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 agents, comprising: (i) at least one PI3K-delta selective inhibitor, wherein said at least one PI3K-delta selective 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-fluorophenyI)-4H-chromen-4-one or a pharmaceutically acceptable salt thereof; (ii) at least one anti-CD20 antibody, wherein said at least one anti-CD20 antibody is ublituximab; and (iii) at least one inhibitor of Bruton's tyrosine kinase (BTK); in the manufacture of a medicament for combination therapy 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 reduce said subject's baseline disease burden by at least 50% by the first efficacy assessment; and wherein said ublituximab is to be administered intravenously on days 1, 8, and 15 of cycle 1 and day 1 of cycles 2, 3, 4, 5, 6, 9, and 12, wherein each cycle is 28 days.

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

(i) TGR-1202;

(ii) ublituximab; and

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

in the manufacture of a medicament for combination therapy 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:

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) agents (i)-(iii) as described herein; and (b) instructions for administering said (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 or a pharmaceutically acceptable salt thereof, in combination with ublituximab, 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)

WHAT IS CLAIMED IS:

1. Use of agents, comprising:

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

(ii) at least one anti-CD20 antibody, wherein said at least one anti-CD20 antibody is ublituximab; and

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

in the manufacture of a medicament for combination therapy 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 reduce said subject's baseline disease burden by at least 50% by the first efficacy assessment; and wherein said ublituximab is to be administered intravenously on days 1, 8, and 15 of cycle 1 and day 1 of cycles 2, 3, 4, 5, 6, 9, and 12, wherein each cycle is 28 days.

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 p-toluenesulfonic acid salt (TGR-1202).

5. The use of claim 4, 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.

6. The use of any one of claims 1-5, 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.

7. The use of claim 6, 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.

8. The use of claim 7, wherein the ublituximab is to be administered at a dose of about 900 mg.

9. The use of any one of claims 1-8, wherein said combination of agents comprises:

(i) TGR-1202;

(ii) ublituximab; and

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

10. The use of any one of claims 1-9, wherein the BTK inhibitor is ibrutinib or acalabrutinib.

11. The use of claim 10, 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.

12. The use of claim 11, wherein ibrutinib is to be administered once daily at a dosage of about 420 mg or about 560 mg per day.

13. The use of any one of claims 1-12, wherein said CLL, MZL, or NHL overexpresses CD20, is refractory to chemotherapy, or has relapsed.

14. The use of claim 13, wherein the CLL, MZL, or NHL is refractory to an anti-CD20 antibody, a PI3K-delta inhibitor, or a BTK inhibitor, when administered as a monotherapy.

15. The use of any one of claims 1-14, wherein said combination of agents i, ii, and iii are to be administered separately and/or sequentially.

16. The use of any one of claims 1-15, 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.

17. The use of any one of claims 1-16, wherein said tumor burden is reduced by at least 75%.

18. Use of agents, comprising:

(i) TGR-1202;

(ii) ublituximab; and

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

in the manufacture of a medicament for combination therapy 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.

19. A kit comprising: (a) agents (i)-(iii) of claim 1; and (b) instructions for administering said (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 or a pharmaceutically acceptable salt thereof, in combination with ublituximab, 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.

20. The kit of claim 19, wherein agent (iii) is ibrutinib or acalabrutinib.

21. The kit of claim 19 or 20, wherein agent (i) is TGR-1202.