**Title:** COMPOSITIONS AND METHODS FOR TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA AND SMALL LYMPHOCYTIC LEUKEMIA USING A BTK INHIBITOR

**Abstract:** Therapeutic methods and pharmaceutical compositions for treating chronic lymphocytic leukemia (CLL) and small lymphocytic leukemia (SLL) are described. In certain embodiments, the invention includes therapeutic methods of treating CLL and SLL using a BTK inhibitor. In certain embodiments, the invention includes therapeutic methods of treating subtypes of CLL and SLL using a BTK inhibitor, including subtypes of CLL in patients sensitive to thrombosis and subtypes of CLL that increase monocytes and NK cells in peripheral blood after treatment with a BTK inhibitor. In certain embodiments, the invention includes pharmaceutical compositions for treating hematological malignancies comprising a combination of a BTK inhibitor and an anti-CD20 anti-body.

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CROSS-REFERENCE TO RELATED APPLICATION

[001] This application claims the benefit of international application number PCT/IB2015/000645 filed on 21 January 2015, which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

[002] Pharmaceutical compositions and therapeutic methods of treating chronic lymphocytic leukemia and other leukemias and lymphomas using a Bruton's tyrosine kinase (BTK) inhibitor are disclosed herein.

BACKGROUND OF THE INVENTION

[003] Bruton's Tyrosine Kinase (BTK or Btk) is a TEC family non-receptor protein kinase expressed in B cells and myeloid cells. The function of BTK in signaling pathways activated by the engagement of the B cell receptor (BCR) and FCER1 on mast cells is well established. Functional mutations in BTK in humans result in a primary immunodeficiency disease characterized by a defect in B cell development with a block between pro- and pre-B cell stages. The result is an almost complete absence of B lymphocytes, causing a pronounced reduction of serum immunoglobulin of all classes. These findings support a key role for BTK in the regulation of the production of auto-antibodies in autoimmune diseases.

[004] Other diseases with an important role for dysfunctional B cells are B cell malignancies. The reported role for BTK in the regulation of proliferation and apoptosis of B cells indicates the potential for BTK inhibitors in the treatment of B cell lymphomas. BTK inhibitors have thus been developed as potential therapies, as described in O. J. D'Cruz and F. M. Uckun, OncoTargets and Therapy 2013, 6. 161-176.

[005] B cell chronic lymphocytic leukemia (CLL) is one of the most prevalent B cell malignancies in adults. CLL is characterized by an expansion of monoclonal mature B cells. CLL patients who relapsed after standard treatments generally experience poor outcomes.
Although survival has been improved by the addition of immunotherapies such as rituximab to standard chemotherapies such as fludarabine and cyclophosphamide, as described in M. Hallek, et al, *Lancet*, 2010, 76, 1164-74, many standard treatments are associated with toxicities and immunosuppression. There is therefore a significant need to identify less toxic and highly efficacious treatments for CLL. Small lymphocytic leukemia (SLL) is closely related to CLL, and differs only in that a lower level of monoclonal lymphocytes is observed in blood than in CLL, along with an enlarged spleen or lymph nodes. There is also a significant need to identify less toxic and highly efficacious treatments for SLL.

**[006]** CLL (and SLL) cells rapidly accumulate and are resistant to apoptosis *in vivo*, but are known to die rapidly *in vitro*. M. Buchner, *et al*, *Blood* 2010, 115, 4497-506. One cause of this effect is from nonmalignant accessory cells in the tumor microenvironment, such as stromal cell contact mediated cell survival. Stromal cells in the bone marrow and lymph nodes are known to have an antiapoptotic and protective effect on CLL cells, protecting them from both chemotherapeutic and spontaneous apoptosis. R. E. Mudry, *et al*, *Blood* 2000, 96, 1926-32.

The chemokine SDFla (CXCL12) directs homing of CLL cells towards protective niches. M. Burger, *et al*, *Blood* 2005, 106, 1824-30. Existing drugs that target the BCR pathway in B cell malignancies can lead to some lymphocytosis, *i.e.* lymphocyte egress from nodal compartments, through disruption of CXCR4-SDFla signaling and other adhesion factors in bone marrow and the resulting mobilization of cells. However, existing therapies may not eradicate residual malignant B cell populations in the microenvironment of the bone marrow and lymph nodes, where protective stromal cells prevent apoptosis. There is thus an urgent need for treatments that reduce or overcome the protective effect of the microenvironment on CLL cells to enable superior clinical responses in patients.


**SUMMARY OF THE INVENTION**

[008] In a preferred embodiment, the invention provides a pharmaceutical composition comprising an anti-CD20 antibody and a Bruton’s tyrosine kinase (BTK) inhibitor, wherein the anti-CD20 antibody is selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof; and wherein the BTK inhibitor is:

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

X is CH, N, O or S;

Y is C(Rₖ), N, O or S;

Z is CH, N or bond;
A is CH or N;

Bi 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_i is RiiC(O), R_i2S(0), R_{13}SO_2 or (Ci_3)alkyl optionally substituted with R_{i4};

R_2 is H, (Ci_{-3})alkyl or (C_3,2)cycloalkyl;

R_3 is H, (Ci_{-6})alkyl or (C_3,2)cycloalkyl; or

R_2 and R_3 form, together with the N and C atom they are attached to, a (C_3,2)heterocycloalkyl optionally substituted with one or more fluorine, hydroxyl, (Ci_{-3})alkyl, (Ci_{-3})alkoxy or oxo;

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

R_5 is H, halogen, cyano, (Ci_{-4})alkyl, (Ci_{-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,io)aryl or (C_{2,6})heterocycloalkyl;

R_e is H or (Ci_{-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 (Ci_{-3})alkyl, or one or more halogen;

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

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

R_7 and R_8 together with the carbon atoms they are attached to, form (C_{6,io})aryl or (Ci_{-3})heteroaryl;

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

R_{io} is H, halogen, (Ci_{-3})alkyl or (Ci_{-3})alkoxy;
Rii is independently selected from the group consisting of (Ci_6)alkyl, (C2_6)alkenyl and (C2_6)alkynyl each alkyl, alkenyl or alkynyl optionally substituted with one or more groups selected from hydroxyl, (Ci_4)alkyl, (C3_2)cycloalkyl, [(Ci_4)alkyl]amino, di[(Ci_4)alkyl]amino, (Ci_3)alkoxy, (C3_2)cycloalkoxy, (C6_10)aryl or (C3_2)heterocycloalkyl; or R11 is (Ci_3)alkyl-C(0)-S-(Ci_3)alkyl; or

R11 is (Ci_3)heteroaryl optionally substituted with one or more groups selected from halogen or cyano;

Ri2 and Ri3 are independently selected from a group consisting of (C2_6)alkenyl or (C2_6)alkynyl both optionally substituted with one or more groups selected from hydroxyl, (Ci_4)alkyl, (C3_2)cycloalkyl, [(Ci_4)alkyl]amino, di[(Ci_4)alkyl]amino, (Ci_3)alkoxy, (C3_2)cycloalkoxy, (C6_10)aryl or (C3_2)heterocycloalkyl; or (Ci_3)heteroaryl optionally substituted with one or more groups selected from halogen or cyano; and

Ri4 is independently selected from a group consisting of halogen, cyano or (C2_6)alkenyl or (C2_6)alkynyl both optionally substituted with one or more groups selected from hydroxyl, (Ci_4)alkyl, (C3_2)cycloalkyl, (Ci_4)alkylamino, di[(Ci_4)alkyl]amino, (Ci_3)alkoxy, (C3_2)cycloalkoxy, (C6_10)aryl, (Ci_3)heteroaryl or (C3_2)heterocycloalkyl.

[009] In a preferred embodiment, the invention provides a pharmaceutical composition comprising an anti-CD20 antibody and a Bruton’s tyrosine kinase (BTK) inhibitor, wherein the anti-CD20 antibody is selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof, wherein the BTK inhibitor is:
or a pharmaceutically-acceptable salt, cocrystal, solvate, or hydrate thereof.

[0010] In a preferred embodiment, the invention provides a pharmaceutical composition comprising an amount of an anti-CD20 antibody of between 25 mg and 2000 mg, and an amount of a BTK inhibitor of between 5 mg and 500 mg.

[0011] In a preferred embodiment, the invention provides a pharmaceutical composition comprising an amount of the BTK inhibitor of between 25 mg and 125 mg.

[0012] In a preferred embodiment, the invention provides a pharmaceutical composition 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.

[0013] 6. The composition of any of Claims 1 to 5, comprising an amount of the anti-CD20 antibody 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.

[0014] 7. The composition of any of Claims 1 to 6, further comprising an anticoagulant or antiplatelet agent, wherein the anticoagulant 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.

[0015] 8. The composition of any of Claims 1 to 7, further comprising at least one pharmaceutically acceptable excipient.

[0016] In an embodiment, the invention includes a method of treating CLL and/or SLL, comprising the step of orally administering, to a human in need thereof, a Bruton's tyrosine kinase (BTK) inhibitor, wherein the BTK inhibitor is (5)-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.

[0017] In an embodiment, the invention includes a method of treating CLL and/or SLL, comprising the step of orally administering, to a human in need thereof, a Bruton's tyrosine kinase (BTK) inhibitor, wherein the BTK inhibitor is (5)-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, wherein the BTK inhibitor is administered once daily at a dose selected from the group consisting of 100 mg, 175 mg, 250 mg, and 400 mg.

[0018] In an embodiment, the invention includes a method of treating CLL and/or SLL, comprising the step of orally administering, to a human in need thereof, a Bruton's tyrosine kinase (BTK) inhibitor, wherein the BTK inhibitor is (5)-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, wherein the BTK inhibitor is administered twice daily at a dose of 100 mg.

[0019] In an embodiment, the invention includes a method of treating CLL and/or SLL, comprising the step of orally administering, to a human in need thereof, a Bruton's tyrosine kinase (BTK) inhibitor, wherein the BTK inhibitor is (5)-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, wherein the CLL increases monocytes and NK cells in peripheral blood after treatment with Formula (II) for a period selected from the group consisting of about 14 days, about 28 days, or about 56 days.
[0020] In an embodiment, the invention includes a method of treating CLL and/or SLL, comprising the step of orally administering, to a human in need thereof, a Bruton's tyrosine kinase (BTK) inhibitor, wherein the BTK inhibitor is (5)-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, wherein the CLL is selected from the group consisting of IgVH mutation negative CLL, ZAP-70 positive CLL, ZAP-70 methylated at CpG3 CLL, CD38 positive CLL, CLL with a 17p13.1 (17p) deletion, CLL with a 1q22.3 (1q) deletion, CLL in a human sensitive to platelet-mediated thrombosis, CLL in a human presently suffering from platelet-mediated thrombosis, CLL in a human previously suffering from platelet-mediated thrombosis, or combinations thereof.

[0021] In an embodiment, the invention includes a method of treating CLL and/or SLL, comprising the step of orally administering, to a human in need thereof, a Bruton's tyrosine kinase (BTK) inhibitor, wherein the BTK inhibitor is (5)-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 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.

[0022] In an embodiment, the invention includes a method of treating CLL and/or SLL, comprising the step of orally administering, to a human in need thereof, a Bruton's tyrosine kinase (BTK) inhibitor, wherein the BTK inhibitor is (5)-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.

[0023] In an embodiment, the invention includes a method of treating CLL and/or SLL, comprising the step of orally administering, to a human in need thereof, a Bruton's tyrosine kinase (BTK) inhibitor, wherein the BTK inhibitor is (5)-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, nadropran,
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.

[0024] In an embodiment, the invention includes a method of treating a hematological
malignancy in a human comprising the step of administering a therapeutically effective dose of a
BTK inhibitor, wherein the BTK inhibitor is (5)-4-(8-amino-3-((1-(but-2-ynoyl)pyrrolidin-2-
yl)imidazo[1,5-a]pyrazin-1-yl) \( \gamma \)-N-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt,
solvate, hydrate, cocrystal, or prodrug thereof, and wherein the hematological malignancy is
selected from the group consisting of non-Hodgkin's lymphoma (NHL), diffuse large B cell
lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Hodgkin's
lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Burkitt's lymphoma, Waldenstrom's
macroglobulinemia (WM), Burkitt's lymphoma, multiple myeloma, or myelofibrosis.

[0025] In an embodiment, the invention includes a method of treating a hematological
malignancy in a human comprising the step of administering a therapeutically effective dose of a
BTK inhibitor, wherein the BTK inhibitor is (5)-4-(8-amino-3-((1-(but-2-ynoyl)pyrrolidin-2-
yl)imidazo[1,5-a]pyrazin-1-yl) \( \gamma \)-N-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt,
solvate, hydrate, cocrystal, or prodrug thereof, and wherein the hematological malignancy is
selected from the group consisting of non-Hodgkin's lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Hodgkin's lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Burkitt's lymphoma, Waldenstrom's macroglobulinemia (WM), Burkitt's lymphoma, multiple myeloma, or myelofibrosis, wherein the BTK inhibitor is administered once daily at a dose selected from the group consisting of 100 mg, 175 mg, 250 mg, and 400 mg.

[0026] In an embodiment, the invention includes a method of treating a hematological malignancy in a human comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is (5)-4-(8-amino-3-((1-(but-2-ynoyl)pyrrolidin-2-yl))imidazo[1,5-a]pyrazin-1-yl)N-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and wherein the hematological malignancy is selected from the group consisting of non-Hodgkin's lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Hodgkin's lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Burkitt's lymphoma, Waldenstrom's macroglobulinemia (WM), Burkitt's lymphoma, multiple myeloma, or myelofibrosis, wherein the BTK inhibitor is administered twice daily at a dose of 100 mg.

[0027] In an embodiment, the invention includes a method of treating a hematological malignancy in a human comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is (5)-4-(8-amino-3-((1-(but-2-ynoyl)pyrrolidin-2-yl))imidazo[1,5-a]pyrazin-1-yl)N-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and wherein the hematological malignancy is selected from the group consisting of non-Hodgkin's lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Hodgkin's lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Burkitt's lymphoma, Waldenstrom's macroglobulinemia (WM), Burkitt's lymphoma, multiple myeloma, or myelofibrosis, wherein the hematological malignancy increases monocytes and NK cells in peripheral blood after treatment with Formula (II) for a period selected from the group consisting of about 14 days, about 28 days, or about 56 days.

[0028] In an embodiment, the invention includes a method of treating a hematological malignancy in a human comprising the step of administering a therapeutically effective dose of a
BTK inhibitor, wherein the BTK inhibitor is (5)-4-(8-amino-3-(l-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-l-yl)N-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and wherein the hematological malignancy is non-Hodgkin's lymphoma (NHL), wherein the NHL is selected from the group consisting of indolent NHL and aggressive NHL.

[0029] In an embodiment, the invention includes a method of treating a hematological malignancy in a human comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is (5)-4-(8-amino-3-(l-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-l-yl)N-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and wherein the hematological malignancy is diffuse large B cell lymphoma (DLBCL), wherein the DLBCL is selected from the group consisting of activated B-cell like diffuse large B-cell lymphoma (DLBCL-ABC) and germinal center B-cell like diffuse large B-cell lymphoma (DLBCL-GCB).

[0030] In an embodiment, the invention includes a method of treating a hematological malignancy in a human comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is (5)-4-(8-amino-3-(l-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-l-yl)N-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and wherein the hematological malignancy is mantle cell lymphoma (MCL), wherein the MCL is selected from the group consisting of mantle zone MCL, nodular MCL, diffuse MCL, and blastoid MCL.

[0031] In an embodiment, the invention includes a method of treating a hematological malignancy in a human comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is (5)-4-(8-amino-3-(l-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-l-yl)N-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and wherein the hematological malignancy is B cell acute lymphoblastic leukemia (B-ALL), wherein the B-ALL is selected from the group consisting of early pre-B cell B-ALL, pre-B cell B-ALL, and mature B cell B-ALL.

[0032] In an embodiment, the invention includes a method of treating a hematological malignancy in a human comprising the step of administering a therapeutically effective dose of a
BTK inhibitor, wherein the BTK inhibitor is (5)-4-(8-amino-3-(l-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and wherein the hematological malignancy is Burkitt's lymphoma, wherein the Burkitt's lymphoma is selected from the group consisting of sporadic Burkitt's lymphoma, endemic Burkitt's lymphoma, and human immunodeficiency virus-associated Burkitt's lymphoma.

[0033] In an embodiment, the invention includes a method of treating a hematological malignancy in a human comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is (5)-4-(8-amino-3-(l-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and wherein the hematological malignancy is multiple myeloma, wherein the multiple myeloma is selected from the group consisting of hyperdiploid multiple myeloma and non-hyperdiploid multiple myeloma.

[0034] In an embodiment, the invention includes a method of treating a hematological malignancy in a human comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is (5)-4-(8-amino-3-(l-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and wherein the hematological malignancy is myelofibrosis, wherein the myelofibrosis is selected from the group consisting of primary myelofibrosis, myelofibrosis secondary to polycythemia vera, and myelofibrosis secondary to essential thrombocythaemia.

[0035] In an embodiment, the invention includes a method of treating a hematological malignancy in a human comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is (5)-4-(8-amino-3-(l-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and wherein the hematological malignancy is selected from the group consisting of non-Hodgkin's lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Hodgkin's lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Burkitt's lymphoma, Waldenstrom's macroglobulinemia (WM), Burkitt's lymphoma, multiple myeloma, or myelofibrosis, 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.

[0036] In an embodiment, the invention includes a method of treating a hematological malignancy in a human comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is (5)-4-[(8-amino-3-(l-(but-2-ynoyl)pyrrolidin-2-y1)imidazo[1,5-a]pyrazin-l-yl )-N-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and wherein the hematological malignancy is selected from the group consisting of non-Hodgkin's lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Hodgkin's lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Burkitt's lymphoma, Waldenstrom's macroglobulinemia (WM), Burkitt's lymphoma, multiple myeloma, or myelofibrosis, further comprising the step of administering a therapeutically effective dose of an anticoagulant or antiplatelet active pharmaceutical ingredient.

[0037] In an embodiment, the invention includes a method of treating a hematological malignancy in a human comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is (5)-4-[(8-amino-3-(l-(but-2-ynoyl)pyrrolidin-2-y1)imidazo[1,5-a]pyrazin-l-yl )-N-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and wherein the hematological malignancy is selected from the group consisting of non-Hodgkin's lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Hodgkin's lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Burkitt's lymphoma, Waldenstrom's macroglobulinemia (WM), Burkitt's lymphoma, multiple myeloma, or myelofibrosis, 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, cloriciromen, 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.

BRIEF DESCRIPTION OF THE DRAWINGS

[0038] 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.

[0039] FIG. 1 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 hours post-dose). BCR is stimulated with IgM and the expression of activation markers CD69 and CD86 are monitored by flow cytometry to determine EC50 values. The results show that Formula (II) is more potent at inhibiting expression of activation makers than ibrutinib.

[0040] FIG. 2 illustrates in vitro potency in whole blood of Formula (II), ibrutinib and CC-292 in inhibition of signals through the B cell receptor.

[0041] FIG. 3 illustrates EGF receptor phosphorylation in vitro for Formula (II) and ibrutinib.

[0042] FIG. 4 illustrates the results of the clinical study of Formula (II) (labeled "BTK inhibitor") in CLL and SLL patients, which are shown in comparison to the results reported for ibrutinib in Figure 1A of J.C. 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.
FIG. 5 shows overall response data shown by SPD of enlarged lymph nodes in CLL and SLL patients as a function of dose of the BTK inhibitor of Formula (II).

FIG. 6 shows a comparison of progression-free survival (PFS) in CLL and SLL patients treated with the BTK inhibitor ibrutinib or the BTK inhibitor of Formula (II). The ibrutinib data is taken from J.C. Byrd, et al., *N. Engl. J. Med.* 2013, 369, 32-42. CLL and SLL patients treated with Formula (II) for at least 8 days are included.

FIG. 7 shows a comparison of number of patients at risk in CLL and SLL patients treated with the BTK inhibitor ibrutinib or the BTK inhibitor of Formula (II). CLL and SLL patients treated with Formula (II) for at least 8 days are included.

FIG. 8 shows a comparison of progression-free survival (PFS) in CLL and SLL 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 J.C. Byrd, et al., *N. Engl. J. Med.* 2013, 369, 32-42.

FIG. 9 shows a comparison of number of patients at risk in CLL and SLL 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 J.C. Byrd, et al., *N. Engl. J. Med.* 2013, 369, 32-42. CLL patients treated with Formula (II) for at least 8 days are included.

FIG. 10 shows improved BTK target occupancy of Formula (II) at lower dosage versus ibrutinib in relapsed/refractory CLL and SLL patients.

FIG. 11 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.

FIG. 12 shows the % change in MDSC (monocytic) level over 28 days versus % ALC change at Cycle 2, day 28 (C2D28) with trendlines.

FIG. 13 shows the % change in natural killer (NK) cell level over 28 days versus % ALC change at Cycle 1, day 28 (C2D28) with trendlines.

FIG. 14 shows the % change in NK cell level over 28 days versus % ALC change at Cycle 2, day 28 (C2D28) with trendlines.
FIG. 15 compares the % change in MDSC (monocytic) level and % change in NK cell level over 28 days versus % ALC change with the % change in level of CD4+ T cells, CD8+ T cells, CD4+/CD8+ T cell ratio, NK-T cells, PD-1+CD4+ T cells, and PD-1+CD8+ T cells, also versus % ALC change, at Cycle 1 day 28 (C1D28). Trendlines are shown for % change in MDSC (monocytic) level and % change in NK cell level.

FIG. 16 compares the % change in MDSC (monocytic) level and % change in NK cell level over 28 days versus % ALC change with the % change in level of CD4+ T cells, CD8+ T cells, CD4+/CD8+ T cell ratio, NK-T cells, PD-1+CD4+ T cells, and PD-1+CD8+ T cells, also versus % ALC change, at Cycle 2 day 28 (C2D28). Trendlines are shown for % change in MDSC (monocytic) level and % change in NK cell level.

FIG. 17 shows an update of the data presented in FIG. 4.

FIG. 18 shows an update of the data presented in FIG. 10, and includes BID dosing results.

FIG. 19 illustrates PFS for patients with 11p deletion.

FIG. 20 illustrates PFS across relapsed/refractory patients with 11p deletion and with 17q deletion and no 11p deletion.

FIG. 21 illustrates PFS for patients with 17q deletion and no 11p deletion.

FIG. 22 illustrates updated SPD results from the clinical study of Formula (II) in relapsed/refractory CLL and SLL patients (N = 58).

FIG. 23 illustrates that treatment of CLL and SLL patients with Formula (II) resulted in increased apoptosis.

FIG. 24 illustrates a decrease in CXCL12 levels observed in patients treated with Formula (II).

FIG. 25 illustrates a decrease in CCL2 levels observed in patients treated with Formula (II).
FIG. 26 illustrates representative photomicrographs and comparison of maximal thrombus size in laser injured arterioles of VWF HAI 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).

FIG. 27 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 of 1 µM.

FIG. 28 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.

FIG. 29 illustrates the effect of the concentration of the tested BTK inhibitors on thrombus formation.

FIG. 30 illustrates the results of platelet collagen receptor glycoprotein VI (GPVI) platelet aggregation studies of Formula (II) (IC₅₀ = 1.15 µM) and ibrutinib (IC₅₀ = 0.13 µM).

FIG. 31 illustrates the results of GPVI platelet aggregation studies of Formula (II) and ibrutinib.

FIG. 32 shows in vitro analysis of antibody-dependent NK cell-mediated INF-γ release with BTK inhibitors. To evaluate NK cell function, purified NK cells were isolated from healthy peripheral blood mononuclear cells and cultured with 0.1 or 1 µM of ibrutinib or 1 µM of Formula (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-γ (IFN-γ). All in vitro experiments were performed in triplicate. Labels are defined as follows: *p = 0.018, **p = 0.002, ***p = 0.001.

FIG. 33 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.

[0072] FIG. 34 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-31 11 ("inhib B," 1 µM). All in vitro experiments were performed in triplicate. Labels are defined as follows: *p = 0.001.

[0073] FIG. 35 shows a summary of the results given in FIG. 34 at the highest concentration of rituximab ("Ab") (10 µg/mL).

[0074] FIG. 36 shows that ibrutinib antagonizes antibody-dependent NK cell-mediated cytotoxicity in primary CLL cells, as with Raji cells in FIG. 34.

[0075] FIG. 37 shows the results of the NK cell degranulation/ADCC assay using whole blood from a normal donor, after pretreatment of the whole blood for 1 hour with the BTK inhibitors and stimulation with MEC-1 cells opsonised with obinutuzumab and cetuximab at 1 µg/mL for 4 hours (n = 3).

[0076] FIG. 38 shows the effects of BTK inhibition on generalized NK cell mediated cytotoxicity.

[0077] FIG. 39 shows that Formula (II) has no adverse effect on T helper 17 (Thl7) cells, which are a subset of T helper cells that produce interleukin-17 (IL17), while ibrutinib strongly inhibits Thl7 cells.

[0078] FIG. 40 shows that Formula (II) has no effect on regulatory T cell (Treg) development, while ibrutinib strongly increases Treg development.

[0079] FIG. 41 shows that Formula (II) has no effect on CD8+ T cell viability, development,
while ibrutinib strongly affects CD8⁺ T cell viability at higher doses.

BRIEF DESCRIPTION OF THE SEQUENCE LISTINGS

[0080] SEQ ID NO: 1 is the heavy chain amino acid sequence of the anti-CD20 monoclonal antibody rituximab.

[0081] SEQ ID NO: 2 is the light chain amino acid sequence of the anti-CD20 monoclonal antibody rituximab.

[0082] SEQ ID NO: 3 is the heavy chain amino acid sequence of the anti-CD20 monoclonal antibody obinutuzumab.

[0083] SEQ ID NO: 4 is the light chain amino acid sequence of the anti-CD20 monoclonal antibody obinutuzumab.

[0084] SEQ ID NO: 5 is the variable heavy chain amino acid sequence of the anti-CD20 monoclonal antibody ofatumumab.

[0085] SEQ ID NO: 6 is the variable light chain amino acid sequence of the anti-CD20 monoclonal antibody ofatumumab.

[0086] SEQ ID NO: 7 is the Fab fragment heavy chain amino acid sequence of the anti-CD20 monoclonal antibody ofatumumab.

[0087] SEQ ID NO: 8 is the Fab fragment light chain amino acid sequence of the anti-CD20 monoclonal antibody ofatumumab.

[0088] SEQ ID NO: 9 is the heavy chain amino acid sequence of the anti-CD20 monoclonal antibody veltuzumab.

[0089] SEQ ID NO: 10 is the light chain amino acid sequence of the anti-CD20 monoclonal antibody veltuzumab.

[0090] SEQ ID NO: 11 is the heavy chain amino acid sequence of the anti-CD20 monoclonal antibody tositumomab.

[0091] SEQ ID NO: 12 is the light chain amino acid sequence of the anti-CD20 monoclonal antibody tositumomab.

[0092] SEQ ID NO: 13 is the heavy chain amino acid sequence of the anti-CD20 monoclonal antibody tositumomab.
antibody ibritumomab.

[0093] SEQ ID NO: 14 is the light chain amino acid sequence of the anti-CD20 monoclonal antibody ibritumomab.

DETAILED DESCRIPTION OF THE INVENTION

[0094] 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.

[0095] 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.

[0096] The terms "co-administration" and "administered in combination with" as used herein, encompass administration of two or more active pharmaceutical ingredients 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.

[0097] The term "in vivo" refers to an event that takes place in a subject's body.

[0098] 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.

[0099] The term "IC_{50}" refers to the half maximal inhibitory concentration, i.e. inhibition of 50% of the desired activity. The term "EC_{50}" refers to the drug concentration at which one-half the maximum response is achieved.

[00100] The term "effective amount" or "therapeutically effective amount" refers to that amount of an active pharmaceutical ingredient or combination of active pharmaceutical ingredients 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, and other factors 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.

[00101] 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.

[00102] The terms "QD," "qd," or "q.d." means quaque die, once a day, or once daily. The terms "BID," "bid," or "b.i.d." mean bis in die, twice a day, or twice daily. The terms "TID," "tid," or "t.i.d." mean ter in die, three times a day, or three times daily. The terms "QID," "qid," or "q.i.d." mean quater in die, four times a day, or four times daily.

[00103] 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, 2-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 selected 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 proton 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.

[00104] "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 active pharmaceutical ingredients is well known in the art. Except insofar as any conventional media or agent is incompatible with the active pharmaceutical ingredient, its use in the therapeutic compositions of the invention is contemplated. Supplementary active ingredients can also be incorporated into the described compositions.

[00105] "Prodrug" is intended to describe a substance that may be converted under physiological conditions or by solvolysis to a biologically active pharmaceutical ingredient 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 pharmaceutical ingredient, 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., H. Bundgaard, Design of Prodrugs, Elsevier, Amsterdam (1985)). The term "prodrug" is also intended to include any covalently bonded carriers, which release the active pharmaceutical ingredient in vivo when administered to a subject. Prodrugs of an active pharmaceutical ingredient, as described herein, may be prepared by modifying functional groups present in the active pharmaceutical ingredient in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to yield the active pharmaceutical ingredient. Prodrugs include, for example, compounds wherein a hydroxy, amino or mercapto group is bonded to any group that, when the prodrug of the active pharmaceutical ingredient 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 pharmaceutical ingredient.

[00106] 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.

[00107] "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., C1-C10 alkyl). Whenever it appears herein, a numerical range such as "1 to 10" refers to each integer in the given range - e.g., "1 to 10 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, etc., up to and including 10 carbon atoms, although the definition is also intended to cover the occurrence of the term "alkyl" where no numerical range is specifically designated. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, sec-butyl isobutyl, tertiary butyl, pentyl, isopentyl, neopentyl, hexyl, septyl, octyl, nonyl and decyl. The alkyl moiety may be attached to the rest of the molecule by a single bond, such as for example, methyl (Me), ethyl (Et), n-propyl (Pr), 1-methylethyl (isopropyl), n-butyl, n-pentyl, 1,1-dimethylethyl (t-butyl) and 3-methylhexyl. Unless stated otherwise specifically in the specification, an alkyl group is optionally substituted by one or more of substituents which are independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, aryalkyl, heteroaryl, heteroaryalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, -ORa, -SRa, -OC(0)-Ra, -N(Ra)2, -C(0)Ra, -C(0)ORa, -OC(0)N(Ra)2, -C(0)N(Ra)2, -N(Ra)C(0)ORa, -
N(R^a)C(0)R^a, -N(R^a)C(0)N(R^a)_2, N(R^a)C(NR^a)N(R^a)_2, -N(R^a)S(0),R^a (where t is 1 or 2), -S(0),OR^a (where t is 1 or 2), -S(0),N(R^a)_2 (where t is 1 or 2), or P0^tR^a where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocycyl, carbocycylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00108] "Alkaryl" 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.

[00109] "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.

[00110] "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.

[00111] 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.

[00112] "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-C_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(0)-R^a, -N(R^a)_2, -C(0)R^a, -C(0)OR^a, -OC(0)N(R^a)_2, -C(0)N(R^a)_2, -N(R^a)C(0)OR^a, -N(R^a)C(0)R^a,
-N(R a )C(0)N(R a ) 2 , N(R a )C(NR a )N(R a ) 2 , -N(R a )S(0),R a (where t is 1 or 2), -S(0),OR a (where t is 1 or 2), -S(0),S(0),N(R a ) 2 (where t is 1 or 2), or P0 3 (R a ) 2 , where each R a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00113] "Alkenyl-cycloalkyl" refers to an -(alkenyl)cycloalkyl radical where alkenyl and cycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for alkenyl and cycloalkyl respectively.

[00114] "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 -C 10 alkynyl). Whenever it appears herein, a numerical range such as "2 to 10" refers to each integer in the given range - e.g., "2 to 10 carbon atoms" means that the alkynyl group may consist of 2 carbon atoms, 3 carbon atoms, etc., up to and including 10 carbon atoms. The alkynyl may be attached to the rest of the molecule by a single bond, for example, ethynyl, propynyl, butynyl, pentynyl and hexynyl. Unless stated otherwise specifically in the specification, an alkynyl group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilyl, -OR a , -SR a , -OC(0)-R a , -N(R a ) 2 , -C(0)R a , -C(0)OR a , -OC(0)N(R a ) 2 , -C(0)N(R a ) 2 , -N(R a )C(0)OR a , -N(R a )C(0)R a , -N(R a )C(0)N(R a ) 2 , N(R a )C(NR a )N(R a ) 2 , -N(R a )S(0),R a (where t is 1 or 2), -S(0),OR a (where t is 1 or 2), -S(0),N(R a ) 2 (where t is 1 or 2), or P0 3 (R a ) 2 , where each R a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00115] "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.

[00116] "Carboxaldehyde" refers to a -(C=0)H radical.

[00117] "Carboxyl" refers to a -(C=0)OH radical.
"Cyano" refers to a -CN radical.

"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$_2$-C$_{10}$ cycloalkyl). Whenever it appears herein, a numerical range such as "3 to 10" refers to each integer in the given range - e.g., "3 to 10 carbon atoms" means that the cycloalkyl group may consist of 3 carbon atoms, etc., up to and including 10 carbon atoms. Illustrative examples of cycloalkyl groups include, but are not limited to the following moieties: cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cyclooctyl, cyclooctenyl, cyclohexyl, 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, ary1, alyarylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilylalkyl, -OR, -SR, -OC(0)-R, -N(R)$^2$, -C(0)R, -C(0)OR, -OC(0)N(R)$^2$, -C(0)N(R)$^2$, -N(R)$^2$C(0)OR, -N(R)$^2$C(0)R, -N(R)$^2$C(0)N(R)$^2$, -N(R)$^2$C(NR)$^2$, -N(R)$^2$S(0),R (where t is 1 or 2), -S(0),OR (where t is 1 or 2), -S(0),N(R)$^2$ (where t is 1 or 2), or P0$_3$(R)$^2$, where each R is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, alyl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

"Cycloalky1-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.

"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.

"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.
[00123] 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, isoproxy, cyclopropoxy and cyclohexyloxy. "Lower alkoxy" refers to alkoxy groups containing one to six carbons.

[00124] 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, heteroarylylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilyl, -OR\textsubscript{a}, -SR\textsubscript{a}, -OC(0)-R\textsubscript{a}, -N(R\textsubscript{a})\textsubscript{2}, -C(0)R\textsubscript{a}, -C(0)OR\textsubscript{a}, -OC(0)N(R\textsubscript{a})\textsubscript{2}, -C(0)N(R\textsubscript{a})\textsubscript{2}, -N(R\textsubscript{a})C(0)R\textsubscript{a}, -N(R\textsubscript{a})C(0)OR\textsubscript{a}, -N(R\textsubscript{a})C(NR\textsubscript{a})N(R\textsubscript{a})\textsubscript{2}, -N(R\textsubscript{a})S(0),R\textsubscript{a} \text{ (where t is 1 or 2)}, -S(0),OR\textsubscript{a} \text{ (where t is 1 or 2)}, -S(0),N(R\textsubscript{a})\textsubscript{2} \text{ (where t is 1 or 2)}, or P0\textsubscript{3}(R\textsubscript{a})\textsubscript{2}, where each R\textsubscript{a} is independently hydrogen, alkyl, fluoroalkyl, carbocycly, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylylalkyl.

[00125] 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 Ci-C\textsubscript{6} alkoxy carbonyl group is an alkoxy group having from 1 to 6 carbon atoms attached through its oxygen to a carbonyl linker. "Lower alkoxy carbonyl" refers to an alkoxy carbonyl group wherein the alkoxy group is a lower alkoxy group.

[00126] The term "substituted alkoxy carbonyl" refers to the group (substituted alkyl)-O-C(0)- 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 alkoxy carbonyl group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilyl, -OR\textsubscript{a}, -SR\textsubscript{a}, -OC(0)-R\textsubscript{a}, -N(R\textsubscript{a})\textsubscript{2}, -C(0)R\textsubscript{a}, -C(0)OR\textsubscript{a}, -OC(0)N(R\textsubscript{a})\textsubscript{2}, -C(0)N(R\textsubscript{a})\textsubscript{2}, -N(R\textsubscript{a})C(0)R\textsubscript{a}, -N(R\textsubscript{a})C(0)OR\textsubscript{a}, -N(R\textsubscript{a})C(NR\textsubscript{a})N(R\textsubscript{a})\textsubscript{2}, -N(R\textsubscript{a})S(0),R\textsubscript{a} \text{ (where t is 1 or 2)}, -S(0),OR\textsubscript{a} \text{ (where t is 1 or 2)}, -S(0),N(R\textsubscript{a})\textsubscript{2} \text{ (where t is 1 or 2)}, or P0\textsubscript{3}(R\textsubscript{a})\textsubscript{2}, where each R\textsubscript{a} is
independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroarylyl or heteroarylylalkyl.

[00127] "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, heteroarylalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilyl, -OR, -SR, -OC(0)-R, -N(R)2, -C(0)R, -C(0)OR, -OC(0)N(R)2, -C(0)N(R)2, -N(R)C(0)OR, -N(R)C(0)N(R)2, N(R)C(NR)N(R)2, -N(R)S(0), R (where t is 1 or 2), -S(0), OR (where t is 1 or 2), -S(0), N(R)2 (where t is 1 or 2), or PO3(R)2, where each R2 is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroarylyl or heteroarylylalkyl.

[00128] "Acyloxy" refers to a R(C=0)O- radical wherein R is alkyl, aryl, heteroaryl, heteroarylyl 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, heteroarylyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilyl, -OR, -SR, -OC(0)-R, -N(R)2, -C(0)R, -C(0)OR, -OC(0)N(R)2, -C(0)N(R)2, -N(R)C(0)OR, -N(R)C(0)N(R)2, N(R)C(NR)N(R)2, -N(R)S(0), R (where t is 1 or 2), -S(0), OR (where t is 1 or 2), -S(0), N(R)2 (where t is 1 or 2), or PO3(R)2, where each R2 is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroarylyl or heteroarylylalkyl.

[00129] "Amino" or "amine" refers to a -N(R)2 radical group, where each R2 is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroarylyl or heteroarylylalkyl, unless stated otherwise specifically in the
specification. When a \(-\text{N}(\text{R}^a)^2\) group has two \(\text{R}^a\) substituents other than hydrogen, they can be combined with the nitrogen atom to form a 4-, 5-, 6- or 7-membered ring. For example, \(-\text{N}(\text{R}^a)^2\) 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, trimethylsilyl, \(-\text{OR}^a\), \(-\text{SR}^a\), \(-\text{OC}(\text{O})\text{R}^a\), \(-\text{N}(\text{R}^a)^2\), \(-\text{C}(\text{O})\text{R}^a\), \(-\text{C}(\text{O})\text{OR}^a\), \(-\text{OC}(\text{O})(\text{R}^a)^2\), \(-\text{C}(\text{O})(\text{R}^a)^2\), \(-\text{N}(\text{R}^a)^2\text{C}(\text{O})\text{OR}^a\), \(-\text{N}(\text{R}^a)^2\text{C}(\text{O})\text{R}^a\), \(-\text{N}(\text{R}^a)^2\text{N}(\text{R}^a)^2\text{N}(\text{R}^a)^2\), \(-\text{N}(\text{R}^a)^2\text{S}(\text{O})\text{R}^a\) (where \(t\) is 1 or 2), \(-\text{S}(\text{O})\text{R}^a\) (where \(t\) is 1 or 2), \(-\text{P}(\text{O})_3(\text{R}^a)^2\) (where each \(\text{R}^a\) is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00130] The term "substituted amino" also refers to \(N\)-oxides of the groups \(-\text{NH}R^d\), and \(\text{NR}^d\text{R}^d\) 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.

[00131] "Amide" or "amido" refers to a chemical moiety with formula \(-\text{C}(\text{O})\text{N}(\text{R})^2\) or \(-\text{NH}C(\text{O})\text{R}\), where \(\text{R}\) is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heterocyclic (bonded through a ring carbon), each of which moiety may itself be optionally substituted. The \(\text{R}_2\) of \(-\text{N}(\text{R})^2\) 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 of Formula (I), 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 T. H. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley & Sons, New York (1999).

[00132] "Aromatic" or "aryl" or "Ar" refers to an aromatic radical with six to ten ring atoms \((\text{e.g., } \text{C}_6\text{-C}_5\text{ aromatic or C}_6\text{-C}_1\text{ aryl})\) which has at least one ring having a conjugated pi electron system which is carbocyclic \((\text{e.g., phenyl, fluorenyl, and naphthyl})\). 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 naphthyldene. 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, alkylnyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, -OR, -SR, -OC(0)-R, -C(0)R, -C(0)OR, -C(0)N(R), -N(R)C(0)R, -N(R)C(0)OR, -N(R)C(0)N(R), N(R)C(NR)N(R), -C(0)N(R), -N(R)C(0)OR, -N(R)C(0)N(R), N(R)C(NR)N(R), N(R)S, R (where t is 1 or 2), -S(R), OR (where t is 1 or 2), -S(R)N(R), P0(R), where each R is independently hydrogen, alkyl, fluoroalkyl, carbocyclyalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00133] "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.

[00134] "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 heterocycloalicyclic (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 T. H. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York (1999). Unless stated otherwise specifically in the specification, an ester group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, -OR, -SR, -
OC(0)-R^a, -N(R^a)_2, -C(0)R^a, -C(0)OR^a, -OC(0)N(R^a)_2, -N(R^a)C(0)OR^a, -N(R^a)C(0)R^a, -C(0)N(R^a)_2, -S(0),OR^a (where t is 1 or 2), -S(0),OR^a (where t is 1 or 2), -S(0),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, carbocycyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00135] "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.

[00136] "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.

[00137] "Heteroalkyl," "heteroalkenyl," and "heteroalkynyl" include optionally substituted alkyl, alkenyl and alkylnyl 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-C4 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, o xo, thioxo, trimethylsilyl, -OR^a, -SR^a, -OC(0)-R^a, -N(R^a)_2, -C(0)R^a, -C(0)OR^a, -OC(0)N(R^a)_2, -C(0)N(R^a)_2, -N(R^a)C(0)OR^a, -N(R^a)C(0)R^a, -N(R^a)C(0)N(R^a)_2

N(R^a)C(NR^a)N(R^a)_2, -N(R^a)S(0),R^a (where t is 1 or 2), -S(0),OR^a (where t is 1 or 2), -S(0),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, carbocycyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.
"Heteroalkylaryl" refers to an -(heteroalkyl)aryl radical where heteroalkyl and aryl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and aryl, respectively.

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

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

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

"Heteroaryl" or "heteroaromatic" or "HetAr" refers to a 5- to 18-membered aromatic radical (e.g., C5-C13 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[<i]thiazolyl, benzothiadiazolyl,
benzo[£][1,4]dioxepinyl, benzo[¾][1,4]oxazinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzoazolyl, benzopyranol, benzo[3,2-d]pyrimidinyl, benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, cyclopenta[d]pyrimidinyl, 6,7-dihydro-5H-cyclopenta[4,5]thieno[2,3-c]pyrimidinyl, 5,6-dihydrobenzo[A]quinazolinyl, 5,6-dihydrobenzo[A]cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furazanyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, 5,8-methano-5,6,7,8-tetrahydroquinazolinyl, naphthyridinyl, 1,6-naphthyridinononyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 5,6,7,8,9,10,10a-octahydrobenzo[A]quinazolinyl, 1-phenyl-1H-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyranol, pyrrolyl, pyrazolyl, pyrazolo[3,4-d]pyrimidinyl, pyridinyl, pyrido[3,2-d]pyrimidinyl, pyrazinyl, pyrimidinyl, pyridazine, pyrrolol, quinazolinyl, quinoxalinyl, quinolinol, isoquinolinol, tetrahydroquinolinol, 5,6,7,8-tetrahydroquinazolinonyl, 5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidinyl, 6,7,8,9-tetrahydro-5H-cyclohepta[4,5]thieno[2,3-c]pyrimidinyl, 5,6,7,8-tetrahydropropyridinol, 5,6-dihydro-5H-cyclohept[4,5]thieno[2,3-c]pyrimidinyl, thiazolyl, thiadiazolyl, thiapyran, triazolyl, tetrazolyl, triazinyl, thieno[2,3-d]pyrimidinyl, thieno[3,2-c]pyrimidinyl, 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, heteroaryalkyl, hydroxy, halo, cyano, nitro, o xo, thio, trimethylsilanyland, -OR, -SR, -OC(O)-R, -N(R)=, -C(0)R, -C(0)OR, -OC(O)N(R)=, -C(0)N(R)=, -N(R)=C(0)OR, -N(R)=C(O)R, -N(R)C(0)N(R), N(R)=C(NR)N(R), N(R)S(O), R (where t is 1 or 2), -S(O)OR (where t is 1 or 2), -P(O)R (where t is 1 or 2), or PO3R (where each R is independently hydrogen, alkyl, fluoroalkyl, carbocycl, carbocyclalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroaryalkyl.

[00143] Substituted heteroaryl also includes ring systems substituted with one or more oxide (-0-) substituents, such as, for example, pyridinyl N-oxides.
"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.

"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, pipеразинил, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuranyl, thithianyl, tetrahydropyranyl, thiomorpholinyl, thiomorpholinyl, 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, alkylnyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, nitro, o xo, thioxo, trimethylsilanyl, -OR, -SR, -OC(O)-R, -N(R)2, -C(0)R, -C(0)OR, -OC(O)N(R)2, -C(0)N(R)2, -N(R)C(O)OR, -N(R)C(0)R, -N(R)C(0)N(R)2, -N(R)C(0)S(0),R (where t is 1 or 2), -S(0),OR (where t is 1 or 2), -S(0),N(R)2 (where t is 1 or 2), or P03(R)2, where each R is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

"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.

[00147] "Isomers" are different compounds that have the same molecular formula. "Stereoisomers" are isomers that differ only in the way the atoms are arranged in space - i.e., having a different stereochemical configuration. "Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic" mixture. The term "(±)" is used to designate a racemic mixture where appropriate. "Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry is specified according to the Cahn-Ingold-Prelog R-S system. When a compound is a pure enantiomer the stereochemistry at each chiral carbon can be specified by either R or S. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain of the compounds described herein contain one or more asymmetric centers and can thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that can be defined, in terms of absolute stereochemistry, as (R)- or (S)-. The present chemical entities, pharmaceutical compositions and methods are meant to include all such possible isomers, including racemic mixtures, optically pure forms and intermediate mixtures. Optically active (R)- and (S)-isomers can be prepared using chiral synths or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

[00148] "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)- and 20% (R)-, 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 the Pirkle alcohol, or derivatization of a compounds using a chiral compound such as Mosher's acid followed by chromatography or nuclear magnetic resonance spectroscopy.

[00149] "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.

[00150] "Nitro" refers to the -N0₂ radical.

[00151] "Oxa" refers to the -O- radical.

[00152] "Oxo" refers to the =O radical.

[00153] "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.

[00154] The terms "enantiomerically enriched," "enantiomerically pure," 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 (7?)-enantiomer, such as at least 75% by weight, 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," "substantially enantiomerically pure," or a "substantially non-racemic" preparation, which refers to preparations of compositions which have at least 85% by weight of one enantiomer relative to the other enantiomer, such as at least 90%, by weight, and such as at least 95% by weight. The terms "diastereomerically enriched" and "diastereomerically pure," as used herein, refer to compositions in which the percent by weight of one diastereomer is greater than the amount of that one diastereomer in a control mixture of diastereomers. In some embodiments, the enrichment can be significantly greater than 80% by weight, providing a "substantially diastereomerically enriched" or "substantially diastereomerically pure" preparation, which refers to preparations of compositions which have at least 85% by weight of one diastereomer relative to other diastereomers, such as at least 90%, by weight, and such as at least 95% by weight.

[00155] In preferred embodiments, the enantiomerically enriched composition has a higher potency with respect to therapeutic utility per unit mass than does the racemic mixture of that composition. Enantiomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred enantiomers can be prepared by asymmetric syntheses. See, for example, Jacques, et al., Enantiomers, Racemates and Resolutions, Wiley Interscience, New York (1981); E. L. Eliel and S. H. Wilen, Stereochemistry of Organic Compounds, Wiley-Interscience, New York (1994).

[00156] 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 toslyloxy groups.

[00157] "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

[00158] "Solvate" refers to a compound in physical association with one or more molecules of a pharmaceutically acceptable solvent.

[00159] "Substituted" means that the referenced group may have attached one or more additional 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, sulfmyl, 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.

[00160] "Sulfanyl" refers to groups that include -S-(optionally substituted alkyl), -S-(optionally substituted aryl), -S-(optionally substituted heteroaryl) and -S-(optionally substituted heterocycloalkyl).

[00161] "Sulfmyl" refers to groups that include -S(0)-(optionally substituted alkyl), -S(0)-(optionally substituted amino), -S(0)-(optionally substituted aryl), -S(0)-(optionally substituted heteroaryl) and -S(0)-(optionally substituted heterocycloalkyl).

[00162] "Sulfonyl" refers to groups that include -S(0₂)-H, -S(0₂)-(optionally substituted alkyl), -S(0₂)-(optionally substituted amino), -S(0₂)-(optionally substituted aryl), -S(0₂)-(optionally substituted heteroaryl), and -S(0₂)-(optionally substituted heterocycloalkyl).

[00163] "Sulfonamidyl" or "sulfonamido" refers to a -S(=0)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(=0)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.

[00164] "Sulfoxyl" refers to a -S(=O)₂OH radical.

[00165] "Sulfonate" refers to a -S(=O)₂OR radical, where R is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon). A sulfonate group is optionally substituted on R by one or more of the substituents described for alkyl, cycloalkyl, aryl, heteroaryl, respectively.

[00166] 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.

[00167] Compounds of the invention also include antibodies. The terms "antibody" and its plural form "antibodies" refer to whole immunoglobulins and any antigen-binding fragment ("antigen-binding portion") or single chains thereof. An "antibody" further refers to a glycoprotein comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds, or an antigen-binding portion thereof. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as V₃) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as V₄) and a light chain constant region. The light chain constant region is comprised of one domain, C₅. The V₃ and V₄ regions of an antibody may be further subdivided into regions of hypervariability, which are referred to as complementarity determining regions (CDR) or hypervariable regions (HVR), and which can be interspersed with regions that are more conserved, termed framework regions (FR). Each V₃ and V₄ is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4.
variable regions of the heavy and light chains contain a binding domain that interacts with an antigen epitope or epitopes. The constant regions of the antibodies may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (e.g., effector cells) and the first component (Clq) of the classical complement system.

[00168] The terms "monoclonal antibody," "mAb," "monoclonal antibody composition," or their plural forms refer to a preparation of antibody molecules of single molecular composition. A monoclonal antibody composition displays a single binding specificity and affinity for a particular epitope. Monoclonal antibodies specific to CD20 can be made using knowledge and skill in the art of injecting test subjects with CD20 antigen and then isolating hybridomas expressing antibodies having the desired sequence or functional characteristics. DNA encoding the monoclonal antibodies is readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the monoclonal antibodies). The hybridoma cells serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as E. coli cells, simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. Recombinant production of antibodies will be described in more detail below.

[00169] The terms "antigen-binding portion" or "antigen-binding fragment" of an antibody (or simply "antibody portion"), as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to an antigen such as CD20. It has been shown that the antigen-binding function of an antibody can be performed by fragments of a full-length antibody. Examples of binding fragments encompassed within the term "antigen-binding portion" of an antibody include (i) a Fab fragment, a monovalent fragment consisting of the V\textsubscript{L}, V\textsubscript{H}, C\textsubscript{L} and CHI domains; (ii) a F(ab')2 fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the V\textsubscript{H} and CHI domains; (iv) a Fv fragment consisting of the V\textsubscript{L} and V\textsubscript{H} domains of a single arm of an antibody, (v) a domain antibody (dAb) fragment (Ward et al., Nature, 1989, 341, 544-546), which may consist of a V\textsubscript{H} or a V\textsubscript{L} domain; and (vi) an isolated complementarity determining region (CDR). Furthermore, although the two domains of the Fv fragment, V\textsubscript{L} and V\textsubscript{H}, are coded for by separate
genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the $V_L$ and $V_H$ regions pair to form monovalent molecules known as single chain Fv (scFv); see, for example, Bird et al., Science 1988, 242, 423-426; and Huston et al., Proc. Natl. Acad. Sci. USA 1988, 85, 5879-5883). Such scFv chain antibodies are also intended to be encompassed within the terms "antigen-binding portion" or "antigen-binding fragment" of an antibody. These antibody fragments are obtained using conventional techniques known to those with skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies.

[00170] The term "human antibody," as used herein, is intended to include antibodies having variable regions in which both the framework and CDR regions are derived from human germline immunoglobulin sequences. Furthermore, if the antibody contains a constant region, the constant region also is derived from human germline immunoglobulin sequences. The human antibodies of the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis in vitro or by somatic mutation in vivo). The term "human antibody", as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

[00171] The term "human monoclonal antibody" refers to antibodies displaying a single binding specificity which have variable regions in which both the framework and CDR regions are derived from human germline immunoglobulin sequences. In one embodiment, the human monoclonal antibodies are produced by a hybridoma which includes a B cell obtained from a transgenic nonhuman animal, e.g., a transgenic mouse, having a genome comprising a human heavy chain transgene and a light chain transgene fused to an immortalized cell.

[00172] The term "recombinant human antibody", as used herein, includes all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as (a) antibodies isolated from an animal (e.g., a mouse) that is transgenic or transchromosomal for human immunoglobulin genes or a hybridoma prepared therefrom (described further below), (b) antibodies isolated from a host cell transformed to express the human antibody, e.g., from a transfectoma, (c) antibodies isolated from a recombinant, combinatorial human antibody library,
and (d) antibodies prepared, expressed, created or isolated by any other means that involve splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies have variable regions in which the framework and CDR regions are derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies can be subjected to in vitro mutagenesis (or, when an animal transgenic for human Ig sequences is used, in vivo somatic mutagenesis) and thus the amino acid sequences of the $V_H$ and $V_L$ regions of the recombinant antibodies are sequences that, while derived from and related to human germline $V_H$ and $V_L$ sequences, may not naturally exist within the human antibody germline repertoire in vivo.

[00173] As used herein, "isotype" refers to the antibody class (e.g., IgM or IgGl) that is encoded by the heavy chain constant region genes.

[00174] The phrases "an antibody recognizing an antigen" and "an antibody specific for an antigen" are used interchangeably herein with the term "an antibody which binds specifically to an antigen."

[00175] The term "human antibody derivatives" refers to any modified form of the human antibody, e.g., a conjugate of the antibody and another agent or antibody. The term "conjugate" or "immunoconjugate" refers to an antibody, or a fragment thereof, conjugated to a therapeutic moiety, such as a bacterial toxin, a cytotoxic drug or a radionuclide-containing toxin. Toxic moieties can be conjugated to antibodies of the invention using methods available in the art.

[00176] The terms "humanized antibody," "humanized antibodies," and "humanized" are intended to refer to antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences. Additional framework region modifications may be made within the human framework sequences. Humanized forms of non-human (for example, murine) antibodies are chimeric antibodies that contain minimal sequence derived from non-human immunoglobulin. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a hypervariable region of the recipient are replaced by residues from a 15 hypervariable region of a non-human species (donor antibody) such as mouse, rat, rabbit or nonhuman primate having the desired specificity, affinity, and capacity. In some instances, Fv framework region (FR) residues of the human immunoglobulin are replaced by corresponding
non-human residues. Furthermore, humanized antibodies may comprise residues that are not found in the recipient antibody or in the donor antibody. These modifications are made to further refine antibody performance. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin sequence. The humanized antibody optionally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see Jones et al, Nature 1986, 321, 522-525; Riechmann et al, Nature 1988, 332, 323-329; and Presta, Curr. Op. Struct. Biol. 1992, 2, 593-596.

[00177] The term "chimeric antibody" is intended to refer to antibodies in which the variable region sequences are derived from one species and the constant region sequences are derived from another species, such as an antibody in which the variable region sequences are derived from a mouse antibody and the constant region sequences are derived from a human antibody.

[00178] A "diabody" is a small antibody fragment with two antigen-binding sites. The fragment comprises a heavy chain variable domain (V_H) connected to a light chain variable domain (V_L) in the same polypeptide chain (V_H^*V_L or V_L^*V_H). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, e.g., European Patent No. EP 404,097, International Patent Publication No.WO 93/1161; and Bolliger et al, Proc. Natl. Acad. Sci. USA 1993, 90, 6444-6448.

[00179] The term "glycosylation" refers to a modified derivative of an antibody. An aglycoslated antibody lacks glycosylation. Glycosylation can be altered to, for example, increase the affinity of the antibody for antigen. Such carbohydrate modifications can be accomplished by, for example, altering one or more sites of glycosylation within the antibody sequence. For example, one or more amino acid substitutions can be made that result in elimination of one or more variable region framework glycosylation sites to thereby eliminate glycosylation at that site. Aglycosylation may increase the affinity of the antibody for antigen, as described in U.S. Patent Nos. 5,714,350 and 6,350,861. Additionally or alternatively, an antibody can be made
that has an altered type of glycosylation, such as a hypofucosylated antibody having reduced amounts of fucosyl residues or an antibody having increased bisecting GlcNac structures. Such altered glycosylation patterns have been demonstrated to increase the ability of antibodies. Such carbohydrate modifications can be accomplished by, for example, expressing the antibody in a host cell with altered glycosylation machinery. Cells with altered glycosylation machinery have been described in the art and can be used as host cells in which to express recombinant antibodies of the invention to thereby produce an antibody with altered glycosylation. For example, the cell lines Ms704, Ms705, and Ms709 lack the fucosyltransferase gene, FUT8 (alpha (1,6) fucosyltransferase), such that antibodies expressed in the Ms704, Ms705, and Ms709 cell lines lack fucose on their carbohydrates. The Ms704, Ms705, and Ms709 FUT8/-/- cell lines were created by the targeted disruption of the FUT8 gene in CHO/DG44 cells using two replacement vectors (see e.g. U.S. Patent Publication No. 2004/01 10704 or Yamane-Ohnuki, et al, Biotechnol. Bioeng., 2004, 87, 614-622). As another example, European Patent No. EP 1,176,195 describes a cell line with a functionally disrupted FUT8 gene, which encodes a fucosyl transferase, such that antibodies expressed in such a cell line exhibit hypofucosylation by reducing or eliminating the alpha 1,6 bond-related enzyme, and also describes cell lines which have a low enzyme activity for adding fucose to the N-acetylglucosamine that binds to the Fc region of the antibody or does not have the enzyme activity, for example the rat myeloma cell line YB2/0 (ATCC CRL 1662). International Patent Publication WO 03/035835 describes a variant CHO cell line, Lec 13 cells, with reduced ability to attach fucose to Asn(297)-linked carbohydrates, also resulting in hypofucosylation of antibodies expressed in that host cell (see also Shields, et al., J. Biol. Chem. 2002, 277, 26733-26740. International Patent Publication WO 99/54342 describes cell lines engineered to express glycoprotein-modifying glycosyl transferases (e.g., beta(l,4)-N-acetylglucosaminyltransferase III (GnTIII)) such that antibodies expressed in the engineered cell lines exhibit increased bisecting GlcNac structures which results in increased ADCC activity of the antibodies (see also Umana, et al, Nat. Biotechn. 1999, 17, 176-180). Alternatively, the fucose residues of the antibody may be cleaved off using a fucosidase enzyme. For example, the fucosidase alpha-L-fucosidase removes fucosyl residues from antibodies as described in Tarentino, et al, Biochem. 1975, 14, 5516-5523.

[00180] "Pegylation" refers to a modified antibody, or a fragment thereof, that typically is reacted with polyethylene glycol (PEG), such as a reactive ester or aldehyde derivative of PEG,
under conditions in which one or more PEG groups become attached to the antibody or antibody fragment. Pegylation may, for example, increase the biological (e.g., serum) half life of the antibody. Preferably, the pegylation is carried out via an acylation reaction or an alkylation reaction with a reactive PEG molecule (or an analogous reactive water-soluble polymer). As used herein, the term "polyethylene glycol" is intended to encompass any of the forms of PEG that have been used to derivatize other proteins, such as mono (C1-C6) alkoxy- or aryloxy-polyethylene glycol or polyethylene glycol-maleimide. The antibody to be pegylated may be an aglycosylated antibody. Methods for pegylation are known in the art and can be applied to the antibodies of the invention. See, for example, European Patent Nos. EP 0154316 and EP 0401384.

[00181] As used herein, an antibody that "specifically binds to human CD20" is intended to refer to an antibody that binds to human CD20 with a K_D of 1×10^{-7} M or less, more preferably 5×10^{-8} M or less, more preferably 1×10^{-8} M or less, more preferably 5×10^{-9} M or less.

[00182] The term "radioisotope-labeled complex" refers to both non-covalent and covalent attachment of a radioactive isotope, such as ^{90}Y, ^{111}In, or ^{131}I, to an antibody.

[00183] The term "biosimilar" means a biological product that is highly similar to a U.S. licensed reference biological product notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product. Furthermore, a similar biological or "biosimilar" medicine is a biological medicine that is similar to another biological medicine that has already been authorized for use by the European Medicines Agency. The term "biosimilar" is also used synonymously by other national and regional regulatory agencies. Biological products or biological medicines are medicines that are made by or derived from a biological source, such as a bacterium or yeast. They can consist of relatively small molecules such as human insulin or erythropoietin, or complex molecules such as monoclonal antibodies. For example, if the reference anti-CD20 monoclonal antibody is rituximab, an anti-CD20 biosimilar monoclonal antibody approved by drug regulatory authorities with reference to rituximab is a "biosimilar to" rituximab or is a "biosimilar thereof" rituximab.
In an embodiment, the BTK inhibitor is a compound of Formula (I):

![Chemical Structure](image)

or a pharmaceutically acceptable salt 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$i$iC(=0), R_i2S(=0), R_i3S(=0) or (C$i$i-$C$i$)alkyl optionally substituted with $R_{14}$;
- $R_2$ is H, (C$i$-$C$)alkyl or (C$_3$-$C_2$)cycloalkyl;
- $R_3$ is H, (C$i$-$C$)alkyl or (C$_3$-$C_2$)cycloalkyl; or
- $R_2$ and $R_3$ form, together with the N and C atom they are attached to, a (C$_3$-$C_2$)heterocycloalkyl optionally substituted with one or more fluorine, hydroxyl, (C$i$-$C$)alkyl, (C$i$-$C$)alkoxy or oxo;
R 4 is H or (Ci₃)alkyl;
R 5 is H, halogen, cyano, (Ci₄)alkyl, (Ci₃)alkoxy, (C₁₋₃)cycloalkyl, any alkyl group of which is optionally substituted with one or more halogen; or R 5 is (C₆-io)aryl or (C₆-io)heteroaryl;
R 6 is H or (Ci₃)alkyl; or
R 5 and R 6 together may form a (C₁₋₃)cycloalkenyl or (C₂₋₆)heterocycloalkenyl, each optionally substituted with (Ci₃)alkyl or one or more halogens;
R 7 is H, halogen, CF₃, (Ci₃)alkyl or (Ci₃)alkoxy;
R 8 is H, halogen, CF₃, (Ci₃)alkyl or (Ci₃)alkoxy; or
R 7 and R 8 together with the carbon atoms they are attached to, form (C₆-io)aryl or (Ci₋₉)heteroaryl;
R 9 is H, halogen, (Ci₃)alkyl or (Ci₃)alkoxy;
R 10 is H, halogen, (Ci₃)alkyl or (Ci₃)alkoxy;
R 11 is independently selected from the group consisting of (Ci₃)alkyl, (C₂₋₆)alkenyl and (C₂₋₆)alkynyl, where each alkyl, alkenyl or alkylnyl is optionally substituted with one or more substituents selected from the group consisting of hydroxyl, (Ci₃)alkyl, (C₆-io)cycloalkyl, [(Ci₃)alkyl]amino, di[(Ci₃)alkyl]amino, (Ci₃)alkoxy, (C₆-io)aryl and (C₂₋₆)heterocycloalkyl; or R 11 is (Ci₋₉)alkyl-C(0)-S-(Ci₋₉)alkyl; or
R 11 is (Ci₅)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 (C₂₋₆)alkenyl or (C₂₋₆)alkynyl, both optionally substituted with one or more substituents selected from the group consisting of hydroxyl, (Ci₃)alkyl, (C₂₋₆)cycloalkyl, [(Ci₃)alkyl]amino, di[(Ci₃)alkyl]amino, (Ci₋₉)alkoxy, (C₂₋₆)cycloalkoxy, (C₆-io)aryl and (C₂₋₆)heterocycloalkyl; or a (Ci₅)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, (C₂₋₆)alkenyl and (C₂₋₆)alkynyl, both optionally substituted with one or more substituents selected from the group consisting of hydroxyl, (Ci₋₉)alkyl, (C₂₋₆)cycloalkyl, (Ci₋₉)alkylamino, di[(Ci₋₉)alkyl]amino, (Ci₋₉)alkoxy, (C₂₋₆)cycloalkoxy, (C₆-io)aryl and (C₂₋₆)heterocycloalkyl; with the proviso that:
0 to 2 atoms of X, Y, Z can simultaneously be a heteroatom;
when one atom selected from X, Y is O or S, then Z is a bond and the other atom selected from X, Y can not be O or S;
when Z is C or N then Y is C(R₆) or N and X is C or N;
0 to 2 atoms of B₁, B₂, B₃, and B₄ are N;
with the terms used having the following meanings:

(Ci₂)alkyl means an alkyl group having 1 to 2 carbon atoms, being methyl or ethyl,
(Ci₃)alkyl means a branched or unbranched alkyl group having 1-3 carbon atoms, being methyl, ethyl, propyl or isopropyl;
(Ci₄)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, (Ci₃)alkyl groups being preferred;
(Ci₅)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, (Ci₄)alkyl groups being preferred. (Ci₆)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. (Ci₅)alkyl groups are preferred, (Ci₄)alkyl being most preferred;
(Ci₂)alkoxy means an alkoxy group having 1-2 carbon atoms, the alkyl moiety having the same meaning as previously defined;
(Ci₃)alkoxy means an alkoxy group having 1-3 carbon atoms, the alkyl moiety having the same meaning as previously defined. (Ci₂)alkoxy groups are preferred;
(Ci₄)alkoxy means an alkoxy group having 1-4 carbon atoms, the alkyl moiety having the same meaning as previously defined. (Ci₃)alkoxy groups are preferred, (Ci₂)alkoxy groups being most preferred;
(C₂₄)alkenyl means a branched or unbranched alkenyl group having 2-4 carbon atoms, such as ethenyl, 2-propenyl, isobutenyl or 2-butenyl;
(C₂₆)alkenyl means a branched or unbranched alkenyl group having 2-6 carbon atoms, such as ethenyl, 2-butenyl, and n-pentenyl, (C₂₄)alkenyl groups being most preferred;
(C₂₄)alkynyl means a branched or unbranched alkynyl group having 2-4 carbon atoms, such as ethynyl, 2-propynyl or 2-butynyl;
(C\textsubscript{2-6})alkynyl means a branched or unbranched alkynyl group having 2-6 carbon atoms, such as ethynyl, propynyl, n-butynyl, n-pentynyl, isopentynyl, isoheptynyl or n-hexynyl. (C\textsubscript{3-6})alkynyl groups are preferred; (C\textsubscript{3-6})cycloalkyl means a cycloalkyl group having 3-6 carbon atoms, being cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl;
(C\textsubscript{3-7})cycloalkyl means a cycloalkyl group having 3-7 carbon atoms, being cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl;
(C\textsubscript{3-5})heterocycloalkyl means a heterocycloalkyl group having 2-6 carbon atoms, preferably 3-5 carbon atoms, and one or two heteroatoms selected from N, O and/or S, which may be attached via a heteroatom if feasible, or a carbon atom; preferred heteroatoms are N or O; also preferred are piperidine, morpholine, pyrrolidine and piperazine; with the most preferred (C\textsubscript{1-5})heterocycloalkyl being pyrrolidine; the heterocycloalkyl group may be attached via a heteroatom if feasible;
(C\textsubscript{3-7})heterocycloalkyl means a heterocycloalkyl group having 3-7 carbon atoms, preferably 3-5 carbon atoms, and one or two heteroatoms selected from N, O and/or S. Preferred heteroatoms are N or O; preferred (C\textsubscript{3-7}) heterocycloalkyl groups are azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl; more preferred (C\textsubscript{3-7})heterocycloalkyl groups are piperidine, morpholine and pyrrolidine; and the heterocycloalkyl group may be attached via a heteroatom if feasible;
(C\textsubscript{3-7})cycloalkoxy means a cycloalkyl group having 3-7 carbon atoms, with the same meaning as previously defined, attached via a ring carbon atom to an exocyclic oxygen atom;
(C\textsubscript{6-10})aryl means an aromatic hydrocarbon group having 6-10 carbon atoms, such as phenyl, naphthyl, tetrahydronaphthyl or indenyl; the preferred (C\textsubscript{6-10})aryl group is phenyl;
(C\textsubscript{i-5})heteroaryl means a substituted or unsubstituted aromatic group having 1-5 carbon atoms and 1-4 heteroatoms selected from N, O and/or S; the (C\textsubscript{i-5})heteroaryl may optionally be substituted; preferred (C\textsubscript{i-5})heteroaryl groups are tetrazolyl, imidazolyl, thiaiazolyl, pyridyl, pyrimidyl, triazinyl, thienyl or furyl, a more preferred (C\textsubscript{i-5})heteroaryl is pyrimidyl;
(C\textsubscript{i-9})heteroaryl means a substituted or unsubstituted aromatic group having 1-9 carbon atoms and 1-4 heteroatoms selected from N, O and/or S; the (C\textsubscript{i-9})heteroaryl may optionally be substituted; preferred (C\textsubscript{i-9})heteroaryl groups are quinoline, isoquinoline and indole;
[(Ci_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 [(Ci_4)alkyl]amino
group is methyramino;
di[(Ci_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[(Ci_4)
alkyl]amino group is dimethylamino;
halogen means fluorine, chlorine, bromine or iodine;
(Ci_3)alkyl-C(0)-S-(Ci_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;
(C3_7)cycloalkenyl means a cycloalkenyl group having 3-7 carbon atoms, preferably 5-7 carbon
atoms; preferred (C3_7)cycloalkenyl groups are cyclopentenyl or cyclohexenyl; cyclohexenyl
groups are most preferred;
(C2_6)heterocycloalkenyl means a heterocycloalkenyl group having 2-6 carbon atoms, preferably
3-5 carbon atoms; and 1 heteroatom selected fromN, O and/or S; preferred (C2_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, 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.
The term "substituted" means that one or more hydrogens on the designated atom/atoms is/are
replaced with a selection from the indicated group, provided that the designated atom's
normal valency under the existing circumstances is not exceeded, and that the substitution
results in a stable compound. Combinations of substituents and/or variables are permissible
only if such combinations result in stable compounds. "Stable compound" or "stable
structure" is defined as a compound or structure that is sufficiently robust to survive isolation
to a useful degree of purity from a reaction mixture, and formulation into a drug product
containing an efficacious active pharmaceutical ingredient.
The term "optionally substituted" means optional substitution with the specified groups, radicals
or moieties.
In an embodiment of Formula (I), B₁ is C(R₇); B₂ is C(R₈); B₃ is C(R₉); B₄ is C(R₆); R₇, R₈, and R₉ are each H; and R₁ is hydrogen or methyl.

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.

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

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

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

In an embodiment of Formula (I), R₁ is selected from the group consisting of hydrogen, fluorine, methyl, methoxyl and trifluoromethyl.

In an embodiment of Formula (I), R₁ is hydrogen.

In an embodiment of Formula (I), R₂ and R₃ together form a heterocycloalkyl ring selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl and morpholinyln, optionally substituted with one or more of fluoro, hydroxyl, (Cᵢ₋₃)alkyl and (Cᵢ₋₃)alkoxy.

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

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

In an embodiment of Formula (I), R₁ is independently selected from the group consisting of (Cᵢ₋₆)alkyl, (C₃₋₆)alkenyl or (C₂₋₆)alkynyl, each optionally substituted with one or more substituents selected from the group consisting of hydroxyl, (Cᵢ₋₃)alkyl, (C₃₋₆)cycloalkyl, [(Cᵢ₋₄)alkyl] amino, di[(Cᵢ₋₄)alkyl] amino, (Cᵢ₋₃)alkoxy, (C₃₋₆)cycloalkoxy, (C₆₋₁₀)aryl and (C₃₋₉)heterocycloalkyl.

In an embodiment of Formula (I), B₁, B₂, B₃ and B₄ are CH; X is N; Y and Z are CH; R₅ is CH₃; A is N; R₂, R₃ and R₄ are H; and R₁ is CO-CH₃.
[00197] 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 \( R_i \) is \( \text{CO-CH}_3\).

[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 CH; \( R_2 \) and \( R_3 \) together form a piperidinyl ring; \( R_4 \) is H; and \( R_i \) is \( \text{CO-ethenyl} \).

[00199] 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 \( R_i \) is \( \text{CO-propynyl} \).

[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 \( \text{CH}_3 \); \( A \) is CH; \( R_2 \) and \( R_3 \) together form a piperidinyl ring; \( R_4 \) is H; and \( R_i \) is \( \text{CO-propynyl} \).

[00201] 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 \( \text{CH}_3 \); \( A \) is CH; \( R_2 \) and \( R_3 \) together form a morpholinyl ring; \( R_4 \) is H; and \( R_i \) is \( \text{CO-ethenyl} \).

[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 \( \text{CH}_3 \); \( A \) is CH; \( R_2 \) and \( R_3 \) together form a morpholinyl ring; \( R_4 \) is H; and \( R_i \) is \( \text{CO-propynyl} \).

[00203] In a preferred embodiment, the BTK inhibitor is a compound of Formula (II):

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The compound of Formula (II) is also known as (5)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide. In an embodiment, the BTK
inhibitor is (5)-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. The preparation of this compound is described at Example 6 of U.S. Patent Application Publication No. US 2014/0155385 Al, the disclosure of which is incorporated herein by reference. Briefly, the preparation of Formula (II) can be accomplished by the following procedure. 1-[Bis(dimethylamino)methylene]-
\( \text{N-H} \) 1,2,3-triazolo[4,5-\( \text{b} \)]pyridin-3-oxid hexafluorophosphate (also known as HATU, \( \text{N} \)-[(Dimethylamino)-1 \text{H}-1,2,3-triazolo-[4,5-\( \text{b} \)]pyridin-1-ylmethylene]-\( \text{N} \)-methylmethanaminium hexafluorophosphate \( \text{N} \)-oxide, and \( \text{O} \)-(1-azabenzotriazol-1-yl)-1,l,3,3-tetramethyluronium hexafluorophosphate) (18.75 mg, 0.049 mmol) was added to a solution of (5)-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, 0.27 mL) and 2-butynoic acid in dichloromethane (2 mL). The mixture was stirred for 30 minutes at room temperature. The mixture was washed with water dried over magnesium sulfate and concentrated under vacuum. The residue was purified by preparative liquid chromatography. Fractions containing product were collected and reduced to dryness to afford 10.5 mg of Formula (II) (18.0% yield).

**Pharmaceutical Compositions**

[00204] In selected embodiments, the invention provides pharmaceutical compositions for treating lymphoma and leukemia, including CLL and SLL.

[00205] The pharmaceutical compositions are typically formulated to provide a therapeutically effective amount of a BTK inhibitor, including the BTK inhibitors of Formula (I) or Formula (II), 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. Where desired, other active ingredients in addition to a BTK inhibitor of Formula (I) or Formula (II) 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.
In selected embodiments, the concentration of the BTK inhibitors of Formula (I) or Formula (II) provided in the pharmaceutical compositions of the invention is 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% or 0.001% w/w, w/v or v/v.

In selected embodiments, the concentration of the BTK inhibitors of Formula (I) or Formula (II) 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%, 1.25%, 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.

In selected embodiments, the concentration of the BTK inhibitors of Formula (I) or Formula (II) 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.

[00209] In selected embodiments, the concentration of the BTK inhibitors of Formula (I) or Formula (II) 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.

[00210] In selected embodiments, the amount of the BTK inhibitors of Formula (I) or Formula (II) is independently equal to or less than 10 g, 9.5 g, 9.0 g, 8.5 g, 8.0 g, 7.5 g, 7.0 g, 6.5 g, 6.0 g, 5.5 g, 5.0 g, 4.5 g, 4.0 g, 3.5 g, 3.0 g, 2.5 g, 2.0 g, 1.5 g, 1.0 g, 0.95 g, 0.9 g, 0.85 g, 0.8 g, 0.75 g, 0.7 g, 0.65 g, 0.6 g, 0.55 g, 0.5 g, 0.45 g, 0.4 g, 0.35 g, 0.3 g, 0.25 g, 0.2 g, 0.15 g, 0.1 g, 0.09 g, 0.08 g, 0.07 g, 0.06 g, 0.05 g, 0.04 g, 0.03 g, 0.02 g, 0.01 g, 0.009 g, 0.008 g, 0.007 g, 0.006 g, 0.005 g, 0.004 g, 0.003 g, 0.002 g or 0.0001 g.

[00211] In selected embodiments, the amount of the BTK inhibitors of Formula (I) or Formula (II) is independently more than 0.0001 g, 0.0002 g, 0.0003 g, 0.0004 g, 0.0005 g, 0.0006 g, 0.0007 g, 0.0008 g, 0.0009 g, 0.001 g, 0.0015 g, 0.002 g, 0.0025 g, 0.003 g, 0.0035 g, 0.004 g, 0.0045 g, 0.005 g, 0.0055 g, 0.006 g, 0.0065 g, 0.007 g, 0.0075 g, 0.008 g, 0.0085 g, 0.009 g, 0.0095 g, 0.01 g, 0.015 g, 0.02 g, 0.025 g, 0.03 g, 0.035 g, 0.04 g, 0.045 g, 0.05 g, 0.055 g, 0.06 g, 0.065 g, 0.07 g, 0.075 g, 0.08 g, 0.085 g, 0.09 g, 0.095 g, 0.1 g, 0.15 g, 0.2 g, 0.25 g, 0.3 g, 0.35 g, 0.4 g, 0.45 g, 0.5 g, 0.55 g, 0.6 g, 0.65 g, 0.7 g, 0.75 g, 0.8 g, 0.85 g, 0.9 g, 0.95 g, 1 g, 1.5 g, 2 g, 2.5, 3 g, 3.5, 4 g, 4.5 g, 5 g, 5.5 g, 6 g, 6.5 g, 7 g, 7.5 g, 8 g, 8.5 g, 9 g, 9.5 g or 10 g.

[00212] The BTK inhibitors of Formula (I) or Formula (II) are effective over a wide dosage range. For example, in the treatment of adult humans, dosages independently ranging from 0.01 to 1000 mg, from 0.5 to 100 mg, from 1 to 50 mg per day, and from 5 to 40 mg per day are examples of dosages that may be used. The exact dosage will depend upon the route of
administration, the form in which the compound is administered, the gender and age of the subject to be treated, the body weight of the subject to be treated, and the preference and experience of the attending physician.

[00213] Described below are non-limiting exemplary pharmaceutical compositions and methods for preparing the same.

**Pharmaceutical Compositions for Oral Administration**

[00214] In selected embodiments, the invention provides a pharmaceutical composition for oral administration containing a BTK inhibitor of Formula (I) or Formula (II), and a pharmaceutical excipient suitable for oral administration.

[00215] In selected embodiments, the invention provides a solid pharmaceutical composition for oral administration containing: (i) an effective amount of a BTK inhibitor of Formula (I) or Formula (II), in combination and (ii) a pharmaceutical excipient suitable for oral administration. In selected embodiments, the composition further contains (iii) an effective amount of at least one additional active ingredient.

[00216] In selected 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, cachets, 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, or a water-in-oil liquid emulsion. 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.

[00217] 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.

[00218] The BTK inhibitors of Formula (I) or Formula (II) 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.

[00219] 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.

[00220] 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.

[00221] 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.

[00222] 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, 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

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aerosol of synthetic silica, or mixtures thereof. A lubricant can optionally be added, in an
amount of less than about 1 weight percent of the pharmaceutical composition.

[00223] 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.

[00224] 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.

[00225] 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.

[00226] 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.

[00227] 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.

[00228] 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.

[00229] 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, lactyl 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.

[00230] Hydrophilic non-ionic surfactants may include, but not limited to, alkylglucosides; alkylmaltosides; alkylthioglucoaldes; 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.

[00231] 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 olate, PEG-30 glyceryl olate, 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-10 oleate, Tween 40, Tween 60, sucrose monostearate, sucrose monolaurate, sucrose monopalmitate, PEG 10-100 nonyl phenol series, PEG 15-100 octyl phenol series, and poloxamers.

[00232] 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.

[00233] 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, such as for 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.

[00234] 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, N-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, ε-caprolactone and isomers thereof, δ-valerolactone and isomers thereof, β-caprolactone and isomers thereof; and other solubilizers known in the art, such as dimethyl acetamide, dimethyl isosorbide, N-methyl pyrrolidones, monoocotanoin, diethylene glycol monoethyl ether, and water.
[00235] 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.

[00236] 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.

[00237] 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.

[00238] 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-toluensulfonic 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. Examples may include, but are not limited to, sodium, potassium, lithium, magnesium, calcium and ammonium.

[00239] 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-toluensulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid and uric acid.

Pharmaceutical Compositions for Injection

[00240] In selected embodiments, the invention provides a pharmaceutical composition for injection containing a BTK inhibitor of Formula (I) or Formula (II), and a pharmaceutical excipient suitable for injection. Components and amounts of agents in the compositions are as described herein.

[00241] 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.
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.

Sterile injectable solutions are prepared by incorporating a BTK inhibitor of Formula (I) or Formula (II) in the required amounts in the appropriate solvent with various other ingredients as enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, certain desirable methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Pharmaceutical Compositions for Topical Delivery

In some embodiments, the invention provides a pharmaceutical composition for transdermal delivery containing the BTK inhibitors of Formula (I) or Formula (II) and a pharmaceutical excipient suitable for transdermal delivery.

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.

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.

[00247] Another exemplary formulation for use in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the BTK inhibitors of Formula (I) or Formula (II) in controlled amounts, either with or without another active pharmaceutical ingredient.

[00248] 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


[00250] Administration of the BTK inhibitors of Formula (I) or Formula (II) or pharmaceutical composition of these compounds can be effected by any method that enables delivery of the compounds to the site of action. These methods include oral routes, intraduodenal routes, parenteral injection (including intravenous, intraarterial, subcutaneous, intramuscular, intravascular, intraperitoneal or infusion), topical (e.g., transdermal application), rectal
administration, via local delivery by catheter or stent or through inhalation. The combination of compounds can also be administered intraadiposally or intrathecally.

[00251] Exemplary parenteral administration forms include solutions or suspensions of active compound in sterile aqueous solutions, for example, aqueous propylene glycol or dextrose solutions. Such dosage forms can be suitably buffered, if desired.

[00252] The invention also provides kits. The kits include the BTK inhibitors of Formula (I) or Formula (II), either alone or in combination in suitable packaging, and written material that can include instructions for use, discussion of clinical studies and listing of side effects. Such kits may also include information, such as scientific literature references, package insert materials, clinical trial results, and/or summaries of these and the like, which indicate or establish the activities and/or advantages of the composition, and/or which describe dosing, administration, side effects, drug interactions, or other information useful to the health care provider. Such information may be based on the results of various studies, for example, studies using experimental animals involving in vivo models and studies based on human clinical trials. The kit may further contain another active pharmaceutical ingredient. Suitable packaging and additional articles for use (e.g., measuring cup for liquid preparations, foil wrapping to minimize exposure to air, and the like) are known in the art and may be included in the kit. Kits described herein can be provided, marketed and/or promoted to health providers, including physicians, nurses, pharmacists, formulary officials, and the like. Kits may also, in selected embodiments, be marketed directly to the consumer. In an embodiment, the invention provides a kit comprising a BTK inhibitor of Formula (I) or Formula (II) for use in the treatment of CLL or SLL, hematological malignancies, or any of the other cancers described herein.

Dosages and Dosing Regimens

[00253] 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.

[00254] In some embodiments, the BTK inhibitor of Formula (I) or Formula (II) is administered in a single dose. Typically, such administration will be by injection - e.g., intravenous injection, in order to introduce the agents quickly. However, other routes may be used as appropriate. A single dose of a BTK inhibitor of Formula (I) or Formula (II) may also be used for treatment of an acute condition.

[00255] In some embodiments, the BTK inhibitor of Formula (I) or Formula (II) is administered in multiple doses. Dosing may be once, twice, three times, four times, five times, six times, or more than six times per day. Dosing may be once a month, once every two weeks, once a week, or once every other day. In other embodiments, a BTK inhibitor of Formula (I) or Formula (II) is administered about once per day to about 6 times per day. In some embodiments a BTK inhibitor of Formula (I) or Formula (II) is administered once daily, while in other embodiments a BTK inhibitor of Formula (I) or Formula (II) is administered twice daily, and in other embodiments a BTK inhibitor of Formula (I) or Formula (II) is administered three times daily.

[00256] Administration of the BTK inhibitor of Formula (I) or Formula (II) may continue as long as necessary. In some embodiments, the BTK inhibitor of Formula (I) or Formula (II) is administered for more than 1, 2, 3, 4, 5, 6, 7, 14, or 28 days. In some embodiments, the the BTK inhibitor of Formula (I) or Formula (II) is administered for less than 28, 14, 7, 6, 5, 4, 3, 2, or 1 day. In some embodiments, the BTK inhibitor of Formula (I) or Formula (II) is administered chronically on an ongoing basis - e.g., for the treatment of chronic effects. In another embodiment the administration of a BTK inhibitor of Formula (I) or Formula (II) 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 embodiments, continuous dosing is achieved and maintained as long as necessary.

[00257] In some embodiments, an effective dosage of a BTK inhibitor of Formula (I) or Formula (II) is in the range of about 1 mg to about 500 mg, about 10 mg to about 300 mg, about 20 mg to about 250 mg, about 25 mg to about 200 mg, about 10 mg to about 200 mg, about 20
mg to about 150 mg, about 30 mg to about 120 mg, about 10 mg to about 90 mg, about 20 mg to about 80 mg, about 30 mg to about 70 mg, about 40 mg to about 60 mg, about 45 mg to about 55 mg, about 48 mg to about 52 mg, about 50 mg to about 150 mg, about 60 mg to about 140 mg, about 70 mg to about 130 mg, about 80 mg to about 120 mg, about 90 mg to about 110 mg, about 95 mg to about 105 mg, about 150 mg to about 250 mg, about 160 mg to about 240 mg, about 170 mg to about 230 mg, about 180 mg to about 220 mg, about 190 mg to about 210 mg, about 195 mg to about 205 mg, or about 198 to about 202 mg. In some embodiments, an effective dosage of a BTK inhibitor of Formula (I) or Formula (II) is about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, or about 500 mg. In some embodiments, an effective dosage of a BTK inhibitor of Formula (I) or Formula (II) is 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 375 mg, 400 mg, 425 mg, 450 mg, 475 mg, or 500 mg.

[00258] In some embodiments, an effective dosage of a BTK inhibitor of Formula (I) or Formula (II) is in the range of about 0.01 mg/kg to about 4.3 mg/kg, about 0.15 mg/kg to about 3.6 mg/kg, about 0.3 mg/kg to about 3.2 mg/kg, about 0.35 mg/kg to about 2.85 mg/kg, about 0.15 mg/kg to about 2.85 mg/kg, about 0.3 mg to about 2.15 mg/kg, about 0.45 mg/kg to about 1.7 mg/kg, about 0.15 mg/kg to about 1.3 mg/kg, about 0.3 mg/kg to about 1.15 mg/kg, about 0.45 mg/kg to about 1 mg/kg, about 0.55 mg/kg to about 0.85 mg/kg, about 0.65 mg/kg to about 0.8 mg/kg, about 0.7 mg/kg to about 0.75 mg/kg, about 0.7 mg/kg to about 2.15 mg/kg, about 0.85 mg/kg to about 2 mg/kg, about 1 mg/kg to about 1.85 mg/kg, about 1.15 mg/kg to about 1.7 mg/kg, about 1.3 mg/kg to about 1.6 mg/kg, about 1.35 mg/kg to about 1.5 mg/kg, about 2.15 mg/kg to about 3.6 mg/kg, about 2.3 mg/kg to about 3.4 mg/kg, about 2.4 mg/kg to about 3.3 mg/kg, about 2.6 mg/kg to about 3.15 mg/kg, about 2.7 mg/kg to about 3 mg/kg, about 2.8 mg/kg to about 3 mg/kg, or about 2.85 mg/kg to about 2.95 mg/kg. In some embodiments, an effective dosage of a BTK inhibitor of Formula (I) or Formula (II) is about 0.35 mg/kg, about 0.7 mg/kg, about 1 mg/kg, about 1.4 mg/kg, about 1.8 mg/kg, about 2.1 mg/kg, about 2.5 mg/kg, about 2.85 mg/kg, about 3.2 mg/kg, or about 3.6 mg/kg.
[00259] In some embodiments, a BTK inhibitor of Formula (I) or Formula (II) is adminstered at a dosage of 10 to 400 mg BID, including a dosage of 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 375 mg, and 400 mg BID.

[00260] An effective amount of the combination of the BTK inhibitor of Formula (I) or Formula (II) 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, sublingual, intranasal and transdermal routes, by intra-arterial injection, intravenously, intraperitoneally, parenterally, intramuscularly, subcutaneously, orally, topically, or as an inhalant.

Methods of Treating Hematological Malignancies, Cancers, and Other Diseases

[00261] In an embodiment, the invention relates to a method of treating CLL in a human that comprises the step of administering to said human a therapeutically effective amount of a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In an embodiment, the invention relates to a method of treating SLL in a human that comprises the step of administering to said human a therapeutically effective amount of a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In an embodiment, the invention relates to a method of treating CLL in a human that comprises the step of administering to said human a therapeutically effective amount of a BTK inhibitor of Formula (I), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In an embodiment, the invention relates to a method of treating SLL in a human that comprises the step of administering to said human a therapeutically effective amount of a BTK inhibitor of Formula (I), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof.

[00262] In an embodiment, the invention relates to a method of treating CLL in a human that comprises the step of administering to said human a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, in a dosing regimen selected from the group consisting of 100 mg QD, 175 mg QD, 250 mg QD, 400 mg QD, and 100 mg BID. In an embodiment, the invention relates to a method of treating CLL in a human that comprises the step of administering to said human a BTK inhibitor of Formula (I), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof,
in a dosing regimen selected from the group consisting of 100 mg QD, 175 mg QD, 250 mg QD, 400 mg QD, and 100 mg BID.

[00263] In an embodiment, the invention relates to a use of a composition of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, in the manufacture of a medicament for treating CLL, wherein the treating comprises the step of administering one or more doses of Formula (II) or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In an embodiment, the invention relates to a use of a composition of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, in the manufacture of a medicament for treating SLL, wherein the treating comprises the step of administering one or more doses of Formula (II) or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In an embodiment, the invention relates to a use of a composition of Formula (I), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, in the manufacture of a medicament for treating CLL, wherein the treating comprises the step of administering one or more doses of Formula (I) or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In an embodiment, the invention relates to a use of a composition of Formula (I), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, in the manufacture of a medicament for treating SLL, wherein the treating comprises the step of administering one or more doses of Formula (I) or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof.

[00264] In an embodiment, the invention relates to a method of treating CLL in a mammal that comprises the step of administering to said mammal a therapeutically effective amount of a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In an embodiment, the invention relates to a method of treating SLL in a mammal that comprises the step of administering to said mammal a therapeutically effective amount of a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In an embodiment, the invention relates to a method of treating CLL in a mammal that comprises the step of administering to said mammal a therapeutically effective amount of a BTK inhibitor of Formula (I), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In an embodiment, the
invention relates to a method of treating SLL in a mammal that comprises the step of administering to said mammal a therapeutically effective amount of a BTK inhibitor of Formula (I), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In an embodiment, the mammal in any of the foregoing embodiments is selected from the group consisting of a human, a canine, a feline, or an equine. In an embodiment, the mammal in any of the foregoing embodiments is a companion animal.

[00265] In an embodiment, the invention relates to a method of treating a subtype of CLL in a human that comprises the step of administering to said mammal a therapeutically effective amount of a BTK inhibitor of Formula (I) or Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. A number of subtypes of CLL have been characterized. CLL is often classified for immunoglobulin heavy-chain variable-region (IgV\textsubscript{H}) mutational status in leukemic cells. R. N. Damle, et al, Blood 1999, 94, 1840-47; T. J. Hamblin, et al, Blood 1999, 94, 1848-54. Patients with IgV\textsubscript{H} mutations generally survive longer than patients without IgV\textsubscript{H} mutations. ZAP70 expression (positive or negative) is also used to characterize CLL. L. Z. Rassenti, et al, N. Engl. J. Med. 2004, 351, 893-901. The methylation of ZAP-70 at CpG3 is also used to characterize CLL, for example by pyrosequencing. R. Claus, et al, J. Clin. Oncol. 2012, 30, 2483-91; J. A. Woyach, et al, Blood 2014, 123, 1810-17. CLL is also classified by stage of disease under the Binet or Rai criteria. J. L. Binet, et al, Cancer 1977, 40, 855-64; K. R. Rai, T. Han, Hematol. Oncol. Clin. North Am. 1990, 4, 447-56. Other common mutations, such as 11p deletion, 13q deletion, and 17p deletion can be assessed using well-known techniques such as fluorescence in situ hybridization (FISH). In an embodiment, the invention relates to a method of treating a CLL in a human that comprises the step of administering to said mammal a therapeutically effective amount of a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, wherein the CLL is selected from the group consisting of IgV\textsubscript{H} mutation negative CLL, ZAP-70 positive CLL, ZAP-70 methylated at CpG3 CLL, CD38 positive CLL, chronic lymphocytic leukemia characterized by a 17p13.1 (17p) deletion, and CLL characterized by a 11q22.3 (11q) deletion.

[00266] In an embodiment, the invention relates to a method of treating a CLL in a human that comprises the step of administering to said mammal a therapeutically effective amount of a BTK
inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, wherein the CLL has undergone a Richter's transformation. Methods of assessing Richter's transformation, which is also known as Richter's syndrome, are described in P. Jain and S. O'Brien, Oncology, 2012, 26, 1146-52. Richter's transformation is a subtype of CLL that is observed in 5-10% of patients. It involves the development of aggressive lymphoma from CLL and has a generally poor prognosis.

[00267] In an embodiment, the invention relates to a method of treating a subtype of CLL in a human, comprising the step of administering to said mammal a therapeutically effective amount of a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, wherein the subtype of CLL is a subtype of CLL that increases monocytes and NK cells in peripheral blood when measured after a period of treatment with Formula (II) selected from the group consisting of about 14 days, about 28 days, about 56 days, about 1 month, about 2 months, about 3 months, about 6 months, and about 1 year, and wherein the term "about" refers to a measurement interval of +/- 2 days.

[00268] In an embodiment, the invention relates to a method of treating chronic lymphocytic leukemia in a patient, wherein the chronic lymphocytic leukemia is chronic lymphocytic leukemia in a patient sensitive to lymphocytosis. In an embodiment, the invention relates to a method of treating chronic lymphocytic leukemia in a patient, wherein the chronic lymphocytic leukemia is chronic lymphocytic leukemia in a patient exhibiting lymphocytosis caused by a disorder selected from the group consisting of a viral infection, a bacterial infection, a protozoal infection, or a post-splenectomy state. In an embodiment, the viral infection in any of the foregoing embodiments is selected from the group consisting of infectious mononucleosis, hepatitis, and cytomegalovirus. In an embodiment, the bacterial infection in any of the foregoing embodiments is selected from the group consisting of pertussis, tuberculosis, and brucellosis.

[00269] The methods described above may be used as first-line cancer therapy, or after treatment with conventional chemotherapeutic active pharmaceutical ingredients, including cyclophosphamide, fludarabine, cyclophosphamide and fludarabine (FC chemotherapy), and chlorambucil. The methods described above may also be supplemented with immunotherapeutic monoclonal antibodies such as the anti-CD52 monoclonal antibody alemtuzumab. In an embodiment, the invention relates to a method of treating CLL in a human that comprises the
step of administering to said human a therapeutically effective amount of a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt, ester, prodrug, cocrystal, solvate or hydrate thereof, and further comprises the step of administering to said human an active pharmaceutical ingredient selected from the group consisting of cyclophosphamide, fludarabine, cyclophosphamide, chlorambucil, salts, esters, prodrugs, cocrystals, solvates, or hydrates thereof, and combinations thereof, and alemtuzumab, antigen-binding fragments, derivatives, conjugates, variants, and radioisotope-labeled complexes thereof.

[00270] In an embodiment, the invention relates to a method of treating hematological malignancies in a human comprising the step of administering to said human a therapeutically effective amount of a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. Hematological malignancies include CLL and SLL, as well as other cancers of the blood, including B cell malignancies. In an embodiment, the invention relates to a method of treating a hematological malignancy selected from the group consisting of non-Hodgkin's lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Hodgkin's lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Waldenstrom's macroglobulinemia (WM), Burkitt's lymphoma, multiple myeloma, or myelofibrosis in a human that comprises the step of administering a therapeutically effective amount of a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof.

[00271] In an embodiment, the invention relates to a method of treating a NHL selected from the group consisting of indolent NHL and aggressive NHL comprising the step of administering a therapeutically effective amount of a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof.

[00272] In an embodiment, the invention relates to a method of treating a DLBCL selected from the group consisting of activated B-cell like diffuse large B-cell lymphoma (DLBCL-ABC) and germinal center B-cell like diffuse large B-cell lymphoma (DLBCL-GCB), comprising the step of administering a therapeutically effective amount of a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof.

[00273] In an embodiment, the invention relates to a method of treating an MCL selected from the group consisting of mantle zone MCL, nodular MCL, diffuse MCL, and blastoid MCL (also
known as blastic variant MCL), comprising the step of administering a therapeutically effective amount of a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof.

[00274] In an embodiment, the invention relates to a method of treating a B-ALL selected from the group consisting of early pre-B cell B-ALL, pre-B cell B-ALL, and mature B cell B-ALL (also known as Burkitt's leukemia), comprising the step of administering a therapeutically effective amount of a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof.

[00275] In an embodiment, the invention relates to a method of treating a Burkitt's lymphoma selected from the group consisting of sporadic Burkitt's lymphoma, endemic Burkitt's lymphoma, and human immunodeficiency virus-associated Burkitt's lymphoma, comprising the step of administering a therapeutically effective amount of a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof.

[00276] In an embodiment, the invention relates to a method of treating a multiple myeloma selected from the group consisting of hyperdiploid multiple myeloma and non-hyperdiploid multiple myeloma, comprising the step of administering a therapeutically effective amount of a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof.

[00277] In an embodiment, the invention relates to a method of treating a myelofibrosis selected from the group consisting of primary myelofibrosis (also known as chronic idiopathic myelofibrosis) and myelofibrosis secondary to polycythemia vera or essential thrombocythaemia, comprising the step of administering a therapeutically effective amount of a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof.

[00278] In an embodiment, the invention relates to a method of treating a subtype of a hematological malignancy in a human, comprising the step of administering to said human a therapeutically effective amount of a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, wherein the subtype of a hematological malignancy is a subtype of a hematological malignancy that increases monocytes and NK cells in peripheral blood when measured after a period of treatment with Formula (II)
selected from the group consisting of about 14 days, about 28 days, about 56 days, about 1 month, about 2 months, about 3 months, about 6 months, and about 1 year, wherein the term "about" refers to a measurement interval of +/- 2 days, and wherein the hematological malignancy is selected from the group consisting of non-Hodgkin's lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Hodgkin's lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Waldenstrom's macroglobulinemia (WM), Burkitt's lymphoma, multiple myeloma, or myelofibrosis.

Methods of Treating Cancers in Patients Sensitive to Thrombosis

[00279] In selected 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 anticoagulant or antiplatelet active pharmaceutical ingredient.

[00280] In selected embodiments, the BTK inhibitor of Formula (I) or Formula (II) and the anticoagulant or the antiplatelet active pharmaceutical ingredient are administered sequentially. In selected embodiments, the BTK inhibitor of Formula (I) or Formula (II) and the anticoagulant or the antiplatelet active pharmaceutical ingredient are administered concomitantly. In selected embodiments, the BTK inhibitor of Formula (I) or Formula (II) is administered before the anticoagulant or the antiplatelet active pharmaceutical ingredient. In selected embodiments, the BTK inhibitor of Formula (I) or Formula (II) is administered after the anticoagulant or the antiplatelet active pharmaceutical ingredient.

[00281] In selected 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 CLL, SLL, NHL, DLBCL, FL, MCL, Hodgkin's lymphoma, B-ALL, WM, Burkitt's lymphoma, multiple myeloma, or myelofibrosis that comprises the step of administering a therapeutically effective amount of a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof.

[00282] In selected 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 acute myeloid leukemia, squamous cell carcinoma including chronic myelocytic leukemia, bladder cancer, head and neck tumor, pancreatic ductal adenocarcinoma (PDA), pancreatic cancer, colon carcinoma, mammary carcinoma, breast cancer, fibrosarcoma, mesothelioma cancer, renal cell carcinoma, lung carcinoma, thyma, prostate cancer, colorectal cancer, ovarian cancer, thymus cancer, brain cancer, squamous cell cancer, skin cancer, eye cancer, retinoblastoma, melanoma, intraocular melanoma, oral cavity and oropharyngeal cancers, gastric cancer, stomach cancer, cervical cancer, renal cancer, kidney cancer, liver cancer, ovarian cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, acquired immune deficiency syndrome (AIDS)-related cancers (e.g., lymphoma and Kaposi's sarcoma), viral-induced cancer, glioblastoma, esophageal tumors, hematological neoplasms, non-small-cell lung cancer, esophagus tumor, hepatitis C virus infection, hepatocellular carcinoma, metastatic colon cancer, multiple myeloma, ovary tumor, pancreas tumor, renal cell carcinoma, small-cell lung cancer, and stage IV melanoma.

[00283] 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 Formula (II), or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof, wherein the cancer is a hematogolical malignancy, and wherein the hematological malignancy is selected from the group consisting of chronic lymphocytic leukemia, B cell acute lymphoblastic
leukemia, and non-Hodgkin's lymphoma.

[00284] 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 anticoagulant or antiplatelet active pharmaceutical ingredient, wherein the cancer is a hematological malignancy, and wherein the hematological malignancy is selected from the group consisting of chronic lymphocytic leukemia, B cell acute lymphoblastic leukemia, and non-Hodgkin's lymphoma.

[00285] Preferred anti-platelet and anticoagulant 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). Examples of anti-platelet active pharmaceutical ingredients for use in the methods of the present invention include acenocoumarol, anagrelide, anagrelide hydrochloride, abciximab, alopixprin, antithrombin, apixaban, argatroban, aspirin, aspirin with extended-release dipyridamole, beraprost, betrixaban, bivalirudin, carbasalate calcium, cilostazol, clopidogrel, clopidogrel bisulfate, cloricoxen, dabigatran etexilate, darexaban, dalteparin, dalteparin sodium, defibrotide, dicumarol, diphenadione, dipyridamole, dixatole, 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, nadroprarin, 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, triflusol, vorapaxar, warfarin, warfarin sodium, ximelagatran, salts thereof, solvates thereof, hydrates thereof, cocrystals thereof, prodrugs thereof, and combinations thereof.

[00286] 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 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 dipiridamole, beraprost, betrixaban, bivalirudin, carbasalate calcium, cilostazol, clopidogrel, clopidogrel bisulfate, cloridrromen, dabigatran etexilate, darexaban, dalteparin, dalteparin sodium, defibrotide, dicumarol, diphendiamine, dipiridamole, ditaizole, 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, triflusul, vorapaxor, warfarin, warfarin sodium, ximelagatran, salts thereof, solvates thereof, hydrates thereof, cocrystals thereof, prodrugs thereof, and combinations thereof.

Combinations of BTK Inhibitors and Anti-CD20 Antibodies

[00287] The BTK inhibitors of Formula (I) and Formula (II) 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 Bl) is found on the surface of normal "pre-B" and mature B lymphocytes, including malignant B lymphocytes. L. M. Nadler, et al, J. Clin. Invest. 1981, 67, 134-40; P. 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. T. F. 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. S. H. Lim, et. al., Haematologica 2010, 95, 135-43; S. A. Beers, et. al., Sem. Hematol. 2010, 47, 107-14; C. Klein, et al, mAbs 2013, 5, 22-33.

[00288] In an embodiment, the invention relates to a method of treating a hematological malignancy 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 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, and wherein the anti-CD20 antibody specifically binds to human CD20 with a $K_D$ selected from the group consisting of $1 \times 10^{-7}$ M or less, $5 \times 10^{-8}$ M or less, $1 \times 10^{-8}$ M or less, and $5 \times 10^{-9}$ M or less.

[00289] In an embodiment, the invention relates to a method of treating CLL or SLL 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 CLL or SLL 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, and
wherein the anti-CD20 antibody specifically binds to human CD20 with a $K_D$ selected from the group consisting of $1 	imes 10^{-7}$ M or less, $5 	imes 10^{-8}$ M or less, $1 	imes 10^{-8}$ M or less, and $5 	imes 10^{-9}$ M or less.

[00290] In selected embodiments, the BTK inhibitor of Formula (I) or Formula (II) and the anti-CD20 monoclonal antibody are administered sequentially. In selected embodiments, the BTK inhibitor of Formula (I) or Formula (II) and the anti-CD20 monoclonal antibody are administered concomitantly. In selected embodiments, the BTK inhibitor of Formula (I) or Formula (II) is administered before the anti-CD20 monoclonal antibody. In selected embodiments, the BTK inhibitor of Formula (I) or Formula (II) is administered after the anticoagulant or the antiplatelet active pharmaceutical ingredient. In selected embodiments, the BTK inhibitor of Formula (I) or Formula (II) 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.

[00291] 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 IgGl 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 W. Rastetter, et al., *Ann. Rev. Med.* **2004**, *55*, 477-503, and in G. L. Plosker and D. P. Figgett, *Drugs*, **2003**, *63*, 803-43. In an embodiment, the anti-CD20 monoclonal antibody is an anti-CD20 biosimilar monoclonal antibody approved by drug regulatory authorities with reference to rituximab. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 90% to SEQ ID NO:1. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 90% to SEQ ID NO:2. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 95% to SEQ ID NO:1. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 95% to SEQ ID NO:2. In an embodiment, the anti-
CD20 monoclonal antibody has a heavy chain sequence identity of greater than 98% to SEQ ID NO: 1. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 98% to SEQ ID NO: 2. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 99% to SEQ ID NO: 1. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 99% to SEQ ID NO: 2.

[00292] 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 T. Robak, Curr. Opin. Investig. Drugs 2009, 10, 588-96. In an embodiment, the anti-CD20 monoclonal antibody is an anti-CD20 biosimilar monoclonal antibody approved by drug regulatory authorities with reference to obinutuzumab. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 90% to SEQ ID NO: 3. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 90% to SEQ ID NO: 4. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 95% to SEQ ID NO: 3. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 95% to SEQ ID NO: 4. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 98% to SEQ ID NO: 3. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 98% to SEQ ID NO: 4. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 99% to SEQ ID NO: 3. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 99% to SEQ ID NO: 4. In an embodiment, the anti-CD20 monoclonal antibody

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

[00293] 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 B. D. 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 J. Du, et al., Mol. Immunol. 2009, 46, 2419-2423. Ofatumumab is commercially available, and its preparation, properties, and use in cancer and other diseases is described in more detail in U.S. Patent No. 8,529,202 B2, the disclosure of which is incorporated herein by reference. In an embodiment, the anti-CD20 monoclonal antibody is an anti-CD20 biosimilar monoclonal antibody approved by drug regulatory authorities with reference to ofatumumab. In an embodiment, the anti-CD20 monoclonal antibody has a variable heavy chain sequence identity of greater than 96% 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:7. 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 Gl, anti-(human B-lymphocyte antigen CD20 (membrane-spanning 4-domains subfamily A member 1, B-lymphocyte surface antigen Bl, Leu-16 or Bp35)); human monoclonal ofatumumab-CD20 γ1 heavy chain (225-214')-disulfide with human monoclonal ofatumumab-CD20 κ light chain, dimer (231-231":234-234")-bisdisulfide antibody.

[00294] 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 D. M. Goldenberg, et al., Leuk. Lymphoma 2010, 51, 747-55. In an embodiment, the anti-CD20 monoclonal antibody is an anti-CD20 biosimilar monoclonal antibody approved by drug regulatory authorities with reference to veltuzumab. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 90% to SEQ ID NO:9. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 90% to SEQ ID NO:10. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 95% to SEQ ID NO:9. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 95% to SEQ ID NO:10. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 98% to SEQ ID NO:9. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 98% to SEQ ID NO:10. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 99% to SEQ ID NO:9. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 99% to SEQ ID NO:10. In an embodiment, the anti-CD20 monoclonal antibody ofatumumab is an immunoglobulin Gl, anti-(human B-lymphocyte antigen CD20 (membrane-spanning 4-domains subfamily A member 1, Leu-16, Bp35)); [218-arginine,360-glutamic acid,362-methionine]humanized mouse monoclonal hA20 γ1 heavy chain (224-213')-disulfide with humanized mouse monoclonal hA20 κ light chain (230-230":233-233")-bisdisulfide dimer.
binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof. In an embodiment, the anti-CD20 monoclonal antibody is $^{131}$I-labeled tositumomab. In an embodiment, the anti-CD20 monoclonal antibody is an anti-CD20 biosimilar monoclonal antibody approved by drug regulatory authorities with reference to tositumomab. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 90% to SEQ ID NO: 11. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 90% to SEQ ID NO: 12. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 95% to SEQ ID NO: 11. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 95% to SEQ ID NO: 12. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 98% to SEQ ID NO: 11. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 98% to SEQ ID NO: 12. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 99% to SEQ ID NO: 11. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 99% to SEQ ID NO: 12.

[00296] In an embodiment, the anti-CD20 monoclonal antibody is ibritumomab, or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof. The active form of ibritumomab used in therapy is ibritumomab tiuxetan. When used with ibritumomab, the chelator tiuxetan (diethylene triamine pentaacetic acid) is complexed with a radioactive isotope such as $^{90}$Y or $^{111}$In. In an embodiment, the anti-CD20 monoclonal antibody is ibritumomab tiuxetan, or radioisotope-labeled complex thereof. In an embodiment, the anti-CD20 monoclonal antibody is an anti-CD20 biosimilar monoclonal antibody approved by drug regulatory authorities with reference to tositumomab. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 90% to SEQ ID NO: 13. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 90% to SEQ ID NO: 14. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 95% to SEQ ID NO: 13. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 95% to SEQ ID NO: 14. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 98% to SEQ ID NO: 13. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 98% to SEQ ID NO: 14.
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.

[00297] 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 administered weekly. In an embodiment, the anti-CD20 antibody is administered monthly. In an embodiment, the anti-CD20 antibody is administered at a lower initial dose, which is escalated when administered at subsequent intervals administered monthly. For example, the first infusion can deliver 300 mg of anti-CD20 antibody, and subsequent weekly doses could deliver 2,000 mg of anti-CD20 antibody for eight weeks, followed by monthly doses of 2,000 mg of anti-CD20 antibody. During any of the foregoing embodiments, the BTK inhibitors of Formula (I) or Formula (II) may be administered daily, twice daily, or at different intervals as described above, at the dosages described above.

[00298] In an embodiment, the invention provides a kit comprising a composition comprising a BTK inhibitor of Formula (I) or Formula (II) and a composition comprising an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, and ibritumomab, or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof, for use in the treatment of CLL or SLL, hematological malignancies, B cell malignancies, or 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.
EXAMPLES

[00299] The embodiments encompassed herein are now described with reference to the following examples. These examples are provided for the purpose of illustration only and the disclosure encompassed herein should in no way be construed as being limited to these examples, but rather should be construed to encompass any and all variations which become evident as a result of the teachings provided herein.

Example 1 - Preclinical Study of a Second Generation BTK Inhibitor for Use in CLL/SLL


[00301] 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-agent 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.

[00302] 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 \textit{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.

[00303] 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 1, a kinome screen (performed by Life Technologies or based on literature data) is shown that compares these compounds.

**TABLE 1. Kinome Screen for BTK Inhibitors (IC\textsubscript{50}, nM)**

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

[00304] The results shown in Table 1 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.

[00305] A comparison of the \textit{in vivo} potency results for the BTK inhibitors of Formula (II) and ibrutinib is shown in FIG. 1. CD86 and CD69 are cell surface proteins that are BCR activation markers. To obtain the \textit{in vivo} potency results, mice were gavaged at increasing drug concentration and sacrificed at one time point (3 hours post-dose). BCR was stimulated with
IgM and the expression of activation marker CD69 and CD86 are monitored by flow cytometry and to determine EC50 values.

[00306] Formula (II) has been evaluated in a study of canine spontaneous B-cell lymphoma. Twenty-one dogs were treated with the BTK inhibitor of Formula (II) at dosages of 2.5 mg/kg once daily to 20 mg/kg twice daily, with a median time on study of 24 days. Intra-subject dose escalation was allowed. Six of the 11 dogs that initiated at 2.5 or 5 mg/kg once daily were escalated and completed the study with dosages of 10 mg/kg twice daily. Among all the dose cohorts, 8 dogs had shrinkage of target lesions >20%; the best tumor responses were between 45-49% reduction in the sum of target lesions in two dogs. Complete responses ("CR") were defined as disappearance of all evidence of disease per evaluator judgment, and absence of new lesions. Vali, et al., Vet. Comp. Oncol. 2010, 8, 28-37. CRs were not observed in the study.

[00307] 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 an 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-a-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 of through 300 mg/kg (the highest dose level) revealed no adverse effects on neurobehavioral effects or body temperature at any dose level. A study of respiratory function in rats also indicated no treatment-related adverse effects at doses through 300 mg/kg (the highest dose level). In a cardiovascular function study in awake telemeterized male beagle dogs, single doses of Formula (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.

[00308] 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 ¹⁴C-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.

[00309] 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. 2. The EC₅₀ 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.

[00310] 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 min to induce EGFR phosphorylation (p-EGFR). Cells were fixed with 1.6% paraformaldehyde and permeabilized with 90% MeOH. Phosphoflow cytometry was performed with p-EGFR (Y1069). MFI values were normalized so that 100% represents the p-EGFR level in stimulated cells without inhibitor, while 0% represents the unstimulated/no drug condition. The results are shown in FIG. 3. EGF-induced p-EGFR inhibition was determined to be 7% at 10 µM for Formula (II), while ibrutinib
has an EC50 of 66 nM. The much more potent inhibition of EGF-induced p-EGFR by ibrutinib may be associated with increased side effects including diarrhea and rash.

Example 2 - Clinical Study of a Second Generation BTK Inhibitor for Use in CLL/SLL

[00311] 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).

[00312] 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.

[00313] 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.

[00314] The secondary objective of the clinical study is to evaluate tumor responses in patients treated with Formula (II).
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)

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.

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.

[00318] 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.

[00319] 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.

[00320] 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. M. Hallek, et al, Blood 2008, 111, 5446-5456.
The schedule of assessments is as follows, with all days stated in the following meaning the given day or +/- 2 days from the given day. A physical examination, including vital signs and weight, are performed at screening, during cycle 1 at 1, 8, 15, 22, and 28 days, during cycle 2 at 15 and 28 days, during cycles 3 to 24 at 28 days, and at follow up (after the last dose). The screening physical examination includes, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. Symptom-directed physical exams are done thereafter. Vital signs (blood pressure, pulse, respiratory rate, and temperature) are assessed after the subject has rested in the sitting position. Eastern Cooperative Oncology Group (ECOG) status is assessed at screening, during cycle 1 at 1, 8, 15, 22, and 28 days, during cycle 2 at 15 and 28 days, during cycles 3 to 24 at 28 days, and at follow up, using the published ECOG performance status indications described in M. M. Oken, et al., Am. J. Clin. Oncol. 1982, 5, 649-655. ECG testing is performed at screening, during cycle 1 at 1, 2, 8, 15, 22, and 28 days, during cycle 2 at 15 and 28 days, during cycles 3 to 24 at 28 days, and at follow up. The 12-lead ECG test will be done in triplicate (> 1 minute apart) at screening. The calculated QTc average of the 3 ECGs must be <480 ms for eligibility. On cycle 1, day 1 and cycle 1, day 8, single ECGs are done predose and at 1, 2, 4, and 6 hours postdose. The single ECG on Cycle 1 Day 2 is done predose. On cycle 1, day 15, day 22, and day 28, a single ECG is done 2 hours post-dose. Starting with cycle 2, a single ECG is done per visit. Subjects should be in supine position and resting for at least 10 minutes before study-related ECGs. Two consecutive machine-read QTc > 500 ms or > 60 ms above baseline require central ECG review. Hematology, including complete blood count with differential and platelet and reticulocyte counts, is assessed at screening, during cycle 1 at 1, 8, 15, 22, and 28 days, during cycle 2 at 15 and 28 days, during cycles 3 to 24 at 28 days, and at follow up. Serum chemistry is assessed at screening, during cycle 1 at 1, 8, 15, 22, and 28 days, during cycle 2 at 15 and 28 days, during cycles 3 to 24 at 28 days, and at follow up. Serum chemistry includes albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphate, potassium, sodium, total bilirubin, total protein, and uric acid. Cell counts and serum immunoglobulin are performed at screening, at cycle 2, day 28, and at every 6 months thereafter until last dose and include T/B/NK/monocyte cell counts (CD3, CD4, CD8, CD14, CD19, CD19, CD16/56, and
others as needed) and serum immunoglobulin (IgG, IgM, IgA, and total immunoglobulin). Bone marrow aspirates are performed at cycle 12. Pharmacodynamics samples are drawn during cycle 1 at 1, 2, and 8 days, and at follow up. On days 1 and 8, pharmacodynamic samples are drawn pre-dose and 4 hours (±10 minutes) post-dose, and on day 2, pharmacodynamic samples are drawn pre-dose. Pharmacokinetics samples are drawn during cycle 1 at 1, 2, 8, 15, 22, and 28 days. Pharmacokinetic samples for Cycle 1 Day 1 are drawn pre-dose and at 0.5, 1, 2, 4, 6 and 24 hours (before dose on Day 2) post-dose. Samples for Cycle 1 Day 8 are drawn pre-dose and at 0.5, 1, 2, 4, and 6 hours post-dose. On Cycle 1 Day 15, 22, and 28, a PK sample is drawn pre-dose and the second PK sample must be drawn before (up to 10 minutes before) the ECG acquisition, which is 2 hours postdose. Pretreatment radiologic tumor assessments are performed within 30 days before the first dose. A computed tomography (CT) scan (with contrast unless contraindicated) is required of the chest, abdomen, and pelvis. In addition, a positron emission tomography (PET) or PET/CT must done for subjects with SLL. Radiologic tumor assessments are mandatory at the end of Cycle 2 (-7 days), Cycle 4 (-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.

TABLE 2. Response Assessment Criteria for CLL. Abbreviations: ANC = absolute neutrophil count; CR = complete remission; CRi = CR with incomplete blood count recovery; PR = partial remission.

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

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

[00323] The response assessment criteria for SLL are summarized in Table 3.
TABLE 3. Response Assessment Criteria for SLL. Abbreviations: CR = complete remission, CT = computed tomography, FDG = \[^{18}\text{F}\]fluorodeoxyglucose, PET = positron-emission tomography, PR = partial remission, SD = stable disease, SPD = sum of the product of the diameters.

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

[00324] 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(o-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(o-24): Area under the plasma concentration-time curve from 0 to 24 hours, calculated using linear trapezoidal summation,

AUC(o-∞): Area under the plasma concentration-time curve from 0 to infinity, calculated using the formula: \[ AUC(o_∞) = AUC(o-t) + \frac{Ct}{\lambda \zeta}, \]

where \( \lambda \zeta \) is the apparent terminal elimination rate constant,

\( C_{\text{max}} \): Maximum observed plasma concentration,

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

\( t_{\frac{1}{2}} \): Terminal elimination half-life (whenever possible),

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

\( C_{\text{L/F}} \): Oral clearance.

[00325] 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.

[00326] 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.

[00327] The following definitions are used for the safety and efficacy analysis sets: Safety analysis set: All enrolled subjects who receive \( \geq 1 \) dose of study drug; Per-protocol (PP) analysis set: All enrolled subjects who receive \( \geq 1 \) dose of study drug and with \( \geq 1 \) tumor response assessment after treatment. The safety analysis set will be used for evaluating the safety parameters in this study. The PP analysis sets will be analyzed for efficacy parameters in this study.

[00328] 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.

[00329] 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.

[00330] 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.

[00331] 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).

[00332] The study scheme is a sequential cohort escalation. Each cohort consists of six subjects. The sample size of the study is 24 to 36 subjects, depending on dose escalation into subsequent cohorts. Cohort 1 (N = 6) consists of Formula (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.

[00333] 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).

[00334] 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).
The baseline characteristics for the patients enrolled in the clinical study are given in Table 4.

**TABLE 4. Relapsed/refractory CLL baseline characteristics.**

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

The results of the clinical study in relapsed/refractory CLL patients are summarized in Table 5.

**TABLE 5. Activity of Formula (II) in relapsed/refractory CLL.** (PR = partial response; PR+L = partial response with lymphocytosis; SD = stable disease; PD = progressive disease.)

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

Median (range) Cycles: 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)
FIG. 4 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 J. C. 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/SLL 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. 5, and in all cases shows significant responses.

A Kaplan-Meier curve showing PFS from the clinical CLL/SLL study of Formula (II) is shown in FIG. 6. 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. 7. Both FIG. 6 and FIG. 7 show the results for Formula (II) in comparison to the results reported for ibrutinib in J. C. 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.

Based on the data and comparisons shown in FIG. 4 to FIG. 7, the CLL study with Formula (II) showed that the efficacy of Formula (II) was surprisingly superior to that of ibrutinib.

In the literature study of ibrutinib, increased disease progression was associated with patients with high-risk cytogenetic lesions (17p13.1 deletion or 11q22.3 deletion), as shown in Figure 3A in J. C. 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. 8, the PFS is shown for Formula (II) in patients with the 17p deletion in comparison to the results obtained for ibrutinib in J. C. Byrd, et al, N. Engl. J. Med. 2013, 369, 32-42. A p-value of 0.0696 was obtained. In FIG. 9, the number of patients at risk with the 17p deletion is compared. To date, no 17p patients have progressed on Formula (II).
The adverse events observed in the clinical study in relapsed/refractory CLL/SLL are given in Table 6. 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 6. Treatment-related adverse events reported in the clinical study of Formula (II) in relapsed/refractory CLL. (Reported in ≥ 5% of patients.)

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

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).

BTK target occupancy was measured for relapsed/refractory CLL patients with the results shown in FIG. 10. 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/SLL patients than ibrutinib.

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. 11, FIG. 12, FIG. 13, FIG. 14, FIG. 15, and FIG. 16. PBMC samples from CLL/SLL 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. 11 and FIG. 12, 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. 13 and FIG. 14, 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. 11 to FIG. 14 are observed in multiple cohorts, at doses including 100 mg BID, 200 mg QD, and 400 mg QD. In FIG. 15 and FIG. 16, 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.

[00345] 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.
Updated clinical results from the CLL/SLL study are shown in FIG. 1 to FIG. 22. FIG. 17 shows an update of the data presented in FIG. 4. FIG. 18 shows an update of the data presented in FIG. 10, 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. 19, FIG. 20, and FIG. 21. Updated SPD results are illustrated in FIG. 22.

Treatment of CLL/SLL patients with Formula (II) also resulted in increased apoptosis, as illustrated in FIG. 23. 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/SLL 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. 24 and FIG. 25, respectively.

Overall, Formula (II) shows superior efficacy to first generation BTK inhibitors such as ibrutinib, or to monotherapy with PI3K-5 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-5 inhibitors, treatment with Formula (II) does not affect NK cell function. Finally, treatment with Formula (II) leads to a CLL/SLL tumor microenvironmental effect by excluding MDSC cells from the marrow and lymph nodes and reducing their number.

Example 3 - Effects of BTK Inhibitors on Thrombosis

Clinical studies have shown that targeting the BCR signaling pathway by inhibiting BTK produces significant clinical benefit (J. C. Byrd, et al, N. Engl. J. Med. 2013, 369, 32-42; M. L. Wang, et al, N. Engl. J. Med. 2013, 369, 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).

[00350] 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 CC-292 and ibrutinib (PCI-32765), in clinical development. CC-292 refers to \(N-(3-(5-fluoro-2-((4-(2-methoxyethoxy)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide\), or a pharmaceutically acceptable salt thereof, including a hydrochloride salt or besylate salt thereof. Importantly, early stage clinical trials have found ibrutinib to be particularly active in chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL), suggesting that this class of inhibitors may play a significant role in various types of cancers (Aalipour and Advani, Br. J. Haematol. 2013, 163, 436-43). However, their effects are not limited to leukemia or lymphomas as platelets also rely on the Tec kinases family members BTK and Tec for signal transduction in response to various thrombogenic stimuli (Oda, et al, Blood 2000, 95(5), 1663-70; Atkinson, et al. Blood 2003, 102(10), 3592-99). In fact, both Tec and BTK play an important role in the regulation of phospholipase \(C_\gamma2\) (PLCy2) downstream of 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 \(\alpha\text{IIb}\beta3\) integrin and PI3K activity (Laffargue, et al., FEBSLett. 1999, 443(1), 66-70). It has also been implicated in GPIba-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.

[00351] Administration of anesthesia, insertion of venous and arterial catheters, fluorescent labeling and administration of human platelets (5 x 10⁹/ml), and surgical preparation of the
cremaster muscle in mice have been previously described (Chen, *et al.*, *Nat Biotechnol.* 2008, 26(1), 114-19). Injury to the vessel wall of arterioles (-40-65 mm diameter) was performed using a pulsed nitrogen dye laser (440 nm, Photonic Instruments) applied through a 20× water-immersion Olympus objective (LUMPlanFl, 0.5 numerical aperture (NA)) of a Zeiss Axiovert 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 (µm²) of coverage determined (Image IQ, Andor Technology). For the Formula (II), CC-292, ibrutinib inhibition studies, the BTK inhibitors were added to purified human platelets for 30 minutes before administration.

[00352] The *in vivo* thrombus effects of the BTK inhibitors, Formula (II), CC-292, and ibrutinib, were evaluated on human platelet-mediated thrombosis by utilizing the *in vivo* human thrombus formation in the VWF HA1 mice model, which has been previously described (Chen, *et al.*, *Nat Biotechnol.* 2008, 26(1), 114-19). Purified human platelets were preincubated with various concentrations of the BTK inhibitors (0.1 µM, 0.5 µM, or 1 µM) or DMSO and then administered to VWF HA1 mice, followed by laser-induced thrombus formation. The BTK inhibitor-treated human platelets were fluorescently labeled and infused continuously through a catheter inserted into the femoral artery. Their behavior in response to laser-induced vascular injury was monitored in real time using two-channel confocal intravital microscopy (Furie and Furie, *J. Clin. Invest.* 2005, 115(12), 2255-62). Upon induction of arteriole injury untreated platelets rapidly formed thrombi with an average thrombus size of 6,450 ± 292 mm² (mean ± s.e.m.), as shown in FIG. 26, FIG. 27, and FIG. 28. Similarly, Formula (II) (1 µM) treated platelets formed a slightly smaller but not significantly different thrombi with an average thrombus size of 5733 ± 393 mm² (mean ± s.e.m.). In contrast, a dramatic reduction in thrombus size occurred in platelets pretreated with 1 µM of ibrutinib, 2600 ± 246 mm² (mean ± s.e.m.), resulting in a reduction in maximal thrombus size by approximately 61% compared with control (P > 0.001) (FIG. 26 and 28). Similar results were obtained with platelets pretreated with 500 nM of Formula (II) or ibrutinib: thrombus size of 5946 ± 283 mm², and 2710 ± 325 mm² respectively. These initial results may provide some mechanic background and explanation on the reported 44% bleeding related adverse event rates in the Phase III RESONATE™ study.
comparing ibrutinib with ofatumumab. The results obtained for CC-292 were similar to that for ibrutinib, as shown in FIG. 26, FIG. 27, and FIG. 28. The effect of the BTK inhibitor concentration is shown in FIG. 29. These results demonstrate the surprising advantage of the BTK inhibitor of Formula (II), which does not interfere with thrombus formation, while the BTK inhibitors CC-292 and ibrutinib interfere with thrombus formation.

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

GPVI platelet aggregation was measured for Formula (II) and 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 Na2HP04, 5 mmol/L KCl, 2 mmol/L MgCl2, 1 mmol/L CaCl2, and 0.1% glucose, at pH 7.4. Stock solutions of Convulxin (CVX) GPVI were prepared on the day of experimentation and added to platelet suspensions 5 minutes (37 °C, 1200 rpm) before the induction of aggregation. Aggregation was assessed with a Chronolog Lumi-Aggregometer (model 540 VS; Chronolog, Havertown, PA) and permitted to proceed for 6 minutes after the addition of agonist. The results are reported as maximum percent change in light transmittance from baseline with platelet buffer used as a reference. The results are shown in FIG. 30.

In FIG. 31, 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.

[00356] The results depicted in FIG. 30 and FIG. 31 indicate that the BTK inhibitor 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 4 - Effects of BTK Inhibition on Antibody-Dependent NK Cell Mediated Cytotoxicity Using Rituximab**

[00357] 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.

[00358] 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-γ was reduced by 48% (p = 0.018) and 72% (p = 0.002) in cultures treated with ibrutinib at 0.1 and 1.0 μM respectively and NK cell degranulation was significantly (p = 0.002) reduced, compared with control cultures. Formula (II) treatment at 1 μM, a clinically relevant concentration, did not inhibit IFN-γ or NK cell degranulation. Rituximab-mediated ADCC was evaluated in NK cells from healthy volunteers as well as assays of NK cells from CLL patients targeting autologous CLL cells. In both cases, ADCC was not inhibited by Formula (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/SLL.


**Given the homology between BTK and interleukin-2 inducible tyrosine kinase (ITK), it has been recently confirmed that ibrutinib irreversibly binds ITK.** J. A. Dubovsky, *et al.*, *Blood*
ITK expression in Fc receptor (FcR)-stimulated NK cells leads to increased calcium mobilization, granule release, and cytotoxicity. D. 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-γ secretion, degranulation by CD107a mobilization, and cytotoxicity by chromium release using CD20+ cell lines and autologous patient samples with CLL.

[00362] 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 1). 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.

[00363] Cell culture conditions were as follows. Cell lines Raji and DHL-4 were maintained in RPMI 1630 supplemented with fetal bovine serum, L-glutamine, 2-mercaptoethanol and penicillin-streptomycin at 37 °C in a humidified incubator. The HER18 cells were maintained in DEM supplemented with fetal bovine serum, penicillin-streptomycin and. Prior to assay, HER18 cells were harvested using trypsin-EDTA (ethylenediaminetetraacetic acid), 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.

[00364] 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 °C. Triplicate cultures were performed on NK cells from donors. After incubation, supernatants were harvested, centrifuged briefly, and then analyzed for interferon-γ using an enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Minneapolis, MN, USA).

[00365] Lytic granule release was determined as follows. NK cells from healthy donors were enriched and cultured in the presence of target cells, monoclonal antibodies and test articles as described above. After 4 hours, the cultures were harvested and cells were pelleted, washed, and then stained for flow cytometry evaluation. Degranulation was evaluated via by flow cytometry by externalization of CD107a, a protein normally present on the inner leaflet of lytic granules, and gating on NK cells (CD3-CD16+ lymphocytes). The percentage of CD107a positive NK cells was quantified by comparison with a negative control (isotype control, unstained cells/FMO). Control cultures (NK cells cultured without target cells, or NK, target cell co-cultures in the absence of appropriate monoclonal antibody) were also evaluated; all experiments were performed in triplicate.

[00366] ADCC assays were performed as follows. Briefly, target cells (Raji or primary CLL) were labeled by incubation at 37 °C with 100 µCi 51Cr for 4 hours prior to co-culture with NK cells. Cells were washed, enumerated, and then added in triplicate to prepared 96-well plates containing treated NK cells at an effector:target (E:T) ratio of 25:1. Rituximab (Genentech) was added to ADCC wells at concentrations of 0.1, 1.0 or 10 µg/mL and the assays were briefly mixed and then centrifuged to collect cells at the bottom of the wells. The effect of NK cell natural cytotoxicity was assessed in wells containing no rituximab. Cultures were incubated at
37 °C for 4 hours, and then centrifuged. Supernatants were harvested and 51Cr release was measured by liquid scintillation counting. All experiments were performed in triplicate.

[00367] Ibrutinib-inhibited rituximab-induced NK cell cytokine secretion in a dose-dependent manner (0.1 and 1 µM) (FIG. 32: 48% p = 0.018; 72% p = 0.002, respectively). At 1 µM, Formula (II) did not significantly inhibit cytokine secretion (FIG. 32: 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. 33). 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. 30 and FIG. 31: ***p = 0.004, **p = 0.002).

[00368] In Raji cells 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. 34). A plot highlighting the differences between Formula (II) and ibrutinib at 10 µM is shown in FIG. 35. 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. 36). In contrast, addition of 1 µM ibrutinib completely inhibited ADCC, with less than 10% cell lysis at any rituximab concentration and no increase in cell lysis in the presence of rituximab, compared with cultures without rituximab. The difference between Formula (II) and ibrutinib was highly significant in this assay (p = 0.001).

[00369] 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. 34). 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. The difference between Formula (II) and ibrutinib was highly significant in this assay (p = 0.001).

[00370] 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 agent than ibrutinib to use in combination with antibodies that have ADCC as a mechanism of action.

Example 5 - Effects of BTK Inhibition on Antibody-Dependent NK Cell Mediated Cytotoxicity Using Obinutuzumab

[00371] Previous studies have determined that ibrutinib undesirably antagonizes rituximab ADCC effects mediated by NK cells. As noted previously, this may be due to ibrutinib's secondary irreversible binding to ITK, which is required for FcR-stimulated NK cell function including calcium mobilization, granule release, and overall ADCC. H. E. Kohrt, et al., Blood 2014, 123, 1957-60. The potential for ibrutinib antagonization of obinutuzumab (GA-101) ADCC as mediated by NK cells was explored and compared to the effects of Formula (II).

[00372] 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 x10^6 WBC/mL was measured, MEC-1 cells were re-suspended at 6 x 10^6 cells/mL, to allow for a final WBC:MEC-1 cell ratio of 1:1). The ibrutinib control and two blinded BTK inhibitors were diluted in X-VIVO 15 serum-free hematopoietic cell medium (Lonza Group, Ltd.) to concentrations of 200 μM, 20 μM and 2 μM. 170 μL aliquots of unmanipulated whole blood were incubated with 10 μL BTK inhibitors or X-VIVO 15 medium for one hour into a plate. Cetuximab and obinutuzumab (GA-101) were
diluted in X-VIVO 15 medium to a concentration of 20 µg/mL. Equal volumes of MEC-1 cells and antibodies were incubated for 5 minutes. After incubation, 20 µL of MEC-1 cells and antibodies was added to whole blood and the BTK inhibitors/X-VIVO 15 medium (for a final volume of 200 µL). The samples were placed in a 5% CO₂ incubator for 4 hours at 37 °C. The experimental conditions thus achieved a WBC:MEC-1 cell ratio of 1:1, with final concentrations of the BTK inhibitors in the assay of 10 µM, 1 µM and 0.1 µM and final concentrations of the antibodies of 1 µg/mL.

[00373] 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-CD 107a-PE antibody was added. The samples were incubated for 20 minutes at room temperature in the dark. An aliquot of 2 mL of FACS lysing solution (BD Biosciences) was added. The samples were again incubated for 5 minutes, and then centrifuged at 2000 rpm for 5 minutes. Supernatant was discarded and the cell pellet was resuspended in 500 µL of PBS. The samples were analyzed on the flow cytometer for CD107a+ NK cells (CD56+).

[00374] The NK cell degranulation results are summarized in FIG. 37 for n = 3 experiments, which shows the effects of the BTK inhibitors 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) unexpectedly shows much less antagonism towards NK cells. These results support a potential synergistic combination of obinutuzumab and Formula (II) in treatment of human B cell malignancies.

Example 6 - Effects of BTK Inhibition on Generalized NK Cell Mediated Cytotoxicity

[00375] 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 5×10⁵ cells were labeled in 100 µL of assay medium (IMDM with 10% FCS and penicillin/streptomycin)
with 100 µCi 51Cr 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 51Cr 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. 38.

Example 7 - Effects of BTK Inhibition on T Cells

[00376] 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-TCRp (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 Thl7 and Treg cultures are grown for 4 days before analysis. The cells are maintained for an additional 3 days with skewing cytokines (Thl7; 20 ng/mL IL-6, 0.5 ng/mL TGF-β, 5 µg/mL IL-4, 5 µg/mL IFN-γ and Treg; 0.5 ng/mL TGF-β, 5 µg/mL IL-4, 5 µg/mL IFN-γ) and are supplemented with IL2 as a growth factor.

[00377] The results are shown in FIG. 39 and FIG. 40, 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 Thl7 and Treg development was observed. Since ibrutinib inhibits both Itk and Txk, a profound inhibition of Thl7 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.

[00378] 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. 41, 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.

Example 8 - Clinical Study of a BTK Inhibitor in Leukemia/Lymphoma in Combination with Obinutuzumab (GA-101)

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/SLL, (2) to determine the ORR at 12 months with the combination of Formula (II) and obinutuzumab in patients with treatment-naive CLL/SLL, and (3) to establish the safety and feasibility of the combination of Formula (II) and obinutuzumab.

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 IgVH 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 patients; and (9) to determine trajectory of psychological and behavioral responses to Formula (II) and covariation with response to therapy.

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.

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.

[00383] 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.
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.

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.

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


[00387] 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.

[00388] In this Phase IB 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-naive subjects can begin in Cohort 2. Once safety is established for Cohort 2, then the cohort will be expanded to 19 subjects.

[00389] 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.

[00390] The inclusion criteria for patient eligibility are as follows: (1) Patients with a diagnosis of intermediate or high risk CLL (or variant immunophenotype), SLL, or B-PLL by IWCLL 2008 criteria' who have: (a) COHORT 1: Previously received at least one therapy for their disease; (b) COHORT 2: Previously untreated disease and > 65 years old OR under 65 years old and refuse or are ineligible for chemoimmunotherapy; (2) Patients on Cohort 1 may have received previous ibrutinib (or another BTK inhibitor) as long as discontinuation was for a reason other than "on-treatment" disease progression; (3) All patients must satisfy one of the following criteria for active disease requiring therapy: (a) Evidence of marrow failure as manifested by the development or worsening of anemia or thrombocytopenia (not attributable to autoimmune hemolytic anemia or thrombocytopenia); (b) Massive (> 6 cm below the costal margin), progressive or symptomatic splenomegaly; (c) Massive nodes (> 10 cm) or progressive or symptomatic lymphadenopathy; (d) Constitutional symptoms, which include any of the following: Unintentional weight loss of 10% or more within 6 months, Significant fatigue limiting activity, Fevers > 100.5 degrees F for 2 weeks or more without evidence of infection, Night sweats > 1 month without evidence of infection; (4) Measurable nodal disease by computed tomography (CT). Measurable nodal disease is defined as > 1 lymph node > 1.5 cm in the longest diameter in a site; (5) Patients with a history of Richter's syndrome are eligible if they now have evidence of CLL only, with < 10% large cells in the bone marrow; (6) Subjects must
have adequate organ function, defined as creatinine < 2.5 times the upper limit of normal (ULN), ALT and AST < 3.0 x ULN, and bilirubin < 2.5 x ULN; (7) Platelets > 50 x 10^9/L. In subjects with CLL involvement of the marrow, > 30 x 10^9/L; (8) ANC > 750/mm^3 In subjects with CLL involvement of the marrow, ANC > 500/mm^3; (9) Subject must have an ECOG performance status < 2; (10) Subject must not have secondary cancers that result in a life expectancy of < 2 years or that would confound assessment of toxicity in this study; (11) Subjects must be > 18 years of age; (12) Subject must provide written informed consent. A signed copy of the consent form will be retained in the patient's chart; (13) Subject must be able to receive outpatient treatment and follow-up at the treating institution; (14) Subject must have completed all CLL therapies > 4 weeks prior to first study dose. Palliative steroids are allowed, but must be at a dose equivalent of < 20 mg prednisone daily for at least 1 week prior to treatment initiation; (15) Subjects capable of reproduction and male subjects who have partners capable of reproduction must agree to use an effective contraceptive method during the course of the study and for 2 months following the completion of their last treatment. Females of childbearing potential must have a negative β-hCG pregnancy test result within 3 days of first study dose. Female patients who are surgically sterilized or who are > 45 years old and have not experienced menses for > 2 years may have their β-hCG pregnancy test waived; (16) Subjects must be able to swallow whole capsules.

[00391] 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 (e.g., phenprocoumon) within 28 days of first dose of study drug; (12) Requires treatment with long-acting proton pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole); (13) Subjects with active infections requiring IV antibiotic/anti viral 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.

[00392] 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 7.
TABLE 7. Dosing of obinutuzumab during 6 treatment cycles each of 28 days duration.

<table>
<thead>
<tr>
<th>Day of Treatment Cycle</th>
<th>Dose of Obinutuzumab</th>
<th>Rate of Infusion (In the absence of infusion reactions/ hypersensitivity during previous infusions)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cycle 2</strong> (loading doses)</td>
<td>Day 1</td>
<td>100 mg</td>
</tr>
<tr>
<td></td>
<td>Day 2</td>
<td>900 mg</td>
</tr>
<tr>
<td></td>
<td>Day 8</td>
<td>1000 mg</td>
</tr>
<tr>
<td></td>
<td>Day 15</td>
<td>1000 mg</td>
</tr>
<tr>
<td><strong>Cycles 3-7</strong></td>
<td>Day 1</td>
<td>1000 mg</td>
</tr>
</tbody>
</table>

[00393] 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. Sequelea 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.

[00394] The results of the ongoing 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 × 10⁹/L. No cases of serious or Grade 3-4 IRRs have been reported. Only 2 patients have had obinutuzumab temporarily held for chills and arthralgias/sluured, respectively, and were able to complete the planned infusion. An additional 3 patients had adverse events within 24 hours of the infusion, all grade 1 (terms: flushing, palpitations in one patient, rash, and restlessness and headache). Consequently, there has been a substantial decrease in serious or Grade 3-4 IRRs with the one month lead-in of Formula (II), which could potentially lead to higher efficacy for the combination as well as better tolerability, leading to a decrease in medical resource utilization.
We claim:

1. A method of treating chronic lymphocytic leukemia (CLL) or small lymphocytic leukemia (SLL) comprising the step of orally administering, to a human in need thereof, the Bruton's tyrosine kinase (BTK) inhibitor, wherein the BTK inhibitor is:

![Chemical Structure](image)

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

wherein:
- X is CH or S;
- Y is C(R₆);
- Z is CH or bond;
- A is CH;
- B₁ is N or C(R₇);
- B₂ is N or C(R₈);
- B₃ is N or CH;
- B₄ is N or CH;
- R₁ is R₁₁C(=O),
R₂ is (C₃₋₅)alkyl;
R₃ is (C₃₋₅)alkyl; or
R₂ and R₃ form, together with the N and C atom they are attached to, a (C₃₋₅)heterocycloalkyl ring selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, and morpholmyl, optionally substituted with one or more fluorine, hydroxyl, (C₃₋₅)alkyl, or (C₃₋₅)alkoxy;
R₄ is H;
R₅ is H, halogen, cyano, (C₄₋₉)alkyl, (C₃₋₅)alkoxy, (C₃₋₉)cycloalkyl, or any alky group which is optionally substituted with one or more halogen;
Rₑ is H or (C₃₋₅)alkyl;
R₇ is H, halogen or (C₃₋₅)alkoxy;
R₈ is H or (C₃₋₅)alkyl; or
R₇ and R₈ form, together with the carbon atom they are attached to a (C₆₋₁₀)aryl or (C₆₋₁₀)heteroaryl;
R₅ and R₆ together may form a (C₃₋₅)cycloalkenyl or (C₂₋₅)heterocycloalkenyl, each optionally substituted with (C₃₋₅)alkyl or one or more halogen;
R₁₁ is independently selected from the group consisting of (C₂₋₆)alkenyl and (C₂₋₆)alkynyl, where each alkenyl or alkynyl is optionally substituted with one or more substituents selected from the group consisting of hydroxyl, (C₃₋₅)alkyl, (C₃₋₅)cycloalkyl, [(C₄₋₉)alkyl]amino, di[(C₄₋₉)alkyl]amino, (C₃₋₅)alkoxy, (C₃₋₅)cycloalkoxy, (C₆₋₁₀)aryl and (C₃₋₅)heterocycloalkyl;
with the proviso that
0 to 2 atoms of B₁, B₂, B₃ and B₄ are N.
2. The method of Claim 1, wherein the BTK inhibitor is:
or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

3. The method of Claim 1, wherein the BTK inhibitor is:

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

4. The method of Claim 1, wherein the BTK inhibitor is:
or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

5. The method of Claim 1, wherein the BTK inhibitor is:

![Chemical Structure]

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

6. The method of Claim 1, wherein the BTK inhibitor is:

![Chemical Structure]
a pharmaceutically acceptable salt, solvate, or hydrate thereof.

7. The method of any one of Claims 1 to 6, wherein the BTK inhibitor is administered once daily at a dose selected from the group consisting of 100 mg, 175 mg, 250 mg, and 400 mg.

8. The method of any one of Claims 1 to 6, wherein the BTK inhibitor is administered twice daily at a dose of 100 mg.

9. The method of any one of Claims 1 to 6, wherein the CLL or SLL increases monocytes and NK cells in peripheral blood after treatment with Formula (II) for a period selected from the group consisting of about 14 days, about 28 days, or about 56 days.

10. The method of any one of Claims 1 to 6, wherein the CLL or SLL is selected from the group consisting of IgV_H mutation negative CLL or SLL, ZAP-70 positive CLL or SLL, ZAP-70 methylated at CpG3 CLL or SLL, CD38 positive CLL or SLL, CLL or SLL with a 17pl3.1 (17p) deletion, CLL or SLL with a 1ql22.3 (1q) deletion, CLL or SLL with a 11q deletion and no 17p deletion, CLL or SLL in a human sensitive to platelet-mediated thrombosis, CLL or SLL in a human presently suffering from platelet-mediated thrombosis, CLL or SLL in a human previously suffering from platelet-mediated thrombosis, or combinations thereof.

11. The method of any one of Claims 1 to 10, 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.

12. The method of any one of Claims 1 to 10, 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. A method of treating a hematological malignancy in a human comprising the step of orally administering, to a human in need thereof, the Bruton's tyrosine kinase (BTK) inhibitor, wherein the BTK inhibitor is:
or a pharmaceutically acceptable salt, solvate, or hydrate thereof,
wherein:
X is CH or S;
Y is C(R_6);
Z is CH or bond;
A is CH;
B_i is N or C(R_j);
B_2 is N or C(R_8);
B_3 is N or CH;
B_4 is N or CH;
R_1 is R_11C(=O),
R_2 is (C_i_3)alkyl;
R_3 is (C_i_3)alkyl; or
R_2 and R_3 form, together with the N and C atom they are attached to, a (C_3-_)heterocycloalkyl ring selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, and morpholmyl, optionally substituted with one or more fluorine, hydroxyl, (C_i_3)alkyl, or (C_i_3)alkoxy;
R_4 is H;
R₅ is H, halogen, cyano, (Ci_4)alkyl, (Ci_3)alkoxy, (C₃₋₆)cycloalkyl, or any alkyl group which is optionally substituted with one or more halogen;
Rₑ is H or (Ci₋₃)alkyl;
R₇ is H, halogen or (Ci₋₃)alkoxy;
R₉ is H or (Ci₋₃)alkyl; or
R₇ and R₉ form, together with the carbon atom they are attached to a (C₆-io)aryl or (Ci₋₉)heteroaryl;
R₅ and R₆ together may form a (C₃₋₇)cycloalkenyl or (C₂₋₆)heterocycloalkenyl, each optionally substituted with (Ci₋₃)alkyl or one or more halogen;
R₁₁ is independently selected from the group consisting of (C₁₋₄)alkenyl and (C₂₋₆)alkynyl, where each alkenyl or alkynyl is optionally substituted with one or more substituents selected from the group consisting of hydroxyl, (Ci₋₄)alkyl, (C₃₋₇)cycloalkyl, [(Ci₋₄)alkyl]amino, di[(Ci₋₄)alkyl]amino, (Ci₋₃)alkoxy, (C₂₋₆)cycloalkoxy, (C₆-io)aryl and (C₃₋₇)heterocycloalkyl;
with the proviso that
0 to 2 atoms of B₁, B₂, B₃ and B₄ are N;
and wherein the hematological malignancy is selected from the group consisting of non-Hodgkin's lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Hodgkin's lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Burkitt's lymphoma, Waldenstrom's macroglobulinemia (WM), Burkitt's lymphoma, multiple myeloma, or myelofibrosis.

15. The method of Claim 14, wherein the BTK inhibitor is:

DB1/ 8j 819064.1
or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

16. The method of Claim 14, wherein the BTK inhibitor is: [Chemical Structure Image]

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

17. The method of Claim 14, wherein the BTK inhibitor is: [Chemical Structure Image]
or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

18. The method of Claim 14, wherein the BTK inhibitor is:

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

19. The method of Claim 14, wherein the BTK inhibitor is:
a pharmaceutically acceptable salt, solvate, or hydrate thereof.

20. The method of any one of Claims 14 to 19, wherein the BTK inhibitor is administered once daily at a dose selected from the group consisting of 100 mg, 175 mg, 250 mg, and 400 mg.

21. The method of any one of Claims 14 to 19, wherein the BTK inhibitor is administered twice daily at a dose of 100 mg.

22. The method of any one of Claims 14 to 19, wherein the hematological malignancy increases monocytes and NK cells in peripheral blood after treatment with Formula (II) for a period selected from the group consisting of about 14 days, about 28 days, or about 56 days.

23. The method of any one of Claims 14 to 19, wherein the NHL is selected from the group consisting of indolent NHL and aggressive NHL.

24. The method of any one of Claims 14 to 19, wherein the DLBCL is selected from the group consisting of activated B-cell like diffuse large B-cell lymphoma (DLBCL-ABC) and germinal center B-cell like diffuse large B-cell lymphoma (DLBCL-GCB).

25. The method of any one of Claims 14 to 19, wherein the MCL is selected from the group consisting of mantle zone MCL, nodular MCL, diffuse MCL, and blastoid MCL.

26. The method of any one of Claims 14 to 19, wherein the B-ALL is selected from the group
consisting of early pre-B cell B-ALL, pre-B cell B-ALL, and mature B cell B-ALL.

27. The method of any one of Claims 14 to 19, wherein the Burkitt's lymphoma is selected from the group consisting of sporadic Burkitt's lymphoma, endemic Burkitt's lymphoma, and human immunodeficiency virus-associated Burkitt's lymphoma.

28. The method of any one of Claims 14 to 19, wherein the multiple myeloma is selected from the group consisting of hyperdiploid multiple myeloma and non-hyperdiploid multiple myeloma.

29. The method of any one of Claims 14 to 19, wherein the myelofibrosis is selected from the group consisting of primary myelofibrosis, myelofibrosis secondary to polycythemia vera, and myelofibrosis secondary to essential thrombocythaemia.

30. The method of any one of Claims 14 to 19, 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.

31. The method of any one of Claims 14 to 19, further comprising the step of administering a therapeutically effective dose of an anticoagulant or antiplatelet active pharmaceutical ingredient.

32. The method of Claim 31, 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, cloridronic, dabigatran etexilate, darexaban, dalteparin, dalteparin sodium, desfibrotide, dicumarol, diphenadione, dipyridamole, ditazole, desirudin, edoxaban, enoxaparin, enoxaparin sodium, eptifibatide, fonaparinux, 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, trifiusal, vorapaxar, warfarin, warfarin sodium, ximelagatran, salts thereof, solvates thereof, hydrates thereof, and combinations thereof.
FIG. 1

- CD86: 0.34 (BTK INHIBITOR), 0.91 (ibrutinib)
- CD69: 0.16 (BTK INHIBITOR), 0.45 (ibrutinib)

EC50 (mg/kg)

Expression in B cells (3h)
Example: Donor 1

FIG. 2
FIG. 3
FIG. 4
FIG. 5
FIG. 6
FIG. 10
FIG. 12
FIG. 15
FIG. 17
FIG. 18
Figure Kaplan-Meier Curves for PFS
Relapsed/Refractory Treated Subjects with Deletion 17p

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

FIG. 19
Figure Kaplan-Meier Curves for PFS
Relapsed/Refractory Treated Subjects

Months from Initiation of Study Treatment

Progression-Free Survival (Proportion)

GROUP: 1: Del17p  2: Del11q and no Del17p

Number At Risk
1: 19 17 13 13 12 11 9 9 9 7 6 6 2 2 1 0
2: 16 15 12 12 10 6 6 6 3 3 2 1 1 0

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

FIG. 20
Figure Kaplan-Meier Curves for PFS
Relapsed/Refractory Treated Subjects with Deletion 11q (and no Deletion 17p)

Progression-Free Survival (Proportion)

0.0 0.2 0.4 0.6 0.8 1.0

Censored

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Months from Initiation of Study Treatment

Number At Risk
16 15 12 12 12 10 6 6 6 3 3 2 1 1 1 0

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

FIG. 21
Sum of Product Diameters of Enlarged Lymph Nodes* in R/R Patients

R/R (N= 58 )

Percent Change in SPD

-100 -75 -50 -25 0 25

- Partial Remission - Partial Remission + Lymphocytosis
- Stable Disease

*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, 01-005 = SD, 06-004 = SD

FIG. 22
FIG. 23
FIG. 24
FIG. 25
FIG. 26
FIG. 28
FIG. 29
FIG. 30
FIG. 31

GPVI INDUCED AGGREGATION

% INHIBITION

FORMULA II
ibrutinib

COMPOUND [nM]

0 500 1000 1500 2000
FIG. 32
FIG. 33
FIG. 35
FIG. 37

- obinutuzumab + ibrutinib
- obinutuzumab + Formula (II) (blinded)
- obinutuzumab + ibrutinib (blinded)
- cetuximab + ibrutinib
- cetuximab + Formula (II) (blinded)
- cetuximab + ibrutinib (blinded)
FIG. 38
FIG. 39
FIG. 41

Graph showing % viability of CD8+ cells treated with different concentrations of formula and ibudinb.
## INTERNATIONAL SEARCH REPORT

### A. CLASSIFICATION OF SUBJECT MATTER

INV.  
A61K31/4985  A61K31/519  A61K45/06  A61P35/00  A61P35/02
A61P35/04  A61P43/00

### ADD.

According to International Patent Classification (IPC) into 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, CHEM ABS Data, MEDLINE, EMBASE, BIOSIS

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>
| X         | wo 2013/010868  AI (MSD OSS BV [NL] ; BARF TJEERD A [NL] ; JANS CHRISTIAAN GERARDUS JOHANNES) 24 January 2013 (2013-01-24) cited in the application on abstract page 1, line 6 - line 9 page 2, line 35 - page 4, line 28 page 21, line 5 - line 24 page 22, line 15 - line 20 examples 1,3,6,35 ,36 claims 1-17 ----- /
|           |                                                                                   | 1-32                 |

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

**T** later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

**X** document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

**Y** document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

**A** document member of the same patent family

Date of the actual completion of the international search

28 January 2016

Date of mailing of the international search report

03/02/2016

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Tayl or, Mark
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