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

CROSS-REFERENCE

[0001] This application claims priority to U.S. Provisional Patent Application No. 61/549,067, titled "THE USE OF INHIBITORS OF BRUTON'S TYROSINE KINASE (BTK)" and filed October 19, 2011, which is incorporated herein by reference in its 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-α production in macrophages, IgE receptor (FcεRI) 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

[0003a] In one aspect, there is proviced use of a combination of:

a therapeutically effective amount of ibrutinib; and

a therapeutically effective amount of GA101;

in the manufacture of a medicament for the treatment of a hematological malignancy in an individual in need thereof, wherein

the therapeutically effective amount of ibrutinib is 420 mg/day or 560 mg/day; and

the ibrutinib and the GA101 are in separate dosage forms.

[0003b] In another aspect, there is proviced use of a combination of:

a therapeutically effective amount of ibrutinib; and

a therapeutically effective amount of GA101;

in the manufacture of a medicament for the treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) in an individual in need thereof, wherein

the therapeutically effective amount of ibrutinib is 420 mg/day; and

the ibrutinib and the GA101 are in separate dosage forms.

[0003c] In another aspect, there is provided a kit for treating a hematological malignancy in an individual, wherein the kit comprises:

(a) ibrutinib; and

(b) GA101; wherein

the therapeutically effective amount of ibrutinib is 420 mg/day or 560 mg/day; and

the ibrutinib and the GA101 are in separate dosage forms.

[0003d] In another aspect, there is provided a kit for treating chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) in an individual, wherein the kit comprises:

(a) ibrutinib; and

(b) GA101; wherein

the therapeutically effective amount of ibrutinib is 420 mg/day; and

the ibrutinib and the GA101 are in separate dosage forms.

[0004] Disclosed herein, in certain examples, is a method for treating a hematological malignancy in an individual in need thereof, comprising: (a) administering to the individual a first treatment comprising an amount of an irreversible Btk inhibitor sufficient to mobilize a plurality of cells from the malignancy; (b) analyzing the mobilized plurality of cells in a sample obtained from the individual; and (c) administering a second treatment to the individual. 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 a B-cell malignancy. In some examples, the hematological malignancy is a leukemia, lymphoproliferative disorder, or myeloid disorder. 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 is a method further

comprises administering the second treatment 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 treatment 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 the second treatment 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 the second treatment after the number of mobilized plurality of cells in the peripheral blood increases as compared to the number before administration of the Btk inhibitor. In some examples, administering the second treatment 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 the second treatment 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, 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: 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 the second treatment based on the biomarker profile. In some examples, the method further comprises predicting the efficacy of the second treatment 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, Waldenström'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 acute or chronic myelogenous (or myeloid) leukemia, myelodysplastic syndrome, 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 irreversible Btk inhibitor covalently binds to Cys 481 of Btk. In some examples, the irreversible Btk inhibitor is a compound of (A), (A1), (B), (B1), (C), (C1), (D), (D1), (E) or (F). In some examples, the irreversible Btk inhibitor is a compound of Formula (D). 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 (i.e. PCI-32765/ibrutinib). In some examples, the second treatment comprises lenalidomide. In some examples, the second treatment comprises bortezomib. In some examples, the second treatment comprises sorafenib. In some examples, the second treatment comprises gemcitabine. In some examples, the second treatment comprises dexamethasone. In some examples, the second treatment comprises bendamustine. In some examples, the second treatment comprises R-406. In some examples, the second treatment comprises taxol. In some examples, the second treatment comprises vincristine. In some examples, the second treatment comprises doxorubicin. In some examples, the second treatment comprises temsirolimus. In some examples, the second treatment comprises carboplatin. In some examples, the second treatment comprises ofatumumab. In some examples, the second treatment comprises rituximab. In some examples, the second treatment comprises GA101. In some examples, the second treatment comprises R-ICE (ifosfamide, carboplatin, etoposide). In some examples, the method comprises using an analytical instrument to analyze the mobilized plurality of cells in a sample obtained from the individual. In some examples, the absolute lymphocyte count in the peripheral blood of the individual increases by at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 125% 150%, 175%, or 200% following administration of an irreversible Btk inhibitor to the individual. In some examples, the absolute lymphocyte count in the peripheral blood of the individual increases by at least about 10%-50% following administration of an irreversible Btk inhibitor to the individual. In some examples, the mobilized cells have decreased expression of CD38 and CXCR4. In some examples, the mobilized cells are CD19+CD5+ cells.

[0005] Disclosed herein, in certain examples, is a method for treating a hematological malignancy in an individual in need thereof, comprising administering to the individual an anti-cancer treatment, wherein the individual is identified as having an increased

mobilization of a plurality of cells from the malignancy following administration of an irreversible Btk inhibitor to the individual. In some examples, the irreversible Btk inhibitor covalently binds to Cys 481 of Btk. In some examples, the irreversible Btk inhibitor is a compound of (A), (A1), (B), (B1), (C), (C1), (D), (D1), (E) or (F). In some examples, the irreversible Btk inhibitor is a compound of Formula (D). 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 (PCI-32765/ibrutinib). In some examples, the hematological malignancy is a B-cell malignancy. In some examples, the hematological malignancy is a leukemia, lymphoproliferative disorder, or myeloid disorder. In some examples, the hematological malignancy is a non-Hodgkin's lymphoma. In some examples, the hematological malignancy is a chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, non-CLL/SLL lymphoma, follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), Waldenstrom's macroglobulinemia, multiple myeloma (MM), marginal zone lymphoma, Burkitt's lymphoma, non-Burkitt high grade B cell lymphoma, extranodal marginal zone B cell lymphoma, acute or chronic myelogenous (or myeloid) leukemia, myelodysplastic syndrome, 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 mobilized cells are myeloid cells or lymphoid cells. In some examples, the individual has a higher peripheral blood concentration of mobilized cells following administration of the Btk inhibitor as compared to the concentration before administration of the Btk inhibitor. In some examples, the second treatment is administered after the peripheral blood concentration of the mobilized plurality of cells has increased for a predetermined length of time. In some examples, identification of cell mobilization is based on detection of the presence, expression or level of expression of one or more biomarkers. 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 second treatment comprises lenalidomide, bortezomib, sorafenib, gemcitabine, dexamethasone, bendamustine, R-406, taxol, vincristine, doxorubicin, temsirolimus, carboplatin, ofatumumab, rituximab, GA101, R-ICE (ifosfamide, carboplatin, etoposide), R-CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone), BR (bendamustine and rituximab), FCR (fludarabine,

cyclophosphamide, and rituximab) or any combination thereof. In some examples, the absolute lymphocyte count in the peripheral blood of the individual increases by at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 125% 150%, 175%, or 200% following administration of an irreversible Btk inhibitor to the individual. In some examples, the absolute lymphocyte count in the peripheral blood of the individual increases by at least about 10%-50% following administration of an irreversible Btk inhibitor to the individual. In some examples, the mobilized cells have decreased expression of CD38 and CXCR4. In some examples, the mobilized cells are CD19+CD5+ cells.

[0006] Disclosed herein, in certain examples, is a method for treating an indolent hematological malignancy in an individual in need thereof, comprising: (a) administering to the individual a first treatment comprising an amount of an irreversible Btk inhibitor sufficient to mobilize a plurality of cells from the indolent hematological malignancy; (b) analyzing the mobilized plurality of cells in a sample obtained from the individual; and (c) administering a second treatment to the individual. 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 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 the second treatment 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 treatment 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 the second treatment 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 the second treatment after the number of mobilized plurality of cells in the peripheral blood increases as compared to the number before administration of the Btk inhibitor. In some examples, administering the second treatment 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 the second treatment 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, 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: 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 the second treatment based on the biomarker profile. In some examples, the method further comprises predicting the efficacy of the second treatment based on the biomarker profile. In some examples, the irreversible Btk inhibitor covalently binds to Cys 481 of Btk. In some examples, the irreversible Btk inhibitor is a compound of (A), (A1), (B), (B1), (C), (C1), (D), (D1), (E) or (F). In some examples, the irreversible Btk inhibitor is a compound of Formula (D). 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 (i.e. PCI-32765/ibrutinib). In some examples, the second treatment comprises lenalidomide. In some examples, the second treatment comprises rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone (R-CHOP). In some examples, the second treatment comprises temsirolimus. In some examples, the method comprises using an analytical instrument to analyze the mobilized plurality of cells in a sample obtained from the individual. In some examples, the absolute lymphocyte count in the peripheral blood of the individual increases by at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 125% 150%, 175%, or 200% following administration of an irreversible Btk inhibitor to the individual. In some examples, the absolute lymphocyte count in the peripheral blood of the individual increases by at least about 10%-50% following administration of an irreversible Btk inhibitor to the individual. In some examples, the mobilized cells have decreased expression of CD38 and CXCR4. In some examples, the mobilized cells are CD19+CD5+ cells.

[0007] Disclosed herein, in certain examples, is a method for treating a non-Hodgkin's lymphoma in an individual in need thereof, comprising: (a) administering to the individual a first treatment comprising an amount of an irreversible Btk inhibitor sufficient to mobilize a plurality of cells from the non-Hodgkin's lymphoma; (b) analyzing the mobilized plurality of cells in a sample obtained from the individual; and (c) administering a second

treatment to the individual. 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 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 the second treatment 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 treatment 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 the second treatment 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 the second treatment after the number of mobilized plurality of cells in the peripheral blood increases as compared to the number before administration of the Btk inhibitor. In some examples, administering the second treatment 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 the second treatment 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, 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: 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 the second treatment based on the biomarker profile. In some examples, the method further comprises predicting the efficacy of the second treatment based on the biomarker profile. In some examples, the irreversible

Btk inhibitor covalently binds to Cys 481 of Btk. In some examples, the irreversible Btk inhibitor is a compound of (A), (A1), (B), (B1), (C), (C1), (D), (D1), (E) or (F). In some examples, the irreversible Btk inhibitor is a compound of Formula (D). 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 (i.e. PCI-32765/ibrutinib). In some examples, the second treatment comprises bortezomib. In some examples, the second treatment comprises bendamustine and rituximab (BR). In some examples, the method comprises using an analytical instrument to analyze the mobilized plurality of cells in a sample obtained from the individual. In some examples, the absolute lymphocyte count in the peripheral blood of the individual increases by at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 125% 150%, 175%, or 200% following administration of an irreversible Btk inhibitor to the individual. In some examples, the absolute lymphocyte count in the peripheral blood of the individual increases by at least about 10%-50% following administration of an irreversible Btk inhibitor to the individual. In some examples, the mobilized cells have decreased expression of CD38 and CXCR4. In some examples, the mobilized cells are CD19+CD5+ cells.

[0008] Disclosed herein, in certain examples, is a method for treating a diffuse large b-cell lymphoma (DLBCL) in an individual in need thereof, comprising: (a) administering to the individual a first treatment comprising an amount of an irreversible Btk inhibitor sufficient to mobilize a plurality of cells from the DLBCL; (b) analyzing the mobilized plurality of cells in a sample obtained from the individual; and (c) administering a second treatment to the individual. 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 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 the second treatment 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 treatment 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 the second treatment 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 the second treatment after the number of mobilized plurality of cells in the peripheral blood increases as compared to the number before administration of the Btk inhibitor. In some examples, administering the second treatment 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 the second treatment 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, 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: 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 the second treatment based on the biomarker profile. In some examples, the method further comprises predicting the efficacy of the second treatment based on the biomarker profile. In some examples, the irreversible Btk inhibitor covalently binds to Cys 481 of Btk. In some examples, the irreversible Btk inhibitor is a compound of (A), (A1), (B), (B1), (C), (C1), (D), (D1), (E) or (F). In some examples, the irreversible Btk inhibitor is a compound of Formula (D). 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 (i.e. PCI-32765/ibrutinib). In some examples, the second treatment comprises bortezomib. In some examples, the second treatment comprises lenalidomide. In some examples, the second treatment comprises rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone (R-CHOP). In some examples, the second treatment comprises temsirolimus. In some examples, the DLBCL is DLBCL, ABC subtype (ABC-DLBCL). In some examples, the DLBCL is DLBCL, GCB subtype (GCB-DLBCL). In some examples, the method comprises using an analytical instrument to analyze the mobilized plurality of cells in a sample obtained from the individual. In some examples, the absolute lymphocyte count in the peripheral blood of the individual increases by at least about 10%, 20%, 30%, 40%, 50%,

60%, 70%, 80%, 90%, 100%, 125% 150%, 175%, or 200% following administration of an irreversible Btk inhibitor to the individual. In some examples, the absolute lymphocyte count in the peripheral blood of the individual increases by at least about 10%-50% following administration of an irreversible Btk inhibitor to the individual. In some examples, the mobilized cells have decreased expression of CD38 and CXCR4. In some examples, the mobilized cells are CD19+CD5+ cells.

[0009] Disclosed herein, in certain examples, is a method for treating a follicular lymphoma (FL) in an individual in need thereof, comprising: (a) administering to the individual a first treatment comprising an amount of an irreversible Btk inhibitor sufficient to mobilize a plurality of cells from the follicular lymphoma; (b) analyzing the mobilized plurality of cells in a sample obtained from the individual; and (c) administering a second treatment to the individual. 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 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 the second treatment 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 treatment 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 the second treatment 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 the second treatment after the number of mobilized plurality of cells in the peripheral blood increases as compared to the number before administration of the Btk inhibitor. In some examples, administering the second treatment 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 the second treatment 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, 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: 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 the second treatment based on the biomarker profile. In some examples, the method further comprises predicting the efficacy of the second treatment based on the biomarker profile. In some examples, the irreversible Btk inhibitor covalently binds to Cys 481 of Btk. In some examples, the irreversible Btk inhibitor is a compound of (A), (A1), (B), (B1), (C), (C1), (D), (D1), (E) or (F). In some examples, the irreversible Btk inhibitor is a compound of Formula (D). 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 (i.e. PCI-32765/ibrutinib). In some examples, the second treatment comprises lenalidomide. In some examples, the second treatment comprises rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone (R-CHOP). In some examples, the second treatment comprises temsirolimus. In some examples, the method comprises using an analytical instrument to analyze the mobilized plurality of cells in a sample obtained from the individual. In some examples, the absolute lymphocyte count in the peripheral blood of the individual increases by at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 125% 150%, 175%, or 200% following administration of an irreversible Btk inhibitor to the individual. In some examples, the absolute lymphocyte count in the peripheral blood of the individual increases by at least about 10%-50% following administration of an irreversible Btk inhibitor to the individual. In some examples, the mobilized cells have decreased expression of CD38 and CXCR4. In some examples, the mobilized cells are CD19+CD5+ cells.

[0010] Disclosed herein, in certain examples, is a method for treating a CLL or SLL in an individual in need thereof, comprising: (a) administering to the individual a first treatment comprising an amount of an irreversible Btk inhibitor sufficient to mobilize a plurality of cells from the CLL or SLL; (b) analyzing the mobilized plurality of cells in a sample obtained from the individual; and (c) administering a second treatment to the individual. 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 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 the second treatment 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 treatment 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 the second treatment 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 the second treatment after the number of mobilized plurality of cells in the peripheral blood increases as compared to the number before administration of the Btk inhibitor. In some examples, administering the second treatment 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 the second treatment 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, 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: 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 the second treatment based on the biomarker profile. In some examples, the method further comprises predicting the efficacy of the second treatment based on the biomarker profile. In some examples, the irreversible Btk inhibitor covalently binds to Cys 481 of Btk. In some examples, the irreversible Btk inhibitor is a compound of (A), (A1), (B), (B1), (C), (C1), (D), (D1), (E) or (F). In some

examples, the irreversible Btk inhibitor is a compound of Formula (D). In some examples, wherein 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 (i.e. PCI-32765/ibrutinib). In some examples, the second treatment comprises lenalidomide. In some examples, the second treatment comprises bendamustine and rituximab (BR). In some examples, the second treatment comprises fludarabine, cyclophosphamide, and rituximab (FCR). In some examples, the second treatment comprises ofatumumab. In some examples, the second treatment comprises rituximab. In some examples, the method comprises using an analytical instrument to analyze the mobilized plurality of cells in a sample obtained from the individual. In some examples, the absolute lymphocyte count in the peripheral blood of the individual increases by at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 125% 150%, 175%, or 200% following administration of an irreversible Btk inhibitor to the individual. In some examples, the absolute lymphocyte count in the peripheral blood of the individual increases by at least about 10%-50% following administration of an irreversible Btk inhibitor to the individual. In some examples, the mobilized cells have decreased expression of CD38 and CXCR4. In some examples, the mobilized cells are CD19+CD5+ cells.

[0011] Disclosed herein, in certain examples, is a method for treating a mantel cell lymphoma in an individual in need thereof, comprising: (a) administering to the individual a first treatment comprising an amount of an irreversible Btk inhibitor sufficient to mobilize a plurality of cells from the mantel cell lymphoma; (b) analyzing the mobilized plurality of cells in a sample obtained from the individual; and (c) administering a second treatment to the individual. 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 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 the second treatment 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 treatment 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 the second treatment 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 the second treatment after the number of mobilized plurality of cells in the peripheral blood increases as compared to the number before administration of the Btk inhibitor. In some examples, administering the second treatment 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 the second treatment 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, 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: 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 the second treatment based on the biomarker profile. In some examples, the method further comprises predicting the efficacy of the second treatment based on the biomarker profile. In some examples, the irreversible Btk inhibitor covalently binds to Cys 481 of Btk. In some examples, the irreversible Btk inhibitor is a compound of (A), (A1), (B), (B1), (C), (C1), (D), (D1), (E) or (F). In some examples, the irreversible Btk inhibitor is a compound of Formula (D). 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 (i.e. PCI-32765/ibrutinib). In some examples, the second treatment comprises temsirolimus. In some examples, the method comprises using an analytical instrument to analyze the mobilized plurality of cells in a sample obtained from the individual. In some examples, the absolute lymphocyte count in the peripheral blood of the individual increases by at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 125% 150%, 175%, or 200% following administration of an irreversible Btk inhibitor to the individual. In some examples, the absolute lymphocyte count in the peripheral blood of the individual increases by at least about 10%-50% following administration of an irreversible Btk inhibitor to the individual. In some examples, the mobilized cells have decreased expression of CD38 and CXCR4. In some examples, the mobilized cells are CD19+CD5+ cells.

[0012] Disclosed herein, in certain examples, is a method for treating a Waldenstrom's macroglobulinemia in an individual in need thereof, comprising: (a) administering to the individual a first treatment comprising an amount of an irreversible Btk inhibitor sufficient to mobilize a plurality of cells from the mantel cell lymphoma; (b) analyzing the mobilized plurality of cells in a sample obtained from the individual; and (c) administering a second treatment to the individual. 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 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 the second treatment 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 treatment 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 the second treatment 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 the second treatment after the number of mobilized plurality of cells in the peripheral blood increases as compared to the number before administration of the Btk inhibitor. In some examples, administering the second treatment 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 the second treatment 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, 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: 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 the second treatment based on the biomarker profile. In some examples, the method further comprises predicting the efficacy of the second treatment based on the biomarker profile. In some examples, the irreversible Btk inhibitor covalently binds to Cys 481 of Btk. In some examples, the irreversible Btk inhibitor is a compound of (A), (A1), (B), (B1), (C), (C1), (D), (D1), (E) or (F). In some examples, the irreversible Btk inhibitor is a compound of Formula (D). 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 (i.e. PCI-32765/ibrutinib). In some examples, the second treatment comprises rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone (R-CHOP). In some examples, the method comprises using an analytical instrument to analyze the mobilized plurality of cells in a sample obtained from the individual. In some examples, the absolute lymphocyte count in the peripheral blood of the individual increases by at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 125% 150%, 175%, or 200% following administration of an irreversible Btk inhibitor to the individual. In some examples, the absolute lymphocyte count in the peripheral blood of the individual increases by at least about 10%-50% following administration of an irreversible Btk inhibitor to the individual. In some examples, the mobilized cells have decreased expression of CD38 and CXCR4. In some examples, the mobilized cells are CD19+CD5+ cells.

[0013] Disclosed herein, in certain examples, is a method for treating a multiple myeloma (MM) in an individual in need thereof, comprising: (a) administering to the individual a first treatment comprising an amount of an irreversible Btk inhibitor sufficient to mobilize a plurality of cells from the MM; (b) analyzing the mobilized plurality of cells in a sample obtained from the individual; and (c) administering a second treatment to the individual. 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 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 the second treatment 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 treatment 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 the second treatment 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 the second treatment after the number of mobilized plurality of cells in the peripheral blood increases as compared to the number before administration of the Btk inhibitor. In some examples, administering the second treatment 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 the second treatment 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, 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: 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 the second treatment based on the biomarker profile. In some examples, the method further comprises predicting the efficacy of the second treatment based on the biomarker profile. In some examples, the irreversible Btk inhibitor covalently binds to Cys 481 of Btk. In some examples, the irreversible Btk inhibitor is a compound of (A), (A1), (B), (B1), (C), (C1), (D), (D1), (E) or (F). In some examples, the irreversible Btk inhibitor is a compound of Formula (D). 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 (i.e. PCI-32765/ibrutinib). In some examples, the second treatment comprises lenalidomide. In some examples, the method comprises using an analytical instrument to analyze the mobilized plurality of cells in a sample obtained from the individual. In some examples, the absolute lymphocyte count in the peripheral blood of the individual increases by at least about 10%, 20%, 30%, 40%, 50%,

60%, 70%, 80%, 90%, 100%, 125% 150%, 175%, or 200% following administration of an irreversible Btk inhibitor to the individual. In some examples, the absolute lymphocyte count in the peripheral blood of the individual increases by at least about 10%-50% following administration of an irreversible Btk inhibitor to the individual. In some examples, the mobilized cells have decreased expression of CD38 and CXCR4. In some examples, the mobilized cells are CD19+CD5+ cells.

[0014] Disclosed herein, in certain examples, is a method for treating a hematological malignancy in an individual in need thereof, comprising: (a) administering to the individual a first treatment comprising an amount of an irreversible Btk inhibitor sufficient to mobilize a plurality of cells from the malignancy; and (b) preparing a biomarker profile for a population of cells isolated from the 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 biomarker expression profile is used to diagnose, determine a prognosis, or create a predictive profile of a hematological malignancy. In some examples, 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 profile indicates if a hematological malignancy involves Btk signaling. In some examples, the biomarker profile indicates if survival of a hematological malignancy involves Btk signaling. In some examples, the biomarker profile indicates that a hematological malignancy does not involve Btk signaling. In some examples, the biomarker profile indicates that survival of a hematological malignancy does not involve Btk signaling. In some examples, the biomarker profile indicates if a hematological malignancy involves BCR signaling. In some examples, the biomarker profile indicates if survival of a hematological malignancy involves BCR signaling. In some examples, the biomarker profile indicates that a hematological malignancy does not involve BCR signaling. In some examples, the biomarker profile indicates that survival of a hematological malignancy does not involve BCR signaling. 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 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 the second

treatment based on the biomarker profile. In some examples, the method further comprises predicting the efficacy of the second treatment based on the biomarker profile.

BRIEF DESCRIPTION OF THE FIGURES

[0015] Figure 1 depicts the role of Btk activity in a number of processes in a chronic lymphocytic leukemia (CLL) cell that contribute to the pathogenesis of the disease.

[0016] Figure 2 depicts the lymph node (LN) response in a patient suffering from CLL. Left panel depicts LN prior to treatment with an irreversible Btk inhibitor (PCI-32765) and Right panel depicts LN post-treatment with an irreversible Btk inhibitor (PCI-32765).

[0017] Figure 3 depicts the percentage change in tumor burden over the course treatment in a clinical trial involving administration of an irreversible Btk inhibitor (PCI-32765) in relapsed refractory (R/R) CLL/SLL patients at 420 mg/day or 840 mg/day.

[0018] Figure 4 presents the absolute lymphocyte count (ALC) and the sum of the product of the diameters (SPD) of the lymph nodes (LN) during the course of treatment with an irreversible Btk inhibitor (PCI-32765) in treatment naïve (dotted line) or R/R CLL/SLL (solid line) patients administered 420 mg/day PCI-32765.

[0019] Figure 5 presents the cumulative best response in treatment naïve patients administered 420 mg/day PCI-32765 over successive cycles of treatment. CR= complete response. PR=partial response.

[0020] Figure 6 presents the cumulative best response in R/R CLL/SLL patients administered 420 mg/day PCI-32765 over successive cycles of treatment. CR= complete response. PR=partial response.

[0021] Figure 7 presents a comparison between the cumulative best response in R/R CLL/SLL patients (RR) versus treatment naïve (TN) patients administered 420 mg/day PCI-32765 over successive cycles of treatment. CR= complete response. PR=partial response.

[0022] Figure 8 depicts the absolute lymphocyte count (ALC)/109 L vs. Cycle Day after administering a Btk inhibitor to individuals with follicular lymphoma who achieved complete or partial response (CR/PR). The Y Axis shows the Absolute Lymphocyte Counts (ALC) at each time point by cycle number and day in the X axis. All Patients (except Pt 32009) were treated on schedule of 4 weeks on treatment followed by one week off. Thus, day1 of each cycle follows one week off drug for these patients. Note the increases of ALC during most cycles of most patients, and the fall of ALC at the beginning of subsequent cycles. This pattern is often blunted in later cycles as patients responded to treatment. Patient 32009 received treatment without interruption and did not show this cyclic pattern, but did show an increase at Cycle 1, day15, and gradual increases during Cycles 2 to 5.

WHAT IS CLAIMED IS:

1. Use of a combination of:

a therapeutically effective amount of ibrutinib; and

a therapeutically effective amount of GA101;

in the manufacture of a medicament for the treatment of a hematological malignancy in an individual in need thereof, wherein

the therapeutically effective amount of ibrutinib is 420 mg/day or 560 mg/day; and

the ibrutinib and the GA101 are in separate dosage forms.

2. Use of a combination of:

a therapeutically effective amount of ibrutinib; and

a therapeutically effective amount of GA101;

in the manufacture of a medicament for the treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) in an individual in need thereof, wherein

the therapeutically effective amount of ibrutinib is 420 mg/day; and

the ibrutinib and the GA101 are in separate dosage forms.

3. The use according to claim 1, wherein the hematological malignancy is a B-cell malignancy.

4. The use according to claim 3, wherein the hematological malignancy is mantle cell lymphoma and the therapeutically effective amount of ibrutinib is 560 mg/day.

5. The use according to claim 3, wherein the hematological malignancy is Waldenström's macroglobulinemia and the therapeutically effective amount of ibrutinib is 420 mg/day.

6. The use according to claim 3, wherein the hematological malignancy is diffuse large B-cell lymphoma (DLBCL) and the therapeutically effective amount of ibrutinib is 560 mg/day.

7. The use according to claim 3, wherein the hematological malignancy is follicular lymphoma (FL) and the therapeutically effective amount of ibrutinib is 560 mg/day.

8. A kit for treating a hematological malignancy in an individual, wherein the kit comprises:

(a) ibrutinib; and

(b) GA101; wherein

the therapeutically effective amount of ibrutinib is 420 mg/day or 560 mg/day; and

the ibrutinib and the GA101 are in separate dosage forms.

9. A kit for treating chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) in an individual, wherein the kit comprises:

(a) ibrutinib; and

(b) GA101; wherein

the therapeutically effective amount of ibrutinib is 420 mg/day; and

the ibrutinib and the GA101 are in separate dosage forms.

10. The kit of claim 8, wherein the kit further comprises

(c) an agent for detecting the presence, expression, or level of expression of a biomarker selected from CXCR4, Ki67, MDC, MIP-1β, CXCL13, CXCL17, IL-10, MIP-1α, CCL17, and CCL21.

11. The kit according to claim 8, wherein the hematological malignancy is a B-cell malignancy.

12. The kit according to claim 11, wherein the hematological malignancy is mantle cell lymphoma and the therapeutically effective amount of ibrutinib is 560 mg/day.

13. The kit according to claim 11, wherein the hematological malignancy is Waldenström's macroglobulinemia and the therapeutically effective amount of ibrutinib is 420 mg/day.

14. The kit according to claim 11, wherein the hematological malignancy is diffuse large B-cell lymphoma (DLBCL) and the therapeutically effective amount of ibrutinib is 560 mg/day.

15. The kit according to claim 11, wherein the hematological malignancy is follicular lymphoma (FL) and the therapeutically effective amount of ibrutinib is 560 mg/day.