blind placebo-controlled multicenter trial of Rituximab in patients with primary progressive multiple sclerosis.

SUMMARY

Reported herein is a bispecific antibody comprising

a) one (full length) antibody comprising two pairs each of a (full length) antibody light chain and a (full length) antibody heavy chain, wherein the binding sites formed by each of the pairs of the (full length) heavy chain and the (full length) light chain specifically bind to a first antigen, and

b) one additional Fab fragment, wherein the additional Fab fragment is fused to any C-terminus of one heavy chain of the (full length) antibody, wherein the binding site of the additional Fab fragment specifically binds to a second antigen,

wherein each of the (full length) antibody light chains comprises in the constant light chain domain (CL) at position 123 the amino acid residue arginine (instead of the wild-type glutamic acid residue; E123R mutation) and at position 124 the amino acid residue lysine (instead of the wild-type glutamine residue; Q124K mutation) (numbering according to Kabat),

wherein each of the (full length) antibody heavy chains comprises in the first constant heavy chain domain (CH1) at position 147 an glutamic acid residue (instead of the wild-type lysine residue; K147E mutation) and at position 213 an glutamic acid residue (instead of the wild-type lysine amino acid residue; K213E mutation) (numbering according to Kabat EU index),

wherein the additional Fab fragment specifically binding to the second antigen comprises a domain crossover such that the constant light chain domain (CL) and the constant heavy chain domain 1 (CH1) are replaced by each other, and

wherein the first antigen is human CD20 and the second antigen is human transferrin receptor.

In one example the additional Fab fragment is fused to the C-terminus of the heavy chain by a peptidic linker.

In one example the N-terminus of the heavy chain variable domain of the Fab fragment is fused to the C-terminus of the (full length) heavy chain or the C-terminus of the peptidic linker.

In one example

a) the (full length) heavy chain that is fused to the additional Fab fragments has as C-terminal (heavy chain) amino acid residues the tripeptide LSP wherein the proline thereof is directly fused to the first amino acid residue of the additional Fab fragment or of the peptidic linker via a peptide bond, and

b) the (full length) heavy chain that is not fused to the additional Fab fragments has as C-terminal (heavy chain) amino acid residues the tripeptide LSP, or SPG, or PGK.

In one example the (full length) antibody is

a) a full length antibody of the human subclass IgG1,

b) a full length antibody of the human subclass IgG4,

c) a full length antibody of the human subclass IgG1 with the mutations L234A, L235A and P329G,

d) a full length antibody of the human subclass IgG4 with the mutations S228P, L235E and P329G,

e) a full length antibody of the human subclass IgG1 with the mutations L234A, L235A and P329G in both heavy chains and the mutations i) T366W, and ii) S354C or Y349C, in one heavy chain and the mutations i) T366S, L368A, and Y407V, and ii) Y349C or S354C, in the respective other heavy chain,

f) a full length antibody of the human subclass IgG4 with the mutations S228P, L235E and P329G in both heavy chains and the mutations i) T366W, and ii) S354C or Y349C, in one heavy chain and the mutations i) T366S, L368A, and Y407V, and ii) Y349C or S354C, in the respective other heavy chain,

g) a full length antibody of the human subclass IgG1 with the mutations L234A, L235A, P329G, I253A, H310A and H435A in both heavy chains and the mutations i) T366W, and ii) S354C or Y349C, in one heavy chain and the mutations i) T366S, L368A, and Y407V, and ii) Y349C or S354C, in the respective other heavy chain, or

h) a full length antibody of the human subclass IgG1 with the mutations L234A, L235A, P329G, M252Y, S254T and T256E in both heavy chains and the mutations i) T366W, and ii) S354C or Y349C, in one heavy chain and the mutations i) T366S, L368A, and Y407V, and ii) Y349C or S354C, in the respective other heavy chain, or

i) a full length antibody of the human subclass IgG1 with the mutations L234A, L235A, P329G, H310A, H433A and Y436A in both heavy chains and the mutations i) T366W, and ii) S354C or Y349C, in one heavy chain and the mutations i) T366S, L368A, and Y407V, and ii) Y349C or S354C, in the respective other heavy chain.

In one example the additional Fab fragment is fused to the C-terminus of the heavy chain comprising the mutation T366W, or to the C-terminus of the heavy chain comprising the mutations T366S, L368A, and Y407V.

In one example

the (full length) antibody is of the human subclass IgG1 with the mutations L234A, L235A and P329G in both heavy chains and the mutations T366W and S354C in one heavy chain and the mutations T366S, L368A, Y407V and Y349C in the respective other heavy chain, and

the additional Fab fragment is fused to the C-terminus of the heavy chain comprising the mutation T366W, or to the C-terminus of the heavy chain comprising the mutations T366S, L368A, and Y407V.

In one example the bispecific antibody comprises

i) a light chain that has a sequence identity to SEQ ID NO: 01 of 70 % or more,

ii) a heavy chain that has a sequence identity to SEQ ID NO: 02 of 70 % or more,

GTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY
SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC.

Reported herein is a bispecific antibody comprising a (full length) light chain that has the amino acid sequence of SEQ ID NO: 01, a (full length) heavy chain that has the amino acid sequence of SEQ ID NO: 02, a (full length) light chain that has the amino acid sequence of SEQ ID NO: 03, and an antibody Fab fragment comprising the amino acid sequences of SEQ ID NO: 04.

In one example the bispecific antibody is monoclonal.

Reported herein is a bispecific antibody comprising

a) a first and a second Fab fragment, wherein each binding site of the first and the second Fab fragment specifically bind to a first antigen,

b) a third Fab fragment, wherein the binding site of the third Fab fragment specifically binds to a second antigen, and wherein the third Fab fragment comprises a domain crossover such that the variable light chain domain (VL) and the variable heavy chain domain (VH) are replaced by each other, and

c) an Fc-region comprising a first Fc-region polypeptide and a second Fc-region polypeptide,

wherein the first and the second Fab fragment each comprise a heavy chain fragment and a full length light chain,

wherein the C-terminus of the heavy chain fragment of the first Fab fragment is fused to the N-terminus of the first Fc-region polypeptide,

wherein the C-terminus of the heavy chain fragment of the second Fab fragment is fused to the N-terminus of the variable light chain domain of the third Fab fragment and the C-terminus of the heavy chain constant domain 1 of the third Fab fragment is fused to the N-terminus of the second Fc-region polypeptide,

wherein each of the full length light antibody chains of the first and second Fab fragment comprises in the constant light chain domain (CL) at position 123 the amino acid residue arginine (instead of the wild-type glutamic acid

residue; E123R mutation) and at position 124 the amino acid residue lysine (instead of the wild-type glutamine residue; Q124K mutation) (numbering according to Kabat),

wherein each of the heavy chain fragments of the first and second Fab fragment comprises in the first constant heavy chain domain (CH1) at position 147 an glutamic acid residue (instead of the wild-type lysine residue; K147E mutation) and at position 213 an glutamic acid residue (instead of the wild-type lysine amino acid residue; K213E mutation) (numbering according to Kabat EU index),

wherein the first antigen is human CD20 and the second antigen is human transferrin receptor.

In one example the first and the second Fc-region polypeptide is

a) of the human subclass IgG1,

b) of the human subclass IgG4,

c) of the human subclass IgG1 with the mutations L234A, L235A and P329G,

d) of the human subclass IgG4 with the mutations S228P, L235E and P329G,

e) of the human subclass IgG1 with the mutations L234A, L235A and P329G in both Fc-region polypeptides and the mutations T366W and S354C in one Fc-region polypeptide and the mutations T366S, L368A, Y407V and Y349C in the respective other Fc-region polypeptide,

f) of the human subclass IgG4 with the mutations S228P, L235E and P329G in both Fc-region polypeptides and the mutations T366W and S354C in one Fc-region polypeptide and the mutations T366S, L368A, Y407V and Y349C in the respective other Fc-region polypeptide,

g) of the human subclass IgG1 with the mutations L234A, L235A, P329G, I253A, H310A and H435A in both Fc-region polypeptides and the mutations T366W and S354C in one Fc-region polypeptide and the

mutations T366S, L368A, Y407V and Y349C in the respective other Fc-region polypeptide, or

h) of the human subclass IgG1 with the mutations L234A, L235A, P329G, M252Y, S254T and T256E in both Fc-region polypeptides and the mutations T366W and S354C in one Fc-region polypeptide and the mutations T366S, L368A, Y407V and Y349C in the respective other Fc-region polypeptide, or

i) of the human subclass IgG1 with the mutations L234A, L235A, P329G, H310A, H433A and Y436A in both Fc-region polypeptides and the mutations T366W and S354C in one Fc-region polypeptide and the mutations T366S, L368A, Y407V and Y349C in the respective other Fc-region polypeptide.

In one example one of the chains of the third Fab fragment is fused to the Fc-region polypeptide comprising the mutation T366W, or to the Fc-region polypeptide comprising the mutations T366S, L368A, and Y407V.

In one example the bispecific antibody comprises

i) a light chain that has a sequence identity to SEQ ID NO: 14 of at least 70 %, or at least 80 %, or at least 90 %, or 95 % or more,

ii) a heavy chain that has a sequence identity to SEQ ID NO: 15 of at least 70 %, or at least 80 %, or at least 90 %, or 95 % or more,

iii) a crossed antibody chain that has a sequence identity to SEQ ID NO: 16 of at least 70 %, or at least 80 %, or at least 90 %, or 95 % or more, and

iv) a modified heavy chain that has a sequence identity to SEQ ID NO: 17 of at least 70 %, or at least 80 %, or at least 90 %, or 95 % or more,

wherein

SEQ ID NO: 14 has the amino acid sequence
DIVMTQTPLSLPVTPGEPASISCRSSKSLLHSNGITYLYWYLQKPGQSP
QLLIYQMSNLVSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCAQN
LELPYTFGGGTKVEIKRTVAAPSVFIFPPSDRKLKSGTASVVCLLNNF

Reported herein is a bispecific antibody comprising two full length light chains that each has the amino acid sequence of SEQ ID NO: 14, a full length heavy chain that has the amino acid sequence of SEQ ID NO: 15, a crossed antibody chain that has the amino acid sequence of SEQ ID NO: 16, and a modified heavy chain that has the amino acid sequence of SEQ ID NO: 17.

In one example the bispecific antibody is monoclonal.

In one aspect, reported herein is a bispecific antibody for binding human CD20 and human transferrin receptor comprising

a) one antibody comprising two pairs each of an antibody light chain and an antibody heavy chain, wherein the binding sites formed by each of the pairs of the heavy chain and the light chain specifically bind to a first antigen, and

b) one additional Fab fragment, wherein the binding site of the additional Fab fragment specifically binds to a second antigen,

said bispecific antibody comprising

- SEQ ID NO: 06 to 09, or

- SEQ ID NO: 11 to 13 and SEQ ID NO: 22, or

- SEQ ID NO: 14 to 17.

Reported herein is an isolated nucleic acid encoding the bispecific antibody as reported herein. In another aspect, reported herein is an isolated nucleic acid encoding the antibody as described herein.

Reported herein is a host cell comprising the nucleic acid as reported herein encoding the bispecific antibody as reported herein. In another aspect, reported herein is a host cell comprising the nucleic acid as described herein.

Reported herein is a method of producing a bispecific antibody as reported herein comprising the following steps:

a) culturing the host cell as reported herein so that the bispecific antibody is produced, and

b) recovering the bispecific antibody from the cell or the cultivation medium and thereby producing the bispecific antibody as reported herein.

Reported herein is an immunoconjugate comprising the bispecific antibody as reported herein and a cytotoxic agent.

Reported herein is a pharmaceutical formulation comprising the bispecific antibody as reported herein and a pharmaceutically acceptable carrier. In another aspect, reported herein is a pharmaceutical formulation for binding human CD20 and human transferrin receptor comprising the antibody as described herein and a pharmaceutically acceptable carrier.

In another aspect, reported herein is the antibody as reported herein for use as a medicament.

Reported herein is the antibody as reported herein for the treatment of cancer.

Reported herein is the bispecific antibody as reported herein for use in treating B-cell proliferative disease.

Reported herein is the bispecific antibody as reported herein for use in inhibiting growth of tumor cells expressing CD20. In one example the inhibiting is in the brain.

Reported herein is the bispecific antibody as reported herein for use in treating carcinoma. In one preferred example the carcinoma is carcinoma of/in the brain.

Reported herein is the bispecific antibody as reported herein for use in treating lymphoma. In one preferred example the lymphoma is primary central nervous system lymphoma (PCNSL).

Reported herein is the bispecific antibody as reported herein for use in treating an autoimmune disease. In one example the autoimmune disease is multiple sclerosis. In one preferred example the autoimmune disease is secondary progressive multiple sclerosis.

Reported herein is the bispecific antibody as reported herein for use in depleting tumor cells expressing CD20. In one example the depleting is in the brain.

Reported herein is the bispecific antibody as reported herein for use in depleting circulating B-cells expressing CD20. In one example the depleting is in the brain.

Reported herein is the bispecific antibody as reported herein for use in depleting brain sequestered B-cells expressing CD20.

Reported herein is the use of the bispecific antibody as reported herein in the manufacture of a medicament.

In one example the medicament is for the treatment of a proliferative type disease. In one example the proliferative type disease is a B-cell proliferative disease. In one example the proliferative type disease is B-cell lymphoma. In one preferred example the proliferative type disease is primary central nervous system lymphoma.

In one example the medicament is for the treatment of a tumor.

In one example the medicament is for the treatment of human carcinoma.

In one example the medicament is for the treatment of an autoimmune disease. In one example the autoimmune disease is selected from the group consisting of inflammatory responses such as inflammatory skin diseases including psoriasis and dermatitis (e.g. atopic dermatitis); systemic scleroderma and sclerosis; responses associated with inflammatory bowel disease (such as Crohn's disease and ulcerative colitis); respiratory distress syndrome (including adult respiratory distress syndrome; ARDS); dermatitis; meningitis; encephalitis; uveitis; colitis; glomerulonephritis; allergic conditions such as eczema and asthma and other conditions involving infiltration of T-cells and chronic inflammatory responses; atherosclerosis; leukocyte adhesion deficiency; rheumatoid arthritis; systemic lupus erythematosus (SLE); diabetes mellitus (e.g. Type I diabetes mellitus or insulin dependent diabetes mellitus); multiple sclerosis; Reynaud's syndrome; autoimmune thyroiditis; allergic encephalomyelitis; Sjogren’s syndrome; juvenile onset diabetes; and immune responses associated with acute and delayed hypersensitivity mediated by cytokines and T-lymphocytes typically found in tuberculosis, sarcoidosis, polymyositis, granulomatosis and vasculitis; pernicious anemia (Addison's disease); diseases involving leukocyte diapedesis; central nervous system (CNS) inflammatory disorder; multiple organ injury syndrome; hemolytic anemia (including, but not limited to cryoglobinemia or Coombs positive anemia); myasthenia gravis; antigen-antibody complex mediated diseases; anti-glomerular basement membrane disease; anti-phospholipid syndrome; allergic neuritis; Graves' disease; Lambert-Eaton myasthenic syndrome; pemphigoid bullous; pemphigus; autoimmune polyendocrinopathies; Reiter's disease; stiff-man syndrome; Bechet disease; giant cell arteritis; immune complex nephritis; IgA nephropathy; IgM polyneuropathies; immune thrombocytopenic purpura (ITP) or autoimmune thrombocytopenia. In one example the medicament is for treatment of multiple sclerosis. In one preferred example the medicament is for the treatment of secondary progressive multiple sclerosis.

In one example the medicament is for depleting tumor cells expressing CD20. In one example the depleting is in the brain.

In one example the medicament is for depleting circulating B-cells expressing CD20. In one example the depleting is in the brain.

In one example the medicament is for depleting brain sequestered B-cells expressing CD20.

In another aspect, reported herein is use of the antibody as described herein in the manufacture of a medicament for the treatment of a proliferative disease.

In another aspect, reported herein is use of the antibody as described herein in the manufacture of a medicament for the treatment of a B-cell proliferative disease.

In another aspect, reported herein is use of the antibody as described herein in the manufacture of a medicament for the treatment of a B-cell lymphoma.

In another aspect, reported herein is use of the antibody as described herein in the manufacture of a medicament for the treatment of a primary central nervous system lymphoma.

In another aspect, reported herein is use of the antibody as described herein in the manufacture of a medicament for the treatment of a tumor.

In another aspect, reported herein is use of the antibody as described herein in the manufacture of a medicament for the treatment of human carcinoma.

In another aspect, reported herein is use of the antibody as described herein in the manufacture of a medicament for the treatment of an autoimmune disease.

In another aspect, reported herein is use of the antibody as described herein in the manufacture of a medicament for the treatment of an autoimmune disease selected from the group consisting of inflammatory responses such as inflammatory skin diseases including psoriasis and dermatitis (e.g. atopic dermatitis); systemic scleroderma and sclerosis; responses associated with inflammatory bowel disease (such as Crohn's disease and ulcerative colitis); respiratory distress syndrome (including adult respiratory distress syndrome; ARDS); dermatitis; meningitis; encephalitis; uveitis; colitis; glomerulonephritis; allergic conditions such as eczema and asthma and other conditions involving infiltration of T-cells and chronic inflammatory responses; atherosclerosis; leukocyte adhesion deficiency; rheumatoid arthritis; systemic lupus erythematosus (SLE); diabetes mellitus (e.g. Type I diabetes mellitus or insulin dependent diabetes mellitus); multiple sclerosis; Reynaud's syndrome; autoimmune thyroiditis; allergic encephalomyelitis; Sjogren's syndrome; juvenile onset diabetes; and immune responses associated with acute and delayed hypersensitivity mediated by cytokines and T-lymphocytes typically found in tuberculosis, sarcoidosis, polymyositis, granulomatosis and vasculitis; pernicious anemia (Addison's disease); diseases involving leukocyte diapedesis; central nervous system (CNS) inflammatory disorder; multiple organ injury syndrome; hemolytic anemia (including, but not limited to cryoglobinemia or Coombs positive anemia); myasthenia gravis; antigen-antibody complex mediated diseases; anti-glomerular basement membrane disease; anti-phospholipid syndrome; allergic neuritis; Graves' disease; Lambert-Eaton myasthenic syndrome; pemphigoid bullous; pemphigus; autoimmune polyendocrinopathies; Reiter's disease; stiff-man syndrome; Bechet disease; giant cell arteritis; immune complex nephritis; IgA nephropathy; IgM polyneuropathies; immune thrombocytopenic purpura (ITP) and autoimmune thrombocytopenia.

In another aspect, reported herein is use of the antibody as described herein in the manufacture of a medicament for the treatment of multiple sclerosis.

In another aspect, reported herein is use of the antibody as described herein in the manufacture of a medicament for the treatment of secondary progressive multiple sclerosis.

In another aspect, reported herein is use of the antibody as described herein in the manufacture of a medicament for the depletion of tumor cells expressing CD20.

In another aspect, reported herein is use of the antibody as described herein in the manufacture of a medicament for the depletion of tumor cells expressing CD20 in the brain.

In another aspect, reported herein is use of the antibody as described herein in the manufacture of a medicament for the depletion of circulating B-cells expressing CD20.

In another aspect, reported herein is use of the antibody as described herein in the manufacture of a medicament for the depletion of circulating B-cells expressing CD20 in the brain.

In another aspect, reported herein is use of the antibody as described herein in the manufacture of a medicament for the depletion of brain sequestered B-cells expressing CD20.

Reported herein is a method of treating an individual having a proliferative type disease comprising administering to the individual an effective amount of the bispecific antibody as reported herein. In one example the proliferative type disease is a B-cell proliferative disease.

Reported herein is a method of treating an individual having carcinoma comprising administering to the individual an effective amount of the bispecific antibody as reported herein. In one preferred example the carcinoma is carcinoma of/in the brain.

Reported herein is a method of treating an individual having lymphoma comprising administering to the individual an effective amount of the bispecific antibody as reported herein. In one preferred example the lymphoma is primary central nervous system lymphoma (PCNSL).

Reported herein is a method of treating an individual having an autoimmune disease comprising administering to the individual an effective amount of the bispecific antibody as reported herein. In one example the autoimmune disease is multiple sclerosis. In one preferred example the autoimmune disease is secondary progressive multiple sclerosis.

Reported herein is a method for inhibiting growth of tumor cells expressing CD20 in an individual comprising administering to the individual an effective amount of the bispecific antibody as reported herein to inhibit growth of tumor cells expressing CD20. In one example the inhibiting is in the brain.

Reported herein is a method for depleting tumor cells expressing CD20 in an individual comprising administering to the individual an effective amount of the bispecific antibody as reported herein to deplete tumor cells expressing CD20. In one example the inhibiting is in the brain.

Reported herein is a method for depleting circulating B-cells expressing CD20 in an individual comprising administering to the individual an effective amount of the bispecific antibody as reported herein to deplete circulating B-cells expressing CD20. In one example the inhibiting is in the brain.

Reported herein is a method for depleting brain sequestered B-cells expressing CD20 in an individual comprising administering to the individual an

effective amount of the bispecific antibody as reported herein to deplete brain sequestered B-cells expressing CD20.

Reported herein is a method of treating multiple sclerosis in a human comprising administering to the human a therapeutically effective amount of an antibody as reported herein which binds to human CD20 and depletes B-cells, and wherein the antibody is not conjugated with a cytotoxic agent.

DETAILED DESCRIPTION OF EMBODIMENTS OF THE INVENTION

The knobs into holes dimerization modules and their use in antibody engineering are described in Carter P.; Ridgway J.B.B.; Presta L.G.: Immunotechnology, Volume 2, Number 1, February 1996 , pp. 73-73. The additional disulfide bridge in the CH3 domain is reported in Merchant, A.M., et al., Nat. Biotechnol. 16 (1998) 677-681.

General information regarding the nucleotide sequences of human immunoglobulins light and heavy chains is given in: Kabat, E.A., et al., Sequences of Proteins of Immunological Interest, 5th ed., Public Health Service, National Institutes of Health, Bethesda, MD (1991).

As used herein, the amino acid positions of all constant regions and domains of the heavy and light chain are numbered according to the Kabat numbering system described in Kabat, et al., Sequences of Proteins of Immunological Interest, 5th ed., Public Health Service, National Institutes of Health, Bethesda, MD (1991) and is referred to as “numbering according to Kabat” herein. Specifically, the Kabat numbering system (see pages 647-660) of Kabat, et al., Sequences of Proteins of Immunological Interest, 5th ed., Public Health Service, National Institutes of Health, Bethesda, MD (1991) is used for the light chain constant domain CL of kappa and lambda isotype, and the Kabat EU index numbering system (see pages 661-723) is used for the constant heavy chain domains (CH1, Hinge, CH2 and CH3, which is herein further clarified by referring to “numbering according to Kabat EU index” in this case).

I. DEFINITIONS

The "blood-brain-barrier" or "BBB" refers to the physiological barrier between the peripheral circulation and the brain and spinal cord which is formed by tight junctions within the brain capillary endothelial plasma membranes, creating a tight

Patent Claims

1. A bispecific antibody for binding human CD20 and human transferrin receptor comprising

   a) one antibody comprising two pairs each of an antibody light chain and an antibody heavy chain, wherein the binding sites formed by each of the pairs of the heavy chain and the light chain specifically bind to a first antigen, and

   b) one additional Fab fragment, wherein the binding site of the additional Fab fragment specifically binds to a second antigen,

   said bispecific antibody comprising

   - SEQ ID NO: 06 to 09, or

   - SEQ ID NO: 11 to 13 and SEQ ID NO: 22, or

   - SEQ ID NO: 14 to 17.

2. The antibody according to claim 1, wherein

   a) the heavy chain that is fused to the additional Fab fragments has as C-terminal heavy chain amino acid residues the tripeptide LSP wherein the proline thereof is directly fused to the first amino acid residue of the additional Fab fragment or of the peptidic linker via a peptide bond, and

   b) the heavy chain that is not fused to the additional Fab fragments has as C-terminal heavy chain amino acid residues the tripeptide LSP, or SPG, or PGK.

3. The antibody according to claim 1, wherein the antibody is monoclonal.

4. A pharmaceutical formulation for binding human CD20 and human transferrin receptor comprising the antibody according to any one of claims 1 to 3 and a pharmaceutically acceptable carrier.

5. The antibody according to any one of claims 1 to 3 for use as a medicament.

6. Use of the antibody according to any one of claims 1 to 3 in the manufacture of a medicament for the treatment of a proliferative disease.

7. Use of the antibody according to any one of claims 1 to 3 in the manufacture of a medicament for the treatment of a B-cell proliferative disease.

8. Use of the antibody according to any one of claims 1 to 3 in the manufacture of a medicament for the treatment of a B-cell lymphoma.

9. Use of the antibody according to any one of claims 1 to 3 in the manufacture of a medicament for the treatment of a primary central nervous system lymphoma.

10. Use of the antibody according to any one of claims 1 to 3 in the manufacture of a medicament for the treatment of a tumor.

11. Use of the antibody according to any one of claims 1 to 3 in the manufacture of a medicament for the treatment of human carcinoma.

12. Use of the antibody according to any one of claims 1 to 3 in the manufacture of a medicament for the treatment of an autoimmune disease.

13. Use of the antibody according to any one of claims 1 to 3 in the manufacture of a medicament for the treatment of an autoimmune disease selected from the group consisting of inflammatory responses such as inflammatory skin diseases including psoriasis and dermatitis (e.g. atopic dermatitis); systemic scleroderma and sclerosis; responses associated with inflammatory bowel disease (such as Crohn's disease and ulcerative colitis); respiratory distress syndrome (including adult respiratory distress syndrome; ARDS); dermatitis; meningitis; encephalitis; uveitis; colitis; glomerulonephritis; allergic conditions such as eczema and asthma and other conditions involving infiltration of T-cells and chronic inflammatory responses; atherosclerosis; leukocyte adhesion deficiency; rheumatoid arthritis; systemic lupus erythematosus (SLE); diabetes mellitus (e.g. Type I diabetes mellitus or insulin dependent diabetes mellitus); multiple sclerosis; Reynaud's syndrome; autoimmune thyroiditis; allergic encephalomyelitis; Sjogren's syndrome; juvenile onset diabetes; and immune responses associated with acute and delayed hypersensitivity mediated by cytokines and T-lymphocytes typically found in tuberculosis, sarcoidosis, polymyositis, granulomatosis and

vasculitis; pernicious anemia (Addison's disease); diseases involving leukocyte diapedesis; central nervous system (CNS) inflammatory disorder; multiple organ injury syndrome; hemolytic anemia (including, but not limited to cryoglobinemia or Coombs positive anemia); myasthenia gravis; antigen-antibody complex mediated diseases; anti-glomerular basement membrane disease; anti-phospholipid syndrome; allergic neuritis; Graves' disease; Lambert-Eaton myasthenic syndrome; pemphigoid bullous; pemphigus; autoimmune polyendocrinopathies; Reiter's disease; stiff-man syndrome; Bechet disease; giant cell arteritis; immune complex nephritis; IgA nephropathy; IgM polyneuropathies; immune thrombocytopenic purpura (ITP) or autoimmune thrombocytopenia.

14. Use of the antibody according to any one of claims 1 to 3 in the manufacture of a medicament for the treatment of multiple sclerosis.

15. Use of the antibody according to any one of claims 1 to 3 in the manufacture of a medicament for the treatment of secondary progressive multiple sclerosis.

16. Use of the antibody according to any one of claims 1 to 3 in the manufacture of a medicament for the depletion of tumor cells expressing CD20.

17. Use of the antibody according to any one of claims 1 to 3 in the manufacture of a medicament for the depletion of tumor cells expressing CD20 in the brain.

18. Use of the antibody according to any one of claims 1 to 3 in the manufacture of a medicament for the depletion of circulating B-cells expressing CD20.

19. Use of the antibody according to any one of claims 1 to 3 in the manufacture of a medicament for the depletion of circulating B-cells expressing CD20 in the brain.

20. Use of the antibody according to any one of claims 1 to 3 in the manufacture of a medicament for the depletion of brain sequestered B-cells expressing CD20.

21. An isolated nucleic acid encoding the antibody according to any one of claims 1 to 3.

22. A host cell comprising the nucleic acid according to claim 21.