THE USE OF INHIBITORS OF BRUTON'S TYROSINE KINASE (BTK)

RELATED APPLICATIONS

[0001] The present application claims the benefit of priority from U.S. Provisional Patent Application No. 61/351,130, filed June 3, 2010; U.S. Provisional Patent Application No. 61/351,655, filed June 4, 2010; U.S. Provisional Patent Application No. 61/351,793, filed June 4, 2010; U.S. Provisional Patent Application No. 61/351,762, filed June 4, 2010; U.S. Provisional Patent Application No. 61/419,764, filed December 3, 2010; and U.S. Provisional Patent Application No. 61/472,138, filed April 5, 2011; all of which are herein incorporated by reference in their entirety.

BACKGROUND OF THE INVENTION

[0002] Bruton's tyrosine kinase (Btk), a member of the Tec family of non-receptor tyrosine kinases, is a key signaling enzyme expressed in all hematopoietic cells types except T lymphocytes and natural killer cells. Btk plays an essential role in the B-cell signaling pathway linking cell surface B-cell receptor (BCR) stimulation to downstream intracellular responses.

[0003] Btk is a key regulator of B-cell development, activation, signaling, and survival (Kurosaki, *Curr Op Imm,* **2000,** 276-281; Schaeffer and Schwartzberg, *Curr Op Imm* **2000,** 282-288). In addition, Btk plays a role in a number of other hematopoietic cell signaling pathways, e.g., Toll like receptor (TLR) and cytokine receptor–mediated TNF-a production in macrophages, IgE receptor (FcepsilonRI) signaling in Mast cells, inhibition of Fas/APO-1 apoptotic signaling in B-lineage lymphoid cells, and collagen-stimulated platelet aggregation. *See, e.g.,* C. A. Jeffries, et al., (2003), *Journal of Biological Chemistry* 278:26258-26264; N. J. Horwood, et al., (2003), *The Journal of Experimental Medicine* 197:1603-1611; Iwaki *et al*. (2005), *Journal of Biological Chemistry* 280(48):40261-40270; Vassilev *et al.* (1999), *Journal of Biological Chemistry* 274(3):1646-1656, and Quek *et al*. (1998), *Current Biology* 8(20):1137-1140.

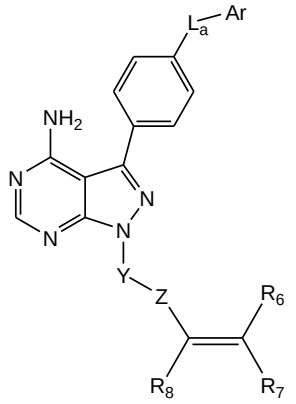
SUMMARY

[0004] Disclosed herein is a method for treating a hematological malignancy in an individual in need thereof, comprising: (a) administering to the individual an amount of an irreversible Btk inhibitor sufficient to mobilize a plurality of cells from the malignancy; and (b) analyzing the mobilized plurality of cells. In some examples, the amount of the irreversible Btk inhibitor is sufficient to induce lymphocytosis of a plurality of cells from the malignancy. In some examples, the hematological malignancy is CLL. In some examples, the treating the hematological malignancy comprises managing the

cy. In some examples, the hematological malignancy is a B-cell malignancy. In some examples, the hematological malignancy is a leukemia, lymphoproliferative disorder, or myeloid. In some examples, the mobilized cells are myeloid cells or lymphoid cells. In some examples, analyzing the mobilized plurality of cells comprises measuring the peripheral blood concentration of the mobilized plurality of cells. In some examples, the method further comprises administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells increases as compared to the concentration before administration of the Btk inhibitor. In some examples, administering the second cancer treatment regimen occurs after a subsequent decrease in peripheral blood concentration of the mobilized plurality of cells. In some examples, analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the peripheral blood concentration of the mobilized plurality of cells as compared to the concentration before administration of the Btk inhibitor. In some examples, the method further comprises administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells has increased for a predetermined length of time. In some examples, analyzing the mobilized plurality of cells comprises counting the number of mobilized plurality of cells in the peripheral blood. In some examples, the method further comprises administering a second cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood increases as compared to the concentration before administration of the Btk inhibitor. In some examples, administering the second cancer treatment regimen occurs after a subsequent decrease in the number of mobilized plurality of cells in the peripheral blood. In some examples, analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the number of mobilized plurality of cells in the peripheral blood as compared to the number before administration of the Btk inhibitor. In some examples, the method further comprises administering a second cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood has increased for a predetermined length of time. In some examples, analyzing the mobilized plurality of cells comprises preparing a biomarker profile for a population of cells isolated from the plurality of cells, wherein the biomarker profile indicates the expression of a biomarker, the expression level of a biomarker, mutations in a biomarker, or the presence of a biomarker. In some examples, the biomarker is any cytogenetic, cell surface molecular or protein or RNA expression marker. In some examples, the biomarker is: ZAP70; t(14,18); β-2 microglobulin; p53 mutational status; ATM mutational status; del(17)p; del(11)q; del(6)q; CD5; CD11c; CD19; CD20; CD22; CD25; CD38; CD103; CD138; secreted, surface or cytoplasmic immunoglobulin expression; V_H mutational status; or a combination thereof. In some

examples, the method further comprises providing a second cancer treatment regimen based on the biomarker profile. In some examples, the method further comprises not administering based on the biomarker profile. In some examples, the method further comprises predicting the efficacy of a treatment regimen based on the biomarker profile. In some examples, the hematological malignancy is a chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, or a non-CLL/SLL lymphoma. In some examples, the hematological malignancy is follicular lymphoma, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, Waldenstrom's macroglobulinemia, multiple myeloma, marginal zone lymphoma, Burkitt's lymphoma, non-Burkitt high grade B cell lymphoma, or extranodal marginal zone B cell lymphoma. In some examples, the hematological malignancy is chronic myelogenous (or myeloid) leukemia, or acute lymphoblastic leukemia. In some examples, the hematological malignancy is relapsed or refractory diffuse large B-cell lymphoma (DLBCL), relapsed or refractory mantle cell lymphoma, relapsed or refractory follicular lymphoma, relapsed or refractory CLL; relapsed or refractory SLL; relapsed or refractory multiple myeloma. In some examples, the Btk inhibitor forms a covalent bond with a cysteine sidechain of a Bruton's tyrosine kinase, a Bruton's tyrosine kinase homolog, or a Btk tyrosine kinase cysteine homolog. In some examples, the irreversible Btk inhibitor is (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one. In some examples, the amount of the irreversible Btk inhibitor is from 300 mg/day up to, and including, 1000 mg/day. In some examples, the amount of the irreversible Btk inhibitor is from 420 mg/day up to, and including, 840 mg/day. In some examples, the amount of the irreversible Btk inhibitor is about 420 mg/day, about 560 mg/day, or about 840 mg/day. In some examples, the amount of the irreversible Btk inhibitor is about 420 mg/day. In some examples, the AUC_{0-24} of the Btk inhibitor is between about 150 and about 3500 ng*h/mL. In some examples, the AUC_{0-24} of the Btk inhibitor is between about 500 and about 1100 ng*h/mL. In some examples, the Btk inhibitor is administered orally. In some examples, the Btk inhibitor is administered once per day, twice per day, or three times per day. In some examples, the Btk inhibitor is administered until disease progression, unacceptable toxicity, or individual choice. In some examples, the Btk inhibitor is administered daily until disease progression, unacceptable toxicity, or individual choice. In some examples, the Btk inhibitor is administered every other day until disease progression, unacceptable toxicity, or individual choice. In some examples, the Btk inhibitor is a front line therapy, second line therapy, third line therapy, fourth line therapy, fifth line therapy, or

sixth line therapy. In some examples, the Btk inhibitor treats a refractory hematological malignancy. In some examples, the Btk inhibitor is a maintenance therapy. In some examples, the second cancer treatment regimen comprises a chemotherapeutic agent, a steroid, an immunotherapeutic agent, a targeted therapy, or a combination thereof. In some examples, the second cancer treatment regimen comprises a B cell receptor pathway inhibitor. In some examples, the B cell receptor pathway inhibitor is a CD79A inhibitor, a CD79B inhibitor, a CD19 inhibitor, a Lyn inhibitor, a Syk inhibitor, a PI3K inhibitor, a Blnk inhibitor, a PLCy inhibitor, a PKCP inhibitor, or a combination thereof. In some examples, the second cancer treatment regimen comprises an antibody, B cell receptor signaling inhibitor, a PI3K inhibitor, an IAP inhibitor, an mTOR inhibitor, a radioimmunotherapeutic, a DNA damaging agent, a proteosome inhibitor, a histone deacetylase inhibitor, a protein kinase inhibitor, a hedgehog inhibitor, an Hsp90 inhibitor, a telomerase inhibitor, a Jak1/2 inhibitor, a protease inhibitor, a PKC inhibitor, a PARP inhibitor, or a combination thereof. In some examples, the second cancer treatment regimen comprises chlorambucil, ifosphamide, doxorubicin, mesalazine, thalidomide, lenalidomide, temsirolimus, everolimus, fludarabine, fostamatinib, paclitaxel, docetaxel, ofatumumab, rituximab, dexamethasone, prednisone, CAL-101, ibritumomab, tositumomab, bortezomib, pentostatin, endostatin, or a combination thereof. In some examples, the second cancer treatment regimen comprises cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone, and optionally, rituximab. In some examples, the second cancer treatment regimen comprises bendamustine, and rituximab. In some examples, the second cancer treatment regimen comprises fludarabine, cyclophosphamide, and rituximab. In some examples, the second cancer treatment regimen comprises cyclophosphamide, vincristine, and prednisone, and optionally, rituximab. In some examples, the second cancer treatment regimen comprises etoposide, doxorubicin, vinristine, cyclophosphamide, prednisolone, and optionally, rituximab. In some examples, the second cancer treatment regimen comprises dexamethasone and lenalidomide. In some examples, the inhibitor of Bruton’s tyrosine kinase is a reversible inhibitor. In some examples, the inhibitor of Bruton’s tyrosine kinase is an irreversible inhibitor. In some examples, the inhibitor of Bruton’s tyrosine kinase forms a covalent bond with a cysteine sidechain of a Bruton’s tyrosine kinase, a Bruton’s tyrosine kinase homolog, or a Btk tyrosine kinase cysteine homolog. In some examples, the inhibitor of Bruton’s tyrosine kinase has the structure of Formula (D):



Formula (D)

wherein:

L_a is CH_2, O, NH or S;

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

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

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

R_7 and R_8 are independently H; or

R_7 and R_8 taken together form a bond;

R_6 is H; and pharmaceutically active metabolites, or pharmaceutically acceptable solvates, pharmaceutically acceptable salts, or pharmaceutically acceptable prodrugs thereof. In some examples, the Bruton's tyrosine kinase inhibitor is (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one. In some examples, La is O. In some examples, Ar is phenyl. In some examples, Z is C(=O), NHC(=O), or $S(=O)_2$. In some examples, each of R_7 and R_8 is H. In some examples, Y is a 4-, 5-, 6-, or 7-membered cycloalkyl ring; or Y is a 4-, 5-, 6-, or 7-membered heterocycloalkyl ring.

[0005] Disclosed herein is a method for treating relapsed or refractory non-Hodgkin's lymphoma in an individual in need thereof, comprising: administering to the individual a therapeutically-effective amount of (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one. In some examples, the non-Hodgkin's lymphoma is relapsed or refractory diffuse large B-cell lymphoma (DLBCL), relapsed or refractory mantle cell lymphoma, or relapsed or refractory follicular lymphoma. In some examples, the amount of (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is from 300 mg/day up to, and including, 1000 mg/day. In some examples, the amount of (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is from 420 mg/day up to, and

including, 840 mg/day. In some examples, the amount of (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is about 420 mg/day, about 560 mg/day, or about 840 mg/day. In some examples, the amount of the irreversible Btk inhibitor is about 420 mg/day. In some examples, the AUC_{0-24} of the Btk inhibitor is between about 150 and about 3500 ng*h/mL. In some examples, the AUC_{0-24} of the Btk inhibitor is between about 500 and about 1100 ng*h/mL. In some examples, (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is administered orally. In some examples, (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is administered once per day, twice per day, or three times per day. In some examples, (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is administered until disease progression, unacceptable toxicity, or individual choice. In some examples, (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is administered until disease progression, unacceptable toxicity, or individual choice. In some examples, (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is administered daily until disease progression, unacceptable toxicity, or individual choice. In some examples, (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is administered every other day until disease progression, unacceptable toxicity, or individual choice. In some examples, (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is a second line therapy, third line therapy, fourth line therapy, fifth line therapy, or sixth line therapy. In some examples, the Btk inhibitor is a maintenance therapy. In some examples, the method further comprises administering a second cancer treatment regimen. In some examples, the second cancer treatment regimen is administered after mobilization of a plurality of lymphoid cells from the non-Hodgkin's lymphoma. In some examples, the second cancer treatment regimen is administered after lymphocytosis of a plurality of lymphoid cells from the non-Hodgkin's lymphoma. In some examples, the second cancer treatment regimen comprises a chemotherapeutic agent, a steroid, an immunotherapeutic agent, a targeted therapy, or a combination thereof. In some examples, the second cancer treatment regimen comprises a B cell receptor pathway inhibitor. In some examples, the B cell receptor pathway inhibitor is a CD79A inhibitor, a CD79B inhibitor, a CD19 inhibitor, a Lyn inhibitor, a Syk inhibitor, a PI3K inhibitor, a Blnk inhibitor, a PLCy inhibitor, a PKCP inhibitor, or a combination thereof. In

some examples, the second cancer treatment regimen comprises an antibody, B cell receptor signaling inhibitor, a PI3K inhibitor, an IAP inhibitor, an mTOR inhibitor, a radioimmunotherapeutic, a DNA damaging agent, a proteosome inhibitor, a histone deacetylase inhibitor, a protein kinase inhibitor, a hedgehog inhibitor, an Hsp90 inhibitor, a telomerase inhibitor, a Jak1/2 inhibitor, a protease inhibitor, a PKC inhibitor, a PARP inhibitor, or a combination thereof. In some examples, the second cancer treatment regimen comprises chlorambucil, ifosphamide, doxorubicin, mesalazine, thalidomide, lenalidomide, temsirolimus, everolimus, fludarabine, fostamatinib, paclitaxel, docetaxel, ofatumumab, rituximab, dexamethasone, prednisone, CAL-101, ibritumomab, tositumomab, bortezomib, pentostatin, endostatin, or a combination thereof. In some examples, the second cancer treatment regimen comprises cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone, and optionally, rituximab. In some examples, the second cancer treatment regimen comprises bendamustine, and rituximab. In some examples, the second cancer treatment regimen comprises fludarabine, cyclophosphamide, and rituximab. In some examples, the second cancer treatment regimen comprises cyclophosphamide, vincristine, and prednisone, and optionally, rituximab. In some examples, the second cancer treatment regimen comprises etoposide, doxorubicin, vinristine, cyclophosphamide, prednisolone, and optionally, rituximab. In some examples, the second cancer treatment regimen comprises dexamethasone and lenalidomide.

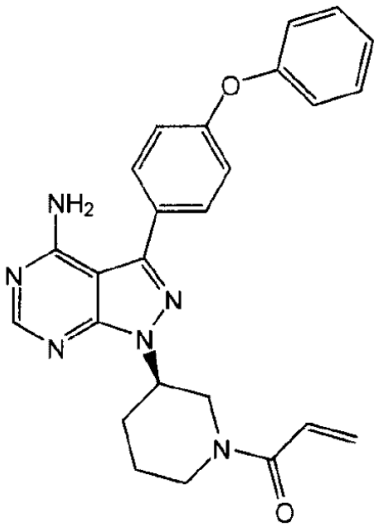
[0006] Disclosed herein is a method for treating diffuse large B-cell lymphoma, activated B cell-like subtype (ABC-DLBCL), in an individual in need thereof, comprising: administering to the individual an irreversible Btk inhibitor in an amount from 300 mg/day up to, and including, 1000 mg/day. In some examples, the method further comprises diagnosing the individual with diffuse large B-cell lymphoma, activated B cell-like subtype (ABC-DLBCL), by determining the gene sequence of one or more biomarkers in a plurality of lymphoid cells isolated from the diffuse large B-cell lymphoma. In some examples, the irreversible Btk inhibitor is (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one. In some examples, the ABC-DLBCL is characterized by a CD79B mutation. In some examples, the CD79B mutation is a mutation of the immunoreceptor tyrosine-based activation motif (ITAM) signaling module. In some examples, the CD79B mutation is a missense mutation of the first immunoreceptor tyrosine-based activation motif (ITAM) tyrosine. In some examples, the CD79B mutation increases surface BCR expression and attenuates Lyn kinase activity. In some examples, the ABC-

DLBCL is characterized by a CD79A mutation. In some examples, the CD79A mutation is in the immunoreceptor tyrosine-based activation motif (ITAM) signaling module. In some examples, the CD79A mutation is a splice-donor-site mutation of the immunoreceptor tyrosine-based activation motif (ITAM) signaling module. In some examples, the CD79A mutation deletes the immunoreceptor tyrosine-based activation motif (ITAM) signaling module. In some examples, the ABC-DLBCL is characterized by a mutation in MyD88, A20, or a combination thereof. In some examples, the MyD88 mutation is the amino acid substitution L265P in the MYD88 Toll/IL-1 receptor (TIR) domain. In some examples, the amount of the irreversible Btk inhibitor is from 420 mg/day up to, and including, 840 mg/day. In some examples, the amount of the irreversible Btk inhibitor is about 420 mg/day, about 560 mg/day, or about 840 mg/day. In some examples, the amount of the irreversible Btk inhibitor is about 420 mg/day. In some examples, the AUC_{0-24} of the Btk inhibitor is between about 150 and about 3500 ng*h/mL. In some examples, the AUC_{0-24} of the Btk inhibitor is between about 500 and about 1100 ng*h/mL. In some examples, the irreversible Btk inhibitor is administered orally. In some examples, the irreversible Btk inhibitor is administered daily until disease progression, unacceptable toxicity, or individual choice. In some examples, the irreversible Btk inhibitor is administered every other day until disease progression, unacceptable toxicity, or individual choice. In some examples, the irreversible Btk inhibitor is a front line therapy, second line therapy, third line therapy, fourth line therapy, fifth line therapy, or sixth line therapy. In some examples, the irreversible Btk inhibitor treats a refractory hematological malignancy. In some examples, the irreversible Btk inhibitor is a maintenance therapy. In some examples, the method further comprises administering at least one additional cancer treatment regimen. In some examples, the additional cancer treatment regimen comprises a chemotherapeutic agent, an immunotherapeutic agent, a steroid, radiation therapy, a targeted therapy, or a combination thereof. In some examples, the second cancer treatment regimen comprises an antibody, B cell receptor signaling inhibitor, a PI3K inhibitor, an IAP inhibitor, an mTOR inhibitor, a radioimmunotherapeutic, is a damaging agent, a proteosome inhibitor, a histone deacetylase inhibitor, a protein kinase inhibitor, a hedgehog inhibitor, an Hsp90 inhibitor, a telomerase inhibitor, a Jak1/2 inhibitor, a protease inhibitor, a PKC inhibitor, a PARP inhibitor, or a combination thereof.

[0007] Disclosed herein is a method of determining a cancer treatment regimen for an individual with a hematological malignancy, comprising: (a) administering to the

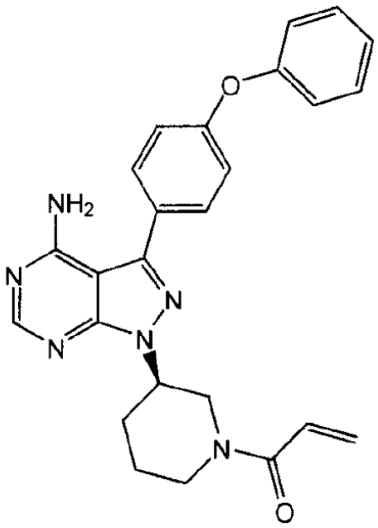
individual an amount of an irreversible Btk inhibitor sufficient to mobilize a plurality of cells from the malignancy; (b) analyzing the mobilized plurality of cells; and (c) selecting a cancer treatment regimen. In some examples, the cancer treatment regimen comprises a chemotherapeutic agent, a steroid, an immunotherapeutic agent, a targeted therapy, or a combination thereof. In some examples, the second cancer treatment regimen comprises a B cell receptor pathway inhibitor. In some examples, the B cell receptor pathway inhibitor is a CD79A inhibitor, a CD79B inhibitor, a CD19 inhibitor, a Lyn inhibitor, a Syk inhibitor, a PI3K inhibitor, a Blnk inhibitor, a PLCy inhibitor, a PKCP inhibitor, or a combination thereof. In some examples, the cancer treatment regimen comprises a B cell receptor pathway inhibitor. In some examples, the cancer treatment regimen comprises a CD79A inhibitor, a CD79B inhibitor, a CD19 inhibitor, a Lyn inhibitor, a Syk inhibitor, a PI3K inhibitor, a Blnk inhibitor, a PLCy inhibitor, a PKCP inhibitor, or a combination thereof. In some examples, the cancer treatment regimen comprises an antibody, B cell receptor signaling inhibitor, a PI3K inhibitor, an IAP inhibitor, an mTOR inhibitor, a radioimmunotherapeutic, a DNA damaging agent, a proteosome inhibitor, a histone deacetylase inhibitor, a protein kinase inhibitor, a hedgehog inhibitor, an Hsp90 inhibitor, a telomerase inhibitor, a Jak1/2 inhibitor, a protease inhibitor, a PKC inhibitor, a PARP inhibitor, or a combination thereof. In some examples, the cancer treatment regimen comprises chlorambucil, ifosphamide, doxorubicin, mesalazine, thalidomide, lenalidomide, temsirolimus, everolimus, fludarabine, fostamatinib, paclitaxel, docetaxel, ofatumumab, rituximab, dexamethasone, prednisone, CAL-101, ibritumomab, tositumomab, bortezomib, pentostatin, endostatin, or a combination thereof. In some examples, the cancer treatment regimen comprises cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone, and optionally, rituximab. In some examples, the cancer treatment regimen comprises bendamustine, and rituximab. In some examples, the cancer treatment regimen comprises fludarabine, cyclophosphamide, and rituximab. In some examples, the cancer treatment regimen comprises cyclophosphamide, vincristine, and prednisone, and optionally, rituximab. In some examples, the cancer treatment regimen comprises etoposide, doxorubicin, vinristine, cyclophosphamide, prednisolone, and optionally, rituximab. In some examples, the cancer treatment regimen comprises dexamethasone and lenalidomide.

[0007a] In one aspect, the present disclosure provides use of a compound in the manufacture of a medicament for treating chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) in an individual who has already received at least one prior therapy for CLL or SLL, wherein the compound has the structure:



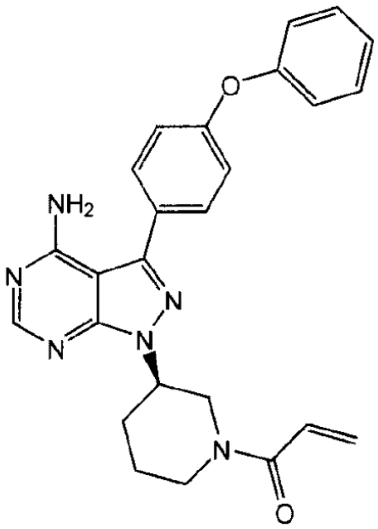
and the compound is adapted for administration once per day in an amount of 420 mg/day.

[0007b] In another aspect, the present disclosure provides a compound for use in treating chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) in an individual who has already received at least one prior therapy for CLL or SLL, wherein the compound has the structure:



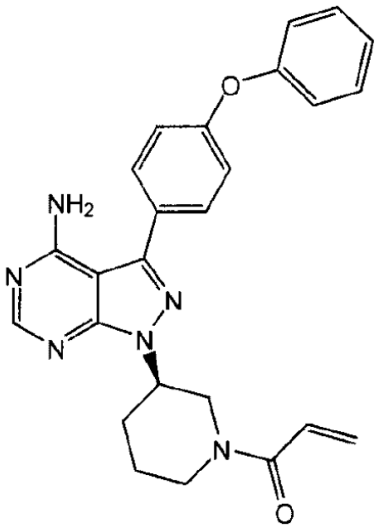
and the compound is adapted for administration once per day in an amount of 420 mg/day.

[0007c] In another aspect, the present disclosure provides use of a compound and an anti-CD20 antibody selected from rituximab and ofatumumab in the manufacture of a medicament for treating relapsed or refractory chronic lymphocytic leukemia, or relapsed or refractory small lymphocytic lymphoma in an individual, wherein the compound has the structure:



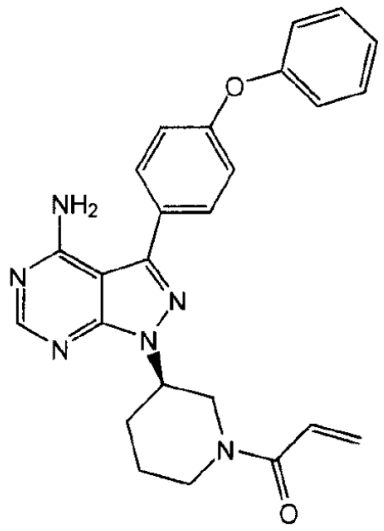
and the compound is adapted for administration once per day in an amount of 420 mg/day.

[0007d] In another aspect, the present disclosure provides a compound and an anti-CD20 antibody selected from rituximab and ofatumumab for use in treating relapsed or refractory chronic lymphocytic leukemia, or relapsed or refractory small lymphocytic lymphoma in an individual, wherein the compound has the structure:



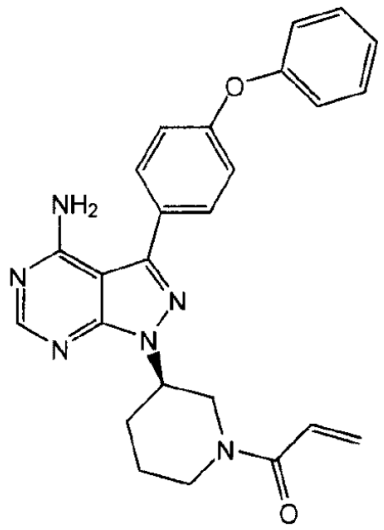
and the compound is adapted for administration once per day in an amount of 420 mg/day.

[0007e] In another aspect, the present disclosure provides use of a compound in the manufacture of a medicament for treating chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) in an individual, wherein the individual is treatment-naïve for CLL or SLL, and wherein the compound has the structure:



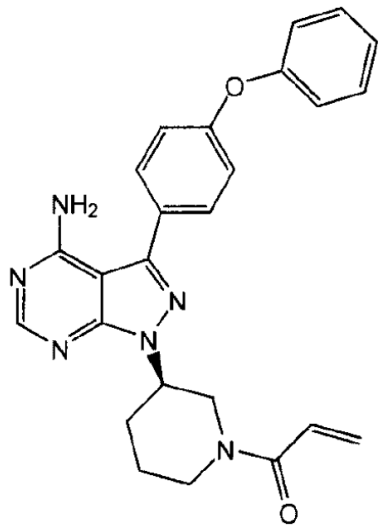
and the compound is adapted for administration once per day in an amount of 420 mg/day.

[0007f]In another aspect, the present disclosure provides a compound for use in treating chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) in an individual, wherein the individual is treatment-naïve for CLL or SLL, and wherein the compound has the structure:



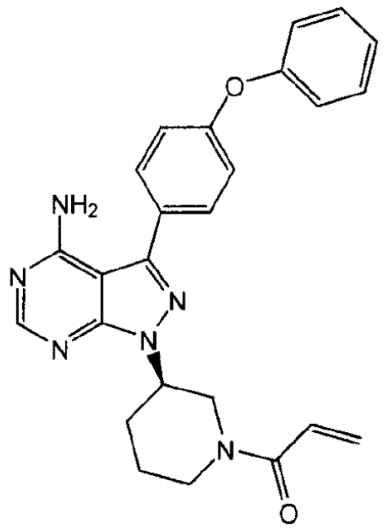
and the compound is adapted for administration once per day in an amount of 420 mg/day.

[0007g] In another aspect, the present disclosure provides use of a compound in the manufacture of a medicament for treating relapsed or refractory chronic lymphocytic leukemia or relapsed or refractory small lymphocytic lymphoma in an individual in need thereof, wherein the compound has the structure:



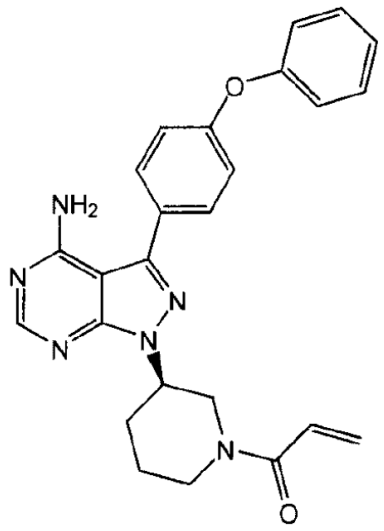
and the compound is adapted for administration once per day in an amount of 420 mg/day.

[0007h] In another aspect, the present disclosure provides use of a compound in the manufacture of a medicament for treating chronic lymphocytic leukemia or small lymphocytic lymphoma in an individual in need thereof, wherein the compound has the structure:



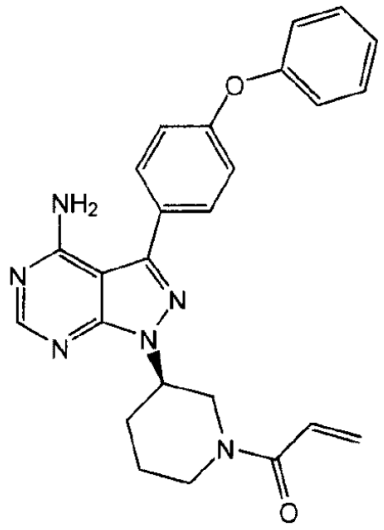
and the compound is adapted for administration once per day in an amount of 420 mg/day.

[0007i]In another aspect, the present disclosure provides a compound for use in treating relapsed or refractory chronic lymphocytic leukemia or relapsed or refractory small lymphocytic lymphoma in an individual in need thereof, wherein the compound has the structure:



and the compound is adapted for administration once per day in an amount of 420 mg/day.

[0007j]In another aspect, the present disclosure provides a compound for use in treating chronic lymphocytic leukemia or small lymphocytic lymphoma in an individual in need thereof, wherein the compound has the structure:



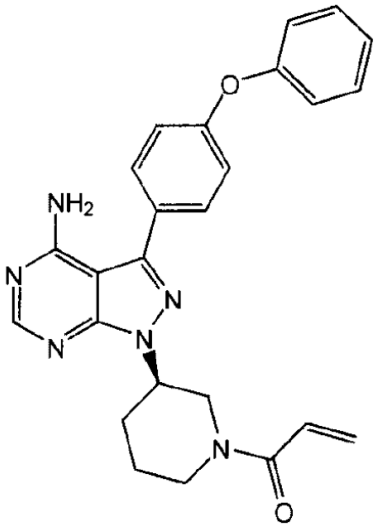
and the compound is adapted for administration once per day in an amount of 420 mg/day.

BRIEF DESCRIPTION OF THE FIGURES

[0008] Fig. 1 depicts the role of Btk activity in a number of processes in a CLL cell that contribute to the pathogenesis of the disease.

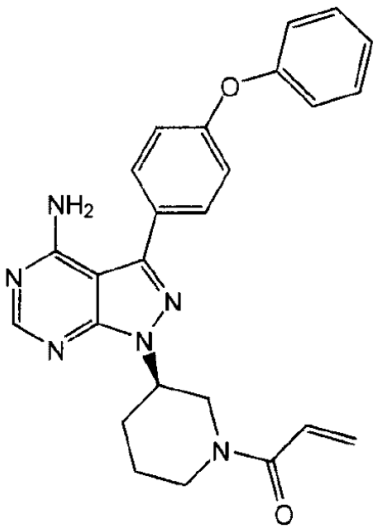
WHAT IS CLAIMED IS:

1. Use of a compound in the manufacture of a medicament for treating chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) in an individual who has already received at least one prior therapy for CLL or SLL, wherein the compound has the structure:



and the compound is adapted for administration once per day in an amount of 420 mg/day.

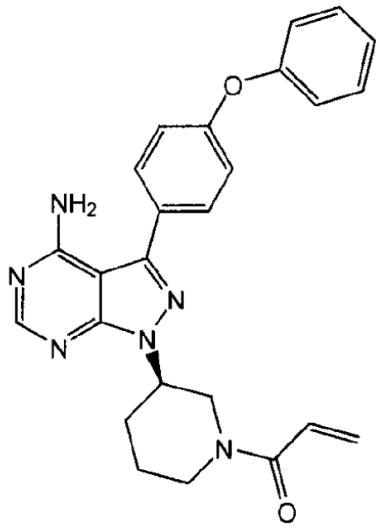
2. A compound for use in treating chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) in an individual who has already received at least one prior therapy for CLL or SLL, wherein the compound has the structure:



and the compound is adapted for administration once per day in an amount of 420 mg/day.

3. Use of a compound and an anti-CD20 antibody selected from rituximab and ofatumumab in the manufacture of a medicament for treating relapsed or refractory chronic lymphocytic

leukemia, or relapsed or refractory small lymphocytic lymphoma in an individual, wherein the compound has the structure:

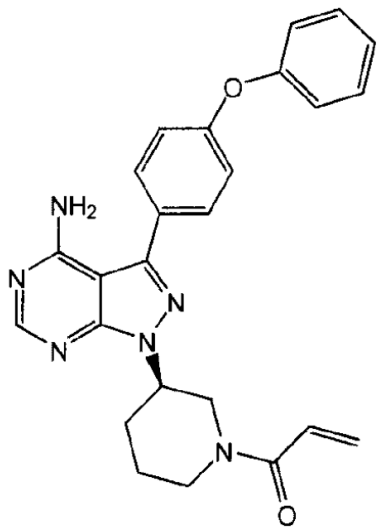


and the compound is adapted for administration once per day in an amount of 420 mg/day.

4. The use of claim 3, further comprising the use of bendamustine.

5. The use of claim 3 or 4, wherein the anti-CD20 antibody is rituximab.

6. A compound and an anti-CD20 antibody selected from rituximab and ofatumumab for use in treating relapsed or refractory chronic lymphocytic leukemia, or relapsed or refractory small lymphocytic lymphoma in an individual, wherein the compound has the structure:

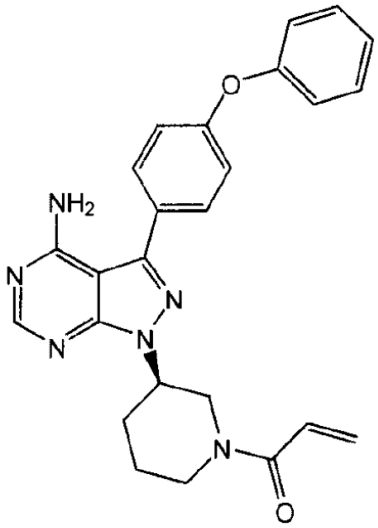


and the compound is adapted for administration once per day in an amount of 420 mg/day.

7. The compound for use of claim 6, further comprising the use of bendamustine.

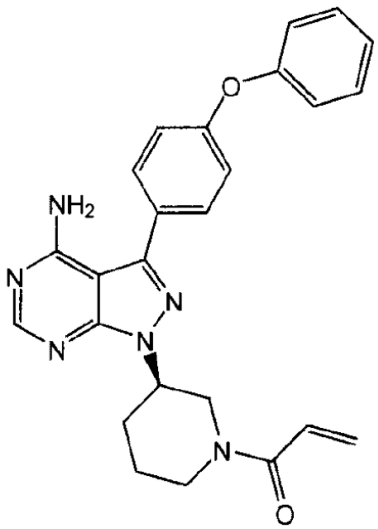
8. The compound for use of claim 6 or 7, wherein the anti-CD20 antibody is rituximab.

9. Use of a compound in the manufacture of a medicament for treating chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) in an individual, wherein the individual is treatment-naïve for CLL or SLL, and wherein the compound has the structure:



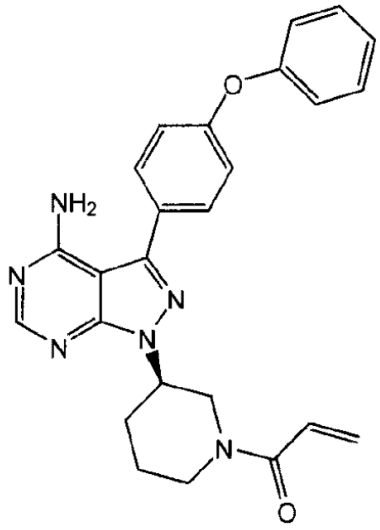
and the compound is adapted for administration once per day in an amount of 420 mg/day.

10. A compound for use in treating chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) in an individual, wherein the individual is treatment-naïve for CLL or SLL, and wherein the compound has the structure:



and the compound is adapted for administration once per day in an amount of 420 mg/day.

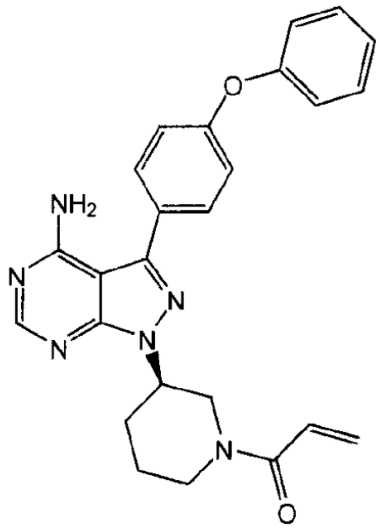
11. Use of a compound in the manufacture of a medicament for treating relapsed or refractory chronic lymphocytic leukemia or relapsed or refractory small lymphocytic lymphoma in an individual in need thereof, wherein the compound has the structure:



and the compound is adapted for administration once per day in an amount of 420 mg/day.

12. The use of claim 11, wherein the individual has high risk for relapsed or refractory chronic lymphocytic leukemia.

13. Use of a compound in the manufacture of a medicament for treating chronic lymphocytic leukemia or small lymphocytic lymphoma in an individual in need thereof, wherein the compound has the structure:



and the compound is adapted for administration once per day in an amount of 420 mg/day.

14. The use of any one of claims 11 to 13, wherein the individual has nucleic acid deletion in chromosome 17.

15. The use of any one of claims 11 to 13, wherein the individual has nucleic acid deletion in chromosome 17p.

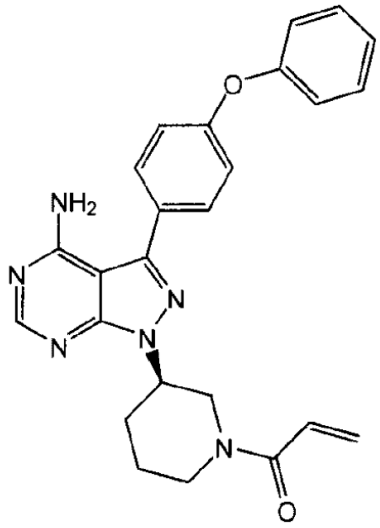
16. The use of any one of claims 11 to 13, wherein the individual has nucleic acid deletion in chromosome 17p13.

17. The use of any one of claims 11 to 13, wherein the individual has nucleic acid deletion in chromosome 11.

18. The use of any one of claims 11 to 13, wherein the individual has nucleic acid deletion in chromosome 11q.

19. The use of any one of claims 11 to 13, wherein the individual has nucleic acid deletion in chromosome 11q22.

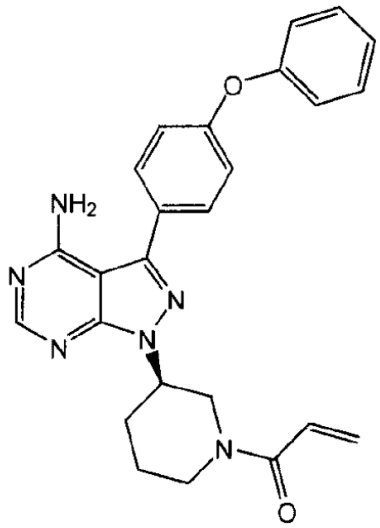
20. A compound for use in treating relapsed or refractory chronic lymphocytic leukemia or relapsed or refractory small lymphocytic lymphoma in an individual in need thereof, wherein the compound has the structure:



and the compound is adapted for administration once per day in an amount of 420 mg/day.

21. The compound for use of claim 20, wherein the individual has high risk for relapsed or refractory chronic lymphocytic leukemia.

22. A compound for use in treating chronic lymphocytic leukemia or small lymphocytic lymphoma in an individual in need thereof, wherein the compound has the structure:



and the compound is adapted for administration once per day in an amount of 420 mg/day.

23. The compound for use of any one of claims 20 to 22, wherein the individual has nucleic acid deletion in chromosome 17.

24. The compound for use of any one of claims 20 to 22, wherein the individual has nucleic acid deletion in chromosome 17p.

25. The compound for use of any one of claims 20 to 22, wherein the individual has nucleic acid deletion in chromosome 17p13.

26. The compound for use of any one of claims 20 to 22, wherein the individual has nucleic acid deletion in chromosome 11.

27. The compound for use of any one of claims 20 to 22, wherein the individual has nucleic acid deletion in chromosome 11q.

28. The compound for use of any one of claims 20 to 22, wherein the individual has nucleic acid deletion in chromosome 11q22.

29. The use of any one of claims 1, 9 and 11 to 19, comprising the use of an additional cancer treatment.

30. The use of claim 29, wherein the additional cancer treatment is bendamustine, bortezomib, CAL-101, chlorambucil, cyclophosphamide, dexamethasone, docetaxel,

doxorubicin, endostatin, everolimus, etoposide, fludarabine, fostamatinib, hydroxydaunorubicin, ibritumomab, ifosphamide, lenalidomide, mesalazine, ofatumumab, paclitaxel, pentostatin, prednisone, rituximab, temsirolimus, thalidomide, tositumomab, vineristine, or a combination thereof.

31. The use of any one of claims 1, 3 to 5, 9 and 11 to 19, wherein the compound is adapted for administration in the form of a solid oral dosage form.

32. The use of claim 31, wherein the solid oral dosage form is a capsule.

33. The use of claim 31, wherein the solid oral dosage form is a tablet.

34. The compound for use of any one of claims 2, 10 and 20 to 28, comprising the use of an additional cancer treatment.

35. The compound for use of claim 34, wherein the additional cancer treatment is bendamustine, bortezomib, CAL-191, chlorambucil, cyclophosphamide, dexamethasone, docetaxel, doxorubicin, endostatin, everolimus, etoposide, fludarabine, fostamatinib, hydroxydaunorubicin, ibritumomab, ifosphamide, lenalidomide, mesalazine, ofatumumab, paclitaxel, pentostatin, prednisone, rituximab, temsirolimus, thalidomide, tositumomab, vineristine, or a combination thereof.

36. The compound for use of any one of claims 2, 6 to 8, 10 and 20 to 28, wherein the compound is adapted for administration in the form of a solid oral dosage form.

37. The compound for use of claim 36, wherein the solid oral dosage form is a capsule.

38. The compound for use of claim 36, wherein the solid oral dosage form is a tablet.

39. The use of any one of claims 1, 3 to 5, 9, 11 to 19 and 29 to 33, wherein the individual achieves a stable disease.

40. The use of any one of claims 1, 3 to 5, 9, 11 to 19 and 29 to 33, wherein the individual achieves a partial response.

41. The use of any one of claims 1, 3 to 5, 9, 11 to 19 and 29 to 33, wherein the individual achieves a complete response.

42. The use of any one of claims 1, 3 to 5, 9, 11 to 19 and 29 to 33, wherein the individual does not experience a progressive disease.