CLAIMS

1. A composition comprising a CD37-specific binding molecule and bendamustine.

2. The composition of claim 1, wherein the CD37-specific binding molecule is a CD37-specific antibody or SMIP.

3. The composition of claim 1, wherein the CD37-specific molecule is a humanized antibody or humanized SMIP.

4. The composition of any one of claims 1 to 3, wherein the CD37-specific binding molecule competes with G28-1 mAb in CD37-specific binding.

5. The composition of claim 1, wherein the CD37-specific binding protein comprises a light chain CDR1 as set forth in SEQ ID NO:61 or 62, a light chain CDR2 as set forth in SEQ ID NO:64, and a light chain CDR3 as set forth in SEQ ID NO:66; and

a heavy chain CDR1 as set forth in SEQ ID NO:63, a heavy chain CDR2 as set forth in SEQ ID NO:65, and a heavy chain CDR3 as set forth in SEQ ID NO:67, 68 or 69.

6. The composition of claim 1, wherein the CD37-specific binding protein comprises, from amino terminus to carboxy terminus:

(i) a humanized heavy chain variable region,

(ii) a linker,

(iii) a humanized light chain variable region,

(iv) an IgG1 hinge, and

(v) a human IgG1 CH2 region, and

(vi) a human IgG1 CH3 region.

7. The composition of claim 1, wherein the CD37-specific binding molecule comprises, from amino terminus to carboxy terminus:

(i) a heavy chain variable region comprising a heavy chain CDR3 as set forth in SEQ ID NO:67 or 68;

(ii) a linker;

(iii) a light chain variable region comprising a light chain CDR1 as set forth in SEQ ID NO:61;

(iv) an IgG1 hinge; and

(v) a human IgG1 CH2 region, and
(vi) a human IgG1 CH3 region.

8. The composition of claim 1, wherein the CD37-specific binding molecule comprises, from amino terminus to carboxy terminus:

(i) a heavy chain variable region comprising a heavy chain CDR1 as set forth in SEQ ID NO:63, a heavy chain CDR2 as set forth in SEQ ID NO:65, and a heavy chain CDR3 as set forth in SEQ ID NO:67 or 68;

(ii) a linker;

(iii) a light chain variable region comprising a light chain CDR1 as set forth in SEQ ID NO:61, a light chain CDR2 as set forth in SEQ ID NO:64, and a light chain CDR3 as set forth in SEQ ID NO:66;

(iv) an IgG1 hinge; and

(v) a human IgG1 CH2 region, and
(vi) a human IgG1 CH3 region.

9. The composition of claim 8, wherein the CD37-specific binding molecule is a humanized CD37-specific binding molecule that comprises from amino

terminus to carboxyl terminus:

(i) a humanized heavy chain variable region,

(ii) a linker as set forth in SEQ ID NO:229,

(iii) a humanized light chain variable region,

(iv) an IgG1 hinge,

(v) a human IgG1 CH2 region, and

(vi) a human IgG1 CH3 region,

wherein

(a) the humanized heavy chain variable region comprising from amino terminus to carboxyl terminus: a human heavy chain FR1, a heavy chain CDR1 as set forth in SEQ ID NO:63, a human heavy chain FR2, a heavy chain CDR2 as set forth in SEQ ID NO:65, a human heavy chain FR3, a heavy chain CDR3 as set forth in SEQ ID NO:67, 68 or 69, and a human heavy chain FR4, and

(b) the humanized light chain variable region comprises from amino terminus to carboxyl terminus: a human light chain FR1, a light chain CDR1 as set forth in SEQ ID NO:61 or 62, a human light chain FR2, a light chain CDR2 as set forth in SEQ ID NO:64, a human light chain FR3, and a light chain CDR3 as set forth in SEQ ID NO:66, and a human light chain FR4.

10. Use of a CD37-specific binding molecule and bendamustine in the manufacture of a medicament for reducing B-cells or treating a disease associated with aberrant B-cell activity.

11. The use of claim 10, wherein the disease associated with aberrant B-cell activity is a B-cell lymphoma, a B-cell leukemia, a B-cell myeloma, a disease characterized by autoantibody production, or a disease characterized by inappropriate T- cell stimulation associated with a B-cell pathway.

12. The use of claim 11, wherein the disease characterized by autoantibody production is idiopathic inflammatory myopathy, rheumatoid arthritis, myasthenia gravis, Grave's disease, type I diabetes mellitus, multiple sclerosis, an autoimmune disease, dermatomyositis, polymyositis, or Waldenstrom's macroglobinemia.

13. The use of claim 10, wherein the disease associated with aberrant B-cell activity is selected from the group consisting of chronic lymphocytic leukemia (CLL), non-Hodgkins lymphoma (NHL), and hairy cell leukemia.

14. The use of claim 10, wherein the CD37-specific binding molecule and bendamustine are administered concurrently.

15. The use of claim 10, wherein the CD37-specific binding molecule and bendamustine are administered sequentially.

16. The use of claim 10, wherein the CD37-specific binding molecule and bendamustine are formulated together.

17. The use of claim 10, wherein the CD37-specific binding molecule is a CD37-specific antibody or SMIP.

18. The use of claim 10, wherein the CD37-specific molecule is a humanized antibody or a humanized SMIP.

19. The use of claim 10, wherein the CD37-specific binding molecule competes with G28-1 mAb in CD37-specific binding.

20. The use of claim 10, wherein the CD37-specific binding molecule is a humanized CD37-specific binding molecule that comprises from amino

terminus to carboxyl terminus:

(i) a humanized heavy chain variable region,

(ii) a linker as set forth in SEQ ID NO:229,

(iii) a humanized light chain variable region,

(iv) an IgG1 hinge,

(v) a human IgG1 CH2 region, and

(vi) a human IgG1 CH3 region, wherein

(a) the humanized heavy chain variable region comprising from amino terminus to carboxyl terminus: a human heavy chain FR1, a heavy chain CDR1 as set forth in SEQ ID NO:63, a human heavy chain FR2, a heavy chain CDR2 as set forth in SEQ ID NO:65, a human heavy chain FR3, a heavy chain CDR3 as set forth in SEQ ID NO:67, 68 or 69, and a human heavy chain FR4, and

(b) the humanized light chain variable region comprises from amino terminus to carboxyl terminus: a human light chain FR1, a light chain CDR1 as set forth in SEQ ID NO:61 or 62, a human light chain FR2, a light chain CDR2 as set forth in SEQ ID NO:64, a human light chain FR3, and a light chain CDR3 as set forth in SEQ ID NO:66, and a human light chain FR4.

CLAIMS

1. A composition comprising a CD37-specific binding molecule and bendamustine.

2. The composition of claim 1, wherein the CD37-specific binding molecule competes with G28-1 mAb in CD37-specific binding.

3. The composition of claim 1 or 2, wherein the CD37-specific binding molecule is humanized.

4. The composition of any one of claims 1 to 3, wherein the CD37-specific binding molecule comprises, from amino to carboxy terminus,

(a) a CD37-specific single-chain Fv (scFV) comprising, from amino to carboxy terminus, (i) a humanized heavy chain variable region comprising a heavy chain CDR3 as set forth in SEQ ID NO: 68, (ii) a linker, and (iii) a humanized light chain variable region;

(b) a hinge region; and

(c) immunoglobulin CH2 and CH3 regions.

5. The composition of any one of claims 1 to 3, wherein the CD37-specific binding molecule comprises, from amino to carboxy terminus,

(a) a CD37-specific single-chain Fv (scFV) comprising, from amino to carboxy terminus, (i) a humanized heavy chain variable region comprising a heavy chain CDR3 as set forth in SEQ ID NO: 67, (ii) a linker, and (iii) a humanized light chain variable region;

(b) a hinge region; and

(c) immunoglobulin CH2 and CH3 regions.

6. The composition of any one of claims 1 to 3, wherein the CD37-specific binding molecule comprises, from amino to carboxy terminus,

(a) a CD37-specific single-chain Fv (scFV) comprising, from amino to carboxy terminus, (i) a humanized heavy chain variable region comprising a heavy chain CDR3 as set forth in SEQ ID NO: 69, (ii) a linker, and (iii) a humanized light chain variable region;

(b) a hinge region; and

(c) immunoglobulin CH2 and CH3 regions.

7. The composition of any one of claims 4 to 6, wherein the humanized light chain variable region comprises a light chain CDR1 as set forth in SEQ ID NO:61.

8. The composition of claim 1, wherein the CD37-specific binding molecule comprises the amino acid sequence set forth in SEQ ID NO: 253.

9. A medicament comprising a CD37-specific binding molecule and bendamustine for reducing B cells or treating a disease or disorder responsive to reducing B cells.

10. The medicament of claim 9 wherein the CD37-specific binding molecule comprises, from amino to carboxy terminus,

(a) a CD37-specific single-chain Fv (scFV) comprising, from amino to carboxy terminus, (i) a humanized heavy chain variable region comprising a heavy chain CDR3 as set forth in SEQ ID NO: 68, (ii) a linker, and (iii) a humanized light chain variable region;

(b) a hinge region; and

(c) immunoglobulin CH2 and CH3 regions.

11.The medicament of claim 9 wherein the CD37-specific binding molecule comprises, from amino to carboxy terminus,

(a) a CD37-specific single-chain Fv (scFV) comprising, from amino to carboxy terminus, (i) a humanized heavy chain variable region comprising a heavy chain CDR3 as set forth in SEQ ID NO: 67, (ii) a linker, and (iii) a humanized light chain variable region;

(b) a hinge region; and

(c) immunoglobulin CH2 and CH3 regions.

12. The medicament of claim 9, wherein the CD37-specific binding molecule comprises, from amino to carboxy terminus,

(a) a CD37-specific single-chain Fv (scFV) comprising, from amino to carboxy terminus, (i) a humanized heavy chain variable region comprising a heavy chain CDR3 as set forth in SEQ ID NO: 69, (ii) a linker, and (iii) a humanized light chain variable region;

(b) a hinge region; and

(c) immunoglobulin CH2 and CH3 regions.

13. The medicament of claim 10, 11 or 12, wherein the humanized light chain variable region comprises a light chain CDR1 as set forth in SEQ ID NO:61.

14. The medicament of claim 9, wherein the CD37-specific binding molecule comprises the amino acid sequence set forth in SEQ ID NO: 253.

15. The medicament of any one of claims 9 to 14, wherein the B cell disease or disorder is 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, Waldenstrom's macroglobinemia, chronic lymphocytic leukemia (CLL), non-Hodgkins lymphoma (NHL), Hairy cell leukemia, small lymphocytic 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, follicular lymphoma, mantle cell lymphoma, diffuse large B-cell lymphoma, mediastinal (thymic) large B-cell lymphoma, intravascular large B-cell lymphoma, primary effusion lymphoma, or Burkitt lymphoma/leukemia.

16. Use of a CD37-specific binding molecule in the manufacture of a medicament for reducing B cells or treating a disease or disorder responsive to reducing B cells, wherein the medicament is comprised of an effective amount of a CD37-specific binding molecule, and wherein the medicament is administered prior to, simultaneous with, or subsequent to an effective amount of bendamustine.

17. Use of bendamustine in the manufacture of a medicament for reducing B cells or treating a disease or disorder responsive to reducing B cells, wherein the medicament is comprised of an effective amount of bendamustine, and wherein the medicament is administered prior to, simultaneous with, or subsequent to an effective amount of a CD37-specific binding molecule.

18. The use of claim 16 or 17, wherein the medicament is administered prior to, simultaneous with, or subsequent to an agent selected from the group consisting of rituximab, fludarabine, vincristine, chlorambucil and cyclophosphamide.

19. The use of any one of claims 16 to 18, wherein the CD37-specific binding molecule comprises, from amino to carboxy terminus,

(a) a CD37-specific single-chain Fv (scFV) comprising, from amino to carboxy terminus, (i) a humanized heavy chain variable region comprising a heavy chain CDR3 as set forth in SEQ ID NO: 68, (ii) a linker, and (iii) a humanized light chain variable region;

(b) a hinge region; and

(c) immunoglobulin CH2 and CH3 regions.

20. The use of any one of claims 16 to 18, wherein the CD37-specific binding molecule comprises, from amino to carboxy terminus,

(a) a CD37-specific single-chain Fv (scFV) comprising, from amino to carboxy terminus, (i) a humanized heavy chain variable region comprising a heavy chain CDR3 as set forth in SEQ ID NO: 67, (ii) a linker, and (iii) a humanized light chain variable region;

(b) a hinge region; and

(c) immunoglobulin CH2 and CH3 regions.

21. The use of any one of claims 16 to 18, wherein the CD37-specific binding molecule comprises, from amino to carboxy terminus,

(a) a CD37-specific single-chain Fv (scFV) comprising, from amino to carboxy terminus, (i) a humanized heavy chain variable region comprising a heavy chain CDR3 as set forth in SEQ ID NO: 69, (ii) a linker, and (iii) a humanized light chain variable region;

(b) a hinge region; and

(c) immunoglobulin CH2 and CH3 regions.

22. The use of claim 19, 20 or 21, wherein the humanized light chain variable region comprises a light chain CDR1 as set forth in SEQ ID NO:61.

23. The use of any one of claims 16 to 18, wherein the CD37-specific binding molecule comprises the amino acid sequence set forth in SEQ ID NO: 253.

24. The use of any one of claims 16 to 23, wherein the B cell disease or disorder is 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, Waldenstrom's macroglobinemia, chronic lymphocytic leukemia (CLL), non-Hodgkins lymphoma (NHL), Hairy cell leukemia, small lymphocytic 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, follicular lymphoma, mantle cell lymphoma, diffuse large B-cell lymphoma, mediastinal (thymic) large B-cell lymphoma, intravascular large B-cell lymphoma, primary effusion lymphoma, or Burkitt lymphoma/leukemia.

25. A kit comprising a CD37-specific binding molecule and bendamustine.

26. A kit of claim 26 25 wherein the CD37-specific binding molecule is a CD37-specific binding molecule according to any one of claims 2 to 8.