COMBINATION OF AN ANTI-CD20 ANTIBODY, PI3 KINASE-DELTA INHIBITOR, AND ANTI-PD-1 OR ANTI-PD-L1 ANTIBODY FOR TREATING HEMATOLOGICAL CANCERS

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 treating or slowing the progression of hematological cancers, by administering to a subject in need thereof a therapeutically effective amount of: (i) at least one inhibitor of PI3 kinase (PI3K)-delta (e.g., TGR-1202); (ii) at least one anti-CD20 antibody (e.g., ublituximab); and (iii) at least one anti-PD1 antibody (e.g., pembrolizumab) or anti-PD-L1 antibody (e.g., atezolizumab).

BACKGROUND OF THE INVENTION

[0002] Despite more than a century of scientific and clinical research, curing cancer remains a medical challenge. 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., nivolumab/Opdivo® for treating squamous cell and non-squamous cell non-small cell lung cancer (NSCLC), and pembrolizumab/Keytruda® for treating NSCLC). Small molecule therapies target dysregulated pathways of cancer cells, e.g., RAS, RAF, PI3K, MEK, JAK, STAT, and BTK.

[0003] While effective hematological cancer therapies exist, suboptimal response, relapsed- refractory disease, and/or resistance to one or more therapeutic agents have remained a challenge. Further, patients with higher risk cytogenetic abnormalities still present with a less than optimal response to approved therapies and shorter duration of response and progression free survival. Accordingly, there is a need for more effective, safe, and durable targeted combination therapies for the treatment of hematological malignancies.

SUMMARY

[0004] The present disclosure provides an innovative combination treatment and treatment regimen for patients with hematological malignancies.

[0005] Disclosed is a method for treating a subject afflicted with chronic lymphocytic leukemia (CLL) comprising administering to the subject in a treatment phase: (i) a therapeutically effective amount of a PI3-kinase delta inhibitor, wherein the PI3-kinase delta inhibitor is (S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrim-idin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one, or a pharmaceutically acceptable salt, solvate, or prodrug thereof; (ii) a therapeutically effective amount of ublituximab; and (iii) a therapeutically effective amount of an anti-PD-1 antibody.

[0006] Disclosed is a PI3-kinase delta inhibitor and/or ublituximab for use in a method for treating a subject afflicted with chronic lymphocytic leukemia (CLL) comprising administering to the subject in a treatment phase: (i) a therapeutically effective amount of the PI3-kinase delta inhibitor, wherein the PI3-kinase delta inhibitor is (S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrim-idin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one, or a pharmaceutically acceptable salt, solvate, or prodrug thereof; (ii) a therapeutically effective amount of ublituximab; and (iii) a therapeutically effective amount of an anti-PD-1 antibody.

[0007] In some embodiments, the anti-PD-1 antibody is pembrolizumab.

[0008] In some embodiments, the PI3-kinase delta inhibitor is in the form of a p-toluenesulfonic acid (PTSA) salt. In some embodiments, the PI3-kinase delta inhibitor is TGR-1202 (umbralisib tosylate).

[0009] In some embodiments, the PI3-kinase delta inhibitor, the ublituximab, and the pembrolizumab are administered to the subject simultaneously, sequentially, or both simultaneously and sequentially.

[0010] In some embodiments, the PI3-kinase delta inhibitor is administered daily at a dose from: about 200 to about 1200 mg, about 400 to about 1000 mg, about 400 to about 800 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, or about 1200 mg.

[0011] In some embodiments, the PI3-kinase delta inhibitor is administered daily at a dose of about 800 mg. In some embodiments, the PI3-kinase delta inhibitor is micronized. In some embodiments, the PI3-kinase delta inhibitor is formulated for oral administration.

[0012] In some embodiments, ublituximab is administered in the treatment phase at a dose from: about 450 to about 1200 mg, about 450 to about 1000 mg, about 500 to about 1200 mg, about 500 to about 1000 mg, about 500 to about 900 mg, about 600 to about 1200 mg, about 600 to about 1000 mg, about 600 to about 900 mg, about 500 mg, about 600 mg, about 700 mg, about 750 mg, about 800 mg, about 900 mg, about 1000 mg, about 1100 mg, or about 1200 mg about once every 4 to 7 weeks, about once every 5 to 7 weeks, about once every 5 to 6 weeks, about once a 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, or about once every 7 weeks.

[0013] In some embodiments, ublituximab is administered at a dose of about 900 mg about once every 6 weeks.

[0021] In some embodiments, the first dose of ublituximab is administered on day 1 of the induction phase. In some embodiments, the first dose of ublituximab, during the induction phase, is divided into 2 or 3 sub-doses to be administered in 2 or 3 consecutive days during the induction phase, or is divided into 2 sub-doses to be administered in 2 consecutive days.

[0022] In some embodiments, the first sub-dose of ublituximab comprises up to 150 mg of ublituximab. In some embodiments, the second sub-dose of ublituximab comprises up to 750 mg of ublituximab.

[0023] In some embodiments, the duration of the induction phase is up to about 12 weeks, up to about 11 weeks, up to about 10 weeks, up to about 9 weeks, or up to about 8 weeks. In some embodiments, the duration of the induction phase is about 8 weeks.

[0024] In some embodiments, the methods described herein further comprise, after the treatment phase, a maintenance phase, which comprises administering to the subject a therapeutically effective amount of a P13-kinase delta inhibitor, or a pharmaceutically acceptable salt, solvate or prodrug thereof. In some embodiments, the PI3-kinase delta inhibitor is administered daily at a dose from: about 200 to about 1200 mg, about 400 to about 1000 mg, about 400 to about 800 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, or about 1200 mg during the maintenance phase. In some embodiments, the PI3-kinase delta inhibitor is administered daily at a dose of about 800 mg during the maintenance phase. In some embodiments, the PI3-kinase delta inhibitor is micronized. In some embodiments, the PI3-kinase delta inhibitor is formulated for oral administration during the maintenance phase.

[0025] In some embodiments, the duration of the maintenance phase is as long as clinical benefit is observed, or until unmanageable toxicity or disease progression occurs. In some embodiments, the maintenance phase ends when disease progression occurs. In some embodiments, the duration of the maintenance phase is at least 3 weeks.

[0026] In some embodiments, the subjects that are treated with the methods described herein are afflicted with relapsed-refractory CLL.

[0027] Disclosed is a method for treating a subject afflicted with relapsed-refractory chronic lymphocytic leukemia (CLL) comprising administering to the subject during a treatment phase: (i) a daily amount of about 800 mg of a PI3-kinase delta inhibitor, wherein the PI3-kinase delta inhibitor is (S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrim-idin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one, or a pharmaceutically acceptable salt, solvate or prodrug thereof; (ii) about 900 mg of ublituximab once every 6 weeks, wherein the first dose of ublituximab is administered on day 1 of the sixth week after the treatment phase is initiated; and (iii) about 100 mg or 200 mg of pembrolizumab once every 3 weeks, wherein the first dose of pembrolizumab is administered on day 1 when the treatment phase is initiated; wherein the duration of the treatment phase is about 12 weeks; and wherein the PI3-kinase delta inhibitor, the ublituximab, and the pembrolizumab are administered to the subject simultaneously, sequentially, or both simultaneously and sequentially.

[0028] Disclosed is a PI3-kinase delta inhibitor and/or ublituximab for use in a method for treating a subject afflicted with relapsed-refractory chronic lymphocytic leukemia (CLL) comprising administering to the subject during a treatment phase: (i) a daily amount of about 800 mg of the PI3-kinase delta inhibitor, wherein the PI3-kinase delta inhibitor is (S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrim-idin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one, or a pharmaceutically acceptable salt, solvate or prodrug thereof; (ii) about 900 mg of ublituximab once every 6 weeks, wherein the first dose of ublituximab is administered on day 1 of the sixth week after the treatment phase is initiated; and (iii) about 100 mg or 200 mg of pembrolizumab once every 3 weeks, wherein the first dose of pembrolizumab is administered on day 1 when the treatment phase is initiated; wherein the duration of the treatment phase is about 12 weeks; and wherein the PI3-kinase delta inhibitor, the ublituximab, and the pembrolizumab are administered to the subject simultaneously, sequentially, or both simultaneously and sequentially.

[0029] In some embodiments, the methods described herein further comprise, prior to the treatment phase, an induction phase, comprising administering to the subject: (i) a daily amount of about 800 mg of a PI3-kinase delta inhibitor, wherein the PI3-kinase delta inhibitor is (S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrim-idin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one, or a pharmaceutically acceptable salt, solvate or prodrug thereof daily; and (ii) about 900 mg of ublituximab once every 1 or 2 weeks; wherein the first dose of ublituximab is administered on day 1 of the induction phase; wherein the duration of the induction phase is about 8 weeks; and wherein the PI3-kinase delta inhibitor and the ublituximab are administered to the subject simultaneously, sequentially, or both simultaneously and sequentially.

[0030] In some embodiments, the first dose of ublituximab is divided into 2 sub-doses during the induction phase, wherein the first sub-dose comprises up to 150 mg of ublituximab; and the second sub-dose comprises up to 750 mg of ublituximab; and wherein the first and second sub-doses are administered on day 1 and day 2 of the induction phase, respectively.

[0031] In some embodiments, the methods of the disclosure further comprise, after the treatment phase, a maintenance phase, comprising administering to the subject daily about 800 mg of a PI3-kinase delta inhibitor, or a pharmaceutically acceptable salt, solvate or prodrug thereof, wherein the duration of the maintenance phase is at least 3 weeks. In some embodiments, the PI3-kinase delta inhibitor is micronized and is formulated for oral administration. In some embodiments, the ublituximab and the pembrolizumab are formulated for intravenous infusion.

[0032] Disclosed is a kit for treating a subject afflicted with relapsed-refractory CLL, the kit comprising: (i) a single dose or multiple doses of ublituximab; (ii) a single dose or multiple doses of a PI3-kinase delta inhibitor, wherein the PI3-kinase delta inhibitor is (S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrim-idin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one, or a pharmaceutically acceptable salt, solvate, or prodrug thereof; (iii) a single dose or

multiple doses of an anti-PD-1 antibody; and (iv) instructions for using said ublituximab, said PI3-kinase delta inhibitor, and said anti-PD-1 antibody according to the methods described herein. In some embodiments, the anti-PD-1 antibody is pembrolizumab.

[0033] Disclosed is a method of treating a subject afflicted with a hematologic cancer, comprising administering to the subject in a treatment phase: (i) a therapeutically effective amount of a PI3 kinase-delta inhibitor; (ii) a therapeutically effective amount of an anti-CD20 antibody; and (iii) a therapeutically effective amount of an anti-PD-1 or anti-PD-L1 antibody.

[0034] Disclosed is a PI3-kinase delta inhibitor and/or ublituximab for use in a method of treating a subject afflicted with a hematologic cancer, comprising administering to the subject in a treatment phase: (i) a therapeutically effective amount of the PI3 kinase-delta inhibitor; (ii) a therapeutically effective amount of an anti-CD20 antibody; and (iii) a therapeutically effective amount of an anti-PD-1 or anti-PD-L1 antibody.

[0034a] In one aspect, there is provided use of a therapeutic combination of agents comprising (i) a therapeutically effective amount of a PI3 kinase-delta inhibitor; (ii) a therapeutically effective amount of an anti-CD20 antibody; and (iii) a therapeutically effective amount of an anti-PD-1 or anti-PD-L1 antibody in the manufacture of a medicament for the treatment of a subject afflicted with a hematologic cancer; wherein said agents are to be administered to the subject in a treatment phase.

[0034b] In another aspect, there is provided a therapeutic combination of agents comprising (i) a therapeutically effective amount of a PI3 kinase-delta inhibitor; (ii) a therapeutically effective amount of an anti-CD20 antibody; and (iii) a therapeutically effective amount of an anti-PD-1 or anti-PD-L1 antibody; for use as a medicament.

[0035] In some embodiments, the PI3 kinase-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, solvate, or prodrug thereof. In some embodiments, the PI3 kinase-delta inhibitor is in the form of a p-toluenesulfonic acid (PTSA) salt. In some embodiments, the PI3 kinase-delta inhibitor is TGR-1202 (umbralisib tosylate).

[0036] In some embodiments, the anti-CD20 antibody is ublituximab or an antibody fragment that binds the same epitope as ublituximab.

[0037] In some embodiments, the anti-PD-1 antibody is nivolumab, pembrolizumab, or pidilizumab.

[0038] In some embodiments, the anti-PD-L1 antibody is CTI-07, CTI-09, CTI-48, CTI-49, CTI-50, CTI-76, CTI-77, CTI-78, CTI-57, CTI-58, CTI-97, CTI-98, CTI-92, CTI-95, CTI-93, CTI-94, CTI-96, durvalumab, BMS-936559, atezolizumab, or avelumab.

[0039] In some embodiments, the anti-PD-L1 antibody is CTI-48.

[0040] In some embodiments, the hematological cancer is lymphoma, leukemia, or myeloma.

[0041] In some embodiments, the hematological cancer is 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), or Richter's transformation.

[0042] In some embodiments, the hematological cancer expresses PD-1 or PD-L1.

[0043] In some embodiments, the hematological cancer is relapsed-refractory disease. In some embodiments, the hematological cancer is relapsed-refractory CLL.

[0044] Disclosed is a method of treating a subject afflicted with a hematologic cancer, comprising administering to the subject in a treatment phase: (i) a therapeutically

effective amount of a PI3-kinase delta inhibitor, wherein the PI3-kinase delta inhibitor is (S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrim-idin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one, or a pharmaceutically acceptable salt, solvate, or prodrug thereof; (ii) a therapeutically effective amount of ublituximab; and (iii) a therapeutically effective amount of an anti-PD-1 antibody or anti-PD-L1 antibody.

[0045] Disclosed is a PI3-kinase delta inhibitor and/or ublituximab for use in a method of treating a subject afflicted with a hematologic cancer, comprising administering to the subject in a treatment phase: (i) a therapeutically effective amount of the PI3-kinase delta inhibitor, wherein the PI3-kinase delta inhibitor is (S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrim-idin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one, or a pharmaceutically acceptable salt, solvate, or prodrug thereof; (ii) a therapeutically effective amount of ublituximab; and (iii) a therapeutically effective amount of an anti-PD-1 antibody or anti-PD-L1 antibody.

[0045a] In another aspect, there is provided use of a therapeutic combination comprising (i) a therapeutically effective amount of a PI3 kinase-delta inhibitor, wherein said PI3 kinase-delta inhibitor is (S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrim-idin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one, or a pharmaceutically acceptable salt, solvate, or prodrug thereof; (ii) a therapeutically effective amount of ublituximab; and (iii) a therapeutically effective amount of an anti-PD-1 antibody or anti-PD-L1 antibody in the manufacture of a medicament for the treatment of a subject afflicted with a hematologic cancer; wherein said agents are to be administered to the subject in a treatment phase.

[0045b] In another aspect, there is provided a therapeutic combination comprising (i) a therapeutically effective amount of a PI3 kinase-delta inhibitor, wherein said PI3 kinase-delta inhibitor is (S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrim-idin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one, or a pharmaceutically acceptable salt, solvate, or prodrug thereof; (ii) a therapeutically effective amount of ublituximab; and (iii) a therapeutically effective amount of an anti-PD-1 antibody or anti-PD-L1 antibody; for use as a medicament.

[0046] In some embodiments, the anti-PD-1 antibody is nivolumab, pembrolizumab, or pidilizumab.

[0047] In some embodiments, the anti-PD-L1 antibody is CTI-07, CTI-09, CTI-48, CTI-49, CTI-50, CTI-76, CTI-77, CTI-78, CTI-57, CTI-58, CTI-97, CTI-98, CTI-92, CTI-95, CTI-93, CTI-94, CTI-96, durvalumab, BMS-936559, atezolizumab, or avelumab.

[0048] In some embodiments, the anti-PD-L1 antibody is CTI-48.

[0049] In some embodiments, the subject treated for a hematological cancer with the methods described herein is a human.

[0050] In some embodiments, the method described herein further comprises, prior to the treatment phase, an induction phase, comprising administering to the subject: (i) a therapeutically effective amount of a PI3 kinase-delta inhibitor, wherein the PI3-kinase delta inhibitor is (S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrim-idin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one, or a pharmaceutically acceptable salt, solvate, or prodrug thereof; and (ii) a therapeutically effective amount of ublituximab. In some embodiments, the PI3 kinase-delta inhibitor is in the form of a p-toluenesulfonic acid (PTSA) salt. In some embodiments, the PI3 kinase-delta inhibitor is TGR-1202 (umbralisib tosylate).

[0051] In some embodiments, the method described herein further comprises, after the treatment phase, a maintenance phase, comprising administering to the subject a therapeutically effective amount of a PI3 kinase-delta inhibitor, or a pharmaceutically acceptable salt, solvate or prodrug thereof.

[0052] In some embodiments, the PI3 kinase-delta inhibitor, the ublituximab, and the anti-PD-1 antibody or anti-PD-L1 antibody are administered to the subject simultaneously, sequentially, or both simultaneously and sequentially.

[0053] Disclosed is a kit for treating a subject afflicted with a hematological cancer, the kit comprising: (i) a single dose or multiple doses of ublituximab; (ii) a single dose or multiple doses of a PI3 kinase-delta inhibitor, wherein the PI3 kinase-delta inhibitor is (S)-2-(1-(4-

amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrim-idin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one, or a pharmaceutically acceptable salt, solvate, or prodrug thereof; (iii) a single dose or multiple doses of an anti-PD-1 or anti-PD-L1 antibody; and (iv) instructions for using said ublituximab, said PI3 kinase-delta inhibitor, and said anti-PD-1 or anti-PD-L1 antibody, according to the methods of the present disclosure.

[0053a] In another aspect, there is provided a kit comprising: (i) a single dose or multiple doses of ublituximab; (ii) a single dose or multiple doses of a PI3 kinase-delta inhibitor, wherein said PI3 kinase-delta inhibitor is (S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrim-idin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one, or a pharmaceutically acceptable salt, solvate, or prodrug thereof; (iii) a single dose or multiple doses of an anti-PD-1 or anti-PD-L1 antibody; and (iv) instructions for using said ublituximab, said PI3 kinase-delta inhibitor, and said anti-PD-1 or anti-PD-L1 antibody, for treatment of a subject afflicted with a hematological cancer according to the use as described herein.

[0054] In some embodiments, the anti-PD-1 antibody in the kit is pembrolizumab. In some embodiments, the anti-PD-L1 antibody in the kit is atezolizumab. In some embodiments, the PI3 kinase-delta inhibitor in the kit is in the form of a p-toluenesulfonic acid (PTSA) salt. In some embodiments, the PI3 kinase-delta inhibitor in the kit is TGR-1202 (umbralisib tosylate).

BRIEF DESCRIPTION OF THE DRAWINGS

[0055] **Figure 1** is a graph showing the percent inhibition of PD-1 binding to PD-L-1+ cells by anti-PD-L1 antibodies, CTI-09, CTI-48, CTI-50, CTI-58, and a clinical control. The results were obtained using FACS analysis.

[0056] **Figures 2A-2C** are graphs showing the binding kinetics of exemplary anti-PD-L1 antibody CTI-48 against human PD-L1 (Fig. 2A), mouse PD-L1 (Fig. 2B), and cyno PD-L1 (Fig. 2C).

[0057] **Figure 3** is a bar graph showing that exemplary anti-PD-L1 antibody CTI-48 exhibits ADCC activity on PD-L1+ lymphoma cells with primary NK cells.

[0058] **Figure 4** is a graph showing the reversal of T-cell inhibition with PD-L1 in a reporter (NFAT) bioassay of immunoblockade with select anti-PD-L1 antibodies, CTI-48 and CTI-49, and a clinical control mAb.

[0059] **Figure 5** is a graph showing blocking of PD-L1 binding to B7.1 by the PD-L1 antibody, CTI-48, and a clinical control mAb.

[0060] **Figure 6** is a bar graph showing the effect of the disclosed PD-L1 antibodies on IFN-γ production. Antibodies were dosed into mixed lymphocyte reaction (MLR) cultures at a concentration of 10 μg/mL. Data were normalized to vehicle control and are presented as combined mean +SEM (n=6). *p<0.05 ** p<0.01, ***p<0.001 indicates statistical significance when compared to appropriate isotype control (hIgG1) using Ordinary one-way ANOVA with Dunnett's multiple comparison post-hoc test. This figure shows a side-by-side comparison of PD-L1 antibody, CTI-48, and a clinical control mAb.

[0061] **Figure 7** is a Kaplan-Meier plot of months of progression-free survival in 9 patients with CLL according to the phase 1/2 study discussed in Example 1.

[0062] **Figure 8** is a graphic parallel representation (a.k.a. "swimmers plot") of each of the 9 patients with CLL studied in Example 1, and their number of days of progression-free survival during each phase (induction/consolidation/maintenance) of the clinical study. Each bar represents each patient in the study.

What is claimed is:

1. Use of a therapeutic combination of agents comprising

(i) a therapeutically effective amount of a PI3 kinase-delta inhibitor;

(ii) a therapeutically effective amount of an anti-CD20 antibody; and

(iii) a therapeutically effective amount of an anti-PD-1 or anti-PD-L1 antibody

in the manufacture of a medicament for the treatment of a subject afflicted with a hematologic cancer; wherein said agents are to be administered to the subject in a treatment phase.

2. The use of claim 1, wherein

(i) the PI3 kinase-delta inhibitor is (S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrim-idin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one, or a pharmaceutically acceptable salt, solvate, or prodrug thereof

(ii) the anti-CD20 antibody is ublituximab or an antibody fragment that binds the same epitope as ublituximab and

(iii) the anti-PD-1 antibody is nivolumab, pembrolizumab, pidilizumab, CTI-07, CTI-09, CTI-48, CTI-49, CTI-50, CTI-76, CTI-77, CTI-78, CTI-57, CTI-58, CTI-97, CTI-98, CTI-92, CTI-95, CTI-93, CTI-94, CTI-96, durvalumab, BMS-936559, atezolizumab, or avelumab.

3. Use of a therapeutic combination comprising

(i) a therapeutically effective amount of a PI3 kinase-delta inhibitor, wherein said PI3 kinase-delta inhibitor is (S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrim-idin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one, or a pharmaceutically acceptable salt, solvate, or prodrug thereof;

(ii) a therapeutically effective amount of ublituximab; and

(iii) a therapeutically effective amount of an anti-PD-1 antibody or anti-PD-L1 antibody

in the manufacture of a medicament for the treatment of a subject afflicted with a hematologic cancer; wherein said agents are to be administered to the subject in a treatment phase.

4. The use of any one of claims 1-3, wherein the duration of the treatment phase is up to about 15 weeks, up to about 14 weeks, up to about 13 weeks, or up to about 12 weeks.

5. The use of claim 4, wherein the duration of the treatment phase is about 12 weeks.

6. The use of claim 3, wherein:

(i) a daily amount of about 800 mg of a PI3-kinase delta inhibitor is to be administered to the subject during a treatment phase, wherein the PI3-kinase delta inhibitor is (S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrim-idin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one, or a pharmaceutically acceptable salt, solvate, or prodrug thereof;

(ii) about 900 mg of ublituximab is to be administered to the subject during a treatment phase once every 6 weeks, wherein the first dose of ublituximab is to be administered on day 1 of the sixth week after the treatment phase is initiated; and

(iii) about 100 mg or 200 mg of pembrolizumab is to be administered to the subject during a treatment phase once every 3 weeks, wherein the first dose of pembrolizumab is to be administered on day 1 when the treatment phase is initiated;

wherein the duration of the treatment phase is about 12 weeks; and

wherein the PI3-kinase delta inhibitor, the ublituximab, and the pembrolizumab are to be administered to the subject simultaneously, sequentially, or both simultaneously and sequentially.

7. The use of any of claims 1-6, wherein, prior to the treatment phase, during an induction phase:

(i) a therapeutically effective amount of a PI3 kinase-delta inhibitor, wherein said PI3 kinase-delta inhibitor is (S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrim-idin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one, or a pharmaceutically acceptable salt, solvate or prodrug thereof; and

(ii) a therapeutically effective amount of ublituximab

are to be administered to the subject.

8. The use of claim 7, wherein the duration of the induction phase is up to about 12 weeks, up to about 11 weeks, up to about 10 weeks, up to about 9 weeks, or up to about 8 weeks.

9. The use of claim 8, wherein the duration of the induction phase is about 8 weeks.

10. The use of claim 7, wherein, prior to the treatment phase, during an induction phase:

(i) a daily amount of about 800 mg of a PI3-kinase delta inhibitor is to be administered to the subject, wherein the PI3-kinase delta inhibitor is (S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrim-idin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one, or a pharmaceutically acceptable salt, solvate, or prodrug thereof; and

(ii) about 900 mg of ublituximab is to be administered to the subject once every 1 or 2 weeks; wherein the first dose of ublituximab is to be administered on day 1 of the induction phase;

wherein the duration of the induction phase is about 8 weeks; and

wherein the PI3-kinase delta inhibitor and the ublituximab are to be administered to the subject simultaneously, sequentially or both simultaneously and sequentially.

11. The use of any one of claims 1-10, wherein the hematological cancer is lymphoma, leukemia, or myeloma.

12. The use of claim 11, wherein the hematological cancer is 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), or Richter's transformation.

13. The use of claims 11 or 12, wherein the hematological cancer is chronic lymphocytic leukemia (CLL).

14. The use of claim 11 or 12, wherein the hematological cancer expresses PD-1 or PD-L1.

15. The use of any one of claims 11-14, wherein the hematological cancer is relapsed-refractory disease.

16. The use of any one of claims 11-15, wherein the hematological cancer is relapsed-refractory CLL.

17. The use of any one of claims 1-16, wherein the PI3 kinase-delta inhibitor is in the form of a p-toluenesulfonic acid (PTSA) salt.

18. The use of any one of claims 1-17, wherein the PI3-kinase delta inhibitor is to be administered daily at a dose from: about 200 to about 1200 mg, about 400 to about 1000 mg, about 400 to about 800 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, or about 1200 mg.

19. The use of of any one of claims 1-18, wherein ublituximab is to be administered at a dose from: about 450 to about 1200 mg, about 450 to about 1000 mg, about 500 to about 1200 mg, about 500 to about 1000 mg, about 500 to about 900 mg, about 600 to about 1200 mg, about 600 to about 1000 mg, about 600 to about 900 mg, about 500 mg, about 600 mg, about 700 mg, about 750 mg, about 800 mg, about 900 mg, about 1000 mg, about 1100 mg, or about 1200 mg, about once every 4 to 7 weeks, about once every 5 to 7 weeks, about once every 5 to 6 weeks, about once a 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, or about once every 7 weeks.

20. The use of any one of claims 1-19, wherein pembrolizumab is to be administered at a dose from: about 100 to about 300 mg, about 100 to about 200 mg, about 100 mg, about 150 mg, about 200 mg, or about 250 mg about once every 2 to 4 weeks, or about once every 3 to 4 weeks, or about once every 3 weeks.

21. The use of any one of claim 1-20, wherein the anti-PD-1 antibody is nivolumab, pembrolizumab, pidilizumab, CTI-07, CTI-09, CTI-48, CTI-49, CTI-50, CTI-76, CTI-77, CTI-78, CTI-57, CTI-58, CTI-97, CTI-98, CTI-92, CTI-95, CTI-93, CTI-94, CTI-96, durvalumab, BMS-936559, atezolizumab, or avelumab.

22. The use of any one of claims 1-21, wherein, after the treatment phase, during a maintenance phase, a therapeutically effective amount of a PI3 kinase-delta inhibitor, or

a pharmaceutically acceptable salt, solvate or prodrug thereof is to be administered to the subject.

23. The use of any one of claims 1-22, wherein the PI3 kinase-delta inhibitor, the ublituximab, and the anti-PD-1 antibody or anti-PD-L1 antibody are to be administered to the subject simultaneously, sequentially, or both simultaneously and sequentially.

24. The use of any one of claims 1-23, wherein the anti-PD-L1 antibody is CTI48.

25. A kit comprising:

(i) a single dose or multiple doses of ublituximab;

(ii) a single dose or multiple doses of a PI3 kinase-delta inhibitor, wherein said PI3 kinase-delta inhibitor is (S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrim-idin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one, or a pharmaceutically acceptable salt, solvate, or prodrug thereof;

(iii) a single dose or multiple doses of an anti-PD-1 or anti-PD-L1 antibody; and

(iv) instructions for using said ublituximab, said PI3 kinase-delta inhibitor, and said anti-PD-1 or anti-PD-L1 antibody, for treatment of a subject afflicted with a hematological cancer according to the use of any one of claims 1-21.

26. The kit of claim 25, wherein said anti-PD-1 antibody is pembrolizumab or atezolizumab.

27. The kit of claims 25 or 26, wherein said PI3 kinase-delta inhibitor is in the form of a p-toluenesulfonic acid (PTSA) salt.

28. The kit of claim 27, wherein said hematological cancer is chronic lymphocytic leukemia (CLL) or is relapsed-refractory chronic lymphocytic leukemia (CLL).

29. A therapeutic combination of agents comprising

(i) a therapeutically effective amount of a PI3 kinase-delta inhibitor;

(ii) a therapeutically effective amount of an anti-CD20 antibody; and

(iii) a therapeutically effective amount of an anti-PD-1 or anti-PD-L1 antibody;

for use as a medicament.

30. A therapeutic combination comprising

(i) a therapeutically effective amount of a PI3 kinase-delta inhibitor, wherein said PI3 kinase-delta inhibitor is (S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrim-idin-1-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one, or a pharmaceutically acceptable salt, solvate, or prodrug thereof;

(ii) a therapeutically effective amount of ublituximab; and

(iii) a therapeutically effective amount of an anti-PD-1 antibody or anti-PD-L1 antibody;

for use as a medicament.