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 P13K-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, there is provided a therapeutic combination of agents comprising (i) at least one P13K-delta selective inhibitor; (ii) at least one anti-CD20 antibody or an antigen-binding fragment thereof; and (iii) at least one inhibitor of Bruton's tyrosine kinase (BTK); for use in the treatment of 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 inhibit proliferation of said B-cells.

[0005b] In another aspect, there is provided use of a therapeutic combination of agents comprising (i) at least one P13K-delta selective inhibitor; (ii) at least one anti-CD20 antibody or an antigen-binding fragment thereof; and (iii) at least one inhibitor of Bruton's tyrosine kinase (BTK); in the manufacture of a medicament for the treatment of a disease or disorder associated with excessive B-cell proliferation in a subject, wherein therapeutically effective amounts of said agent are to be administered to inhibit proliferation of said B-cells.

[0006] In some embodiments, the P13K-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 P13K delta selective inhibitor of Formula A, or a stereoisomer thereof, or a pharmaceutically acceptable salt, solvate, or prodrug thereof:

synthase inhibitors, non-BTK and non-P13K-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 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 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, the proliferation of the B-cell population is associated with 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, hairy cell leukemia (HCL), and Richter's transformation.

[0054] Disclosed is a kit comprising at least one P13K-delta selective inhibitor, at least one anti-CD20 antibody, and at least one inhibitor of BTK; and (b) instruction for using a P13K-delta selective inhibitor in combination with an anti-CD20 antibody and an inhibitor of BTK.

[0054a] In another aspect, there is provided a kit comprising: (a) a combination of agents (i)-(iii) as described herein; and (b) instructions for using said P13K-delta selective inhibitor in combination with an anti-CD20 antibody or fragment thereof, and an inhibitor of BTK.

[0055] Disclosed is a kit comprising at least one P13K-delta selective inhibitor of formula A, at least one anti-CD20 antibody, and at least one inhibitor of BTK. In certain embodiments, other agents that can be used to perform the methods described herein, and combinations thereof, are also included in the kit.

[0056] In some embodiments, the kit comprises (a) a P13K-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)

1. A therapeutic combination of agents comprising

(i) at least one P13K-delta selective inhibitor;

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

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

for use in the treatment of 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 inhibit proliferation of said B-cells.

2. Use of a therapeutic combination of agents comprising

(i) at least one P13K-delta selective inhibitor;

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

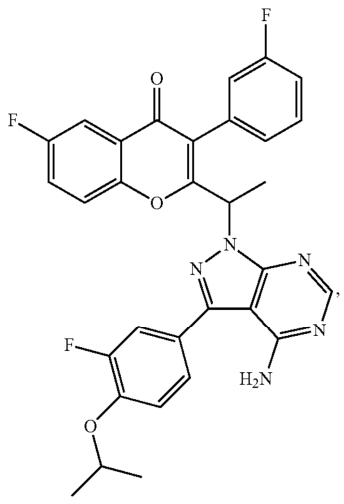
(iii) at least one inhibitor of Bruton's tyrosine kinase (BTK);

in the manufacture of a medicament for the treatment of a disease or disorder associated with excessive B-cell proliferation in a subject, wherein therapeutically effective amounts of said agent are to be administered to inhibit proliferation of said B-cells.

3. The therapeutic combination for use of claim 1, or the use of claim 2, wherein

(i) said at least one P13K-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; or

is idelalisib, duvelisib (IPI-145), ACP-319, INCB-50465, or ME-401;

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

(iii) 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.

4. The therapeutic combination for use of claim 1 or 3, or the use of claim 2 or 3, wherein the P13K-delta inhibitor is to be administered 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.

5. The therapeutic combination for use of claim any one of claims 1, 3 and 4, or the use of any one of claims 2-4, wherein the P13K-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.

6. The therapeutic combination for use of claim 5, or the use of claim 5, wherein the P13K-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).

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

8. The therapeutic combination for use of any one of claims 1 and 3-7, or the use of any one of claims 2-7, wherein said anti-CD20 antibody is ublituximab.

9. The therapeutic combination for use of claim 8, or the use of claim 8, 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.

10. The therapeutic combination for use of claim 8 or 9, or the use of claim 8 or 9, wherein the ublituximab is to be 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 about once every 1 to 9 weeks, about once every week, about twice 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.

11. The therapeutic combination for use of claim 10, or the use of claim 10, wherein the ublituximab is to be administered at a dose of about 900 mg.

12. The therapeutic combination for use of any one of claims 1 and 3-11, or the use of any one of claims 2-11, wherein the BTK inhibitor is ibrutinib or acalabrutinib.

13. The therapeutic combination for use of claim 12, or the use of claim 12, wherein said ibrutinib is to be administered once daily at a dosage from: 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.

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

15. The therapeutic combination for use of claim 1, or the use of claim 2, wherein said combination of agents comprises:

(i) TGR-1202;

(ii) ublituximab; and

(iii) ibrutinib.

16. The therapeutic combination for use of any one of claims 1 and 3-15, or the use of any one of claims 2-15, wherein disease or disorder is a hematological malignancy.

17. The therapeutic combination for use of claim 16, or the use of claim 16, wherein 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.

18. The therapeutic combination for use of claim 16 or 17, or the use of claim 16 or 17, wherein said hematological malignancy overexpresses CD20, said hematological malignancy is refractory to chemotherapy or said hematological malignancy has relapsed.

19. The therapeutic combination for use of claim 18, or the use of claim 18, wherein the hematological malignancy is refractory to an anti-CD20 antibody, a P13K-delta inhibitor, or a BTK inhibitor.

20. The therapeutic combination for use of any one of claims 1 and 3-19, or the use of any one of claims 2-19, wherein said combination of agents i, ii, and iii are to be administered separately and/or sequentially.

21. The therapeutic combination for use of any one of claims 1 and 3-20, or the use of any one of claims 2-20, wherein said agents i and iii are to be administered simultaneously or sequentially once a day, and, optionally, are contained in the same pharmaceutical composition.

22. The therapeutic combination for use of any one of claims 1 and 3-21, or the use of any one of claims 2-21, wherein inhibiting proliferation of said B-cells comprises depleting B-cells, promoting apoptosis, promoting cell-cycle arrest, blocking the B-cell receptor (BCR) signaling pathway, or any combination thereof.

23. A kit comprising: (a) a combination of agents (i)-(iii) of claim 1 or 2; and (b) instructions for using said P13K-delta selective inhibitor in combination with an anti-CD20 antibody or fragment thereof, and an inhibitor of BTK.

24. The kit of claim 23, 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 .

25. The kit of claim 23 or 24, wherein agent (ii) is ublituximab.

26. The kit of any one of claims 23-25, wherein agent (iii) is ibrutinib or acalabrutinib.

27. The kit of any one of claims 23-26, wherein agent (i) is TGR-1202.