CLAIMS

1. A method of reducing the number of B-cells or treating a disease or disorder associated with aberrant B-cell activity in a subject having or suspected having the disease or disorder, comprising treating a subject with a therapeutically effective amount of a CD37-specific binding molecule and a therapeutically effective amount of an mTOR or PI3K inhibitor.

2. The method of claim 1, wherein the method comprises administering to the subject an mTOR inhibitor.

3. The method of claim 2, wherein the mTOR inhibitor is sirolimus, temsirolimus, or a torkinib.

4. The method of claim 2, wherein the mTOR inhibitor is deforolimus, everolimus, tacrolimus, zotarolimus, curcumin, or farnesylthiosalicylic acid.

5. The method of claim 1, wherein the method comprises administering to the subject a PI3K inhibitor.

6. The method of claim 5, wherein the PI3K inhibitor is a P110δ-specific inhibitor.

7. The method of any one of claims 1 to 6, wherein the CD37-specific binding molecule is a CD37-specific antibody or antigen-binding portion thereof, or a SMIP protein.

8. The method of any one of claims 1 to 6, wherein the CD37-specific binding molecule is a humanized antibody or antigen-binding portion thereof, or a humanized SMIP protein.

9. The method of any one of claim 1 to 6, wherein the CD37-specific binding molecule is a humanized CD37-specific SMIP protein comprising an amino acid sequence as set forth in SEQ ID NO:6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 52, 60, 80, 82, 84, 86, or 88.

10. The method of any one of claims 1 to 6, wherein the CD37-specific binding molecule is a humanized CD37-specific SMIP protein comprising an amino acid sequence set forth in SEQ ID NO:253.

11. The method of any one of claims 1 to 6, wherein the CD37-specific binding molecule is a humanized CD37-specific antibody whose light and heavy chains comprise SEQ ID NOS:307 and 308, respectively, or SEQ ID NOS:309 and 310, respectively.

12. The method of claim 2, wherein the CD37-specific binding molecule comprises a SMIP protein having an amino acid sequence as set forth in SEQ ID NO:253, and wherein the mTOR inhibitor is sirolimus or temsirolimus.

13. The method of claim 2, wherein the CD37-specific binding molecule comprises an antibody whose light and heavy chains comprise SEQ ID NOS:307 and 308, respectively, or SEQ ID NOS:309 and 310, respectively, and wherein the mTOR inhibitor is sirolimus, temsirolimus, or a torkinib.

14. The method of any one of claims 1 to 13, wherein the CD37-specific binding molecule and the mTOR or PI3K inhibitor are administered sequentially.

15. The method of any one of claims 1 to 13, wherein the CD37-specific binding molecule and the mTOR or PI3K inhibitor are administered concurrently.

16. The method of claim 15, wherein the CD37-specific binding molecule and the mTOR or PI3K inhibitor are formulated together.

17. The method of any one of claims 1 to 13, wherein the CD37-specific binding molecule is administered parenterally and the mTOR or PI3K inhibitor is administered orally.

18. The method according to any one of claims 1 to 17, wherein the disorder or disease associated with aberrant B-cell activity is a B-cell lymphoma or leukemia such as B-cell non-Hodgkins lymphoma (NHL) (including Burkitt's lymphoma, chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), diffuse large B-cell lymphoma, follicular lymphoma, immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, and mantle cell lymphoma), hairy cell leukemia, Waldenström's macroglobulinemia, B-cell pro-lymphocytic leukemia, CD37+ dendritic cell lymphoma, lymphoplasmacytic lymphoma, splenic marginal zone lymphoma, extra-nodal marginal zone B-cell lymphoma of mucosa-associated (MALT) lymphoid tissue, nodal marginal zone B-cell lymphoma, mediastinal (thymic) large B-cell lymphoma, intravascular large B-cell lymphoma, and primary effusion lymphoma; a disease characterized by autoantibody production such as idiopathic inflammatory myopathy, rheumatoid arthritis, juvenile rheumatoid arthritis, myasthenia gravis, Grave's disease, type I diabetes mellitus, anti-glomerular basement membrane disease, rapidly progressive glomerulonephritis, Berger's disease (IgA nephropathy), systemic lupus erythematosus (SLE), Crohn's disease, ulcerative colitis, idiopathic thrombocytopenic purpura (ITP), anti-phospholipid antibody syndrome, neuromyelitis optica, multiple sclerosis, an autoimmune disease, dermatomyositis, polymyositis, or Waldenstrom's macroglobinemia; or a disease characterized by inappropriate T-cell stimulation associated with a B-cell pathway.

19. The method of any one of claims 1 to 17, wherein the subject further has chromosomal translocation t(11;14)(q13;q32) or cyclin D1 overexpression.

20. The method according to claim 19, wherein the disorder or disease associated with aberrant B-cell activity is mantle cell lymphoma.

21. A kit for treating a non-Hodgkins lymphoma comprising:

(a) a unit dosage of a CD37-specific binding molecule, and

(b) a unit dosage of an mTOR or PI3K inhibitor.

22. The kit of claim 21, further comprising a CD20-specific binding molecule such as TRU-015, rituximab, ofatumumab, ocrelizumab; cytokine; chemokine; growth factor; chemotherapeutic agent such as bendamustine; or radiotherapeutic agent.

23. A composition, comprising:

(a) a CD37-specific binding molecule, and

(b) an mTOR or phosphatidylinositol 3-kinase (PI3K) inhibitor.

24. The composition of claim 23, wherein the composition comprises an mTOR inhibitor.

25. The composition of claim 24, wherein the mTOR inhibitor is sirolimus, temsirolimus, or a torkinib.

26. The composition of claim 2, wherein the mTOR inhibitor is deforolimus, everolimus, tacrolimus, zotarolimus, curcumin, or farnesylthiosalicylic acid.

27. The composition of claim 23, wherein the composition comprises a PI3K inhibitor.

28. The composition of claim 27, wherein the PI3K inhibitor is a p110δ-specific inhibitor.

29. The composition of any one of claims 23 to 28, wherein the CD37-specific binding molecule is a CD37-specific antibody or antigen-binding portion thereof, or a SMIP protein.

30. The composition of any one of claims 23 to 28, wherein the CD37-specific binding molecule is a humanized antibody or antigen-binding portion thereof, or a humanized SMIP protein.

31. The composition of any one of claim 23 to 28, wherein the CD37-specific binding molecule is a humanized CD37-specific SMIP protein comprising an amino acid sequence as set forth in SEQ ID NO:6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 52, 60, 80, 82, 84, 86, or 88.

32. The composition of any one of claims 23 to 28, wherein the CD37-specific binding molecule is a humanized CD37-specific SMIP protein comprising an amino acid sequence set forth in SEQ ID NO:253.

33. The composition of any one of claims 23 to 28, wherein the CD37-specific binding molecule is a humanized CD37-specific antibody whose light and heavy chains comprise SEQ ID NOS:307 and 308, respectively, or SEQ ID NOS:309 and 310, respectively.

34. The composition of claim 24, wherein the CD37-specific binding molecule comprises a SMIP protein with an amino acid sequence as set forth in SEQ ID NO:253, and wherein the mTOR inhibitor is sirolimus, temsirolimus, or a torkinib.

35. The composition of claim 24, wherein the CD37-specific binding molecule whose light and heavy chains comprise SEQ ID NOS:307 and 308, respectively, or SEQ ID NOS:309 and 310, respectively, and wherein the mTOR inhibitor is sirolimus, temsirolimus, or a torkinib.

36. The composition of any one of claims 23 to 35, further comprising a CD20-specific binding molecule such as TRU-015, rituximab, ofatumumab, ocrelizumab; cytokine; chemokine; growth factor; chemotherapeutic agent such as bendamustine; or radiotherapeutic agent.

CLAIMS

1. Use of a CD37-specific binding molecule in the manufacture of a medicament for reducing the number of B-cells or treating a disease or disorder associated with aberrant B-cell activity in a subject having or suspected of having the disease or disorder, wherein the CD37-specific binding molecule is to be administered prior to, simultaneous with, or subsequent to an effective amount of an mTOR or PI3K inhibitor.

2. The use according to claim 1, wherein the medicament is to be administered to the subject prior to, simultaneous with, or subsequent to the mTOR inhibitor.

3. The use according to claim 2, wherein the mTOR inhibitor is sirolimus, temsirolimus, or a torkinib.

4. The use according to claim 2, wherein the mTOR inhibitor is deforolimus, everolimus, tacrolimus, zotarolimus, curcumin, or farnesylthiosalicylic acid.

5. The use according to claim 1, wherein the medicament is to be administered to the subject prior to, simultaneous with, or subsequent to the PI3K inhibitor.

6. The use according to claim 5, wherein the PI3K inhibitor is a P110δ-specific inhibitor.

7. The use according to any one of claims 1 to 6, wherein the CD37-specific binding molecule is a CD37-specific antibody or antigen-binding portion thereof, or a SMIP protein.

8. The use according to any one of claims 1 to 6, wherein the CD37-specific binding molecule is a humanized antibody or antigen-binding portion thereof, or a humanized SMIP protein.

9. The use according to any one of claims 1 to 6, wherein the CD37-specific binding molecule comprises an amino acid sequence as set forth in SEQ ID NO:6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 52, 60, 80, 82, 84, 86, or 88.

10. The use according to any one of claims 1 to 6, wherein the CD37-specific binding molecule comprises an amino acid sequence set forth in SEQ ID NO:253.

11. The use according to any one of claims 1 to 6, wherein the CD37-specific binding molecule comprises antibody light and heavy chains comprising SEQ ID NOS:307 and 308, respectively, or SEQ ID NOS:309 and 310, respectively.

12. The use according to claim 2, wherein the CD37-specific binding molecule comprises an amino acid sequence as set forth in SEQ ID NO:253, and wherein the mTOR inhibitor is sirolimus or temsirolimus.

13. The use according to claim 2, wherein the CD37-specific binding molecule comprises antibody light and heavy chains comprising SEQ ID NOS:307 and 308, respectively, or SEQ ID NOS:309 and 310, respectively, and wherein the mTOR inhibitor is sirolimus, temsirolimus, or a torkinib.

14. The use according to any one of claims 1 to 13, wherein the CD37-specific binding molecule and the mTOR or PI3K inhibitor are to be administered sequentially.

15. The use according to any one of claims 1 to 13, wherein the CD37-specific binding molecule and the mTOR or PI3K inhibitor are to be administered concurrently.

16. The use according to claim 15, wherein the CD37-specific binding molecule and the mTOR or PI3K inhibitor are formulated together.

17. The use according to any one of claims 1 to 13, wherein the CD37-specific binding molecule is to be administered parenterally and the mTOR or PI3K inhibitor is to be administered orally.

18. The use according to according to any one of claims 1 to 17, wherein the disorder or disease associated with aberrant B-cell activity is a B-cell lymphoma or leukemia such as B-cell non-Hodgkins lymphoma (NHL) (including Burkitt's lymphoma, chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), diffuse large B-cell lymphoma, follicular lymphoma, immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, and mantle cell lymphoma), hairy cell leukemia, Waldenström's macroglobulinemia, B-cell pro-lymphocytic leukemia, CD37+ dendritic cell lymphoma, lymphoplasmacytic lymphoma, splenic marginal zone lymphoma, extra-nodal marginal zone B-cell lymphoma of mucosa-associated (MALT) lymphoid tissue, nodal marginal zone B-cell lymphoma, mediastinal (thymic) large B-cell lymphoma, intravascular large B-cell lymphoma, and primary effusion lymphoma; a disease characterized by autoantibody production such as idiopathic inflammatory myopathy, rheumatoid arthritis, juvenile rheumatoid arthritis, myasthenia gravis, Grave's disease, type I diabetes mellitus, anti-glomerular basement membrane disease, rapidly progressive glomerulonephritis, Berger's disease (IgA nephropathy), systemic lupus erythematosus (SLE), Crohn's disease, ulcerative colitis, idiopathic thrombocytopenic purpura (ITP), anti-phospholipid antibody syndrome, neuromyelitis optica, multiple sclerosis, an autoimmune disease, dermatomyositis, polymyositis, or

Waldenstrom's macroglobinemia; or a disease characterized by inappropriate T-cell stimulation associated with a B-cell pathway.

19. The use of according to any one of claims 1 to 17, wherein the subject further has chromosomal translocation t(11;14)(q13;q32) or cyclin D1 overexpression.

20. The use of according to claim 19, wherein the disorder or disease associated with aberrant B-cell activity is mantle cell lymphoma.

21. A kit for treating a non-Hodgkins lymphoma comprising:

(a) a unit dosage of a CD37-specific binding molecule, and

(b) a unit dosage of an mTOR or PI3K inhibitor.

22. The kit of claim 21, further comprising a CD20-specific binding molecule such as TRU-015, rituximab, ofatumumab, ocrelizumab; cytokine; chemokine; growth factor; chemotherapeutic agent such as bendamustine; or radiotherapeutic agent.

23. A composition, comprising:

(a) a CD37-specific binding molecule, and

(b) an mTOR or phosphatidylinositol 3-kinase (PI3K) inhibitor.

24. The composition of claim 23, wherein the composition comprises the mTOR inhibitor.

25. The composition of claim 24, wherein the mTOR inhibitor is sirolimus, temsirolimus, or a torkinib.

26. The composition of claim 24, wherein the mTOR inhibitor is deforolimus, everolimus, tacrolimus, zotarolimus, curcumin, or farnesylthiosalicylic acid.

27. The composition of claim 23, wherein the composition comprises the PI3K inhibitor.

28. The composition of claim 27, wherein the PI3K inhibitor is a p110δ-specific inhibitor.

29. The composition of any one of claims 23 to 28, wherein the CD37-specific binding molecule is a CD37-specific antibody or antigen-binding portion thereof, or a SMIP protein.

30. The composition of any one of claims 23 to 28, wherein the CD37-specific binding molecule is a humanized antibody or antigen-binding portion thereof, or a humanized SMIP protein.

31. The composition of any one of claim 23 to 28, wherein the CD37-specific binding molecule comprises an amino acid sequence as set forth in SEQ ID NO:6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 52, 60, 80, 82, 84, 86, or 88.

32. The composition of any one of claims 23 to 28, wherein the CD37-specific binding molecule comprises an amino acid sequence set forth in SEQ ID NO:253.

33. The composition of any one of claims 23 to 28, wherein the CD37-specific binding molecule comprises antibody light and heavy chains comprising SEQ ID NOS:307 and 308, respectively, or SEQ ID NOS:309 and 310, respectively.

34. The composition of claim 24, wherein the CD37-specific binding molecule comprises an amino acid sequence as set forth in SEQ ID NO:253, and wherein the mTOR inhibitor is sirolimus, temsirolimus, or a torkinib.

35. The composition of claim 24, wherein the CD37-specific binding molecule comprises light and heavy chains comprising SEQ ID NOS:307 and 308, respectively, or SEQ ID NOS:309 and 310, respectively, and wherein the mTOR inhibitor is sirolimus, temsirolimus, or a torkinib.

36. The composition of any one of claims 23 to 35, further comprising a CD20-specific binding molecule such as TRU-015, rituximab, ofatumumab, ocrelizumab; cytokine; chemokine; growth factor; chemotherapeutic agent such as bendamustine; or radiotherapeutic agent.

37. The kit of claim 21 or 22, wherein the CD37-specific binding molecule and the mTOR or PI3K inhibitor are to be administered sequentially to a subject having or suspected of having the non-Hodgkins lymphoma.

38. The kit of claim 21 or 22, wherein the CD37-specific binding molecule and the mTOR or PI3K inhibitor are to be administered concurrently to a subject having or suspected of having the non-Hodgkins lymphoma.

39. The kit of claim 21 or 22, wherein the CD37-specific binding molecule and the mTOR or PI3K inhibitor are formulated together.

40. The kit of claim 21 or 22, wherein the CD37-specific binding molecule is to be administered parenterally and the mTOR or PI3K inhibitor is to be administered orally to a subject having or suspected of having the non-Hodgkins lymphoma.