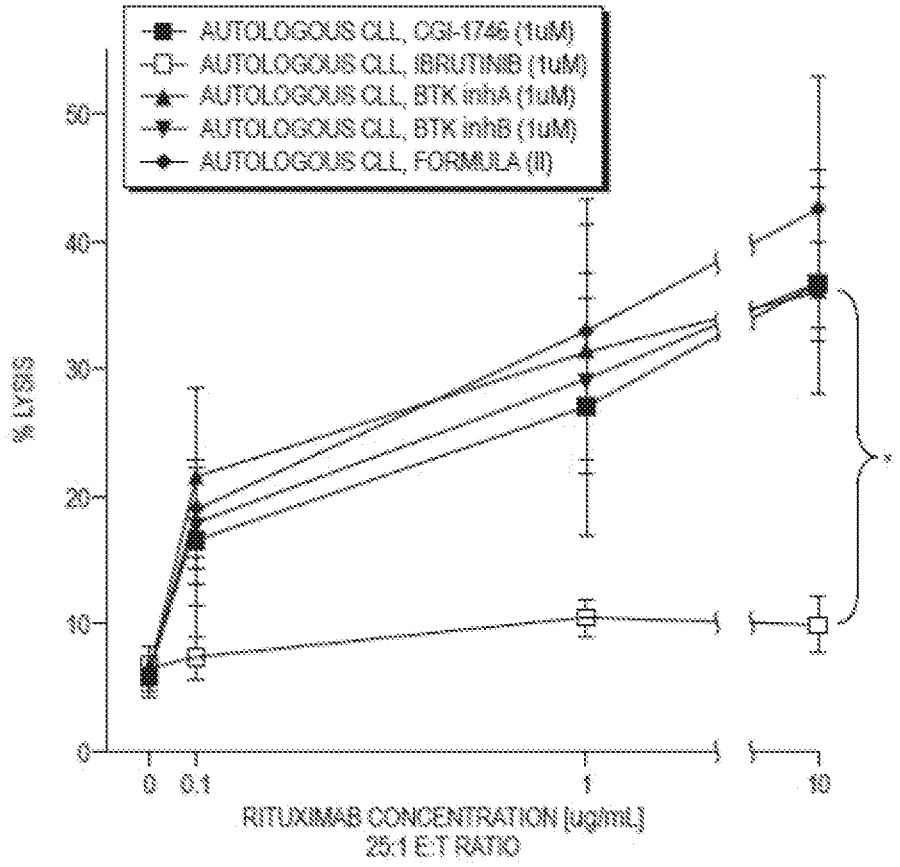

AUTOLOGOUS CLL, CGI-1746 (1uM)
AUTOLOGOUS CLL, IBRUTINIB (1uM)
AUTOLOGOUS CLL, BTK inhA (1uM)
AUTOLOGOUS CLL, BTK inhB (1uM)
AUTOLOGOUS CLL, FORMULA (II)
% LYSIS
50
40
30
20
10
0
0
0.1
1
10
RITUXIMAB CONCENTRATION [ug/mL]
25:1 E:T RATIO

FIG. 33

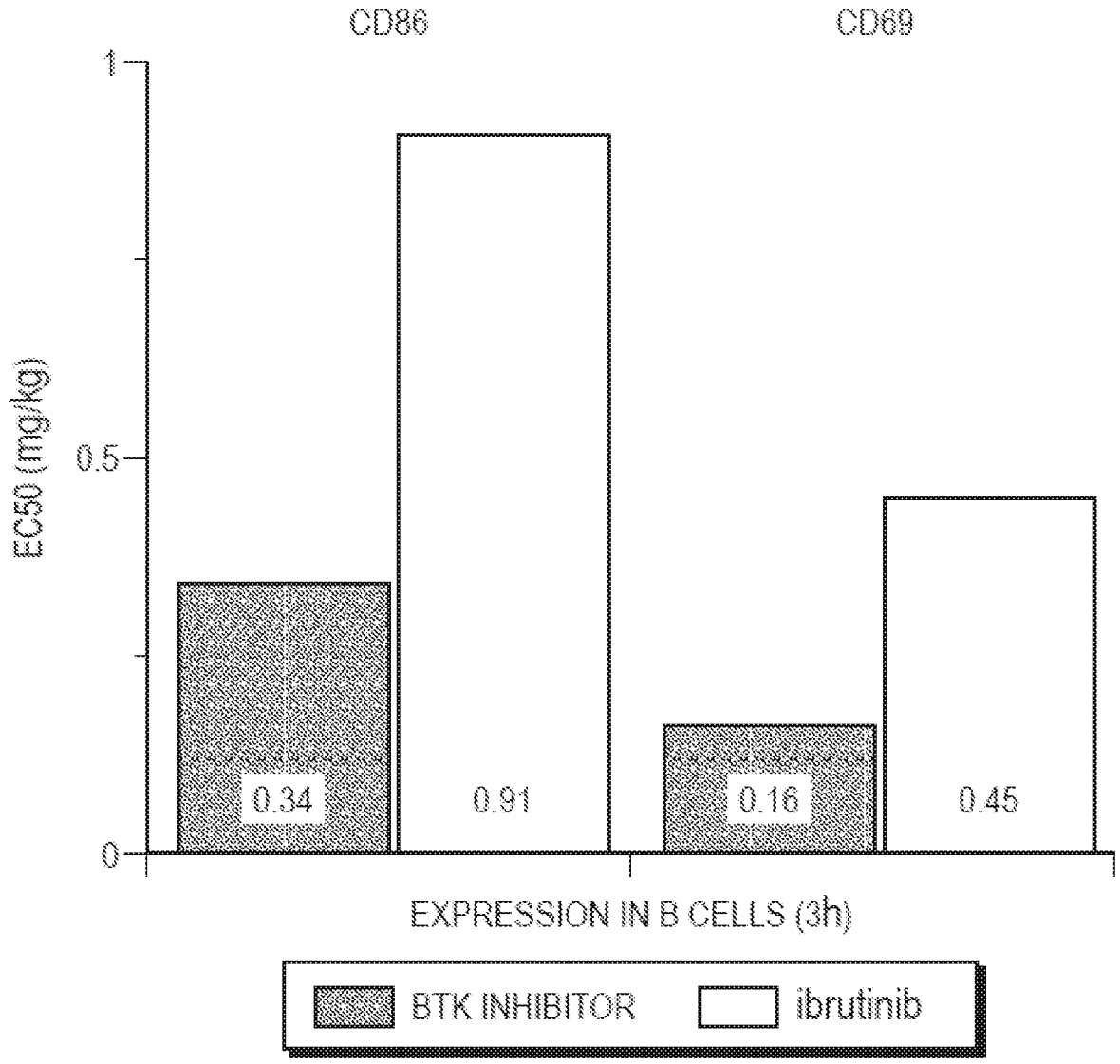

CD86
CD69
1
0.5
0
EC50 (mg/kg)
0.34
0.91
0.16
0.45
EXPRESSION IN B CELLS (3h)
BTK INHIBITOR
ibrutinib

FIG. 34

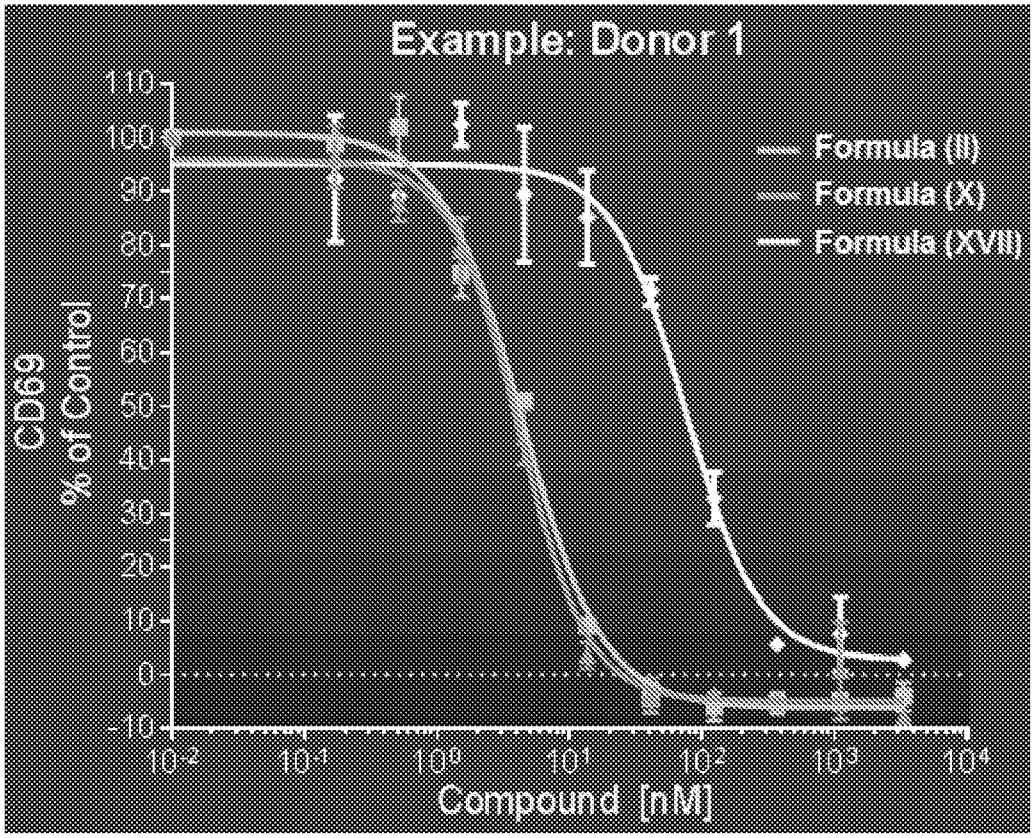

Example: Donor 1
Formula (II)
Formula (X)
Formula (XVII)
CD69
% of Control
110
100
90
80
70
60
50
40
30
20
10
0
-10
10-2
10-1
100
101
102
103
104
Compound [nM]

FIG. 35

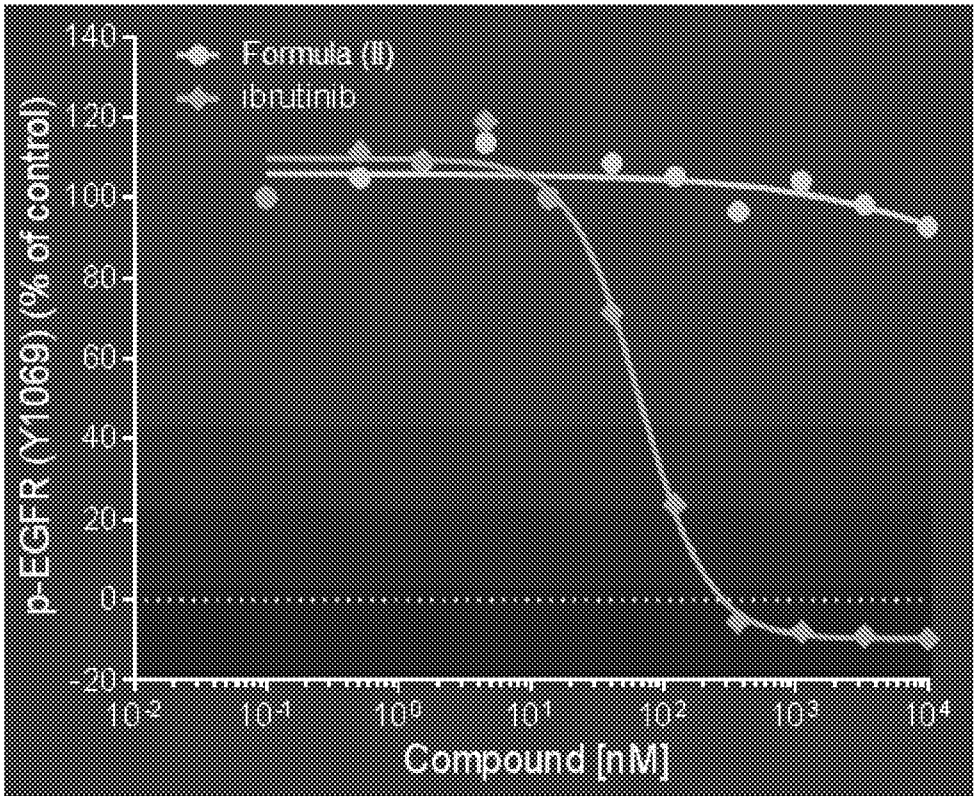

Formula (II)
Ibrutinib
p-EGFR (Y1069) (% of control)
140
120
100
80
60
40
20
0
-20
$10^{-2}$
$10^{-1}$
$10^{0}$
$10^{1}$
$10^{2}$
$10^{3}$
$10^{4}$
Compound [nM]

FIG. 36

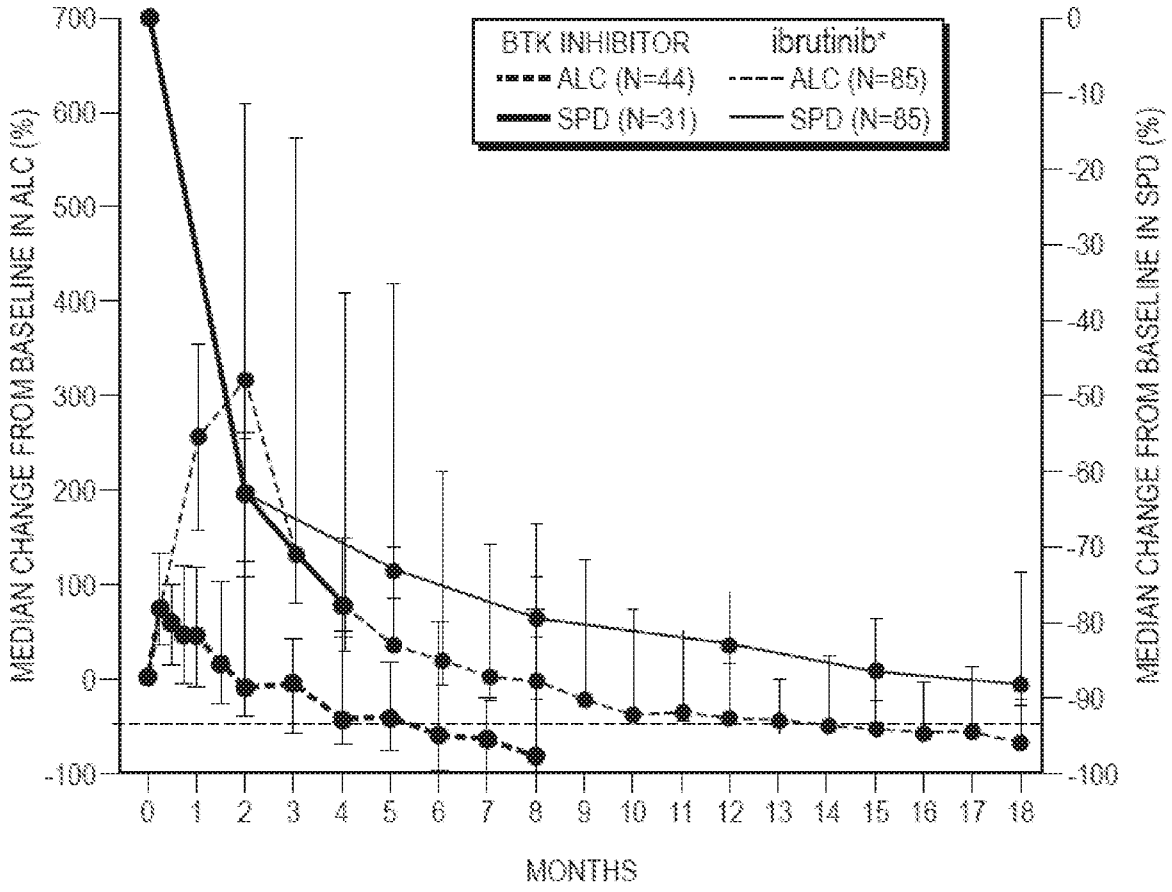

BTK INHIBITOR
ibrutinib*
ALC (N=44)
SPD (N=31)
ALC (N=85)
SPD (N=85)
MEDIAN CHANGE FROM BASELINE IN ALC (%)
MEDIAN CHANGE FROM BASELINE IN SPD (%)
700
600
500
400
300
200
100
0
-100
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
MONTHS

FIG. 37

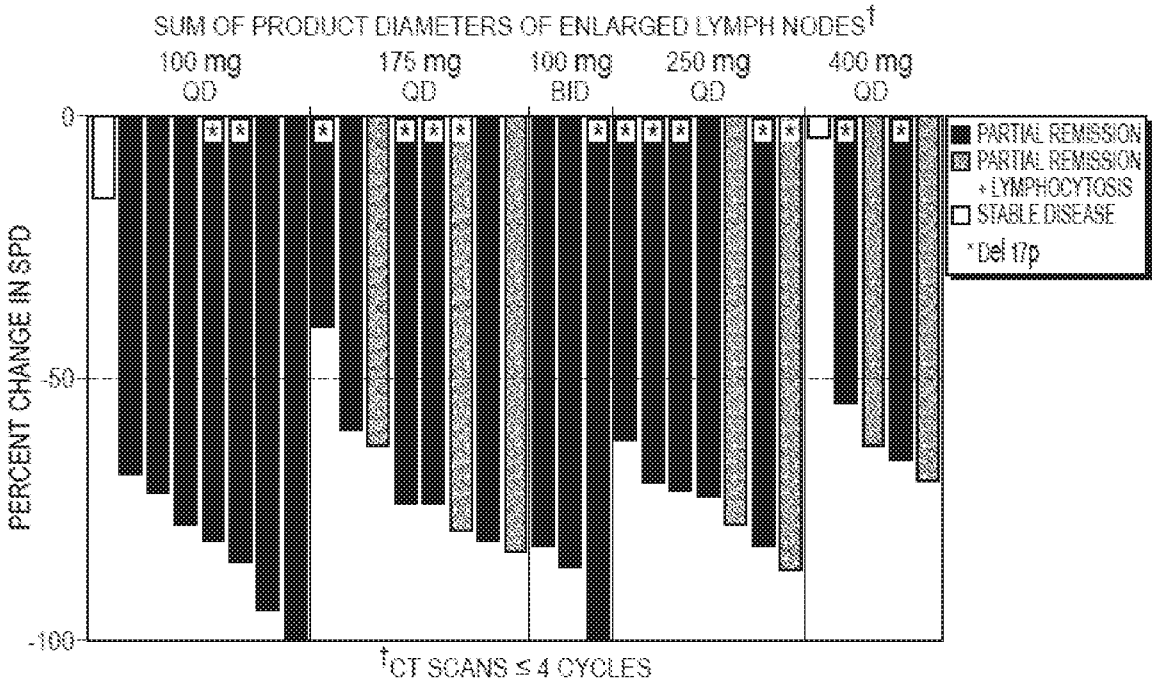

SUM OF PRODUCT DIAMETERS OF ENLARGED LYMPH NODES†
100 mg QD
175 mg QD
100 mg BID
250 mg QD
400 mg QD
0
-50
-100
PERCENT CHANGE IN SPD
PARTIAL REMISSION
PARTIAL REMISSION + LYMPHOCYTOSIS
STABLE DISEASE
* Del 17p
†CT SCANS ≤ 4 CYCLES

FIG. 38

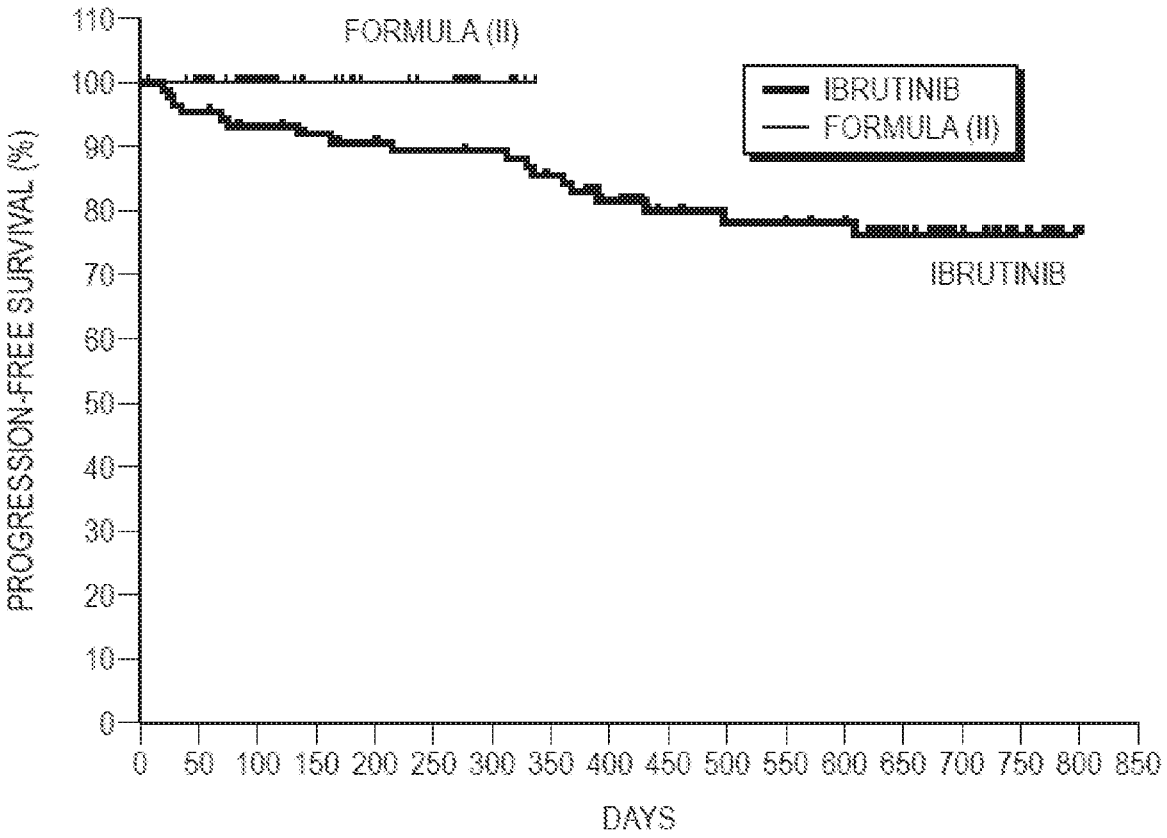

FORMULA (II)
IBRUTINIB
FORMULA (II)
IBRUTINIB
PROGRESSION-FREE SURVIVAL (%)
110
100
90
80
70
60
50
40
30
20
10
0
0 50 100 150 200 250 300 350 400 450 500 550 600 650 700 750 800 850
DAYS

FIG. 39

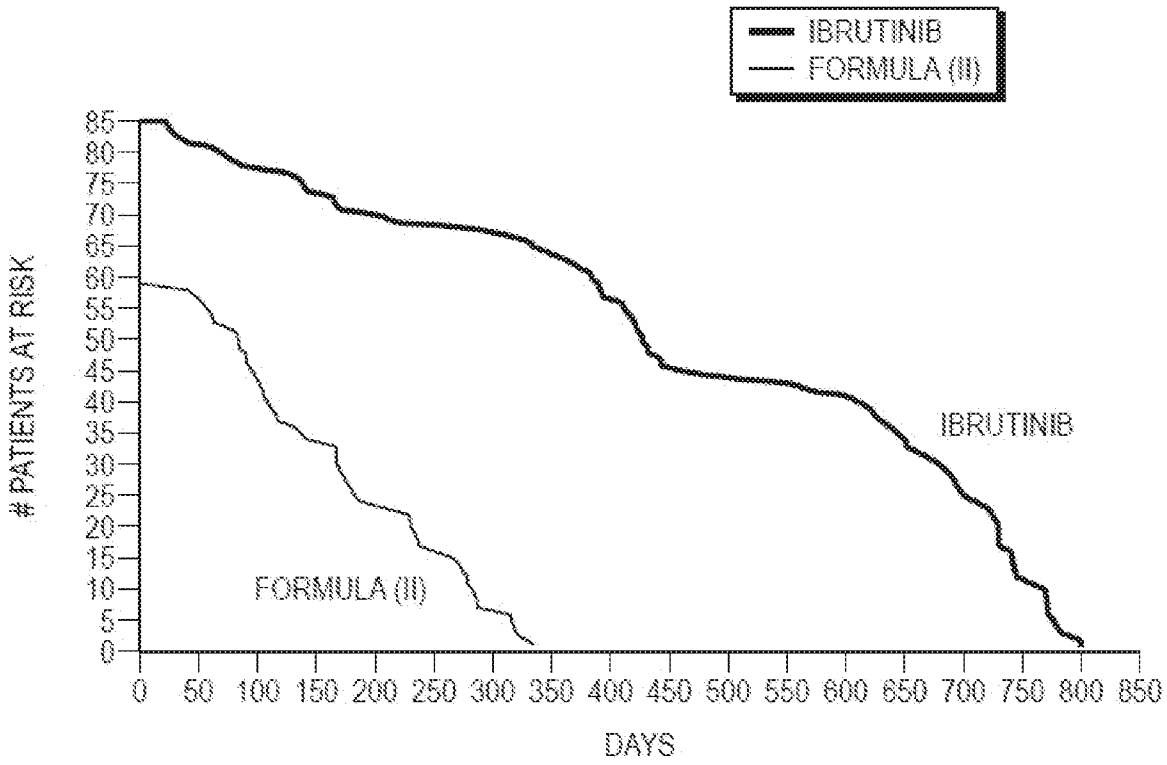

IBRUTINIB
FORMULA (II)
# PATIENTS AT RISK
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
IBRUTINIB
FORMULA (II)
0 50 100 150 200 250 300 350 400 450 500 550 600 650 700 750 800 850
DAYS

FIG. 40

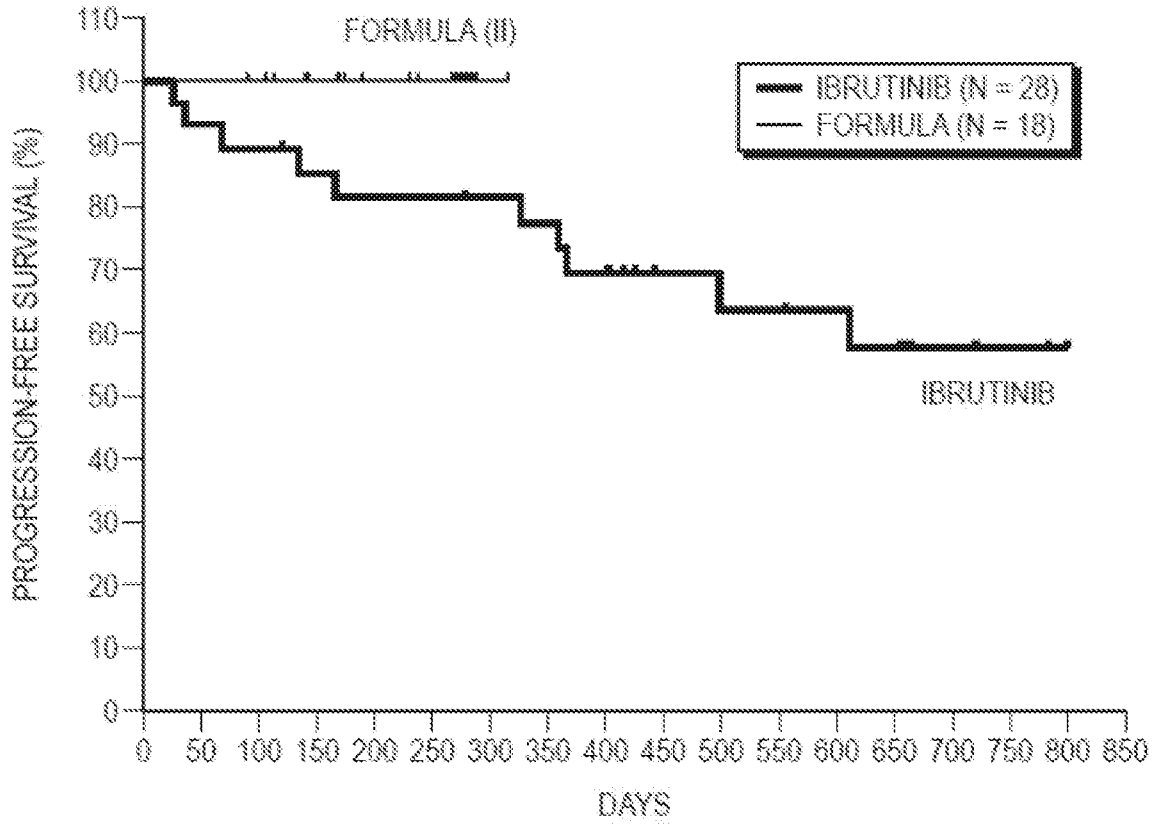

FORMULA (II)
IBRUTINIB (N = 28)
FORMULA (N = 18)
IBRUTINIB
PROGRESSION-FREE SURVIVAL (%)
110
100
90
80
70
60
50
40
30
20
10
0
0 50 100 150 200 250 300 350 400 450 500 550 600 650 700 750 800 850
DAYS

FIG. 41

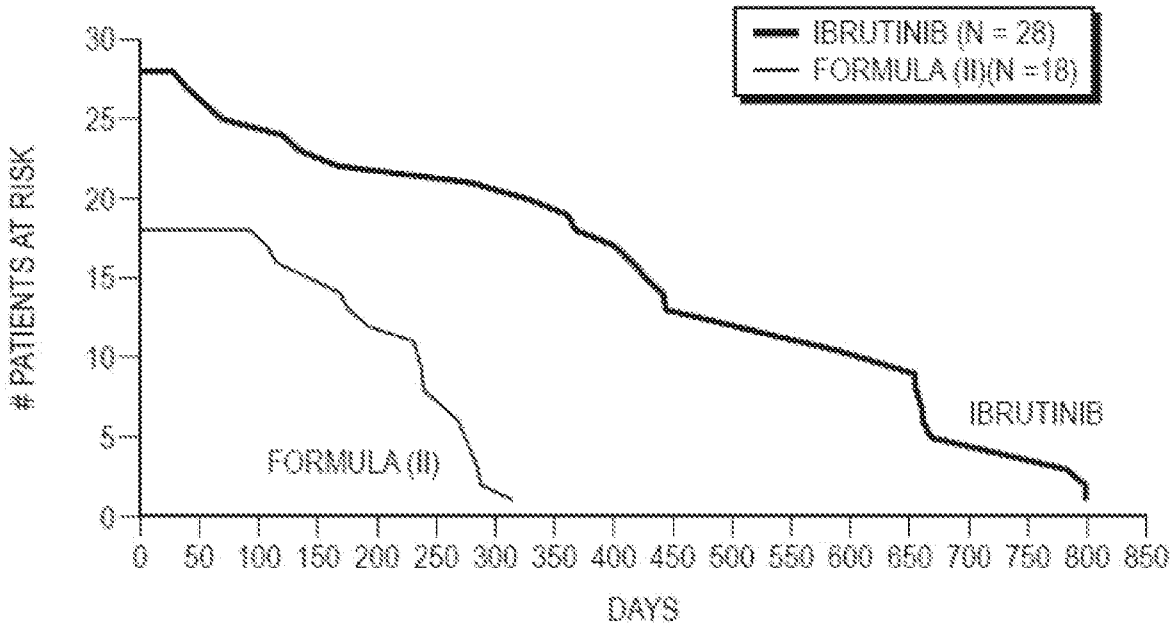

IBRUTINIB (N = 28)
FORMULA (II)(N =18)
# PATIENTS AT RISK
30
25
20
15
10
5
0
IBRUTINIB
FORMULA (II)
0 50 100 150 200 250 300 350 400 450 500 550 600 650 700 750 800 850
DAYS

FIG. 42

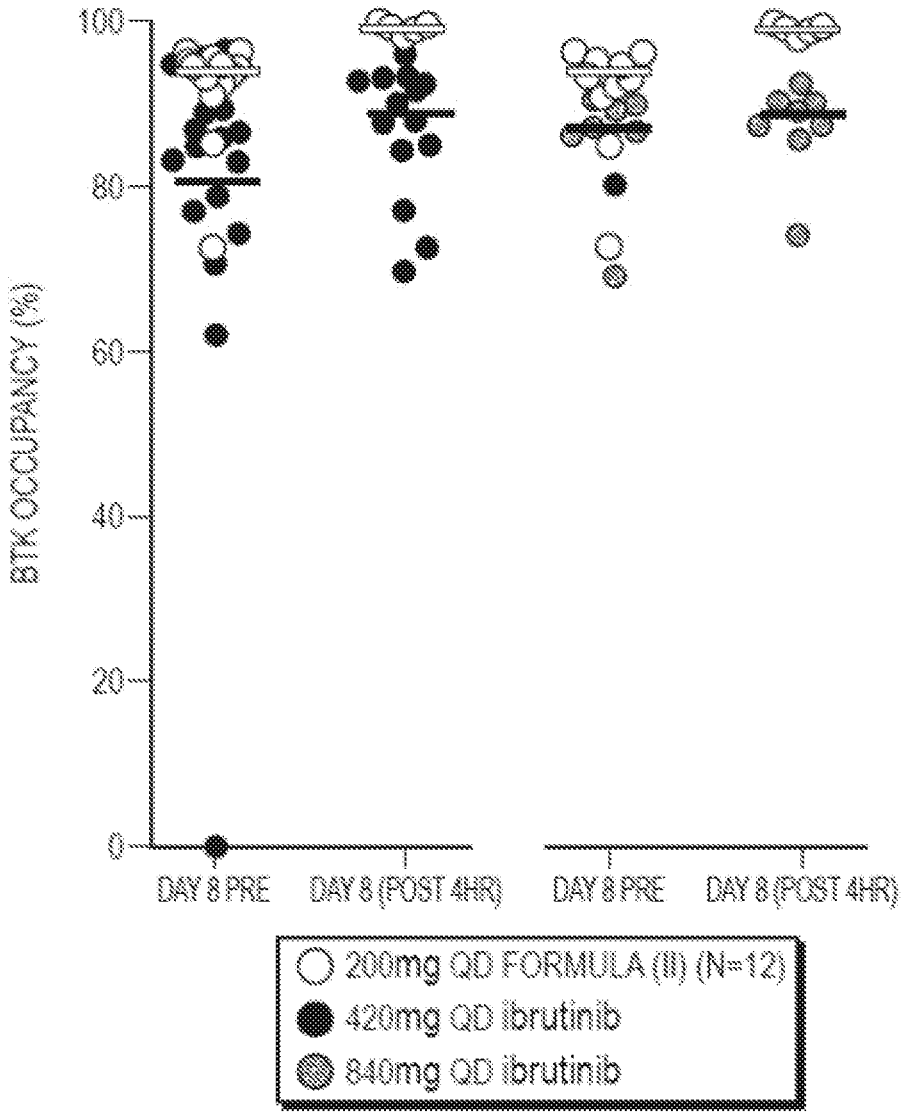

100
80
60
40
20
0
BTK OCCUPANCY (%)
DAY 8 PRE
DAY 8 (POST 4HR)
DAY 8 PRE
DAY 8 (POST 4HR)
200mg QD FORMULA (II) (N=12)
420mg QD ibrutinib
840mg QD ibrutinib

FIG. 43

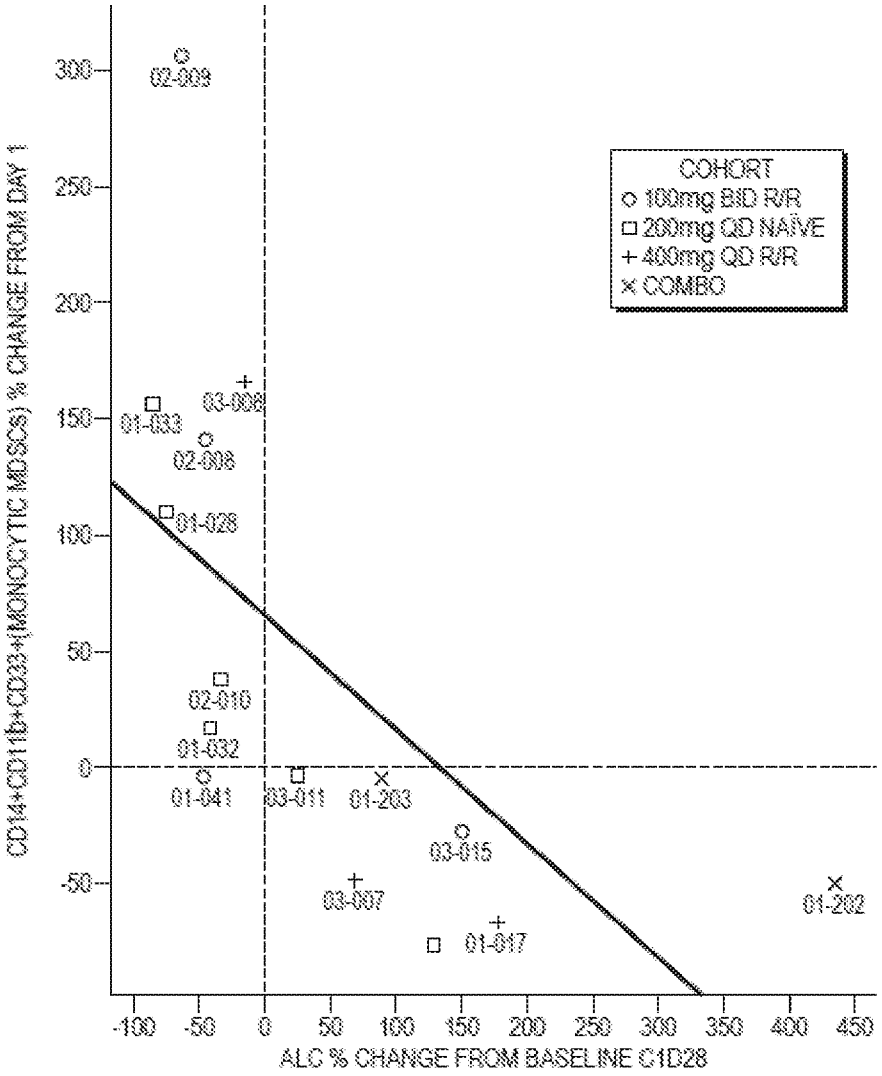

COHORT
100mg BID R/R
200mg QD NAÏVE
400mg QD R/R
COMBO
CD14+CD11b+CD33+(MONOCYTIC MDSCs) % CHANGE FROM DAY 1
ALC % CHANGE FROM BASELINE C1D28
300
250
200
150
100
50
0
-50
-100
-50
0
50
100
150
200
250
300
350
400
450
02-009
03-006
01-033
02-008
01-028
02-010
01-032
01-041
03-011
01-203
03-015
03-007
01-017
01-202

FIG. 44

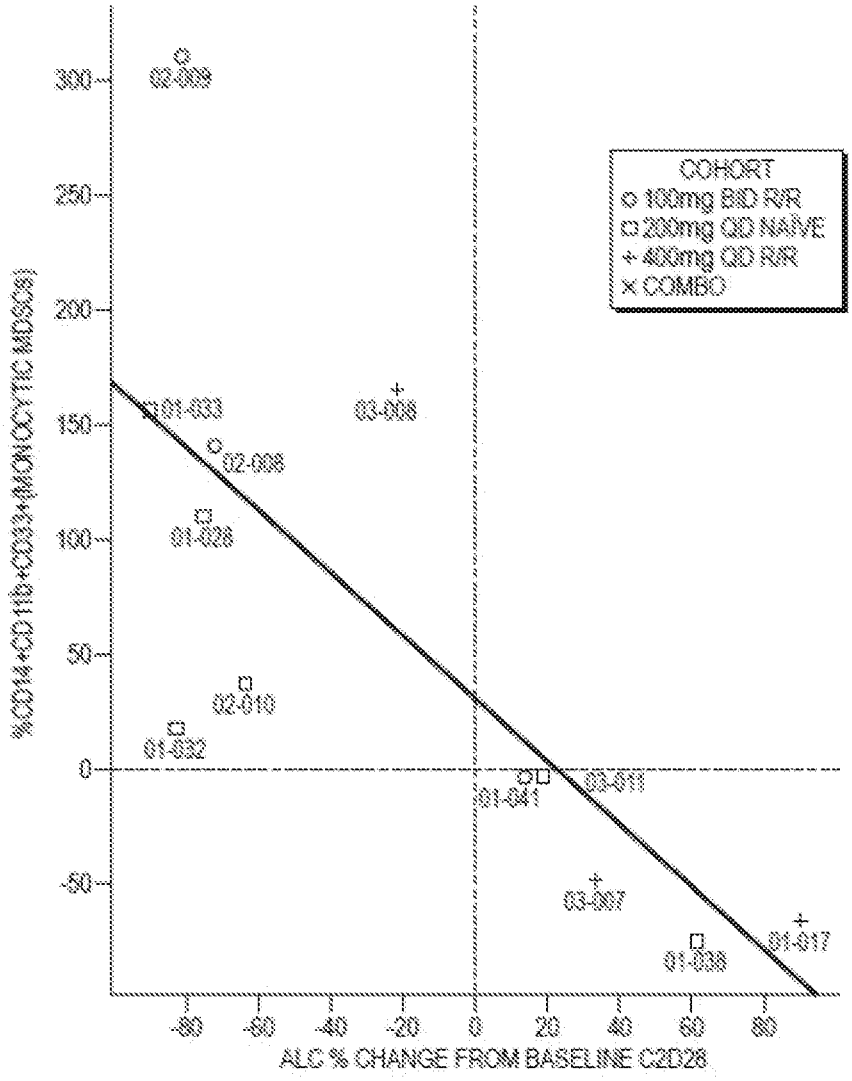

COHORT
100mg BID R/R
200mg QD NAÏVE
400mg QD R/R
COMBO
%(CD14+CD11b+CD33+)MON(CCYTIC MDSCs)
ALC % CHANGE FROM BASELINE C2D28
300
250
200
150
100
50
0
-50
-80
-60
-40
-20
0
20
40
60
80
02-009
01-033
03-008
02-008
01-028
02-010
01-032
01-041
03-011
03-007
01-017
01-038

FIG. 45

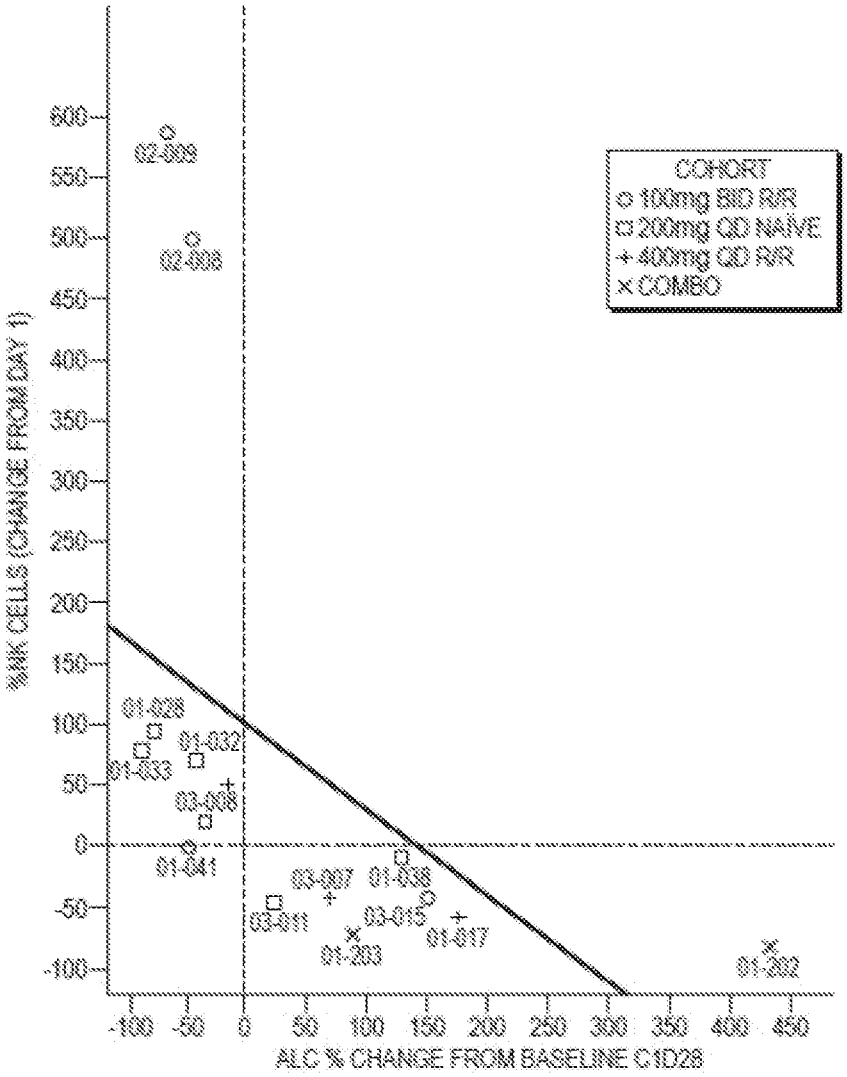

COHORT
100mg BID R/R
200mg QD NAÏVE
400mg QD R/R
COMBO
%NK CELLS (CHANGE FROM DAY 1)
ALC % CHANGE FROM BASELINE C1D28
02-009
02-008
01-028
01-032
01-033
03-006
01-041
03-007
01-038
03-011
03-015
01-017
01-203
01-202

FIG. 46

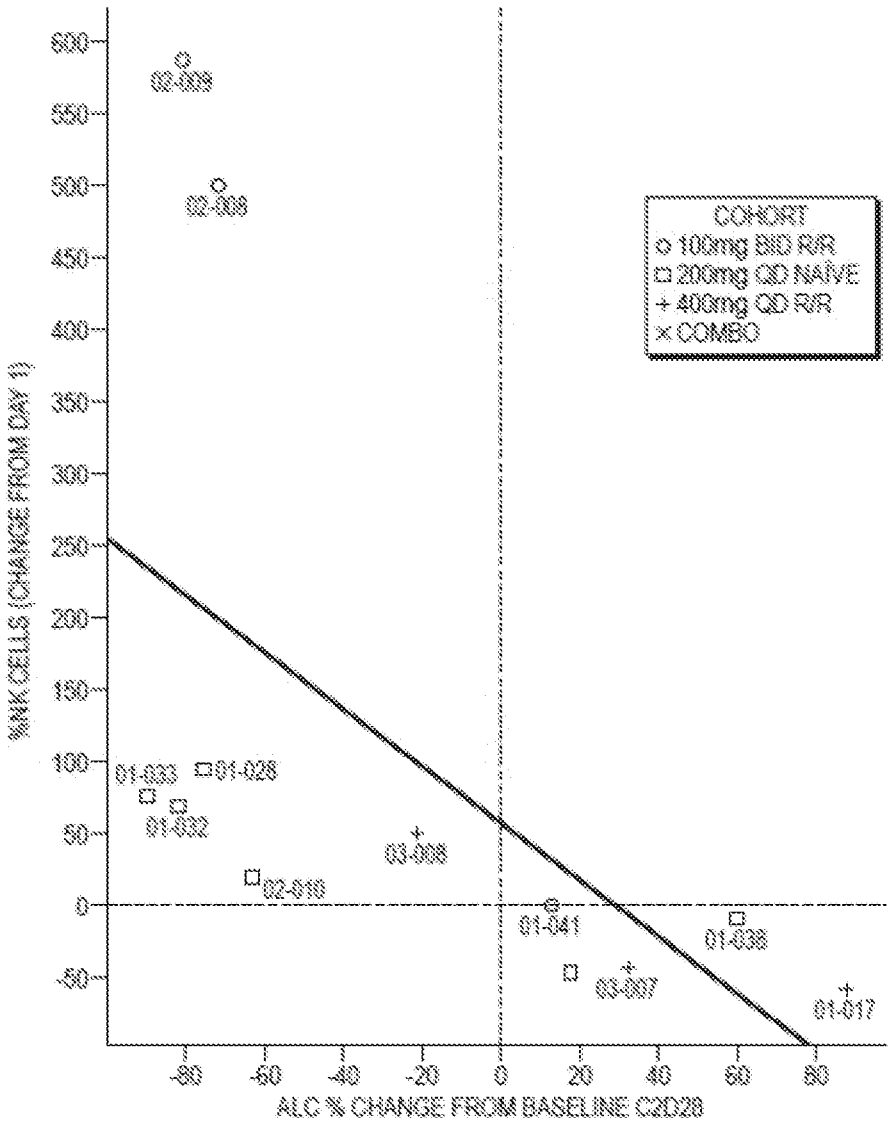

%NK CELLS (CHANGE FROM DAY 1)
ALC % CHANGE FROM BASELINE C2D28
COHORT
100mg BID R/R
200mg QD NAIVE
400mg QD R/R
COMBO
02-009
02-008
01-033
01-028
01-032
03-008
02-010
01-041
01-038
03-007
01-017

FIG. 47

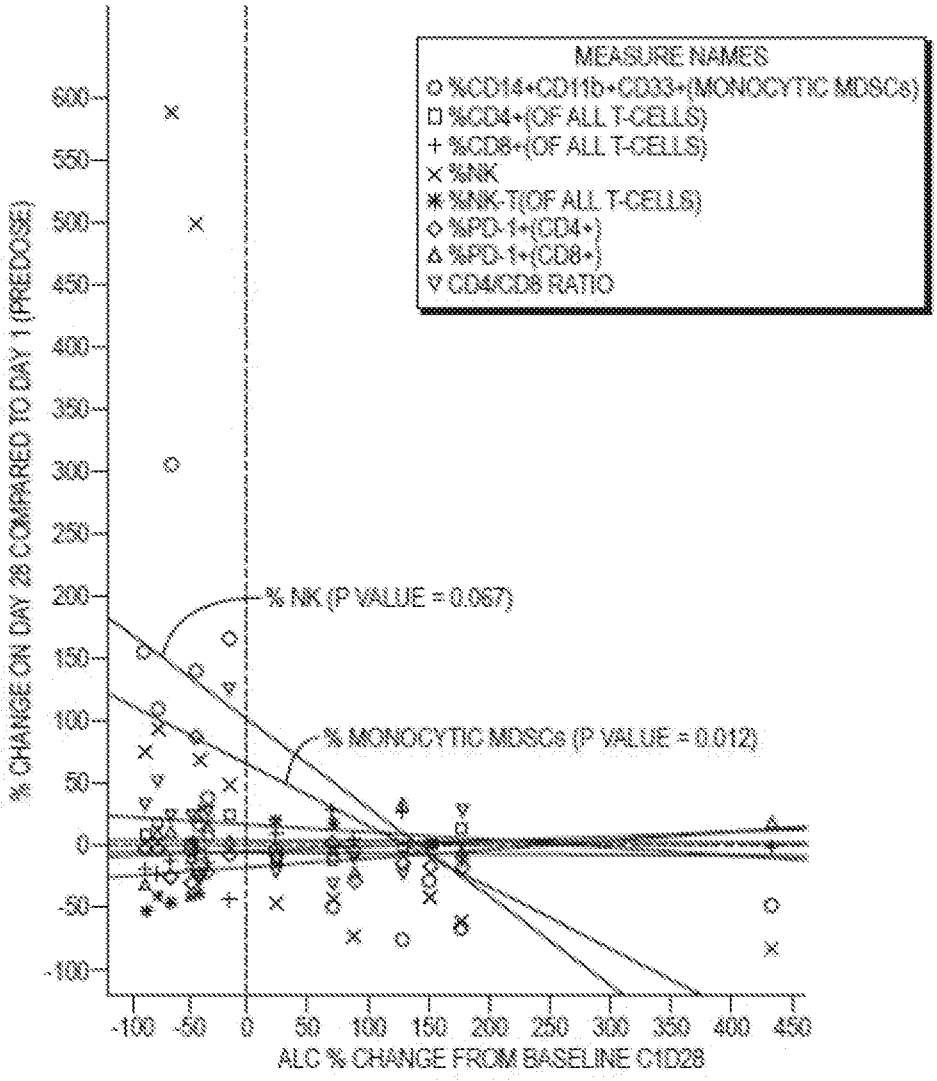

MEASURE NAMES
%CD14+CD11b+CD33+(MONOCYTIC MDSCs)
%CD4+(OF ALL T-CELLS)
%CD8+(OF ALL T-CELLS)
%NK
%NK-T(OF ALL T-CELLS)
%PD-1+(CD4+)
%PD-1+(CD8+)
CD4/CD8 RATIO
% NK (P VALUE = 0.057)
% MONOCYTIC MDSCs (P VALUE = 0.012)
% CHANGE ON DAY 28 COMPARED TO DAY 1 (PREDOSE)
ALC % CHANGE FROM BASELINE C1D28
600
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. 48

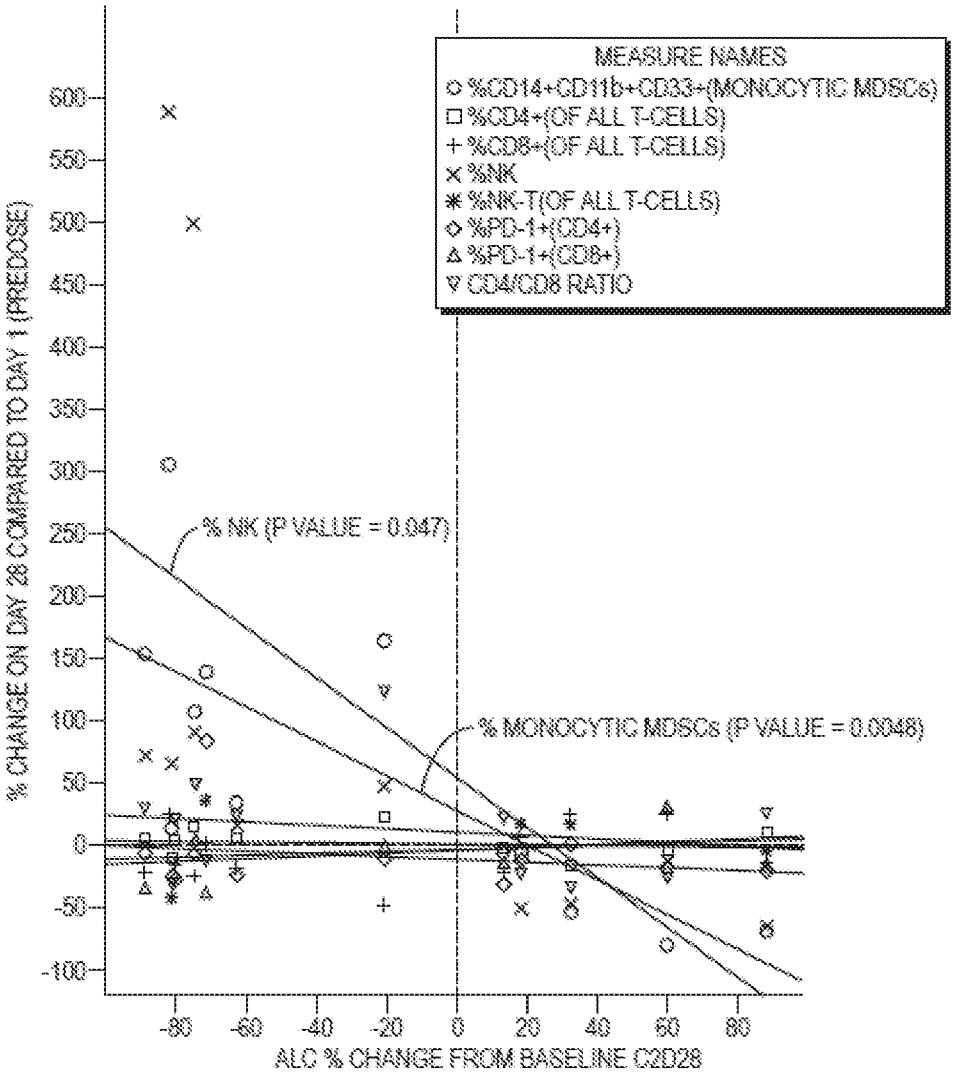

MEASURE NAMES
%CD14+CD11b+CD33+(MONOCYTIC MDSCs)
%CD4+(OF ALL T-CELLS)
%CD8+(OF ALL T-CELLS)
%NK
%NK-T(OF ALL T-CELLS)
%PD-1+(CD4+)
%PD-1+(CD8+)
CD4/CD8 RATIO
% NK (P VALUE = 0.047)
% MONOCYTIC MDSCs (P VALUE = 0.0048)
% CHANGE ON DAY 28 COMPARED TO DAY 1 (PREDOSE)
ALC % CHANGE FROM BASELINE C2D28
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
-100
-80
-60
-40
-20
0
20
40
60
80

FIG. 49

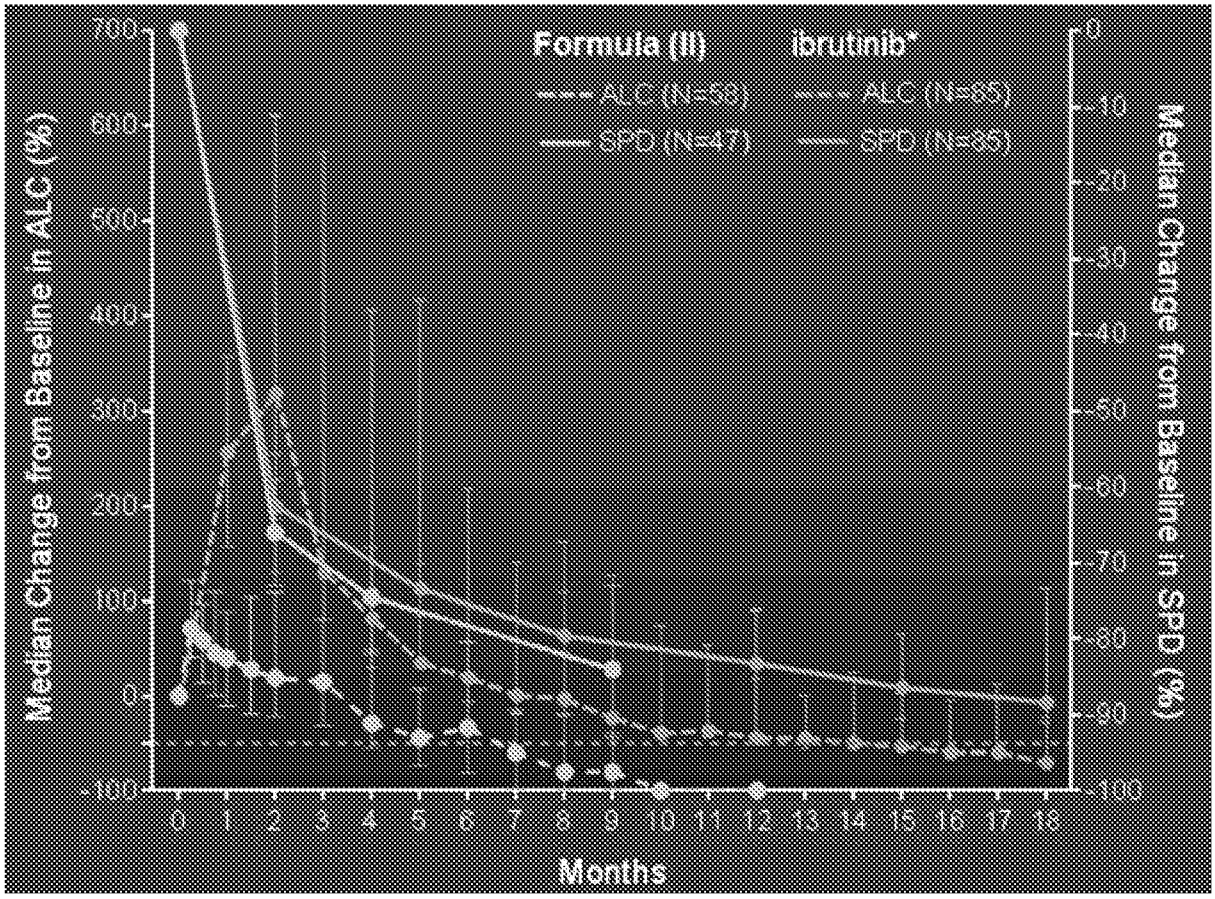

Formula (II)
ALC (N=58)
SPD (N=47)
ibrutinib*
ALC (N=55)
SPD (N=56)
Median Change from Baseline in ALC (%)
Median Change from Baseline in SPD (%)
Months
700
600
500
400
300
200
100
0
-100
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

FIG. 50

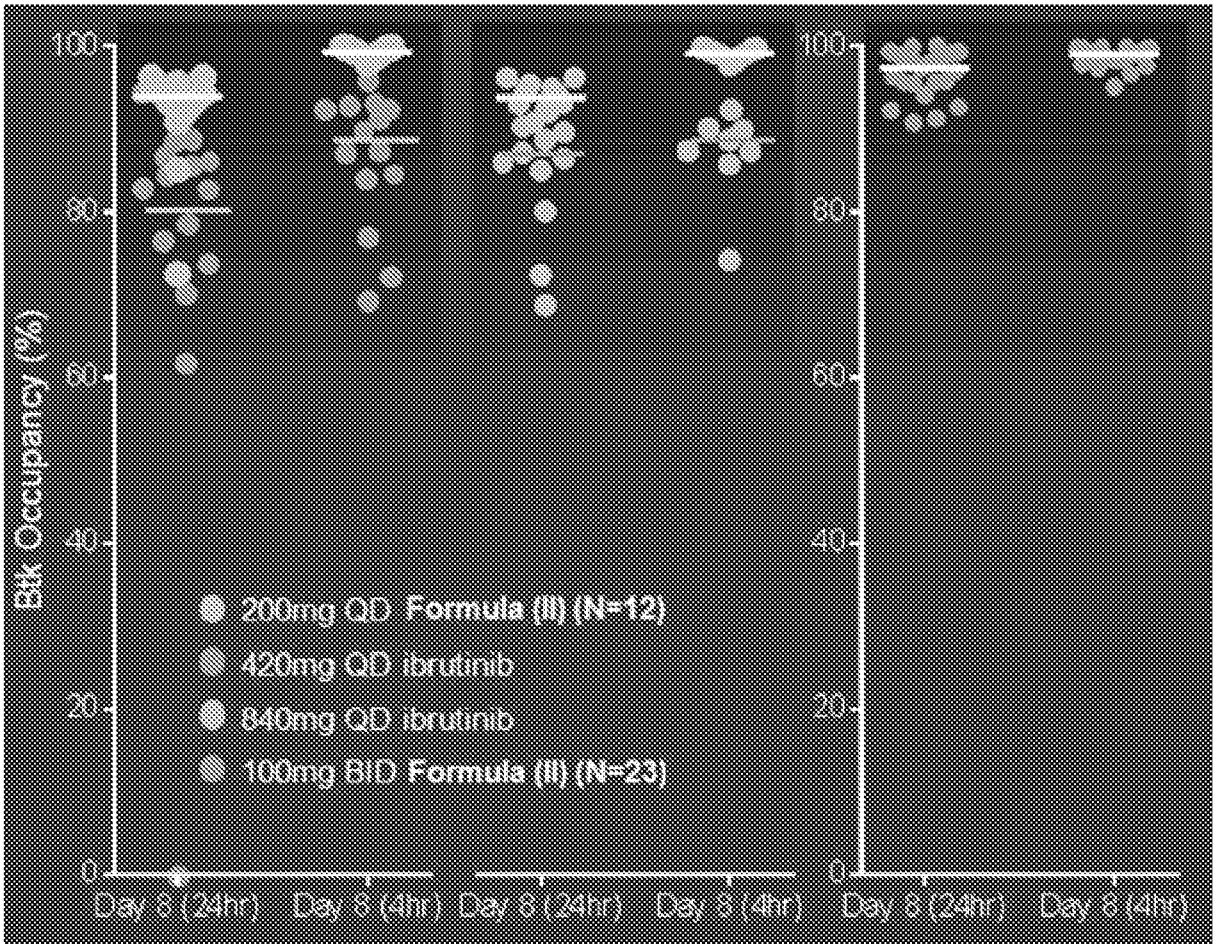
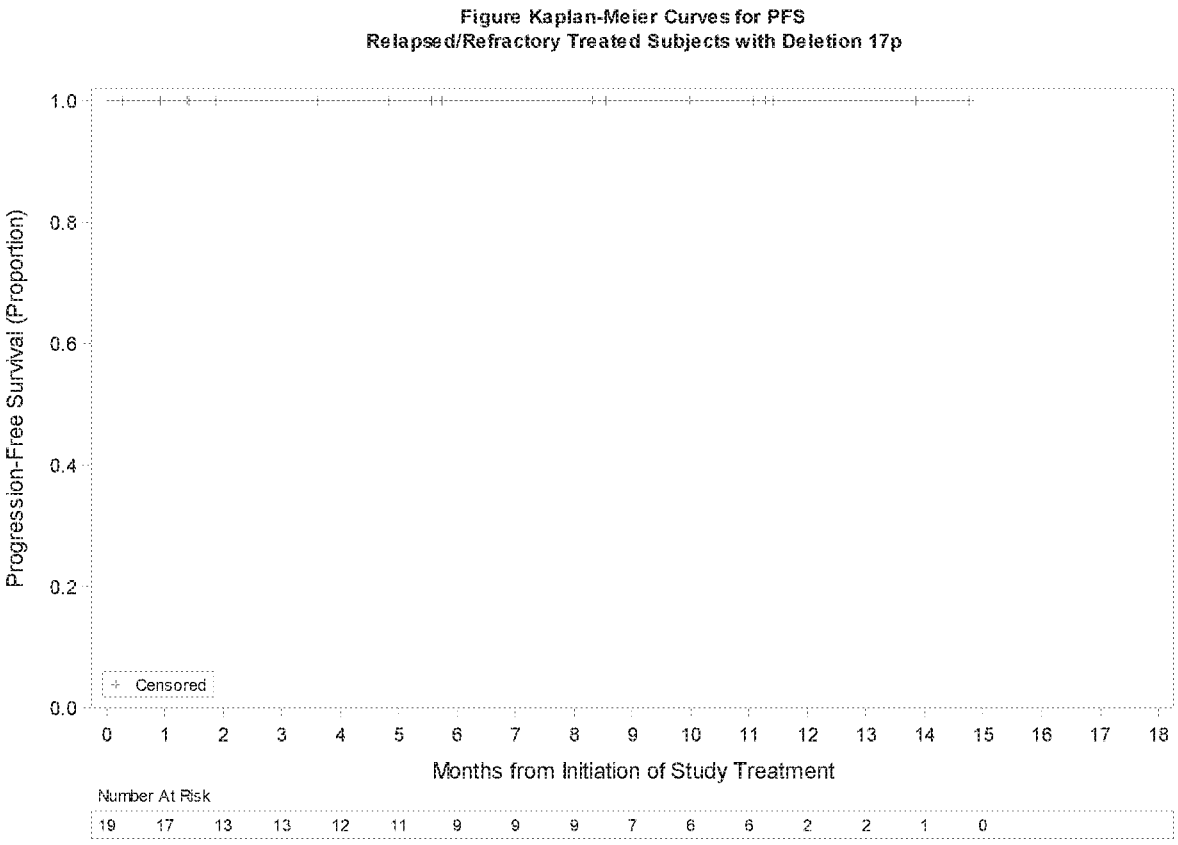
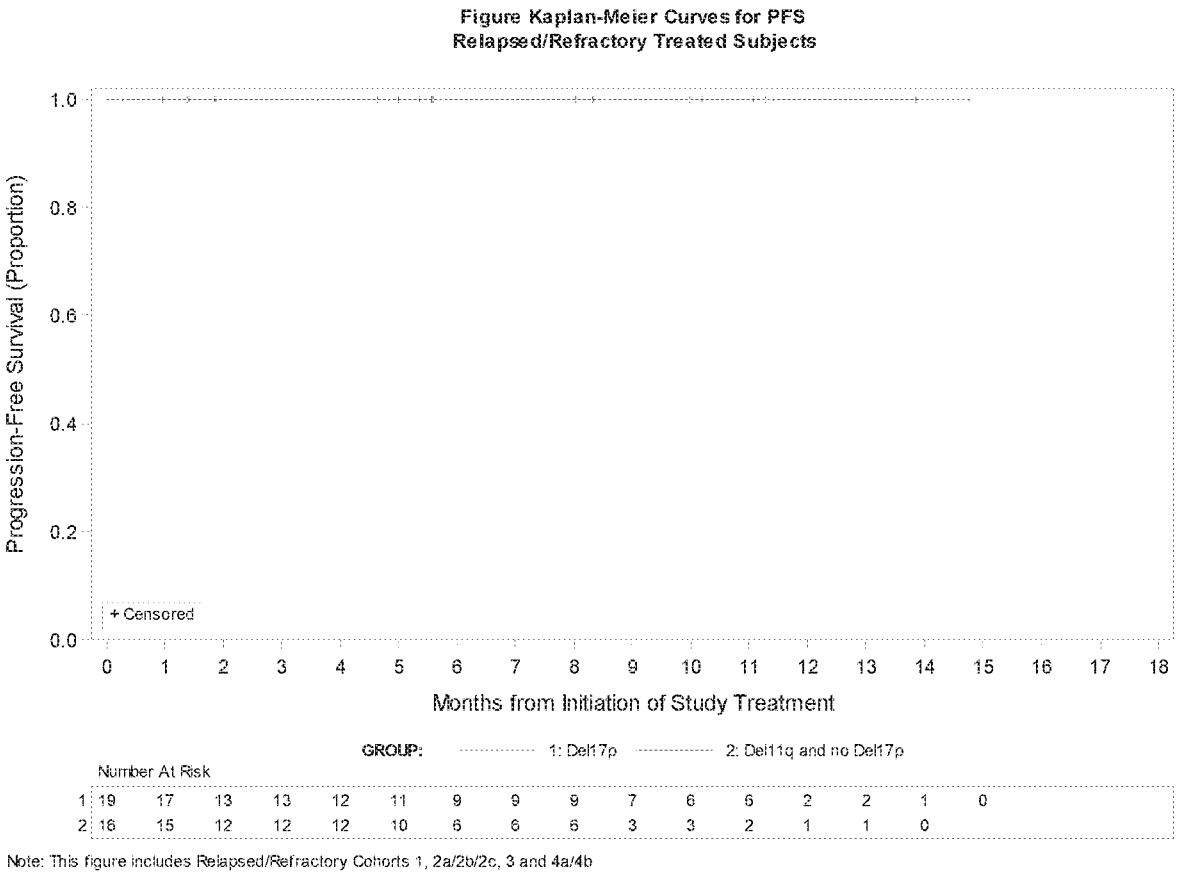

Btk Occupancy (%)
100
80
60
40
20
0
200mg QD Formula (II) (N=12)
420mg QD ibrutinib
840mg QD ibrutinib
100mg BID Formula (II) (N=23)
Day 8 (24hr)
Day 8 (4hr)
Day 8 (24hr)
Day 8 (4hr)
Day 8 (24hr)
Day 8 (4hr)

FIG. 51



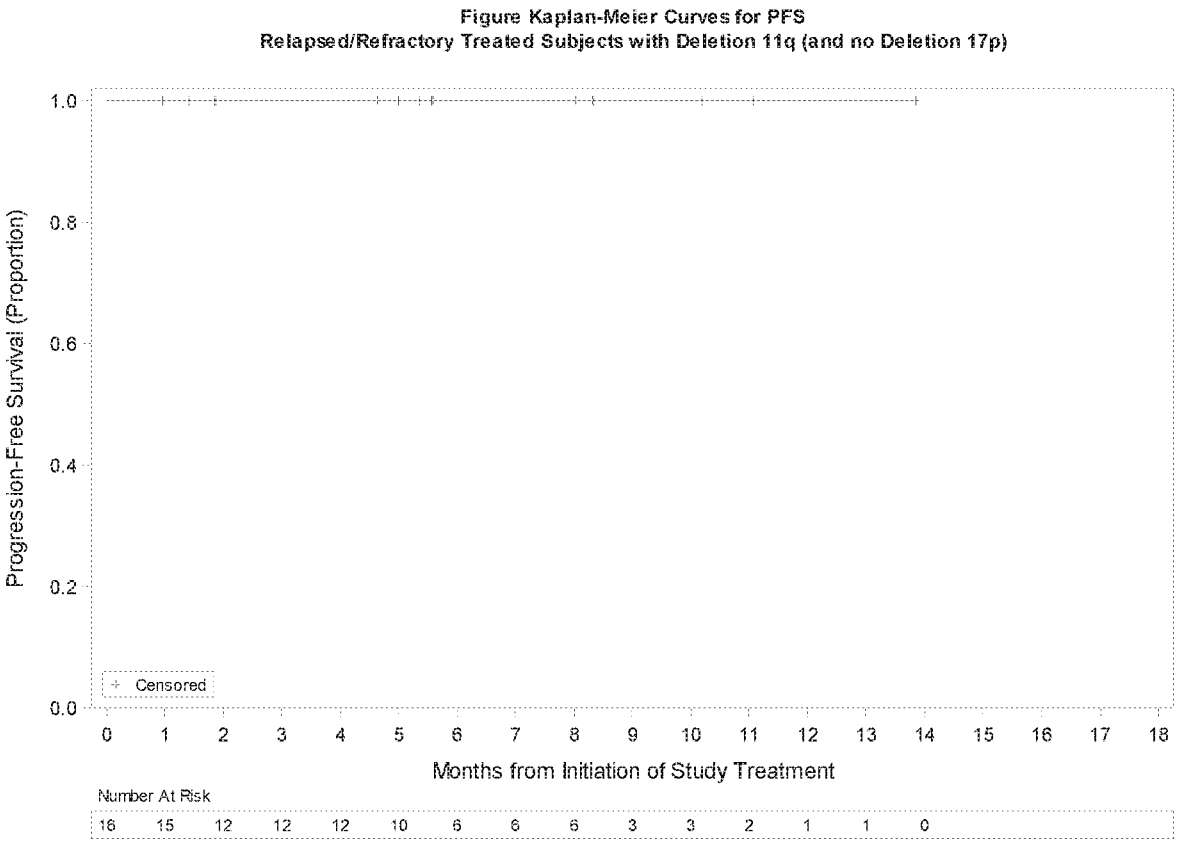

Note: This figure includes Relapsed/Refractory Cohorts 1, 2a/2b/2c, 3 and 4a/4b.

FIG. 52



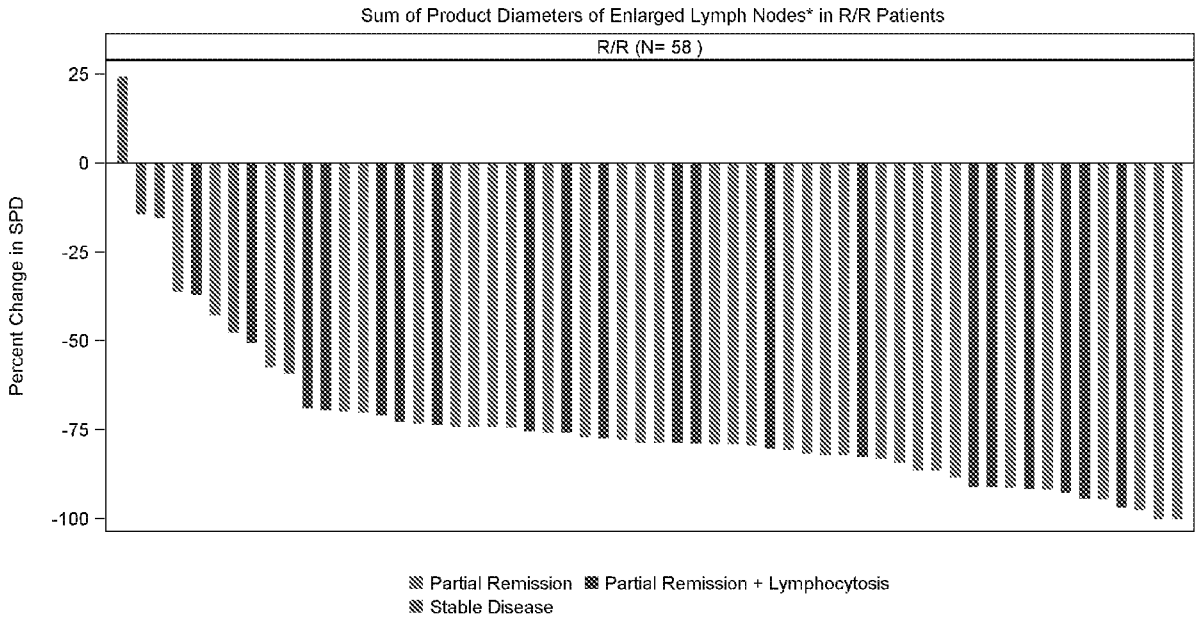

Note: This figure includes Relapsed/Refractory Cohorts 1, 2a/2b/2c, 3 and 4a/4b

FIG. 53




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

FIG. 54




*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. 55

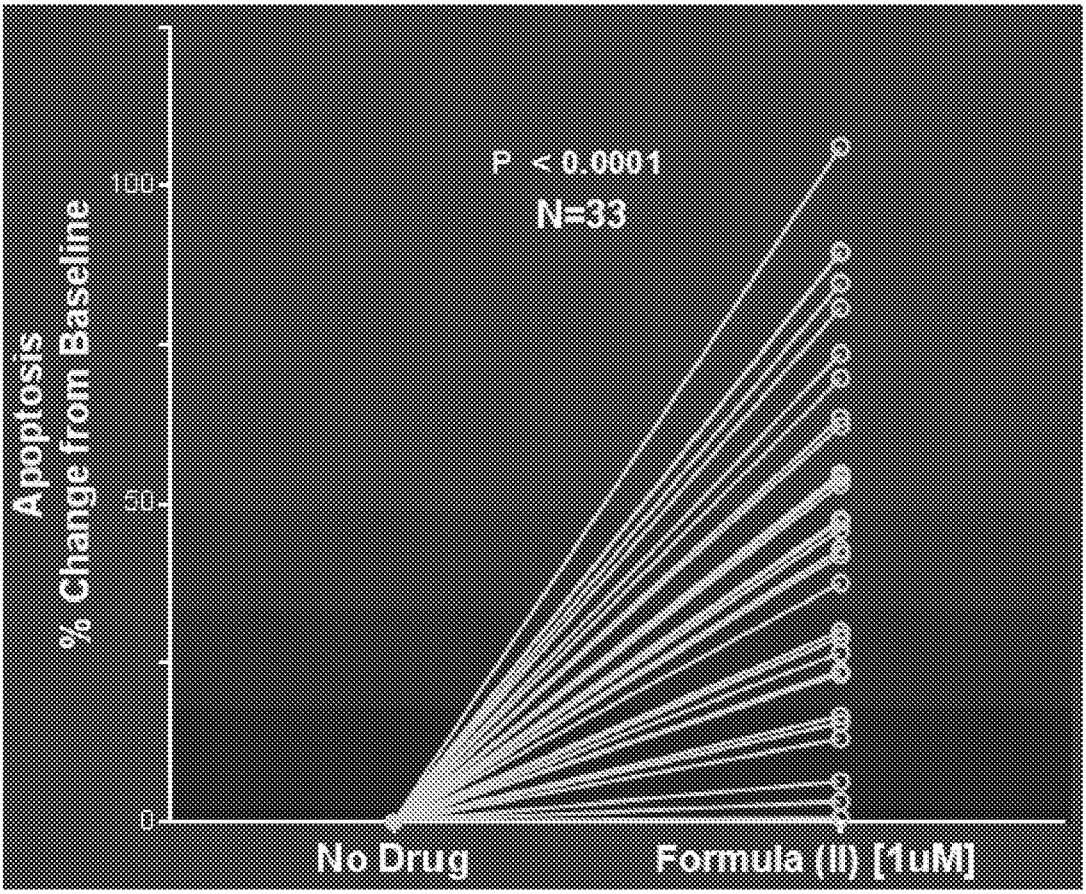

Apoptosis
% Change from Baseline
100
50
0
P < 0.0001
N=33
No Drug
Formula (II) [1uM]

FIG. 56

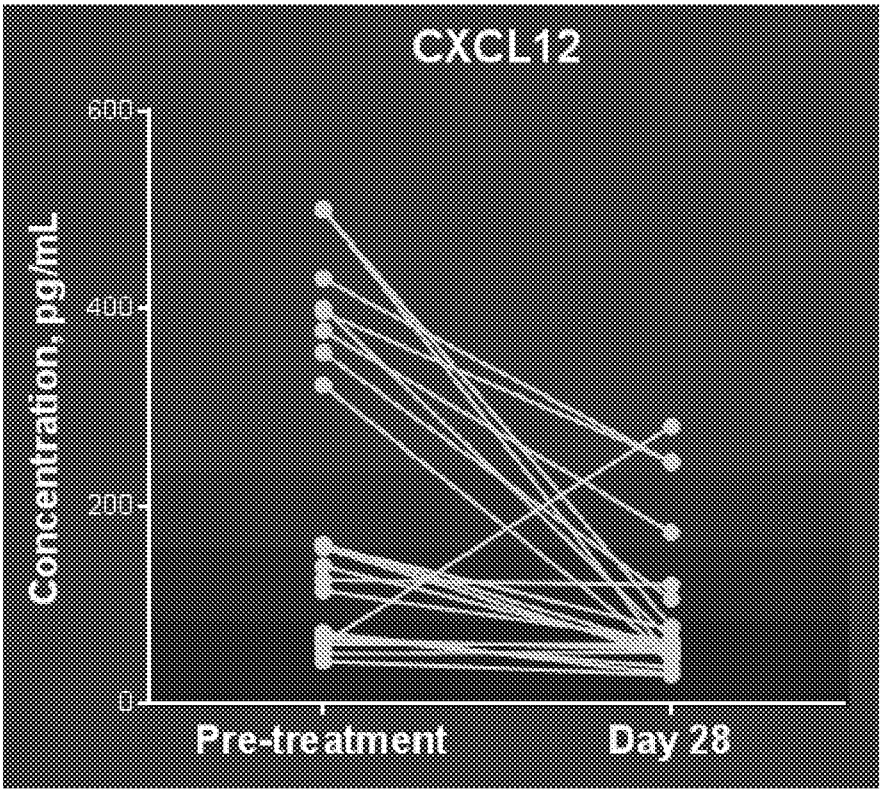

CXCL12
Concentration, pg/mL
600
400
200
0
Pre-treatment
Day 28

FIG. 57

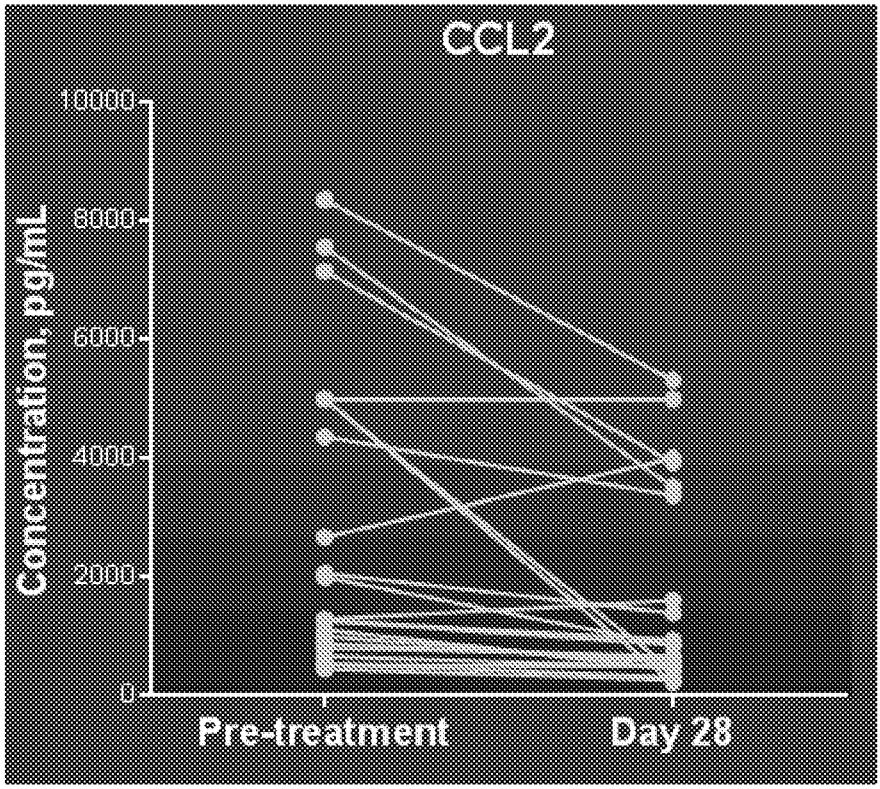

CCL2
Concentration, pg/mL
10000
8000
6000
4000
2000
0
Pre-treatment
Day 28

FIG. 58

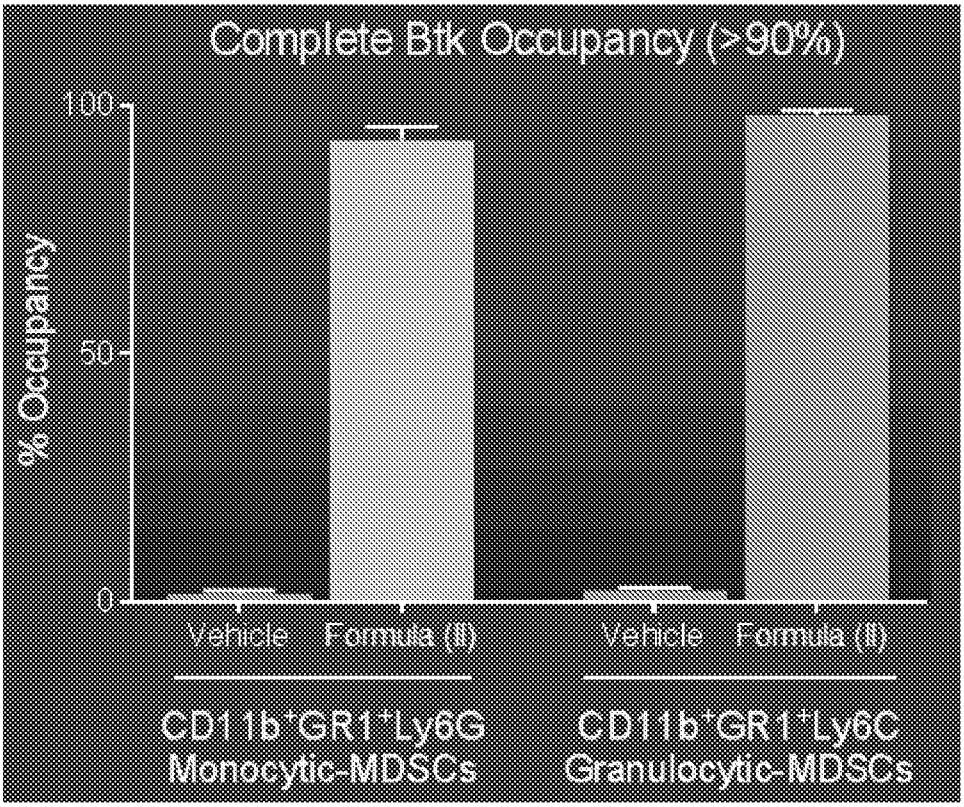

Complete Btk Occupancy (>90%)
% Occupancy
100
50
0
Vehicle
Formula (II)
Vehicle
Formula (II)
CD11b+GR1+Ly6G
Monocytic-MDSCs
CD11b+GR1+Ly6C
Granulocytic-MDSCs

FIG. 59

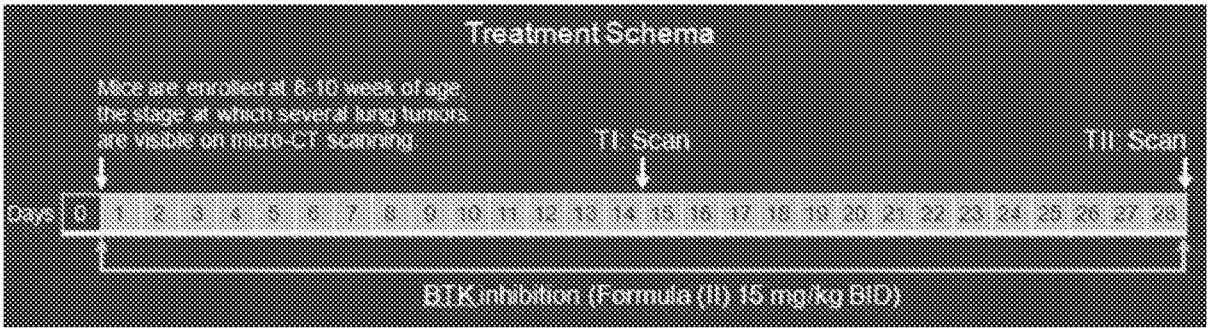

Treatment Schema
Mice are enrolled at 8-10 week of age,
the stage at which several lung tumors
are visible on micro-CT scanning
T1 Scan
T11 Scan
Days
0
BTK inhibition (Formula (II) 15 mg/kg BID)

FIG. 60

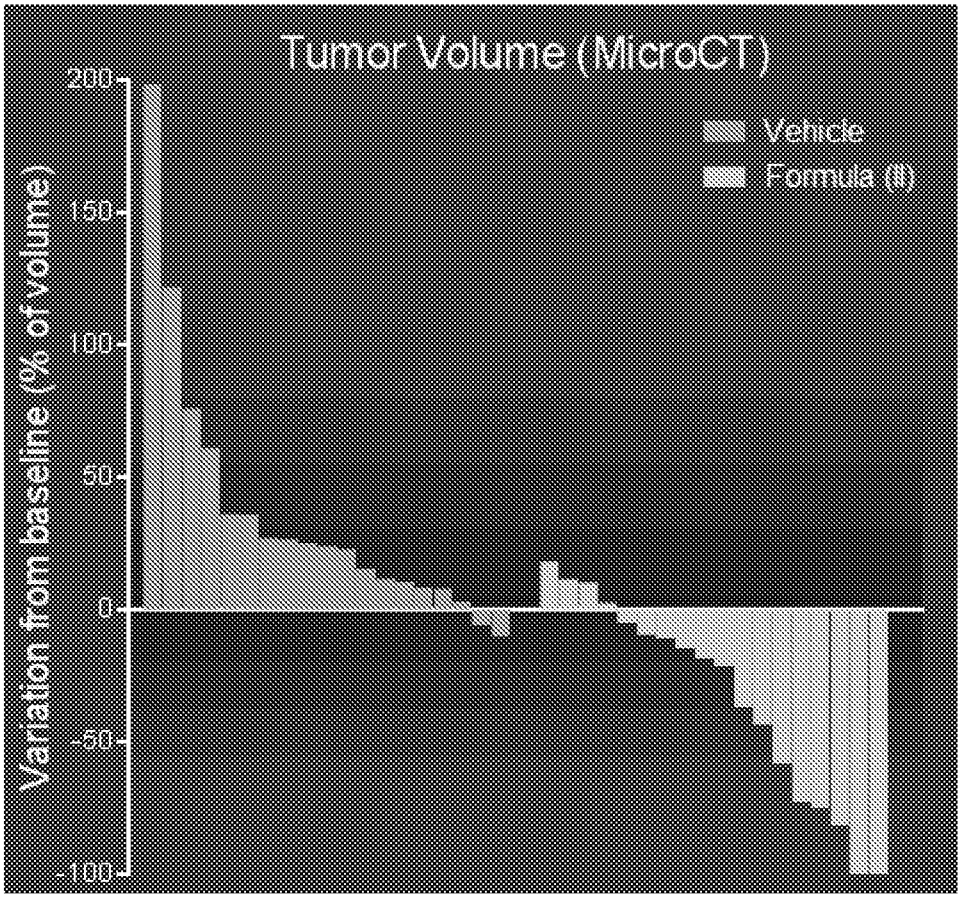

Tumor Volume (MicroCT)
Vehicle
Formula (II)
Variation from baseline (% of volume)
200
150
100
50
0
-50
-100

FIG. 61

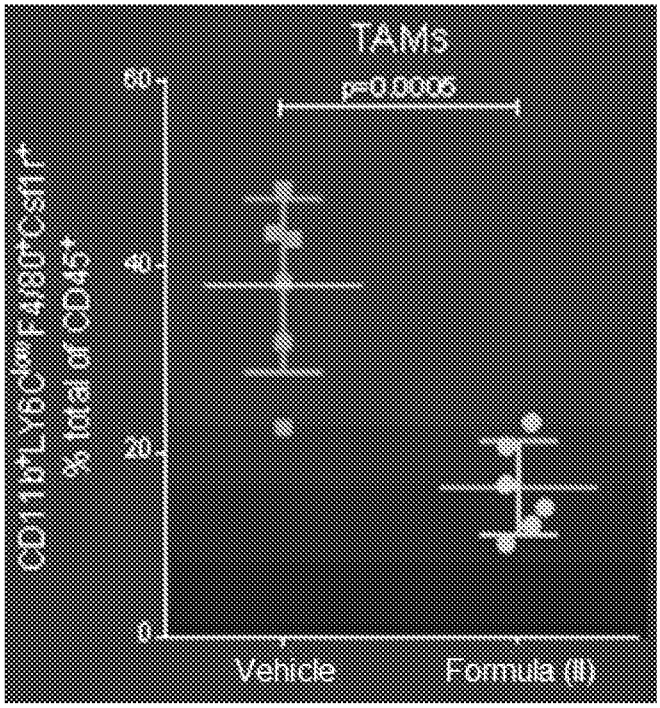

TAMs
p=0.0005
CD11b+Ly6c-F4/80+Csf1r+
% total of CD45+
60
40
20
0
Vehicle
Formula (II)

FIG. 62

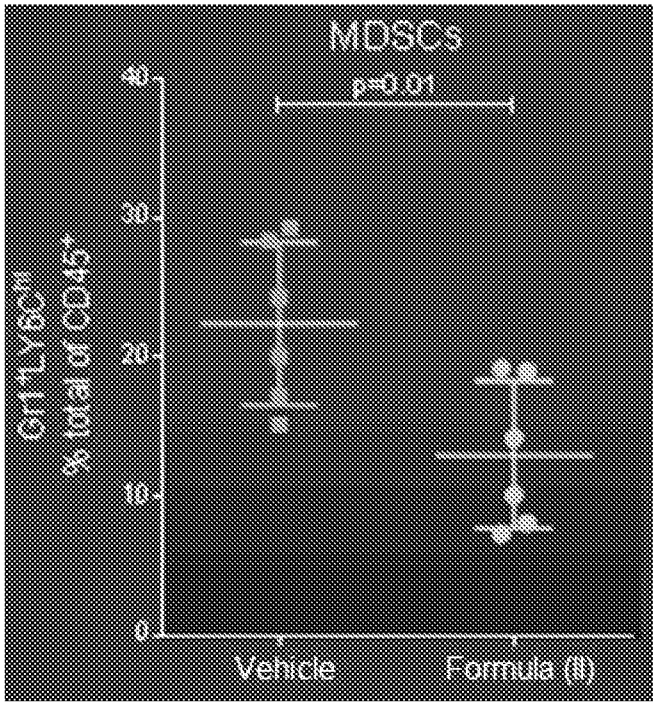

MDSCs
p=0.01
40
30
20
10
0
Gr1+Ly6C+
% total of CD45+
Vehicle
Formula (II)

FIG. 63

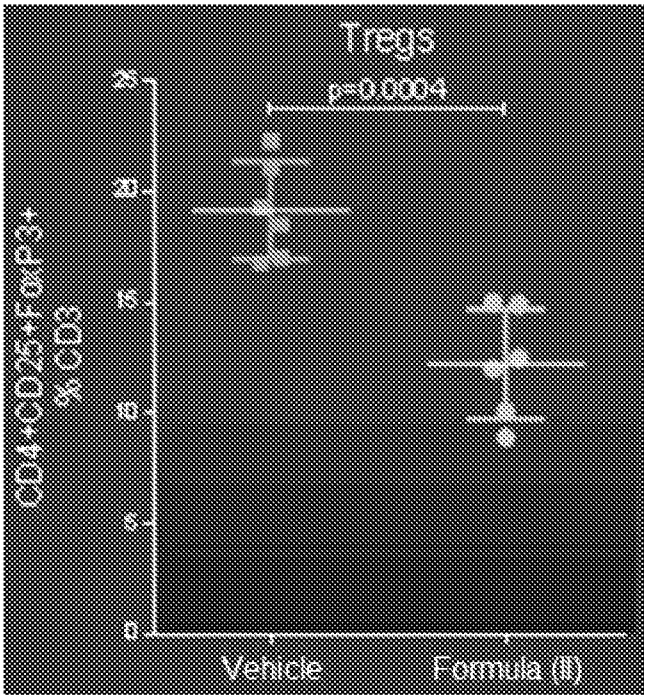

Tregs
p=0.0004
CD4+CD25+Foxp3+
% CD3
25
20
15
10
5
0
Vehicle
Formula (8)

FIG. 64

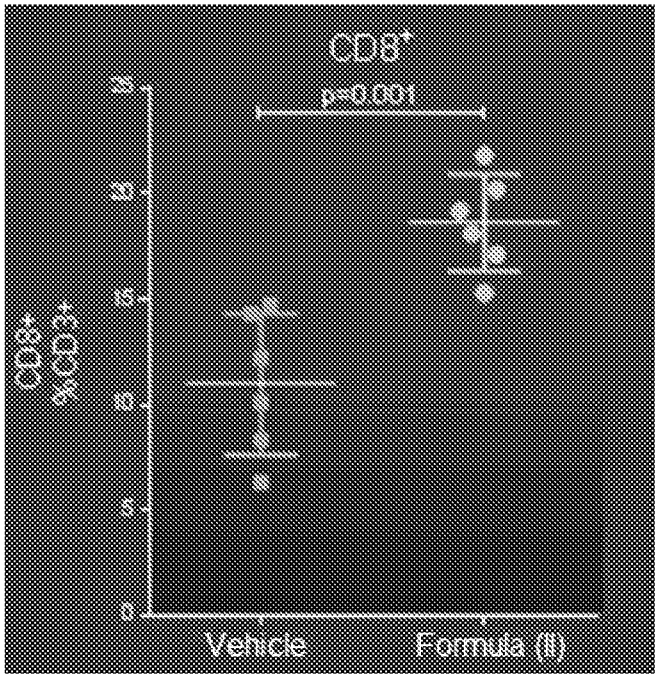



FIG. 65

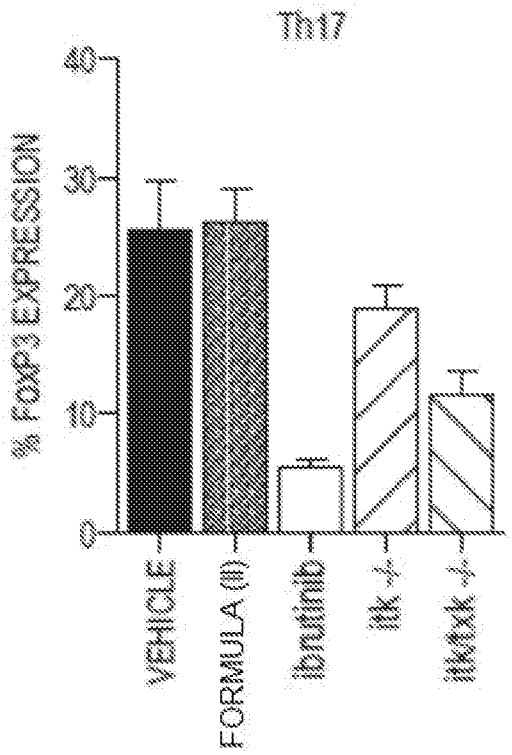

Th17
% FoxP3 EXPRESSION
0
10
20
30
40
VEHICLE
FORMULA (II)
ibrutinib
itk -/-
itk/rlk -/-

FIG. 66

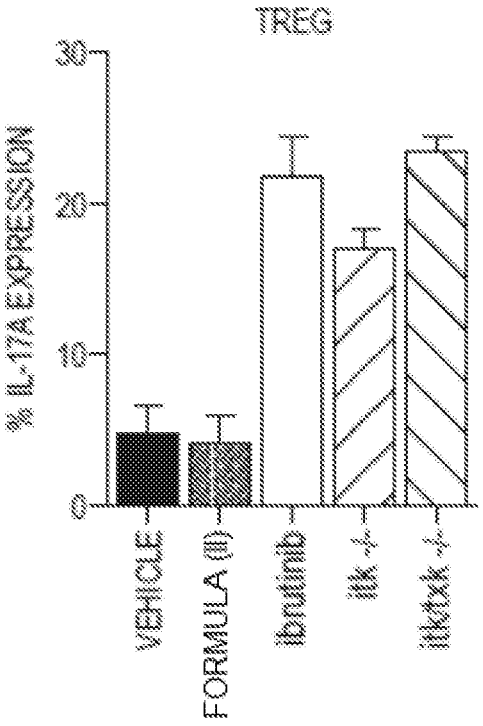

TREG
% IL-17A EXPRESSION
30
20
10
0
VEHICLE
FORMULA (II)
ibrutinib
itk -/-
itktxk -/-

FIG. 67

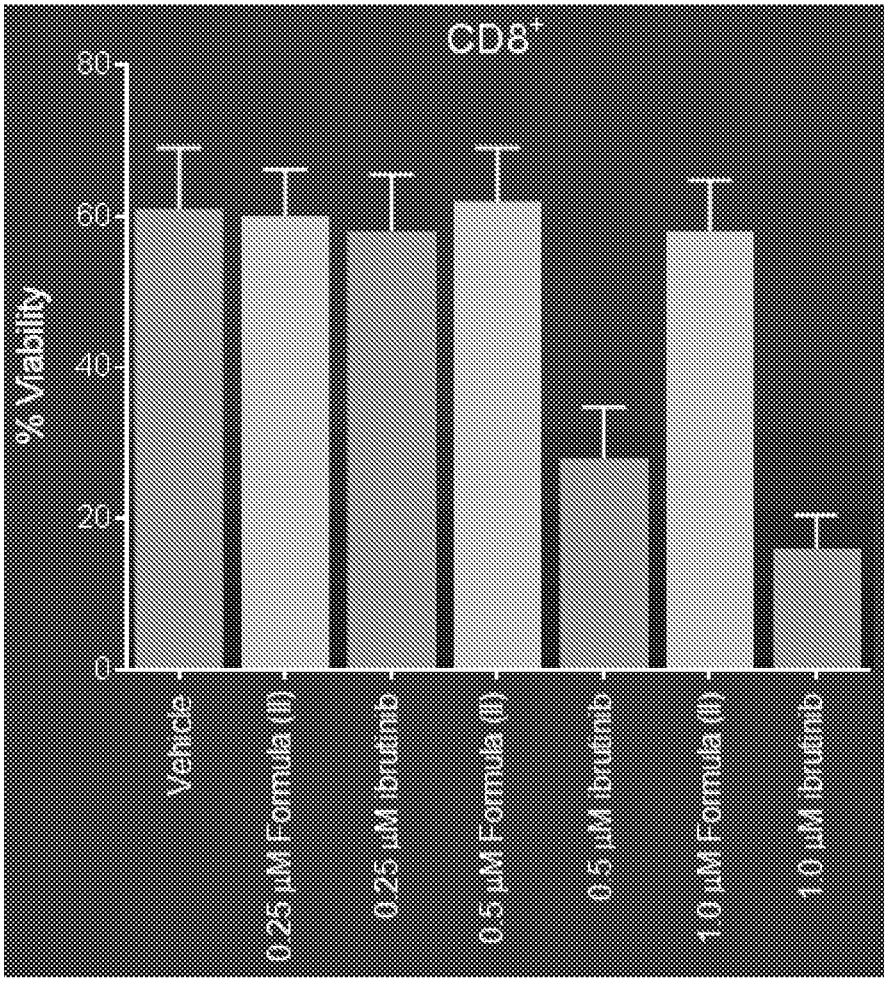

CD8+
% Viability
80
60
40
20
0
Vehicle
0.25 μM Formula (II)
0.25 μM Ibrutinib
0.5 μM Formula (II)
0.5 μM Ibrutinib
1.0 μM Formula (II)
1.0 μM Ibrutinib

FIG. 68

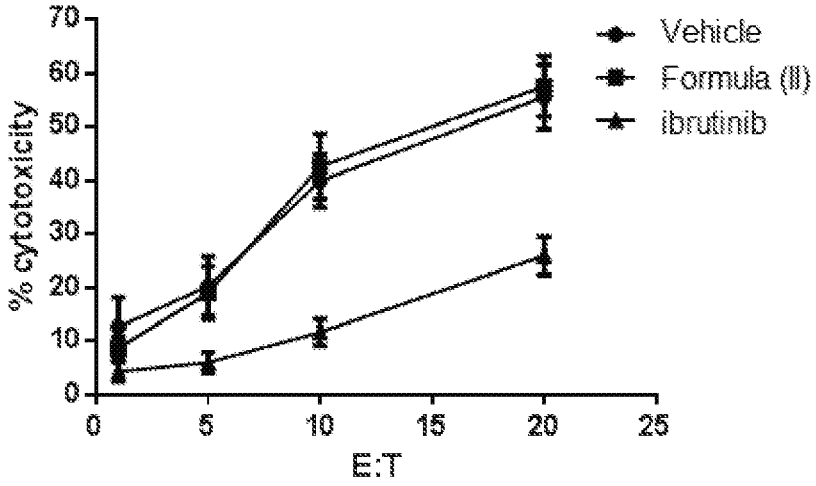

70
60
50
40
30
20
10
0
% cytotoxicity
0
5
10
15
20
25
E:T
Vehicle
Formula (II)
ibrutinib

FIG. 69

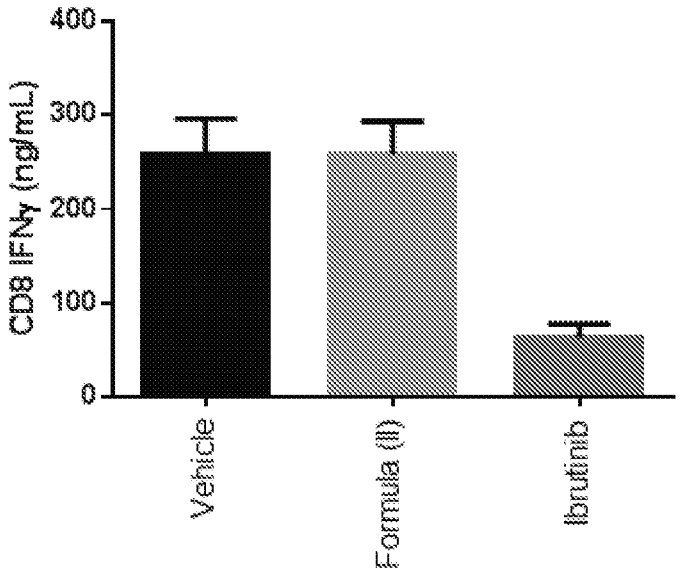



FIG. 70

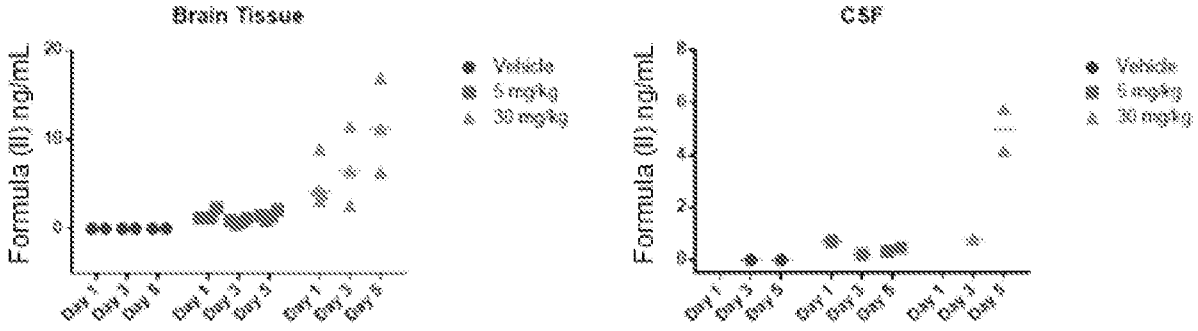

Brain Tissue
Formula (II) ng/mL
Vehicle
5 mg/kg
30 mg/kg
CSF
Formula (II) ng/mL
Vehicle
5 mg/kg
30 mg/kg

FIG. 71

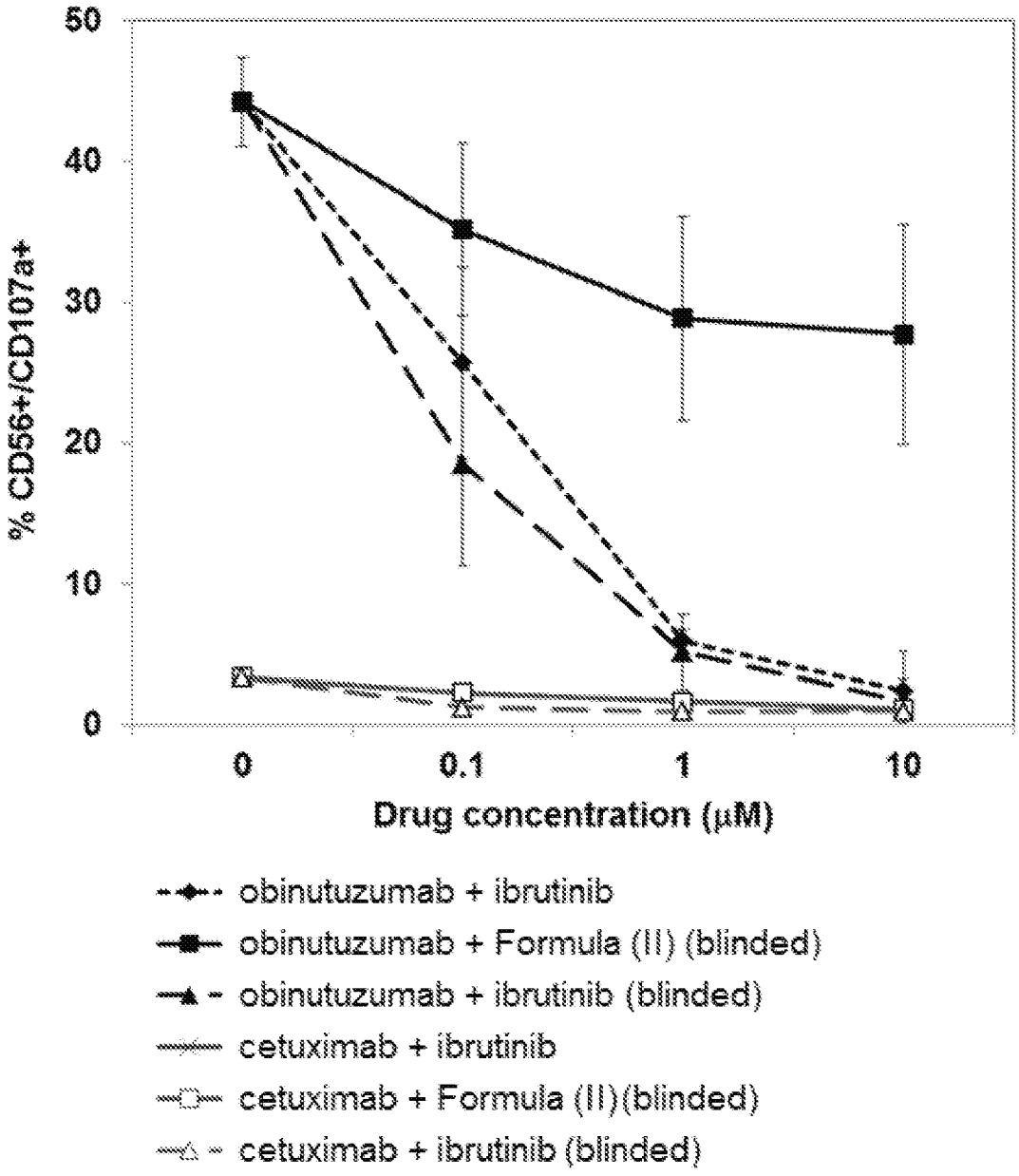

50
40
30
20
10
0
% CD56+/CD107a+
0
0.1
1
10
Drug concentration (μM)
obinutuzumab + ibrutinib
obinutuzumab + Formula (II) (blinded)
obinutuzumab + ibrutinib (blinded)
cetuximab + ibrutinib
cetuximab + Formula (II)(blinded)
cetuximab + ibrutinib (blinded)

FIG. 72

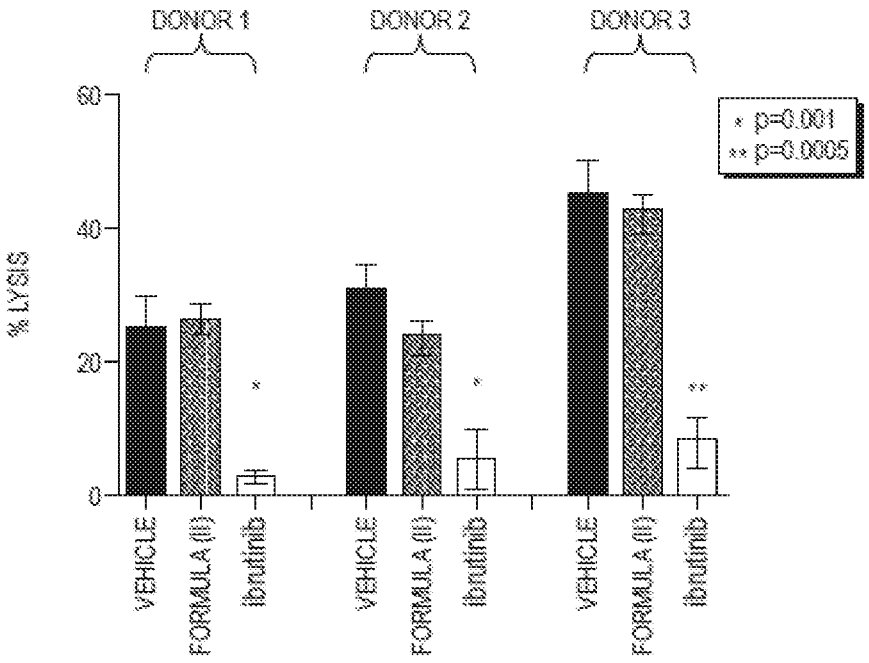

DONOR 1
DONOR 2
DONOR 3
* p=0.001
** p=0.0005
% LYSIS
60
40
20
0
*
*
**
VEHICLE
FORMULA (II)
Ibrutinib
VEHICLE
FORMULA (II)
Ibrutinib
VEHICLE
FORMULA (II)
Ibrutinib

FIG. 73

# INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/056122

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/00 A61K31/4155 A61K31/416 A61K31/454 A61K31/519
A61K39/395 A61K45/06 A61K31/4439 A61K31/4985 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | D'CRUZ OJ ET AL: "Novel Bruton's tyrosine kinase inhibitors currently in development", ONCOTARGETS AND THERAPY, vol. 6, 6 March 2013 (2013-03-06), pages 161-176, XP055217561, GB ISSN: 1178-6930, DOI: 10.2147/OTT.S33732 abstract; table 1 page 168, column 2 | 1,4-6,9, 15-21 |

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-/- .

[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" documentwhich may throw doubts on priority claim(s) orwhich 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 |
|---|---|
| 10 November 2015 | 19/11/2015 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Bonzano, Camilla |

# INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/056122

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | VAN DEN AKKER EMILE ET AL: "The Btk inhibitor LFM-A13 is a potent inhibitor of Jak2 kinase activity" , BIOLOGICAL CHEMISTRY, vol . 385 , no. 5 , May 2004 (2004-05) , pages 409-413 , XP008177694, ISSN: 1431-6730 abstract page 412 , column 1, paragraph 3 | 1,5,9, 15-18, 27,28, 32,33 |
| X, P | W0 2015/083008 Al (ACERTA PHARMA B V [NL] ) 11 June 2015 (2015-06-11) paragraphs [0009] , [0284] examples 3-5 | 1-36 |
| X | US 2012/108612 Al (H0NIGBERG LEE [US] ET AL) 3 May 2012 (2012-05-03) paragraphs [0003] , [0004] claims 22,34,36 | 1,4-6,9 , 10, 16, 23,27 , 28,32 ,34 |
| X | HUANG F ET AL: "Identification of candidate molecular markers predicting sensitivity in solid tumors to dasatinib: Rationale for patient selection" , CANCER RESEARCH , vol . 67, no. 5, 1 March 2007 (2007-03-01) , pages 2226-2238, XP002558115 , AMERICAN ASSOCIATION FOR CANCER RESEARCH , US ISSN: 0008-5472 , D0I : 10. 1158/0008-5472 . CAN-06-3633 abstract page 2226, column 2, paragraph 2 - paragraph 3 | 1,5,9, 15-18, 27,28, 32,33 |
| X, P | MA JIA0 ET AL: "Characterization of ibrutinib-sensitive and -resistant mantle lymphoma cells", BRITISH JOURNAL OF HAEMAT0L0GY, vol . 166, no. 6, September 2014 (2014-09) , pages 849-861 , XP008177889 , WILEY-BLACKWELL PUBLISHING LTD, GB ISSN: 0007-1048, D0I : 10. 1111/BJH . 12974 page 850, column 1, paragraph 1 - paragraph 3 page 859 , column 1, paragraph 4 - column 2, paragraph 1 | 1,4-6,9 , 15-21 |

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# INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/056122

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | J. C. MONTERO ET AL: "Inhibition of Src Family Kinases and Receptor Tyrosine Kinases by Dasatinib: Possible Combinations in Solid Tumors", CLINICAL CANCER RESEARCH, vol. 17, no. 17, 1 September 2011 (2011-09-01), pages 5546-5552, XP055217710, ISSN: 1078-0432, DOI: 10.1158/1078-0432.CCR-10-2616 page 5547, column 1, paragraph 2 - column 2, paragraph 2 | 1,4-6,9, 15-21 |
| X | NICOLE GRABINSKI ET AL: "Ibrutinib (Imbruvica™) potently inhibits ErbB receptor phosphorylation and cell viability of ErbB2-positive breast cancer cells", INVESTIGATIONAL NEW DRUGS., vol. 32, no. 6, 1 August 2014 (2014-08-01), pages 1096-1104, XP055222546, US ISSN: 0167-6997, DOI: 10.1007/S10637-014-0141-2 page 1097, column 1, paragraph 2 | 1,4-6,9, 15-21 |
| X,P | MASSÓ-VALLÉS DANIEL ET AL: "Ibrutinib exerts potent antifibrotic and antitumor activities in mouse models of pancreatic adenocarcinoma.", CANCER RESEARCH 15 APR 2015, vol. 75, no. 8, 15 April 2015 (2015-04-15), pages 1675-1681, XP008177914, ISSN: 1538-7445 page 1679, column 1 - column 2 page 1677, column 1 | 1,4-6,9, 15-21 |
| X | NIEMANN CARSTEN U ET AL: "Cytokine and T-Cell Phenotypic Changes Upon In Vivo Ibrutinib Therapy For CLL - Targeting Both CLL Cells and The Tumor-Microenvironment", BLOOD, vol. 122, no. 21, November 2013 (2013-11), page 2856, XP008177899, & 55TH ANNUAL MEETING OF THE AMERICAN-SOCIETY-OF-HEMATOLOGY; NEW ORLEANS, LA, USA; DECEMBER 07-10, 2013 | 1,4,5, 15-18, 23,27, 28,33,34 |
| Y | abstract | 1-37 |

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# INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/056122

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | TAI YU-TZU ET AL: "Targeting Brouton's Tyrosine Kinase with PCI-32765 Blocks Growth and Survival of Multiple Myeloma and Waldenstrom Macroglobulinemia Via Potent Inhibition of Osteoclastogenesis, Cytokines/Chemokine Secretion, and Myeloma Stem-Like Cells in the Bone Marrow Microenvironment", BLOOD, vol. 118, no. 21, November 2011 (2011-11), page 404, XP008177897, & 53RD ANNUAL MEETING AND EXPOSITION OF THE AMERICAN-SOCIETY-0F-HEMAT0L0GY (ASH); SAN DIEGO, CA, USA; DECEMBER 10-13, 2011 abstract page 2, paragraph 1 | 1,4,5, 15-18, 23,27, 28,33,34 |
| X | HERMAN SARAH E M ET AL: "Ibrutinib inhibits BCR and NF-kappa B signaling and reduces tumor proliferation in tissue-resident cells of patients with CLL", BLOOD, vol. 123, no. 21, May 2014 (2014-05), pages 3286-3295, XP008177906, | 1,4,5, 15-18, 23,27, 28,33,34 |
| Y | page 3292, column 1 | 1-37 |
| X | KITAYAMA J0JI ET AL: "CD90(+) Mesothelial-Like Cells in Peritoneal Fluid Promote Peritoneal Metastasis by Forming a Tumor Permissive Microenvironment", PL0S ONE, vol. 9, no. 1, January 2014 (2014-01), XP008177901, page 86515, column 2 page 86516, column 2, paragraph 2 | 1,4,6,9, 10, 14-16, 18-20, 23,27, 28,32-34 |
| Y | W0 2013/010868 Al (MSD OSS BV [NL]; BARF TJEERD A [NL]; JANS CHRISTIAAN GERARDUS JOHANNES) 24 January 2013 (2013-01-24) page 78 - page 89 | 1-37 |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2015/056122

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
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| | | BR PI0622054 A2 | 09-11-2010 |
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| | | CA 2847852 A1 | 03-04-2008 |
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| | | CN 102887900 A | 23-01-2013 |
| | | DK 2201840 T3 | 20-02-2012 |
| | | DK 2526933 T3 | 18-05-2015 |
| | | EA 200900351 A1 | 30-10-2009 |
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| | | EA 201300246 A1 | 30-01-2014 |
| | | EP 2081435 A2 | 29-07-2009 |
| | | EP 2201840 A1 | 30-06-2010 |
| | | EP 2443929 A1 | 25-04-2012 |
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