COMBINATION OF ANTI-CD20 ANTIBODY, P13 KINASE-DELTA SELECTIVE INHIBITOR, AND BTK INHIBITOR TO TREAT B-CELL PROLIFERATIVE DISORDERS

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] The present invention relates generally to the field of cancer therapy. More particularly, the present invention relates to methods and kits for inhibiting proliferation of a B-cell population and treating B-cell proliferative disorders, such as hematological cancers, by administering to a subject a combination of agents comprising: (i) at least one inhibitor of P13 kinase (PI3K)-delta; (ii) at least one anti-CD20 antibody; and (iii) at least one inhibitor of Bruton's tyrosine kinase (BTK).

[0002]

Background Art

Despite more than a century of dedicated scientific and clinical research, curing cancer remains one of the biggest medical challenges to date. Cancer treatments have mainly relied on the combination of surgery, radiotherapy, and/or cytotoxic chemotherapies. Within the last decade, however, targeted cancer therapies have opened a new era in the field of oncology. Targeted cancer therapies are drugs designed to interfere with specific molecules necessary for tumor growth and progression; they are broadly classified into monoclonal antibodies (mAbs) or small molecules. Some examples of targeted therapies include monoclonal antibodies to CD20 (e.g., rituximab/Rituxan® for treating lymphomas), CD52 (e.g., alemtuzumab/Campath®), VEGF (e.g., bevacizumab/Avastin®), HER2 (e.g., trastuzumab/Herceptin® for treating Her2+ breast and stomach cancers), EGFR (e.g., cetuximab/Erbitux® for treating colorectal cancer), CTLA-4 (e.g., ipilimumab/Yervoy® for treating melanoma), and PD-1 (e.g., MDX-1106, CT-011). Small molecule therapies target dysregulated pathways of cancer cells, e.g., RAS, RAF, PI3K, MEK, JAK, STAT, and BTK.

[0003] While effective B-cell cancer therapies exist (e.g., Rituxan®), suboptimal response and/or resistance to one or more therapeutic agents have remained a challenge.

Accordingly, there is a need in the art for more effective, safe, and durable combination therapies for the treatment of B-cell proliferative diseases, such as B-cell malignancies.

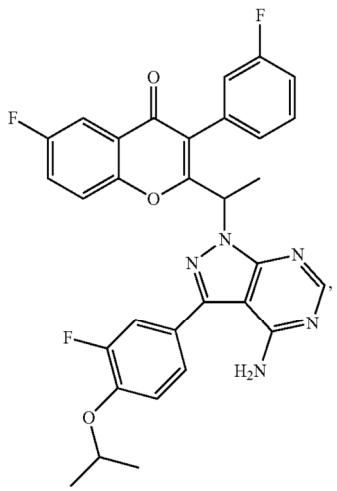
SUMMARY

[0004] The combination treatment described herein is suitable for treating or delaying progression of B-cell proliferative disorders in a subject, such as hematological malignancies.

[0005] Disclosed are methods of inhibiting proliferation of a B-cell population comprising (a) administering to the B-cell population a combination of agents, in therapeutically effective amounts, said combination of agents comprising: (i) at least one PI3K-delta selective inhibitor; (ii) at least one anti-CD20 antibody; and (iii) at least one inhibitor of Bruton's tyrosine kinase (BTK); and (b) inhibiting proliferation of said B-cell population.

[0005a] In one aspect, the present disclosure refers to use of a therapeutic combination of agents comprising (i) at least one PI3K-delta selective inhibitor represented by Formula A, a stereoisomer thereof, a pharmaceutically acceptable salt, or solvate, thereof:

(A)



selected from
(RS)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one; or
(S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyI)-4H-chromen-4-one; (ii) at least one anti-CD20 antibody or an antigen-binding fragment thereof, wherein said anti-CD20 antibody is ublituximab or an anti-CD20 antibody that binds to the same epitope as ublituximab; and (iii) at least one inhibitor of Bruton's tyrosine kinase (BTK); in the manufacture of a medicament for the treatment of chronic lymphocytic leukemia (CLL), marginal zone lymphoma (MZL) or non-Hodgkin's lymphoma (NHL) in a subject, wherein therapeutically effective amounts of said agents are to be administered to inhibit proliferation of B-cells and thereby reduce said subject's baseline disease burden by at least 50% by the first efficacy assessment.

[0005b] In another aspect, the present disclosure refers to use of a therapeutic combination of agents comprising:

(i) at least one PI3K-delta selective inhibitor;

(ii) at least one anti-CD20 antibody or an antigen-binding fragment thereof; and

(iii) at least one Bruton's tyrosine kinase (BTK) inhibitor;

in the manufacture of a medicament to treat a disease or disorder associated with excessive B-cell proliferation in a subject, wherein therapeutically effective amounts of said agents are to be administered to deplete said B-cells by promoting apoptosis, promoting cell-cycle arrest, blocking the B-cell receptor (BCR) signaling pathway, or any combination thereof.

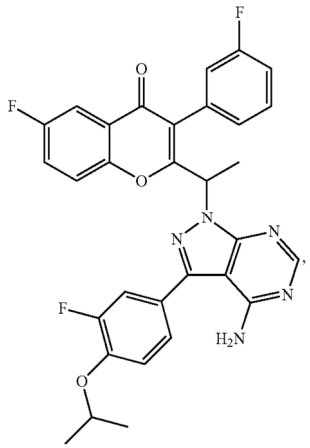
[0006] In some examples, the PI3K-delta inhibitor is selected from the group consisting of TGR-1202 (also known as umbralisib), idelalisib, duvelisib (IPI-145), ACP-319; INCB-50465; and ME-401.

[0007] Disclosed are methods of inhibiting proliferation of a B-cell population comprising,

(a) administering to said B-cell population a combination of agents, in therapeutically effective amounts, said combination of agents comprising:

(i) at least one PI3K delta selective inhibitor of Formula A, or a stereoisomer thereof, or a pharmaceutically acceptable salt, solvate, or prodrug thereof:

(A)



.

selected from one or more of,

(RS)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one;

(S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyI)-4H-chromen-4-one; and

(R)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one;

(ii) at least one anti-CD20 antibody, wherein at least one anti-CD20 antibody is ublituximab or an anti-CD20 antibody or antibody fragment that binds to the same epitope as ublituximab; and

(iii) at least one inhibitor of Bruton's tyrosine kinase (BTK); and

(b) inhibiting proliferation of said B-cell population.

[0008] In some examples, the PI3K-delta inhibitor of Formula A is (S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one.

[0009] In some examples, the PI3K-delta inhibitor of Formula A is (S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one p-toluenesulfonic acid (PTSA) salt (also known as TGR-1202).

[0010] In some examples, the method of inhibiting proliferation of a B-cell population comprises depleting B-cells. In some examples, such a method is used on a patient whose cancer has relapsed.

[0011] In some examples, the method of inhibiting proliferation of a B-cell population comprises promoting apoptosis of said B-cells.

[0012] In some examples, the method of inhibiting proliferation of a B-cell population comprises promoting cell-cycle arrest.

[0013] In some examples, the method of inhibiting proliferation of a B-cell population comprises blocking the B-cell receptor (BCR) signaling pathway.

[0014] In some examples, the PI3K-delta inhibitor is administered daily at a dosage from: about 200 mg to about 1200 mg, about 400 mg to about 1000 mg, about 400 mg to about 800 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, or about 1200 mg.

[0015] In some examples, TGR-1202 is administered at a dose of about 400 mg to about 1200 mg per day. In some examples, the TGR-1202 is administered at a dose of about 400 mg per day. In some examples, the TGR-1202 is administered at a dose of about 600 mg per day. In some examples, the TGR-1202 is administered at a dose of about 800 mg per day.

[0016] In some examples, the PI3K-delta inhibitor is formulated for oral administration. In some examples, the PI3K-delta inhibitor is TGR-1202 and it is formulated for oral administration. In some examples, TGR-1202 is administered in a fed-state.

[0017] In some examples, the anti-CD20 antibody is glycoengineered, exhibits a low fucose content in its Fc region, or is antibody-dependent cellular cytotoxicity (ADCC)-optimized.

[0018] In some examples, the anti-CD20 antibody is ublituximab (also known as TG-1101 and UTX). In some examples, the ublituximab comprises the VH CDR1, CDR2, and CDR3 region of sequences SEQ ID NOS: 1, 2, and 3, and the VL CDR1, CDR2, and CDR3 region of sequences SEQ ID NOS: 6, 7, and 8. In some examples, the ublituximab comprises the VH of SEQ ID NO: 4 and the VL of SEQ ID NO: 9.

[0019] In some examples, the ublituximab is administered at a dose from: about 450 mg to about 1200 mg, about 600 to about 1200 mg, about 600 to about 1000 mg, about 600 to about 900 mg, about 600 mg, about 700 mg, about 800 mg, or about 900 mg.

[0020] Ublituximab may be administered about twice every week, about once every 1 to 9 weeks, about once every week, about once every 2 weeks, about once every 3 weeks,

about once every 4 weeks, about once every 5 weeks, about once every 6 weeks, about once every 7 weeks, about once every 8 week, or about once every 9 weeks. One skilled in the art will appreciate that the dosage of ublituximab and/or frequency of administering ublituximab may change during the course of therapy (lowered or increased) depending upon the patient's clinical response, side effects, etc.

[0021] In some examples, the ublituximab is administered at a dose of about 900 mg. In some examples, the ublituximab is administered intravenously. Preferably, the ublituximab is administered by intravenous infusion.

[0022] In some examples, the BTK inhibitor is selected from the group consisting of 1-[(3R)-3-[4-Amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]piperidin-1-yl]prop-2-en-1-one (Imbruvica®, ibrutinib, or PCI-32765); 1-(R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]piperidin-1-yl]-2,3,-dihydroxypropan-1-one (PCI-45227); 4-{8-Amino-3-[(2S)-1-(2-butynoyl)-2-pyrrolidinyl]imidazo[1,5-a]pyrazin-1-yl}-N-(2-pyridinyl)benzamide (acalabrutinib or ACP-196); (R)-N-(3-(6-((4-(1,4-dimethyl-3-oxopiperazin-2-yl)phenyl)amino)-4-methyl-5-oxo-4,5-dihydropyrazin-2-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide (GDC-0834); (S)-9-(1-acryloylpiperidin-3-yl)-6-amino-7-(4-phenoxyphenyl)-7,9-dihydro-8H-purin-8-one (ONO-4059 or GS-4059); 6-cyclopropyl-8-fluoro-2-[2-(hydroxymethyl)-3-[1-methyl-5-[[5-(4-methylpiperazin-1-yl)pyridin-2-yl]amino]-6-oxopyridin-3-yl]phenyl]isoquinolin-1-one (RN-486); N-(3-((5-fluoro-2-((4-(2-methoxyethoxy)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide (spebrutinib or AVL-292 or CC-292); SNS-062, as developed by Sunesis Pharmaceuticals and Biogen, *see*, Binnerts, M.E. *et al*., 2015 AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, Boston, MA, November 8, 2015*);* N-(3-((2-((4-(4-methylpiperazin-1-yl)phenyl)amino)thieno[3,2-d]pyrimidin-4-yl)oxy)phenyl)acrylamide (HM-71224); 4-(tert-butyl)-N-(3-(8-(phenylamino)imidazo[1,2-a]pyrazin-6-yl)phenyl)benzamide (CGI-560); N-[3-[4,5-dihydro-4-methyl-6-[[4-(4-morpholinylcarbonyl)phenyl]amino]-5-oxopyrazinyl]-2-methylphenyl]-4-(1,1-dimethylethyl)-benzamide (CGI-1746); 4-(4-((4-((3-acrylamidophenyl)amino)-5-fluoropyrimidin-2-yl)amino)phenoxy)-N-methylpicolinamide (CNX-774); 7-benzyl-1-(3-(piperidin-1-yl)propyl)-2-(4-(pyridin-4-yl)phenyl)-1H-imidazo[4,5-g]quinoxalin-6(5H)-one (CTA-056),; α-Cyano-β-hydroxy-β-

[0023] In some examples, the BTK inhibitor is 1-[(3*R*)-3-[4-Amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidin-1-yl]prop-2-en-1-one (ibrutinib).

[0024] In some examples, the BTK inhibitor is 4-{8-Amino-3-[(2*S*)-1-(2-butynoyl)-2-pyrrolidinyl]imidazo[1,5-a]pyrazin-1-yl}-*N*-(2-pyridinyl)benzamide (acalabrutinib or ACP-196).

[0025] In some examples, the ibrutinib is administered once daily at a dosage from: about 200 to about 800 mg, about 400 to about 600 mg, about 400 mg, about 420 mg, about 440 mg, about 480 mg, about 500 mg, about 520 mg, about 540 mg, about 560 mg, about 580 mg, or about 600 mg.

[0026] In some examples, the ibrutinib is administered once daily at a dosage of about 420 mg or about 560 mg per day. In some examples, the ibrutinib is administered once daily at a dosage of about 420 mg per day. In some examples, the ibrutinib is administered once daily at a dosage of about 560 mg per day.

[0027] In some examples, ibrutinib is administered orally.

[0028] In some examples, the B-cell population whose proliferation is to be inhibited is in a human subject. In some examples, the human subject has a disease or disorder associated with excessive B-cell proliferation. In some examples, the disease associated with excessive B-cell proliferation is cancer. In some examples, a human subject has cancer. In some examples, the cancer is a B-cell hematological malignancy. In certain examples, the B-cell hematological malignancy is lymphoma or leukemia.

[0029] In some examples, the B-cell hematological malignancy is selected from the group consisting of acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), acute monocytic leukemia (AMoL), chronic lymphocytic leukemia (CLL), high-risk CLL, small lymphocytic lymphoma (SLL), high-risk SLL, multiple myeloma (MM), non-Hodgkin's lymphoma (NHL), mantle cell lymphoma (MCL), follicular lymphoma (FL), Waldenstrom's macroglobulinemia (WM), diffuse large B-cell lymphoma (DLBCL), marginal zone lymphoma (MZL), Burkitt's lymphoma (BL), hairy cell leukemia (HCL), and Richter's transformation.

[0030] In some examples, the B-cell hematological malignancy is selected from the group consisting of chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma

(SLL), non-Hodgkin's lymphoma (NHL), mantle cell lymphoma (MCL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), and marginal zone lymphoma (MZL).

[0031] In some examples, the hematological malignancy is selected from the group consisting of Burkitt's lymphoma, non-Burkitt high grade B cell lymphoma, primary mediastinal B-cell lymphoma (PMBL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, B cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, plasma cell myeloma, plasmacytoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, Hodgkin's lymphoma, or lymphomatoid granulomatosis.

[0032] In some examples, the cancer overexpresses CD20.

[0033] In some examples, the cancer is refractory to chemotherapy.

[0034] In some examples, the cancer is refractory to any agent described herein, *i.e.*, an anti-CD20 antibody, a PI3K delta selective inhibitor, or a BTK inhibitor, when said agent was administered individually (i.e., used as a monotherapy). In some examples, the cancer is refractory to non-TGR-1202 PI3K-delta inhibitors.

[0035] In some examples, the cancer is refractory to non-ublituximab anti-CD20 antibodies.

[0036] In some examples, the cancer is refractory to rituximab.

[0037] In some examples, the cancer is refractory to a BTK inhibitor.

[0038] In some examples, the cancer is refractory to ibrutinib.

[0039] In some examples, the cancer has relapsed.

[0040] In some examples, the human subject has one or more genetic mutations selected from the group consisting of 17p del, 11q del, p53, unmutated IgVH together with ZAP-70+ and/or CD38+, and trisomy 12.

[0041] In some examples, the agents (i, ii, and iii) of the methods described herein are administered separately.

[0042] In some examples, the agents (i, ii, and iii) of the methods described herein are administered sequentially, though a particular order (or sequence of administration) is not required. In some examples, the agents (i and iii) of the methods described herein are administered simultaneously or sequentially.

[0043] In some examples, the combination of agents is sequentially administered in an induction, consolidation, and/or maintenance regimen.

[0044] In some examples, two of the agents i, ii, or iii, are administered together in order to induce a partial anti-tumor response, followed by administration of the third agent to enhance the anti-tumor response. In some examples, a complete anti-tumor response (CR) is observed following administration of all agents (e.g., i, ii, and iii, as disclosed herein) to said subject. In some examples, a subject administered any of the methods described herein achieves a complete response with minimal residual disease (MRD).

[0045] In some examples, a subject administered any of the methods described herein achieves a partial reponse (PR) when all three agents are administered in combination. In some examples, a subject administered any of the methods described herein achieves a partial response (PR) or a complete response (CR) that is durable for at least two months.

[0046] In some examples, at least one of the agents i, ii, or iii, is administered in a maintenance therapy in order to keep the B-cell proliferative disorder from returning after successful treatment. In some examples, the agent is administered in maintenance therapy for an extended period of time, e.g., until unmanageable toxicity, or disease progression occurs. In some examples, the maintenance therapy ends when disease progression occurs.

[0047] In some examples, the agents (i and iii) of the methods described herein are contained in the same pharmaceutical composition. In some examples, the pharmaceutical composition is for oral administration.

[0048] In some examples, the methods described herein further comprises administering to the subject at least one additional therapeutic agent for inhibiting B-cell proliferation. In some examples, the at least one additional therapeutic agent is selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, anthracyclines, vinca alkaloids, plant alkaloids, nitrogen mustards, proteasome inhibitors, intercalating antibiotics, growth factor inhibitors, cell-cycle inhibitors, biological response modifiers, anti-hormones, angiogenesis inhibitors, anti-androgens, DNA interactive agents, purine analogues, topoisomerase I inhibitors, topoisomerase II inhibitors, tubulin interacting agents, hormonal agents, thymidilate

synthase inhibitors, non-BTK and non-PI3K-delta tyrosine kinase inhibitors, angiogenesis inhibitors, EGF inhibitors, VEGF inhibitors, CDK inhibitors, SRC inhibitors, c-Kit inhibitors, Her1/2 inhibitors, inhibitors of myc, anti-tumor antibodies, monoclonal antibodies directed against growth factor receptors, protein kinase modulators, radioactive isotopes, immunotherapies, glucocorticoids, and combinations thereof.

[0049] In some examples, the at least one additional therapeutic agent is an anti-cancer agent selected from the group consisting of DNA interactive agents, such as cisplatin or doxorubicin; topoisomerase II inhibitors, such as etoposide; topoisomerase I inhibitors such as CPT-11 or topotecan; tubulin interacting agents, such as paclitaxel, docetaxel or the epothilones (for example ixabepilone), either naturally occurring or synthetic; hormonal agents, such as tamoxifen; thymidilate synthase inhibitors, such as 5-fluorouracil; and anti-metabolites, such as methotrexate; other tyrosine kinase inhibitors such as Iressa and OSI-774; angiogenesis inhibitors; EGF inhibitors; VEGF inhibitors; CDK inhibitors; SRC inhibitors; c-Kit inhibitors; Her1/2 inhibitors and monoclonal antibodies directed against growth factor receptors such as erbitux (EGF) and herceptin (Her2); and other protein kinase modulators. Other anti-cancer agents that could be used in the methods and kits of the disclosure will be known to those skilled in the oncology art.

[0050] In some examples, the at least one additional therapeutic agent is selected from the group consisting of a proteasome inhibitor, Bortezomib (Velcade®), Carfilzomib (PR-171), PR-047, disulfiram, lactacystin, PS-519, eponemycin, epoxomycin, aclacinomycin, CEP-1612, MG-132, CVT-63417, PS-341, vinyl sulfone tripeptide inhibitors, ritonavir, PI-083, (+/-)-7-methylomuralide, (-)-7-methylomuralide, lenalidomide, and combinations thereof.

[0051] In some examples, the additional therapeutic agent is a combination of chemotherapies such as, e.g., "CHOP" (a combination including (i) cyclophosphamide such as cytoxan, (ii) doxorubicin or other topoisomerase II inhibitors such as adriamycin, (iii) vincristine or other vincas such as oncovin; and (iv) a steroid such as hydrocortisone or prednisolone); "R-CHOP" (a combination including rituxan, cyclophosphamide, doxorubicin, vincristine, and prednisone); "ICE" (a combination including ifosfamide, carboplatin, and etoposide); "R-ICE" (a combination including rituxan, ifosfamide,

carboplatin, and etoposide); "R-ACVBP" (a combination of rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone); "DA-EPOCH-R" (a combination of dose-adjusted etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone and rituximab); "R-bendamustine" (a combination of bendamustine and rituximab); "GemOx or R-GemOx" (a combination of gemcitabine and oxaliplatin, with or without rituximab); and "DHAP" (a combination including dexamethasone, cytarabine, and cisplatin).

[0052] In some examples, methods of inhibiting proliferation of a B-cell population are provided, comprising, (a) administering to the B-cell population a combination of agents, in therapeutically effective amounts, said combination of agents comprising: (i) TGR-1202; (ii) ublituximab; and (iii) ibrutinib; and (b) inhibiting proliferation of said B-cell population.

[0053] In some examples, the proliferation of the B-cell population is associated with a hematological malignancy. In some examples, the hematological malignancy is selected from the group consisting of acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), multiple myeloma (MM), non-Hodgkin's lymphoma (NHL), mantle cell lymphoma (MCL), follicular lymphoma (FL), Waldenstrom's macroglobulinemia (WM), diffuse large B-cell lymphoma (DLBCL), marginal zone lymphoma (MZL), Burkitt's lymphoma, hairy cell leukemia (HCL), and Richter's transformation.

[0054] Disclosed is a kit comprising at least one PI3K-delta selective inhibitor, at least one anti-CD20 antibody, and at least one inhibitor of BTK; and (b) instruction for using a PI3K-delta selective inhibitor in combination with an anti-CD20 antibody and an inhibitor of BTK.

[0054a] In another aspect, the present disclosure refers to a kit comprising: (a) a combination of agents (i)-(iii) as described herein; and (b) instructions for using said PI3K-delta selective inhibitor in combination with an anti-CD20 antibody or fragment thereof, and an inhibitor of BTK, as a combined preparation for use in the treatment of chronic lymphocytic leukemia (CLL), marginal zone lymphoma (MZL) or non-Hodgkin’s lymphoma (NHL) in a subject.

[0055] Disclosed is a kit comprising at least one PI3K-delta selective inhibitor of formula A, at least one anti-CD20 antibody, and at least one inhibitor of BTK. In certain examples, other agents that can be used to perform the methods described herein, and combinations thereof, are also included in the kit.

[0056] In some examples, the kit comprises (a) a PI3K-delta selective inhibitor of formula A, as described herein, or a stereoisomer thereof, or a pharmaceutically acceptable salt, solvate, or prodrug thereof; an anti-CD20 antibody or fragment thereof that binds to the same epitope as ublituximab; and an inhibitor of BTK; and (b)

instructions for using said PI3K-delta selective inhibitor, in combination with ublituximab or an anti-CD20 antibody or fragment thereof that binds to the same epitope as ublituximab and an inhibitor of BTK.

[0057] In some examples, the inhibitor of BTK in the kit is ibrutinib. In some examples, the inhibitor of BTK in the kit is acalabrutinib.

[0058] In some examples, the PI3K-delta selective inhibitor in the kit is (S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one. In some examples, the PI3K-delta selective inhibitor in the kit is (S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one p-toluenesulfonic acid (PTSA) salt (TGR-1202).

[0059] In some examples, the kit further comprises ublituximab or an anti-CD20 antibody or fragment thereof that binds to the same epitope as ublituximab.

[0060] In some examples, the kit further comprises one or more additional therapeutic agents that can be used to inhibit B-cell proliferation.

BRIEF DESCRIPTION OF THE DRAWINGS/FIGURES

[0061] **Figure 1** is a schematic representation of the study design of a Phase 1/1b clinical trial where TGR1202 + Ublituximab + Ibrutinib were administered to 38 patients with NHL (n=22) and CLL (n=16). Patients with NHL included those with DLBCL, FL, MCL, SLL, and MZL. Details of patient histologies are provided in Example 1. TGR-1202 and Ibrutinib were administered once daily starting on day 1. Ublituximab infusions were given on day 1, 8, and 15 of cycle 1, and day 1 of cycles 2, 3, 4, 5, 6, 9, and 12 (as indicated by the arrow (↓)).

[0062] **Figure 2** is a bar graph depicting *efficacy* of the combination of TGR-1202 + Ublituximab + Ibrutinib in 36 patients with CLL and NHL. Efficacy is reflected in the best percent change from baseline in disease burden in all patients who had received at least one post baseline scan to assess disease/tumor burden, with responses determined according to standard international working group criteria for NHL and CLL (see citations in Example 1).

cancer, the therapeutically effective amount of the agent or drug can reduce the number of cancer cells; reduce the tumor size; inhibit (i.e., slow to some extent and in a certain embodiment, stop) cancer cell infiltration into peripheral organs; inhibit (i.e., slow to some extent and in a certain embodiment, stop) tumor metastasis; inhibit, to some extent, tumor growth; and/or relieve to some extent one or more of the symptoms associated with the cancer. See the definition herein of "treating." To the extent the drug can prevent growth and/or kill existing cancer cells, it can be cytostatic and/or cytotoxic. A "prophylactically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic result. Typically, but not necessarily, since a prophylactic dose is used in subjects prior to or at an earlier stage of disease, the prophylactically effective amount will be less than the therapeutically effective amount.

[0094] Terms such as "treating," "treatment," "to treat," "having a therapeutic effect," alleviating," "to alleviate," or "slowing the progression of" refer to both 1) therapeutic measures that cure, slow down, lessen symptoms of, and/or halt progression of a diagnosed pathologic condition or disorder, such as a hematological malignancy, and 2) prophylactic or preventative measures that prevent and/or slow the development of a targeted pathologic condition or disorder. Thus, those in need of treatment include those already with the disorder; those prone to have the disorder; and those in whom the disorder is to be prevented. In certain embodiments, a subject is successfully "treated" for cancer according to the methods of the present invention if the patient shows one or more of the following: reduction in cachexia, increase in survival time, elongation in time to tumor progression, reduction in tumor mass, reduction in tumor burden and/or a prolongation in time to tumor metastasis, time to tumor recurrence or progressive disease, tumor response, complete response (CR), partial response (PR), stable disease, progression free survival (PFS), overall survival (OS), each as measured by standards set by the National Cancer Institute and the U.S. Food and Drug Administration for the approval of new drugs. *See*, Johnson *et al*, *J. Clin. Oncol. 21*:1404-1411 (2003). In some embodiments, the "therapeutic effect," as defined above, also encompasses a reduction in toxicity or adverse side effects, and/or an improvement in tolerability.

[0095] A "combination" of an anti-CD20 antibody (e.g., ublituximab), a PI3K-delta selective inhibitor (e.g., TGR-1202), and a BTK inhibitor (e.g., ibrutinib), is generally

synonymous with a "combination of agents." A "combination of agents" refers to the administration of at least one of each of these three agents (could be more than one type of each agent) to the same population of B-cells or to the same subject simultaneously, sequentially, or both simultaneously and sequentially. Thus, by way of example, administration of an anti-CD20 antibody preceding or following (e.g., by hour(s), day(s), week(s), or month(s)) administration of a PI3K-delta selective inhibitor, preceding or following (e.g., by hour(s), day(s), week(s), or month(s)) administration of a BTK inhibitor, constitutes administration of a combination of agents. As will be apparent to one skilled in the art from the context, a "combination of agents" can also include an anti-CD20 antibody (e.g., ublituximab), a PI3K-delta selective inhibitor (e.g., TGR-1202), and a BTK inhibitor, and one or more additional therapeutic agents, as described herein. In addition, simultaneous administration of an anti-CD20 antibody or fragment thereof, a PI3K-delta selective inhibitor, and a BTK inhibitor also constitutes administration of a combination of the anti-CD20 antibody or fragment thereof, PI3K-delta selective inhibitor, and a BTK inhibitor, regardless of whether the anti-CD20 antibody or fragment thereof, PI3K-delta inhibitor, and the BTK inhibitor are administered together in a single pharmaceutical formulation or are administered simultaneously in separate pharmaceutical formulations by either the same or different routes of administration. Further, the term "combination of agents" is intended to include treatment regimens in which the agents are administered by the same or different route of administration or at the same or different time.

[0096] As used herein, the term "induction" or "induction therapy" refers to the first agent, or combination of agents, as disclosed herein, administered to treat a B-cell proliferative disorder. If the first agent or combination of agents does not result in a complete response or it causes severe side effects, other agents may be added or used instead (see "consolidation"). Induction is also called primary therapy, or primary treatment, and is administered with the goal of inducing some initial reduction in disease burden. For example, induction therapy can include the use of an anti-CD20 inhibitor and a PI3K delta inhibitor.

[0097] As used herein, "consolidation" or "consolidation therapy" refers to treatment that is given following induction therapy. Consolidation therapy is used to kill any malignant B- cells that may be left in the body following induction therapy. For example, if an anti-

CD20 inhibitor and a PI3K delta inhibitor are used as induction therapy, consolidation therapy can include the use of a BTK inhibitor. Consolidation is also called intensification therapy.

[0098] As used herein, "maintenance" or "maintenance therapy" refers to treatment that is given to help keep the B-cell proliferative disorder from returning after successful treatment with the initial therapy. Maintenance therapy may include treatment with the same agents that were used in the consolidation phase, and the agents in this phase may be administered for an extended period of time.

[0099] A tumor which "does not respond," "responds poorly," or is "refractory" to treatment (with, for example, an anti-CD20 antibody) does not show statistically significant improvement in response to that treatment when compared to no treatment or treatment with a placebo in a recognized animal model or human clinical trial, or which responds to an initial treatment, but grows as treatment continues.

[0100] "Polynucleotide" or "nucleic acid," as used interchangeably herein, refer to polymers of nucleotides of any length, and include DNA and RNA. The nucleotides can be deoxyribonucleotides, ribonucleotides, modified nucleotides or bases, and/or their analogs, or any substrate that can be incorporated into a polymer by DNA or RNA polymerase. A polynucleotide can comprise modified nucleotides, such as methylated nucleotides and their analogs. If present, modification to the nucleotide structure can be imparted before or after assembly of the polymer. The sequence of nucleotides can be interrupted by non-nucleotide components.

[0101] The terms "polypeptide," "peptide," and "protein" are used interchangeably herein to refer to polymers of amino acids of any length. The polymer can be linear or branched, it can comprise modified amino acids, and it can be interrupted by non-amino acids. The terms also encompass an amino acid polymer that has been modified naturally or by intervention; for example, disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation or modification, such as conjugation with a labeling component. Also included within the definition are, for example, polypeptides containing one or more analogs of an amino acid (including, for example, unnatural amino acids, etc.), as well as other modifications known in the art. It is understood that, because the polypeptides of this invention are based upon antibodies, in certain embodiments, the polypeptides can occur as single chains or associated chains.

amino acids; salts of guanidine; and salts of substituted guanidine wherein the substituents are selected from nitro, amino, alkyl, alkenyl, alkynyl, ammonium or substituted ammonium salts and aluminum salts.

[0116] The term "selective inhibitor" as applied to a biologically active agent refers to the agent's ability to selectively reduce the target signaling activity as compared to off-target signaling activity, via direct or indirect interaction with the target.

[0117] The term "PI3K-delta selective inhibitor"(also known as PI3K-δ inhibitor) refers to a compound, which selectively inhibits the activity of the PI3K-delta isoform more effectively than other isoforms of the PI3K family (α, β, and γ). In some embodiments, the PI3K-delta selective inhibitor refers to a compound of Formula A, as described herein, which selectively inhibits the activity of the PI3K-delta isoform more effectively than other isoforms of the PI3K family (α, β, and γ). For instance, a PI3K-delta selective inhibitor of Formula A can be a compound that exhibits a 50% inhibitory concentration (IC_{50}) with respect to the δ type P13-kinase that is at least 20-fold, or lower, than the inhibitor's IC_{50} with respect to the rest of the other types PI3K isoforms (*i.e.*, α, β, and γ).

[0118] The term "Bruton's tyrosine kinase" (also known as "BTK," agammaglobulinemia tyrosine kinase (ATK), or B-cell progenitor kinase (BPK)) refers to a non-receptor tyrosine kinase enzyme in the B-cell antigen receptor (BCR) signaling pathway. BTK, a member of the Tec family of protein tyrosine kinases, is predominantly expressed in B-lymphocytes at various stages of development (except in terminally differentiated plasma cells). BTK is a signal transduction protein that regulates normal B-cell development, differentiation and functioning, and has also been implicated in initiation, survival, and progression of mature B-cell lymphoproliferative disorders, such as B-cell malignancies. Akinleye, A. *et al., J. Hematol. Oncol. 6*:59 (2013). As used herein, BTK is from *homo sapiens*, as disclosed in U.S. Patent No. 6,326,469 (Gen Bank Acc. No. NP_000052).

[0119] An "inhibitor of BTK" or "BTK inhibitor" refers to a small molecule that targets BTK and either inhibits BTK tyrosine phosphorylation and/or B-cell activation and/or otherwise inhibits or diminishes or abolishes the biological activity of a BTK protein. An "irreversible BTK inhibitor" refers to a molecule that upon contact with BTK, causes the formation of a new covalent bond with an amino acid residue of BTK. Both reversible and irreversible inhibitors of BTK can be used in the methods and kits of the present invention.

[0120] The term "synergistic effect," as used herein, refers to a greater-than-additive therapeutic effect produced by a combination administration of compounds wherein the therapeutic effect obtained with the combination exceeds the additive effects that would otherwise result from individual administration the compounds alone. Embodiments of the invention include methods of producing a synergistic effect in the treatment of hematological cancer, wherein said effect is at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 100%, at least 200%, at least 500%, or at least 1000% greater than the corresponding additive effect.

[0121] "Therapeutic synergy," as used herein, means that the combined administration of agents, as described herein, (i.e., an anti-CD20 antibody and a PI3K-delta selective inhibitor of Formula A and a BTK inhibitor) produces a therapeutic effect that is greater than the additive effects of the anti-CD20 antibody, the PI3K-delta selective inhibitor, and the BTK inhibitor, when each is used alone and/or when two agents are combined.

[0122] As used in the present disclosure and claims, the singular forms "a," "an," and "the" include plural forms unless the context clearly dictates otherwise.

[0123] It is understood that wherever embodiments are described herein with the language "comprising," otherwise analogous embodiments described in terms of "consisting of" and/or "consisting essentially of" are also provided.

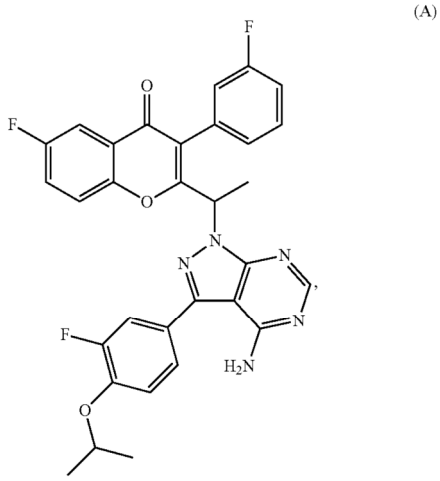
Methods

[0124] In one aspect, provided herein are methods of inhibiting proliferation of a B-cell population comprising (a) administering to the B-cell population a combination of agents, in therapeutically effective amounts, said combination of agents comprising: (i) at least one PI3K-delta selective inhibitor; (ii) at least one anti-CD20 antibody; and (iii) at least one inhibitor of Bruton's tyrosine kinase (BTK); and (b) inhibiting proliferation of said B-cell population.

[0125] In another aspect, provided herein are methods of inhibiting proliferation of a B-cell population comprising,

(a) administering to said B-cell population a combination of agents, in therapeutically effective amounts, said combination of agents comprising:

(i) at least one PI3K-delta selective inhibitor of Formula A, or a stereoisomer thereof, or a pharmaceutically acceptable salt, solvate, or prodrug thereof:



selected from one or more of,

(RS)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one;

(S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyI)-4H-chromen-4-one; and

(R)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one;

(ii) at least one anti-CD20 antibody, wherein at least one anti-CD20 antibody is ublituximab or an anti-CD20 antibody or antibody fragment that binds to the same epitope as ublituximab; and

(iii) at least one inhibitor of Bruton's tyrosine kinase (BTK); and

(b) inhibiting proliferation of said B-cell population.

[0126] In some embodiments, the method of inhibiting proliferation of a B-cell population comprises depleting B-cells. In some embodiments, this method is effective on subjects whose cancer has relapsed.

[0127] In some embodiments, the method of inhibiting proliferation of a B-cell population comprises promoting apoptosis of said B-cells.

[0128] In some embodiments, the method of inhibiting proliferation of a B-cell population comprises promoting cell-cycle arrest.

[0129] In some embodiments, the method of inhibiting proliferation of a B-cell population comprises depleting B-cells.

[0130] In some embodiments, the method of inhibiting proliferation of a B-cell population comprises blocking the B-cell receptor (BCR) signaling pathway.

[0131] In some embodiments, the method of inhibiting proliferation of a B-cell population treats a B-cell proliferative disorder in a subject. In some embodiments, the B-cell proliferative disorder is a hematological malignancy. In some embodiments, the hematological malignancy is selected from the group consisting of acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), multiple myeloma (MM), non-Hodgkin's lymphoma (NHL), mantle cell lymphoma (MCL), follicular lymphoma (FL), Waldenstrom's macroglobulinemia (WM), diffuse large B-cell lymphoma (DLBCL), marginal zone lymphoma (MZL), Burkitt's lymphoma (BL), hairy cell leukemia (HCL), and Richter's transformation.

PI3K-delta selective inhibitor

[0132] The phosphoinositide 3-kinases (PI3Ks) are a family of enzymes that regulate diverse biological functions in every cell type by generating phosphoinositide second-messenger molecules. PI3Ks are involved in various cellular functions, including cell proliferation and survival, cell differentiation, intracellular trafficking, and immunity. As the activity of these phosphoinositide second messengers is determined by their phosphorylation state, the kinases and phosphatises that act to modify these lipids are central to the correct execution of intracellular signaling events. PI3Ks phosphorylate lipids at the 3-hydroxyl residue of an inositol ring (Whitman *et al., Nature* 332:664 (1988)) to generate phosphorylated phospholipids (PIP3s), which act as second messengers recruiting kinases with lipid binding domains (including plekstrin homology (PH) regions), such as Akt and phosphoinositide-dependent kinase-1 (PDK1). Binding of Akt to membrane PIP3s causes the translocation of Akt to the plasma membrane, bringing Akt into contact with PDK1, which is responsible for activating Akt. The tumor-suppressor phosphatase PTEN (Phosphatase and Tensin homolog deleted on chromosome

Ten) dephosphorylates PIP3 and therefore acts as a negative regulator of Akt activation. The PI3Ks Akt and PDK1 are important in the regulation of many cellular processes including cell cycle regulation, proliferation, survival, apoptosis, and motility and are significant components of the molecular mechanisms of diseases such as cancer, diabetes, and immune inflammation (Vivanco *et al., Nature Rev. Cancer* 2:489 (2002); Phillip*s et al., Cancer* 83:41 (1998)).

[0133] The PI3K family is comprised of four different classes: Classes I, II, III, and IV. Classes I- III are lipid kinases and Class IV are serine/threonine protein kinases.

[0134] The members of the Class I family of PI3Ks are dimers of a regulatory and a catalytic subunit. The Class I family consists of four isoforms, determined by the 110 kDa catalytic subunits α, β, γ, and δ. *See* Engelman, J.A., *Nat Rev Genet* 7:606-619 (2006); Carnero, A., *Curr Cancer Drug Targets* 8:187-198 (2008); and Vanhaesebroeck, B., *Trends Biochem Sci* 30:194-204 (2005). Class I can be subdivided into two subclasses: Class Ia, formed by the combination of pl10 α, β, and δ, and a regulatory subunit (p85, p55 or p50); and Class Ib, formed by p110 γ and p101 regulatory subunits. The delta (δ) isoform of PI3K is highly expressed in cells of hematopoietic origin, and strongly upregulated, and often mutated, in various hematologic malignancies.

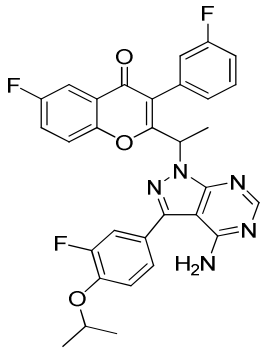
[0135] Studies regarding PI3K and related protein kinase pathways have been published by various groups, including, Liu *et al.*, *Nature Reviews Drug Discovery* 8:627-644 (2009); Nathan *et al*, *Mol. Cancer Ther*. 8(1) (2009); and Marone *et al.*, *Biochimica et Biophysica Acta* 1784:159-185 (2008). Two known inhibitors of PI3K, LY294002 and Wortmannin, are non-specific PI3K inhibitors as they do not distinguish the four members of Class I PI3K: α, β, γ, and δ. A number of PI3K inhibitors have entered clinical trials for the treatment of cancers, and various types of cancers (including breast cancer, non-small cell lung cancer (NSCLC), and hematological cancers), are being considered as areas of therapeutic interest.

[0136] One example of a PI3K-delta selective inhibitor is Idelalisib (trade name Zydelig®), which was approved by the U.S. FDA in 2014 for the treatment of relapsed CLL (in combination with Rituxan®; see, Furman, R.R. *et al*., *N. Eng. J. Med*. 370:997-1007 (2014)), relapsed follicular B-cell non-Hodgkin lymphoma (FL), and relapsed small lymphocytic lymphoma (SLL), another type of non-Hodgkin lymphoma. *See*, Zydelig® full prescribing information (Gilead Sciences). Idelalisib has a unique and limiting

toxicity profile including immune mediated colitis (grade 3 ≥ 5%), pneumonitis (grade 3 ≥ 4%), and transaminitis (grade 3 ≥ 8%). Therefore the FDA's approval of Zydelig® comes with a boxed warning noting the possibility of fatal and serious toxicities including hepatic, severe diarrhea, colitis, pneumonitis and intestinal perforation. *Id.*

[0137] Another example of a PI3K-delta selective inhibitor is duvelisib (IPI-145). *See*, O'Brian, S. *et al.*, *Blood 124*:Abstract 3334 (2014). Although duvelisib targets both PI3K delta and gamma, at the dose under development (25 mg twice daily), it primarily inhibits just the delta isoform. *Id.* Another PI3K-delta selective inhibitor is ACP-319 (previously AMG-319). *See*, Lanasa, M.C. *et al.*, *Blood 122*:Abstract 678 (2013). ACP-319 is currently in development by Acerta Pharma B.V. ME-401 is a new oral PI3K-delta selective inhibitor in development by MEI Pharma. See, Moreno, O. *et al.,*"Clinical Pharmacokinetics and Pharmacodynamics of ME-401, an Oral, Potent, and Selective Inhibitor of Phosphatidylinositol 3-Kinase P110δ, Following Single Ascending Administration to Healthy Volunteers" (Abstract # CT157), presented at the American Association for Cancer Research (AACR) Annual Meeting, New Orleans (April 16-20, 2016). INCB-50465 is another PI3K-delta selective inhibitor in development by Incyte Corporation that is in Phase I/II clinical trials for the treatment of B-cell malignancies. See, Forero-Torres, A. *et al.*, "Preliminary safety, efficacy, and pharmacodynamics of a highly selective PI3Kδ inhibitor, INCB050465, in patients with previously treated B-cell malignancies" (Abstract #CT056), presented at the AACR Annual Meeting, New Orleans (April 16-20, 2016).

[0138] As provided herein, at least one PI3K-delta selective inhibitor is used in the methods (and kits) of the present invention. In one embodiment, the PI3K-delta selective inhibitor that is used in combination with the anti-CD20 antibodies and BTK inhibitors, described herein, is a compound of formula A:



(A)

or a stereoisomer thereof, or a pharmaceutically acceptable salt, solvate, or prodrug thereof. In a preferred embodiment, the compound of Formula A is selected from one or more of,

(RS)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one;

(S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyI)-4H-chromen-4-one; and

(R)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one.

[0139] A PI3K-delta inhibitor of formula A can be prepared using the general synthetic methods as disclosed in International Patent Appl. Publ. No. WO 2011/055215 A2 and U.S. Patent Appl. Publ. No. 2011/0118257 A1.

[0140] In some embodiments, the PI3K-delta inhibitor is administered to a subject daily at a dosage from: about 200 mg to about 1200 mg, about 400 mg to about 1000 mg, about 400 mg to about 800 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, or about 1200 mg.

[0141] In some embodiments, the PI3K-delta inhibitor of Formula A is (S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one.

[0142] In a preferred embodiment, the PI3K-delta inhibitor of Formula A is (S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one p-toluenesulfonic acid (PTSA) salt (also known as (S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo [3, 4-d]

pyrimidin-1-yl)-ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one 4-methylbenzenesulfonate, TGR-1202, and umbralisib).

[0143] The preparation of TGR-1202 is described in International Publ. No. WO 2014/006572 and U.S. Patent Publ. No. 2014/0011819, each of which is incorporated herein by reference in its entirety. In addition to describing the synthesis of TGR-1202, WO 2014/006572 and US 2014/0011819 also disclose the therapeutic activity of this molecule to inhibit, regulate and/or modulate the signal transduction of PI3K. TGR-1202 is also described in U.S. Patent No. 9,150,579, which issued October 6, 2015. International Publ. No. WO 2015/181728, incorporated herein by reference in its entirety, describes a solid state form of TGR-1202 that exhibits enhanced solubility and pharmacokinetics upon oral administration. The entirety of each of these applications and patents is incorporated herein by reference.

[0144] TGR-1202 (or umbralisib) is a next generation PI3K-delta inhibitor with a unique molecular structure and activity profile distinct from other PI3K-delta inhibitors in development, including: (1) greater selectivity to the delta isoform of PI3K; (2) a a prolonged half-life that enables once-daily dosing; and (3) a differentiated safety profile from other PI3K-delta inhibitors, notably with respect to hepatic toxicity and colitis.

[0145] TGR-1202 was evaluated in a single-agent Phase I dose-escalation study in patients with relapsed and refractory hematologic malignancies (*see e.g.*, Burris *et al.*, "Activity of TGR-1202, a novel once-daily PI3Kδ inhibitor, in patients with relapsed or refractory hematologic malignancies," *J. Clinical Oncology (ASCO Annual Meeting Abstracts)* 32 (15): 2513 (2014)). The study reported that TGR-1202 was well-tolerated in patients with relapsed or refractory hematologic malignancies, with no reported hepatic toxicity and signs of clinical activity at doses ≥ 800 mg each day. *Id.* The favorable safety profile of TGR-1202 compared to prior inhibitors has also been demonstrated in long-term follow up. See, Burris, H. *et al*., "Long-term follow-up of the PI3K delta inhibitor TGR-1202 demonstrates a differentiated safety profile and high response rates in CLL and NHL: Integrated-analysis of TGR-1202 monotherapy and combined with ublituximab," American Society of Clinical Oncology Annual Meeting (ASCO), Abstract #7512 (June 3, 2016) .

[0146] In some embodiments, the TGR-1202 is administered at a dose from about 400 mg to about 1200 mg per day. In some embodiments, the TGR-1202 is administered at a

dose of about 400 mg per day. In some embodiments, the TGR-1202 is administered at a dose of about 600 mg per day. In some embodiments, the TGR-1202 is administered at a dose of about 800 mg per day.

[0147] In some embodiments, the PI3K-delta inhibitor is formulated for oral administration. In certain embodiments, the PI3K-delta inhibitor is TGR-1202 and it is formulated for daily oral administration. In certain embodiments, TGR-1202 is administered in a fed-state.

Anti-CD20 Antibodies

[0148] CD20 is a hydrophobic transmembrane phosphoprotein that is expressed predominantly in pre-B cells and mature peripheral B cells in humans and mice. In humans, CD20 is also strongly and homogeneously expressed in most mature B-cell malignancies, including, for example, most non-Hodgkin's B-cell lymphomas (NHL) and B-type Chronic Lymphocytic Leukemia's (B-CLL). The CD20 antigen is not expressed on haematopoietic stem cells or on plasmocytes.

[0149] Anti-CD20 monoclonal antibodies have been, and continue to be, developed for the treatment of B-cell diseases. The chimeric anti-CD20 monoclonal antibody rituximab (Rituxan®) has become the standard therapy for many CD20-positive B-cell lymphomas and was the first mAb approved for any oncology indication. Demarest, SJ *et al., mAbs* 3:338-351 (2011). However, there are a substantial number of patients who are refractory to treatment with rituximab or who develop resistance in the course of prolonged treatment with rituximab (used as a single agent or even in combination with chemotherapeutic regimens).

[0150] As provided herein, anti-CD20 antibodies and antigen-binding fragments thereof can be used in combination with a PI3K-delta selective inhibitor and a BTK inhibitor to treat B-cell proliferative disorders, such as B-cell malignancies. More than one anti-CD20 antibody can be used in the methods and kits of the present invention.

[0151] Aside from rituximab, a number of other anti-CD20 antibodies are known in the art, including, for example, ublituximab, ofatumumab (HuMax; Intracel), ocrelizumab, veltuzumab, GA101 (obinutuzumab), AME-133v (Applied Molecular Evolution), ocaratuzumab (Mentrik Biotech), PRO131921, tositumomab, ibritumomab-tiuxetan,

Methods of treating B-cell proliferative disorders, such as B-cell malignancies

[0210] In some embodiments, the B-cell population whose proliferation is to inhibited is in a human subject. In some embodiments, the human subject has a disease or disorder associated with excessive B-cell proliferation. In some embodiments, the disease associated with excessive B-cell proliferation is cancer. In some embodiments, a human subject has cancer. In some embodiments, the cancer is a hematological malignancy. In certain embodiments, the hematological malignancy is lymphoma, leukemia, or myeloma.

[0211] In some embodiments, the hematological malignancy is selected from the group consisting of acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), multiple myeloma (MM), non-Hodgkin's lymphoma (NHL), mantle cell lymphoma (MCL), follicular lymphoma (FL), Waldenstrom's macroglobulinemia (WM), diffuse large B-cell lymphoma (DLBCL), marginal zone lymphoma (MZL), including extranodal and nodal MZL, hairy cell leukemia (HCL), Burkitt's lymphoma (BL), and Richter's transformation.

[0212] In some embodiments, the hematological malignancy is selected from the group consisting of chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), non-Hodgkin's lymphoma (NHL), mantle cell lymphoma (MCL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), and marginal zone lymphoma (MZL).

[0213] In some embodiments, the cancer overexpresses CD20.

[0214] In some embodiments, the cancer is refractory to chemotherapy.

[0215] In some embodiments, the cancer is refractory to non-TGR-1202 PI3K-delta inhibitors.

[0216] In some embodiments, the cancer is refractory to non-ublituximab anti-CD20 antibodies.

[0217] In some embodiments, the cancer is refractory to any agent described herein, i.e., an anti-CD20 antibody, a PI3K delta selective inhibitor, or a BTK inhibitor, when said agent was administered individually to a subject (i.e, used as a monotherapy).

[0218] In some embodiments, the cancer is refractory to a BTK inhibitor. In some embodiments, the cancer is refractory to ibrutinib.

[0219] In some embodiments, the cancer is refractory to rituximab.

[0220] In some embodiments, the cancer has relapsed.

maintenance therapy for an extended period of time, e.g., until unmanageable toxicity, or disease progression occurs. In some embodiments, the maintenance therapy ends when disease progression occurs. In some embodiments, UTX infusion continues being administered every three months until disease progression. In some embodiments, TGR-1202 single agent therapy is administered daily until disease progression. In some embodiments, ibrutinib single agent therapy is administered daily until disease progression.In some embodiments, TGR-1202 and ibrutinib therapies are administered daily until disease progression.

[0228] In some embodiments, the methods described herein further comprises administering to the subject at least one additional therapeutic agent for inhibiting B-cell proliferation. In some embodiments, the at least one additional therapeutic agent is selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, anthracyclines, vinca alkaloids, plant alkaloids, nitrogen mustards, proteasome inhibitors, intercalating antibiotics, growth factor inhibitors, cell-cycle inhibitors, biological response modifiers, anti-hormones, angiogenesis inhibitors, anti-androgens, DNA interactive agents, purine analogues, topoisomerase I inhibitors, topoisomerase II inhibitors, tubulin interacting agents, hormonal agents, thymidilate synthase inhibitors, non-BTK and non-PI3K-delta tyrosine kinase inhibitors, angiogenesis inhibitors, EGF inhibitors, VEGF inhibitors, CDK inhibitors, SRC inhibitors, c-Kit inhibitors, Her1/2 inhibitors, inhibitors of myc, anti-tumor antibodies, monoclonal antibodies directed against growth factor receptors, protein kinase modulators, radioactive isotopes, immunotherapies, glucocorticoids, and combinations thereof.

[0229] In some embodiments, the at least one additional therapeutic agent is an anti-cancer agent selected from the group consisting of DNA interactive agents, such as cisplatin or doxorubicin; topoisomerase II inhibitors, such as etoposide; topoisomerase I inhibitors such as CPT-11 or topotecan; tubulin interacting agents, such as paclitaxel, docetaxel or the epothilones (for example ixabepilone), either naturally occurring or synthetic; hormonal agents, such as tamoxifen; thymidilate synthase inhibitors, such as 5-fluorouracil; and anti-metabolites, such as methotrexate; other tyrosine kinase inhibitors such as Iressa and OSI-774; angiogenesis inhibitors; EGF inhibitors; VEGF inhibitors; CDK inhibitors; SRC inhibitors; c-Kit inhibitors; Her1/2 inhibitors and monoclonal

[0233] The combination of agents comprising a PI3K-delta inhibitor, an anti-CD20 antibody, and a BTK inhibitor (or more than one of any or all agents) can be administered in any order or at any interval as determined by those skilled in the art. For example, a PI3K-delta inhibitor of formula A, ublituximab or an anti-CD20 antibody that binds to the same epitope as ublituximab, and a BTK inhibitor can be administered sequentially (in any order), simultaneously, or via any combination of sequential and simultaneous administrations. Any combination of a PI3K-delta inhibitor of formula A, ublituximab or an anti-CD20 antibody that binds to the same epitope as ublituximab, and a BTK inhibitor can be administered in the same pharmaceutical compositions or in separate pharmaceutical compositions. For example, a PI3K-delta inhibitor of formula A and a BTK inhibitor can be administered in the same pharmaceutical composition.

[0234] Administration of the combination of agents, whether simultaneous, sequential (in any order) or both, can be performed according to any number of desired intervals of minutes (*e.g.*, 0-60 minutes), hours (*e.g.*, 0-24 hours), days (*e.g.*, 0-7 days), and/or weeks (*e.g.*, 0-52 weeks), as can be decided and determined by one of skill in the art. The dosing can also vary over time, for example, starting with a once weekly dose for a period of time (*e.g.*, for 1, 2, 3, 4, 5, or 6 weeks) followed by dosing once every two weeks, once every three weeks, once every four weeks, once every five weeks, or once every six weeks.

[0235] The PI3K-delta selective inhibitor, the anti-CD20 antibody, and the BTK inhibitor that are to be used in combination in the methods of the invention can be formulated into pharmaceutical compositions for administration to mammals, including humans. The pharmaceutical compositions comprise pharmaceutically acceptable carriers, including, e.g., ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[0236] The agents to be used in combination in accordance with the methods of the invention can be administered by any suitable method, *e.g.*, orally, parenterally, intraventricularly, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The mode of administration for each agent does not have to be the same.

[0237] In a preferred embodiment, the PI3K-delta inhibitor (e.g., TGR-1202) is administered orally.

[0238] In a preferred embodiment, the BTK inhibitor (e.g., Ibrutinib) is administered orally.

[0239] As used herein, the term "parenteral" includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Parenteral formulations can be a single bolus dose, an infusion, or a loading bolus dose followed with a maintenance dose. These compositions can be administered at specific fixed or variable intervals, e.g., once a day, or on an "as needed" basis. In a preferred embodiment, the anti-CD20 antibody ublituximab is administered intravenously (IV), preferably by infusion.

[0240] Certain pharmaceutical compositions can be orally administered in an acceptable dosage form including, e.g., capsules, tablets, aqueous suspensions, or solutions. Certain pharmaceutical compositions also can be administered by nasal aerosol or inhalation. Such compositions can be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, and/or other conventional solubilizing or dispersing agents.

[0241] A specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the particular therapeutic agents used, the patient's age, body weight, general health, sex, and diet, and the time of administration, rate of excretion, drug combination, and the severity of the disease being treated. In some cases, dosages may need to be modified based on scan or biopsy results. Judgment of such factors by medical caregivers is within the ordinary skill in the art. Dosage will also depend on the individual patient to be treated, the route of administration, the type of formulation, the characteristics of the compound used, tumor burden, and the desired

effect. The amount used can be determined by pharmacological and pharmacokinetic principles well known in the art.

[0242] In some embodiments, the anti-CD20 antibody is ublituximab and it is administered at a dose from: about 450 mg to about 1200 mg, about 600 to about 1200 mg, about 600 to about 1000 mg, about 600 to about 900 mg, about 600 mg, about 700 mg, about 800 mg, or about 900 mg. In a preferred embodiment, the ublituximab is administered at a dose of about 900 mg.

[0243] Ublituximab may be administered about twice every week, about once every 1 to 9 weeks, about once every week, about once every 2 weeks, about once every 3 weeks, about once every 4 weeks, about once every 5 weeks, about once every 6 weeks, about once every 7 weeks, about once every 8 week, or about once every 9 weeks. One skilled in the art will appreciate that the dosage of ublituximab and/or frequency of administering ublituximab may change during the course of therapy (lowered or increased) depending upon the patient's clinical response, side effects, etc.

[0244] In some embodiments, ublituximab is administered on day 1, 8, and 15 of cycle 1 and cycle 2 and day 1 on cycles 4, 6, 9, and 12, wherein each cycle is 28 days.

[0245] In some embodiments, a PI3K-delta selective inhibitor of formula A is administered once a day at a dosage from: about 200 mg to about 1200 mg, about 400 mg to about 1000 mg, about 400 mg to about 800 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, or about 1200 mg.

[0246] In some embodiments, the PI3K-delta selective inhibitor of formula A is (S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one PTSA salt (TGR-1202) and it is administered at a dose from about 400 mg to about 1200 mg per day. In some embodiments, the TGR-1202 is administered at a dose of about 400 mg per day. In some embodiments, the TGR-1202 is administered at a dose of about 600 mg per day. In some embodiments, the TGR-1202 is administered at a dose of about 800 mg per day.

[0247] In some embodiments, the BTK inhibitor is 1-[(3*R*)-3-[4-Amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidin-1-yl]prop-2-en-1-one (ibrutinib). In some embodiments, the ibrutinib is administered once daily at a dosage from: about 200 to about 800 mg, about 400 to about 600 mg, about 400 mg, about 420 mg, about 440 mg, about 480 mg, about 500 mg, about 520 mg, about 540 mg, about 560

mg, about 580 mg, or about 600 mg. In some embodiments, the ibrutinib is administered at a dose of about 420 mg per day or about 560 mg per day. In some embodiments, the ibrutinib is administered at a dose of about 420 mg per day. In some embodiments, the ibrutinib is administered at a dose of about 560 mg per day. The dosages of other non-ibrutinab BTK inhibitors that can be used in the methods of the invention can be routinely determined by those skilled in the art based on the scientific/medical literature.

[0248] Supplementary active compounds can also be incorporated into the methods and kits of the present invention. For example, an anti-CD20 antibody, a PI3K-delta selective inhibitor, and a BTK inhibitor can be coformulated with and/or coadministered with one or more additional therapeutic agents. As non-limiting examples, the methods and kits could be coformulated with anti-cancer agents such as DNA interactive agents, such as cisplatin or doxorubicin; topoisomerase II inhibitors, such as etoposide; topoisomerase I inhibitors such as CPT-11 or topotecan; tubulin interacting agents, such as paclitaxel, docetaxel or the epothilones (for example ixabepilone), either naturally occurring or synthetic; hormonal agents, such as tamoxifen; thymidilate synthase inhibitors, such as 5-fluorouracil; and anti-metabolites, such as methotrexate; other tyrosine kinase inhibitors such as Iressa and OSI-774; angiogenesis inhibitors; EGF inhibitors; VEGF inhibitors; CDK inhibitors; SRC inhibitors; c-Kit inhibitors; Her1/2 inhibitors and monoclonal antibodies directed against growth factor receptors such as erbitux (EGF) and herceptin (Her2); and other protein kinase modulators. The additional active agent can also be a proteasome inhibitor, Bortezomib (Velcade®), Carfilzomib (PR-171), PR-047, disulfiram, lactacystin, PS-519, eponemycin, epoxomycin, aclacinomycin, CEP-1612, MG-132, CVT-63417, PS-341, vinyl sulfone tripeptide inhibitors, ritonavir, PI-083, (+/-)-7-methylomuralide, (-)-7-methylomuralide, lenalidomide (Revlimid®), or a combination thereof.

Kits

[0249] In one aspect, provided herein is a kit comprising (a) at least one PI3K-delta selective inhibitor, at least one anti-CD20 antibody, and at least one inhibitor of BTK; and (b) instruction for using a PI3K-delta selective inhibitor in combination with an anti-CD20 antibody and an inhibitor of BTK.

[0250] In another aspect, provided herein is a kit comprising at least one PI3K-delta selective inhibitor of formula A, at least one anti-CD20 antibody that is ublituximab or an antibody that binds to the same epitope as ublituximab, and at least one inhibitor of BTK. In some embodiments, other agents that can be used to perform the methods described herein, and combinations thereof, are included in the kit. Such kits can include, for example, other compounds and/or compositions to treat B-cell malignancies known to those skilled in the art, a device(s) for administering the compounds and/or compositions, and written instructions in a form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products.

[0251] In some embodiments, a kit comprises (a) a PI3K-delta selective inhibitor of formula A (e.g., TGR-1202), or a stereoisomer thereof, or a pharmaceutically acceptable salt, solvate, or prodrug thereof; ublituximab or an anti-CD20 antibody or fragment thereof that binds to the same epitope as ublituximab; and an inhibitor of BTK, and (b) instructions for using said PI3K-delta selective inhibitor in combination with ublituximab or an anti-CD20 antibody or fragment thereof that binds to the same epitope as ublituximab and an inhibitor of BTK.

[0252] In some embodiments, the inhibitor of BTK in the kit is ibrutinib. In some embodiments, the inhibitor of BTK in the kit is acalabrutimib.

[0253] In some embodiments, the PI3K-delta selective inhibitor in the kit is (S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one.

[0254] In some embodiments, the PI3K-delta selective inhibitor in the kit is (S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one PTSA salt (TGR-1202, also known as umbralisib).

[0255] In some embodiments, the kit further comprises ublituximab or an anti-CD20 antibody or fragment thereof that binds to the same epitope as ublituximab.

[0256] In some embodiments, the kit further comprises ublituximab.

[0257] One skilled in the art will readily recognize that the disclosed combination of agents (antibodies and small molecule inhibitors) described herein for use in the methods of the invention can be readily incorporated into one of the established kit formats that are well known in the art.

[0258] Further provided are kits comprising (a) a PI3K-delta selective inhibitor of formula A, an anti-CD20 antibody, a BTK inhibitor, or a combination thereof; and (b) an additional anti-cancer agent. In some embodiments, the kit comprises TGR-1202, ublituximab, and ibrutinib or another inhibitor of BTK (as described herein), and a chemotherapeutic agent selected from the group consisting of DNA interactive agents, such as cisplatin or doxorubicin; topoisomerase II inhibitors, such as etoposide; topoisomerase I inhibitors such as CPT-11 or topotecan; tubulin interacting agents, such as paclitaxel, docetaxel or the epothilones (for example ixabepilone), either naturally occurring or synthetic; hormonal agents, such as tamoxifen; thymidilate synthase inhibitors, such as 5-fluorouracil; and anti-metabolites, such as methotrexate; other tyrosine kinase inhibitors such as Iressa and OSI-774; angiogenesis inhibitors; EGF inhibitors; VEGF inhibitors; CDK inhibitors; SRC inhibitors; c-Kit inhibitors; Her1/2 inhibitors and monoclonal antibodies directed against growth factor receptors such as erbitux (EGF) and herceptin (Her2); and other protein kinase modulators.

Methods of Using Combinations of a PI3K-delta selective inhibitor of Formula A, Ublituximab or an anti-CD20 antibody that binds the same epitope as ublituximab, and a BTK inhibitor

[0259] Combinations of a PI3K-delta selective inhibitor of Formula A, ubltuximab or an anti-CD20 antibody that binds the same epitope as ublituximab, and a BTK inhibitor can be used in methods of treating B-cell proliferative diseases (such as B-cell malignancies) in a subject.

[0260] In some embodiments, a PI3K-delta selective inhibitor of Formula A can be used in the manufacture of a medicament for the treatment of a B-cell proliferative disorder, wherein the PI3K-delta selective inhibitor of Formula A is to be administered in combination (e.g., sequentially or simultaneously) with an anti-CD20 antibody that is ublituximab or an antibody that binds to the same epitope as ublituximab, and a BTK inhibitor. In addition, an anti-CD20 antibody can be used in the manufacture of a medicament for the treatment of a B-cell proliferative disorder, wherein the anti-CD20 antibody is to be administered in combination (e.g., sequentially or simultaneously) with a PI3K-delta selective inhibitor of Formula A and a BTK inhibitor. In some embodiments, the anti-CD20 antibody is ublituximab. In some embodiments, the PI3K-

delta selective inhibitor is TGR-1202. In some embodiments, the anti-CD20 antibody is ublituximab and the PI3K-delta selective inhibitor is TGR-1202.

[0261] The invention further provides a method of inhibiting PI3K-delta isoform and/or CD20, and/or BTK in a subject by administering to the subject an effective amount of the agents of the present invention in combination.

[0262] The invention further provides a method of treating, preventing, and/or inhibiting a PI3K-delta-mediated disease, disorder or condition and/or a CD20-mediated disease, disorder, or condition (such as cancer or other proliferative disease or disorder) and/or a BTK-mediated disease, disorder, or condition in a patient by administering to the a patient an effective amount of the agents of the present invention in combination.

[0263] The invention further provides a method of treating a PI3K-delta isoform- and/or CD20- or BTK-associated disease, disorder or condition in a patient by administering to the patient an effective amount of the agents of the present invention in combination. In some embodiments, the amount of the agents administered in combination is sufficient to treat a PI3K-delta isoform- and/or CD20- and/or BTK-associated disease, disorder, or condition by selective inhibition of PI3K-delta and/or CD20 and/or BTK.

[0264] In some embodiments, the invention further provides a method of treating a B-cell proliferative disease by administering to a patient in need of such treatment an effective amount of at least one PI3K delta selective inhibitor, at least one anti-CD20 antibody, and at least one BTK inhibitor. In some embodiments, the anti-CD20 antibody is ublituximab. In some embodiments, the PI3K-delta selective inhibitor is TGR-1202. In some embodiments, the BTK inhibitor is ibrutinib. In some embodiments, the anti-CD20 antibody is ublituximab and the PI3K-delta selective inhibitor is TGR-1202. In some embodiments, the anti-CD20 antibody is ublituximab, the PI3K-delta selective inhibitor is TGR-1202, and the BTK inhibtor is ibrutinib.

[0265] In some embodiments, the invention further provides a method of treating a B-cell proliferative disease by administering to a patient in need of such treatment an effective amount of at least one PI3K delta selective inhibitor of formula A, at least one anti-CD20 antibody that is ublituximab or an antibody that binds to the same epitope as ublituximab, and at least one BTK inhibitor of the present invention. In some embodiments, the amounts of the agents administered in combination are sufficient to treat the B-cell proliferative disease by selective inhibition of PI3K-delta, and/or inhibition of CD20,

and/or inhibition of BTK. In some embodiments, the B-cell proliferative disorder is a B-cell malignancy (e.g., lymphoma, leukemia, or myeloma). In some embodiments, the anti-CD20 antibody is ublituximab. In some embodiments, the PI3K-delta selective inhibitor is TGR-1202. In some embodiments, the BTK inhibitor is ibrutinib. In some embodiments, the anti-CD20 antibody is ublituximab and the PI3K-delta selective inhibitor is TGR-1202. In some embodiments, the anti-CD20 antibody is ublituximab, the PI3K-delta selective inhibitor is TGR-1202, and the BTK inhibtor is ibrutinib.

[0266] The invention further provides a method for treating a B-cell proliferative disease by administering to a patient in need of such treatment an effective amount of a combination of the agents of the present invention, in further combination (simultaneously or sequentially) with at least one other anti-cancer agent. In one embodiment, the amount of the PI3K-delta selective inhibitor of Formula A administered is sufficient to treat (or facilitate treatment of) the B-cell proliferative disease by selective inhibition of PI3K-delta.

[0267] The combinations of the agents of the present invention are particularly useful in the treatment of a variety of hematological cancers, such as, but not limited to, e.g., acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), multiple myeloma (MM), non-Hodgkin's lymphoma (NHL), mantle cell lymphoma (MCL), follicular lymphoma (FL), Waldenstrom's macroglobulinemia (WM), diffuse large B-cell lymphoma (DLBCL), marginal zone lymphoma (MZL), hairy cell leukemia (HCL), Burkitt's lymphoma (BL), and Richter's transformation.

[0268] Those skilled in the art would appreciate that other types of lymphomas or leukemias would find use in the combination of agents of the invention, such as, *e.g.*, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, plasma cell myeloma/plasmacytoma, Hodgkin's lymphoma, and Burkitt's lymphoma/Burkitt's cell leukemia.

[0269] In some embodiments, Non-Hodgkin's Lymphoma (NHL) is aggressive NHL or indolent NHL. Examples of aggressive NHL include B-cell neoplasms, diffuse large B-cell lymphoma (DLBCL), T/NK cell neoplasms, anaplastic large cell lymphoma, peripheral T-cell lymphomas, precursor B-lymphoblastic leukemia/lymphoma, precursor T-lymphoblastic leukemia/lymphoma, Burkitt's lymphoma, adult T-cell

inhibitors, such as etoposide; topoisomerase I inhibitors such as CPT-11 or topotecan; tubulin interacting agents, such as paclitaxel, docetaxel or the epothilones (for example ixabepilone), either naturally occurring or synthetic; hormonal agents, such as tamoxifen; thymidilate synthase inhibitors, such as 5-fluorouracil; and anti-metabolites, such as methotrexate; other tyrosine kinase inhibitors such as Iressa and OSI-774; angiogenesis inhibitors; EGF inhibitors; VEGF inhibitors; CDK inhibitors; SRC inhibitors; c-Kit inhibitors; Her1/2 inhibitors and monoclonal antibodies directed against growth factor receptors such as erbitux (EGF) and herceptin (Her2); and other protein kinase modulators. The additional active agent can also be a proteasome inhibitor, Bortezomib (Velcade®), Carfilzomib (PR-171), PR-047, disulfiram, lactacystin, PS-519, eponemycin, epoxomycin, aclacinomycin, CEP-1612, MG-132, CVT-63417, PS-341, vinyl sulfone tripeptide inhibitors, ritonavir, PI-083, (+/-)-7-methylomuralide, (-)-7-methylomuralide, lenalidomide (Revlimid®), or a combination thereof.

[0274] The combination of agents of the present invention are also useful in combining (administered together or sequentially) with one or more steroidal anti-inflammatory drugs (e.g, prednisone or prednisolone), non-steroidal anti-inflammatory drugs (NSAIDs) or immune selective anti-inflammatory derivatives (ImSAIDs).

[0275] In some embodiments, a patient has a relapsed or refractory condition (i.e., B-cell cancer). In some embodiments, the subject is refractory to chemotherapy treatment, or in relapse after treatment with chemotherapy. In some embodiments, the subject is refractory to a non-TGR-1202 PI3K-delta inhibitor. In some embodiments, the subject is refractory to an agent (i, ii, or iii) described herein, where the agent was administered individually (i.e., as a monotherapy).

[0276] In some embodiments, the cancer is resistant to treatment with rituximab. In some embodiments, the cancer shows a reduced response to treatment with rituximab. In some embodiments, the subject has previously been treated with rituximab.

[0277] In a particular embodiment, the methods comprise reducing the level of NF-kappa-B activity, reducing SNAIL expression, increasing RKIP activity, increasing PTEN activity, increasing tumor sensitivity to TRAIL-apoptosis, reducing the level of PI3K-delta activity or a combination thereof in a subject.

[0278] In a particular embodiment, the combination of the PI3K-delta inhibitor of formula A, the anti-CD20 antibody ublituximab, and the BTK inhibitor, as described

herein, depletes B-cells from human whole blood. In some embodiments, the described triplet combination depletes B-cells from human whole blood to a greater extent than either the PI3K-delta inhibitor of formula A, the anti-CD20 antibody ublituximab, or the BTK inhibitor alone depletes B-cells from human whole blood. In some embodiments, the combination of the PI3K-delta inhibitor of formula A, the anti-CD20 antibody ublituximab, and the BTK inhibitor depletes B-cells from human whole blood to a greater extent than the sum of the depletion by the PI3K-delta inhibitor of formula A, the depletion by the anti-CD20 antibody ublituximab, and the depletion by the BTK inhibitor.

[0279] In some embodiments, a PI3K-delta inhibitor of formula A, the anti-CD20 antibody, and the BTK inhibitor are used in a method of treating a disease or disorder associated with excessive B-cell proliferation, wherein the method comprises administration of a PI3K-delta inhibitor of formula A, the anti-CD20 antibody ublituximab, and the BTK inhibitor to a subject in need thereof. In some embodiments, a PI3K-delta inhibitor of formula A, the anti-CD20 antibody, and the BTK inhibitor are used in a method of treating a disease or disorder associated with excessive B-cell activity, wherein the method comprises administration of a PI3K-delta inhibitor of formula A, the anti-CD20 antibody, and the BTK inhibitor to a subject in need thereof. In some embodiments, a PI3K-delta inhibitor of formula A, the anti-CD20 antibody, and the BTK inhibitor are used in a method of treating a disease or disorder associated with excessive number of B-cells, wherein the method comprises administration of a PI3K-delta inhibitor of formula A, the anti-CD20 antibody, and the BTK inhibitor to a subject in need thereof. In some embodiments, the anti-CD20 antibody is ublituximab. In some embodiments, the PI3K-delta selective inhibitor is TGR-1202. In some embodiments, the BTK inhibitor is ibrutinib. In some embodiments, the anti-CD20 antibody is ublituximab and the PI3K-delta selective inhibitor is TGR-1202. In some embodiments, the anti-CD20 antibody is ublituximab, the PI3K-delta selective inhibitor is TGR-1202, and the BTK inhibtor is ibrutinib.

[0280] When the agents of the present disclosure are administered to a subject (*e.g.*, a human subject), the agents can be administered as a composition that comprises a pharmaceutically acceptable carrier or excipient, by any appropriate route, such as intradermal, intramuscular, intraperitoneal, parenteral, intravenous, subcutaneous, intranasal, epidural, oral, sublingual, buccal, intracerebral, intravaginal, transdermal,

Examples

Example 1: Triple Combination of a PI3K-delta Inhibitor of Formula A (TGR-1202), an Anti-CD20 Antibody (ublituximab), and a BTK Inhibitor (ibrutinib) to Treat B-cell Malignancies

[0283] Background**:** Novel targeted agents are emerging for B-cell malignancies, but few studies have successfully and safely combined these agents. Ublituximab (UTX) is a novel glycoengineered type 1 chimeric IgG1 mAb targeting a unique epitope on the CD20 antigen that is not targeted by rituximab or ofatumumab. *See*, Miller, J. *et al*., *Blood 120:* Abstract No. 2756 (2012); Deng, C. *et. al*., *J. Clin. Oncol. 31*:Abstract No. 8575 (2013); O'Connor, O.A. *et al*., *J. Clin. Oncol. 32*:5s (2014), (suppl; Abstract No. 8524). Ublituximab was glycoengineered for potent activity, exhibiting a unique primary amino acid sequence and a low fucose content, which was designed to induce superior antibody-dependent cell-mediated cytotoxicity ("ADCC"). Responses with single agent ublituximab have been observed in rituximab refractory patients. *Id.*

[0284] Umbralisib (also known as TGR-1202) is a next generation, highly specific, once daily, orally available, PI3K-delta inhibitor, active in patients with a wide variety of relapsed or refractory (rel/ref) hematologic malignancies. *See*, O' Connor, O.A. *et al*., *Blood 126*: Abstract No. 4154 (2015); Burris, H. *et al*., *J Clin Oncol 33* (2015) (suppl; abstract 7069); Burris, H. *et al*., *J Clin Oncol 32*:5s, (2014) (suppl; abstract 2513); Burris, H. *et al*., *Blood* 124: Abstract No. 1984 (2014). TGR-1202 has a unique molecular structure that provides it with an advantageous safety profile, notably with respect to hepatic toxicity and colitis. *Id*. The favorable safety profile of TGR-1202 compared to prior inhibitors has been demonstrated, including in long-term follow up. Burris, H. *et al*., "Long-term follow-up of the PI3K delta inhibitor TGR-1202 demonstrates a differentiated safety profile and high response rates in CLL and NHL: Integrated-analysis of TGR-1202 monotherapy and combined with ublituximab," American Society of Clinical Oncology Annual Meeting (ASCO), Abstract #7512 (June 3, 2016) . The delta isoform of PI3K is highly expressed in cells of hematopoietic origin, and strongly upregulated, and often mutated, in various hematologic malignancies.

[0285] The orally-administered BTK inhibitor ibrutinib is currently FDA-approved and marketed under the name Imbruvica® for the treatment of a variety of B-cell neoplasms,

such as mantle cell lymphoma, CLL, and Waldenstrom's macroglobulinemia (a form of non-Hodgkin's lymphoma (NHL)). *See*, Imbruvica® full prescribing information (Pharmacyclics LLC and Janssen Biotech, Inc.). Also, see Honigsberg, L.A. *et al., PNAS 107*:13075-13080 (2010) and U.S. Patent Nos. 7,514,444, 8,697,711, 8,703,780, 8,088,309, and 8,088,781.

[0286] The safety, maximum tolerated dose (MTD), and efficacy of the triplet combination of the anti-CD20 antibody, ublituximab, + the PI3K-delta inhibitor, TGR-1202, + the BTK inhibitor, ibrutinib, were evaluated in 38 patients with relapsed and refractory B-cell malignancies, such as chronic lymphocytic leukemia (CLL) and Non-Hodgkins Lymphoma (NHL) in a Phase 1 clinical trial.

[0287] Methods: Patients eligible for the trial had a confirmed diagnosis of chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), or B-cell non-Hodgkin lymphoma (NHL) with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2, and adequate organ system function (i.e., ANC $\geq$ 500/µl; platelets $\geq$ 30K/µl). In general, patients had to have relapsed after, or were refractory to, at least one prior treatment regimen, with no limit on the number of prior therapies. (One exception was treatment naïve CLL/SLL patients). Patients with other B-cell lymphoproliferative disorders (i.e., Richter's Transformation), or patients that were refractory (did not respond) to prior PI3K-delta inhibitors or prior BTK inhibtors were also eligible. Patients that relapsed from prior autologous stem cell transplant after 90 days were also eligible.

[0288] A total of 38 patients (n=38) were administered the triplet combination, including 6 patients with follicular lymphoma (FL), 16 patients with chronic lymphocytic leukemia (CLL), 4 patients with small lymphocytic lymphoma (SLL), 6 patients with diffuse large B-cell lymphoma (DLBCL), 2 patients with marginal zone lymphoma (MZL), and 4 patients with mantle cell lymphoma (MCL). The median patient age was 65 years (range 32-85). The 29 male and 9 female patients had received a median of 3 prior treatment regimens (range 0-6). The number of patients with 3 or more prior therapies was 21 (55%). Regarding the ECOG scale of performance status for the 38 patients studied: 14 patients were at ECOG 0; 21 patients were at ECOG 1; and 3 patients were at ECOG 2. *See*, Oken, M.M. *et al*., *Am J Clin. Oncol. 5*:649-655 (1982). Thirteen patients (34%)

experiencing a Grade 3 or 4 event. Pneumonia and neutropenia were the only Grade 3 or 4 adverse events in greater than 10% of patients.

[0292] Of the 38 patients treated to date, two patients discontinued due to an adverse event (pneumonia and sepsis). One dose limiting toxicity (DLT) was observed in the CLL level 1 cohort (400 mg TGR-1202) due to reactivation of varicella zoster. No other DLT's were observed.

Clinical Activity

[0293] Thirty six (36) of 38 patients were evaluable for efficacy (two patients discontinued prior to the first efficacy assessment – 1 patient was removed per investigator discretion and 1 patient was removed due to pneumonia). The efficacy of treating CLL was examined per the standard international working group guidelines set forth in Hallek, M. *et al*., *Blood 111*:5446-5456 (2008). The efficacy of treating NHL was examined per the standard international working group guidelines set forth in Cheson, B.D. *et al*., *J Clin Oncol 25*:579-586 (2007).

[0294] A clinical response was observed at all three dose levels of TGR-1202.

[0295] **FIG. 2** is a bar graph depicting efficacy as reflected in the best percent change from baseline in disease burden in all patients who had received at least one post baseline scan to assess disease/tumor burden. **FIG. 4** presents efficacy results in terms of the level of clinical response (i.e., CR, PR, ORR, SD, and PD).

[0296] In the CLL/SLL cohort, 100% of patients (19 of 19) achieved an objective response, with 8 out of 16 CLL patients having a 17p and /or 11q deletion (a high risk feature). See, **FIGS. 2** and **4**. Three CLL patients had prior BTK and/or PI3K-delta inhibitor therapy, including one patient refractory to both idelalisib and ibrutinib who attained a complete response that has been ongoing for 1.5 years.

[0297] The two patients with marginal zone lymphoma (MZL) achieved an objective response with one being a complete response (CR) and one being a partial response (PR). See, **FIGS. 2** and **4**.

[0298] In the 5 patients with heavily pre-treated (≥ 4 prior lines of therapy) follicular lymphoma (FL), 80% (4 of 5) achieved an objective response including 2 with prior autologous stem cell transplantation (ASCT), 1 refractory to prior ibrutinib, and 1 with 5 prior lines of rituximab-based therapy. See, **FIG. 2** and **4**.

[0299] Of the four mantle cell lymphoma (MCL) patients, 100% of patients (4 of 4) achieved an objective response with 2 patients achieving a complete response (CR), as determined by radiography with bone marrow confirmation pending, and 2 patients achieving a partial response (PR). See, **FIGS. 2 and 4**. One MCL patient remains on study now for close to 800 days. (**FIG. 3**).

[0300] The 5 patients who showed progressive disease (PD) on study had Diffuse Large B-Cell Lymphoma (DLBCL). The DLBCL patients had a median of four prior therapies, and 4 out of the 6 patients with DLBCL were of the non-germinal center B-cell-like (GCB) subtype. See, **FIG. 4**.

[0301] *Duration of study*: 81% of patients were on the study for more than 6 months. The median time on the study was 11.1 months (range 0.4 - 30.1+ months). (See **FIG. 3**). One CLL patient and one FL patient has been on the study for over 900 days. **FIG. 3.**

[0302] Conclusions**:** This is the first triple combination of an anti-CD20 antibody, a PI3K-delta inhibitor, and a BTK inhibitor used to treat B-cell malignancies. The combination of UTX + TGR-1202 + ibrutinib was well-tolerated with clinical activity observed across heavily pre-treated and high-risk B-cell malignancies.

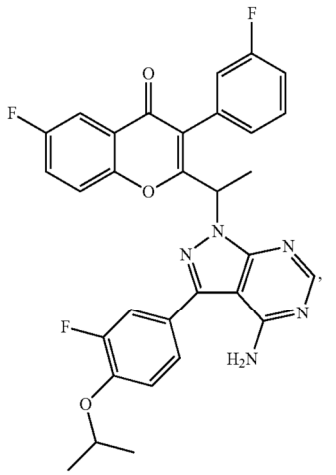
[0303] The present invention has been described above with the aid of functional building blocks illustrating the implementation of specified functions and relationships thereof. The boundaries of these functional building blocks have been arbitrarily defined herein for the convenience of the description. Alternate boundaries can be defined so long as the specified functions and relationships thereof are appropriately performed.

[0304] The foregoing description of the specific embodiments will so fully reveal the general nature of the invention that others can, by applying knowledge within the skill of the art, readily modify and/or adapt for various applications such specific embodiments, without undue experimentation, without departing from the general concept of the present invention. Therefore, such adaptations and modifications are intended to be within the meaning and range of equivalents of the disclosed embodiments, based on the teaching and guidance presented herein. It is to be understood that the phraseology or terminology herein is for the purpose of description and not of limitation, such that the terminology or phraseology of the present specification is to be interpreted by the skilled artisan in light of the teachings and guidance.

1. Use of a therapeutic combination of agents comprising

(i) at least one PI3K-delta selective inhibitor represented by Formula A, a stereoisomer thereof, a pharmaceutically acceptable salt, or solvate, thereof:

(A)



selected from

(RS)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one; or

(S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyI)-4H-chromen-4-one;

(ii) at least one anti-CD20 antibody or an antigen-binding fragment thereof, wherein said anti-CD20 antibody is ublituximab or an anti-CD20 antibody that binds to the same epitope as ublituximab; and

(iii) at least one inhibitor of Bruton's tyrosine kinase (BTK);

in the manufacture of a medicament for the treatment of chronic lymphocytic leukemia (CLL), marginal zone lymphoma (MZL) or non-Hodgkin’s lymphoma (NHL) in a subject, wherein therapeutically effective amounts of said agents are to be administered to inhibit proliferation of B-cells and thereby reduce said subject’s baseline disease burden by at least 50% by the first efficacy assessment.

2. The use of claim 1, wherein

said at least one BTK inhibitor is selected from the group consisting of ibrutinib; acalabrutinib; GDC-0834; ONO-4059; RN-486; spebrutinib; SNS-062; HM-71224; CGI-560; CGI-1746; CTA-056; CNX-774; BGB-3111; LFM-A13; PCI-45227; dasatinib; ONO-WG-307; JTE-051; AVL-263; AVL-291; AVL-101; TP-4207; PCI-45292; PCI-45466; CG-036806; TAS-5567; PCI-45261; KBP-7536; HCI-1684; PLS-123; BMS-488516; BMS-509744; and HY-11066.

3. The use of claim 1 or 2, wherein the PI3K-delta inhibitor is to be administered at a dosage from: 200 mg to 1200 mg, 400 mg to 1000 mg, 400 mg to 800 mg, 400 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, or 1200 mg.

4. The use of any one of claims 1-3, wherein the PI3K-delta inhibitor is (S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one or a pharmaceutically acceptable salt thereof.

5. The use of claim 4, wherein the PI3K-delta inhibitor is (S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one p-toluenesulfonic acid salt (TGR-1202).

6. The use of claim 5, wherein TGR-1202 is to be administered at a dose from (a) 400 mg to 1200 mg per day or (b) 800 mg per day.

7. The use of any one of claims 1-6, wherein said anti-CD20 antibody is ublituximab.

8. The use of claim 7, wherein said ublituximab comprises (i) the VH CDR1, CDR2, and CDR3 region of sequences SEQ ID NOS: 1, 2, and 3, and the VL CDR1, CDR2, and CDR3 region of sequences SEQ ID NOS: 6, 7, and 8, or (ii) the VH of SEQ ID NO: 4 and the VL of SEQ ID NO: 9.

9. The use of claim 7 or 8, wherein the ublituximab is to be administered at a dose from: 450 mg to 1200 mg, 600 to 1200 mg, 600 to 1000 mg, 600 to 900 mg, 600 mg, 700 mg, 800

mg, or 900 mg once every 1 to 9 weeks, once every week, twice every week, once every 2 weeks, once every 3 weeks, once every 4 weeks, once every 5 weeks, once every 6 weeks,once every 7 weeks, once every 8 week, or once every 9 weeks.

10. The use of claim 9, wherein the ublituximab is to be administered at a dose of about 900 mg.

11. The use of any one of claims 1-10, wherein said combination of agents comprises:

(i) TGR-1202;

(ii) ublituximab; and

(iii) a Bruton's tyrosine kinase (BTK) inhibitor.

12. The use of any one of claims 1-11, wherein the BTK inhibitor is ibrutinib or acalabrutinib.

13. The use of claim 12, wherein ibrutinib is to be administered once daily at a dosage from: 400 to 600 mg, 400 mg, 420 mg, 440 mg, 480 mg, 500 mg, 520 mg, 540 mg, 560 mg, 580 mg, or 600 mg.

14. The use of claim 13, wherein ibrutinib is to be administered once daily at a dosage of about 420 mg or about 560 mg per day.

15. The use of any one of claims 1-14, wherein said CLL, MZL or NHL overexpresses CD20, is refractory to chemotherapy or has relapsed.

16. The use of claim 15, wherein the CLL, MZL or NHL is refractory to an anti-CD20 antibody, a PI3K-delta inhibitor, or a BTK inhibitor.

17. The use of any one of claims 1-16, wherein said combination of agents i, ii, and iii are to be administered separately and/or sequentially.

18. The use of any one of claims 1-17, wherein said agents i and iii are to be administered simultaneously or sequentially once a day, and are contained in the same or separate pharmaceutical composition.

19. The use of method of any one of claims 1-18, wherein said tumor burden is reduced by at least 75%.

20. Use of a therapeutic combination of agents comprising:

(i) at least one PI3K-delta selective inhibitor;

(ii) at least one anti-CD20 antibody or an antigen-binding fragment thereof; and

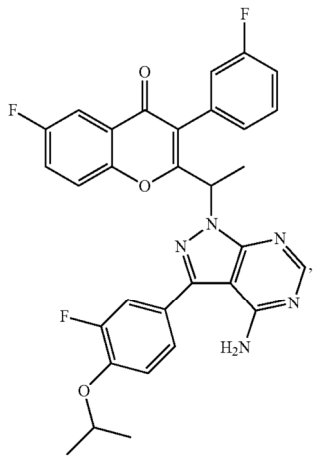
(iii) at least one Bruton's tyrosine kinase (BTK) inhibitor;

in the manufacture of a medicament to treat a disease or disorder associated with excessive B-cell proliferation in a subject, wherein therapeutically effective amounts of said agents are to be administered to deplete said B-cells by promoting apoptosis, promoting cell-cycle arrest, blocking the B-cell receptor (BCR) signaling pathway, or any combination thereof.

21. The use of Claim 20, wherein

said PI3K-delta selective inhibitor is represented by Formula A, a stereoisomer thereof, a pharmaceutically acceptable salt, or solvate, thereof:

(A)



selected from (RS)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one; or (S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyI)-4H-chromen-4-one; and

said at least one anti-CD20 antibody or an antigen-binding fragment thereof, is ublituximab or an anti-CD20 antibody that binds to the same epitope as ublituximab.

22. A kit comprising: (a) a combination of agents (i)-(iii) of claim 1; and (b) instructions for using said PI3K-delta selective inhibitor in combination with an anti-CD20 antibody or fragment thereof, and an inhibitor of BTK, as a combined preparation for use in the treatment of chronic lymphocytic leukemia (CLL), marginal zone lymphoma (MZL) or non-Hodgkin's lymphoma (NHL) in a subject.

23. The kit for use of claim 22, wherein agent (i) is (S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one or a pharmaceutically acceptable salt thereof .

24. The kit for use of claim 23, wherein agent (ii) is ublituximab.

25. The kit for use of any one of claims 22-24, wherein agent (iii) is ibrutinib or acalabrutinib.

26. The kit for use of any one of claims 22-25, wherein agent (i) is TGR-1202.