CLAIMS

1. An isolated antibody, or antigen-binding portion thereof, wherein said antibody, or antigen-binding portion comprises:

(a) an H-CDR1 as set forth in SEQ ID NO:29;

(b) an H-CDR2 as set forth in SEQ ID NO:30;

(c) an H-CDR3 as set forth in SEQ ID NO:31;

(d) an L-CDR1 as set forth in SEQ ID NO:34;

(e) an L-CDR2 as set forth in SEQ ID NO:35; and

(f) an L-CDR3 as set forth in SEQ ID NO:36.

2. The antibody, or antigen-binding portion according to claim 1 wherein said antibody, or antigen-binding portion comprises a V_H region amino acid sequence as set forth in SEQ ID NO:43.

3. The antibody, or antigen-binding portion according to claim 1 wherein said antibody, or antigen-binding portion comprises a V_L region amino acid sequence as set forth in SEQ ID NO:45.

4. The antibody, or antigen-binding portion according to claim 1, comprising a V_H region amino acid sequence as set forth in SEQ ID NO:43 and a V_L region amino acid sequence as set forth in SEQ ID NO:45.

5. The isolated antibody, wherein said antibody comprises a heavy chain amino acid sequence as set forth in SEQ ID NO:44 and further comprises a light chain amino acid sequence set forth in SEQ ID NO:46, with the proviso that the C-terminal lysine residue of SEQ ID NO:44 is optionally absent.

6. The isolated antibody according to any of claims 1 to 5, which is an IgG2.

7. A pharmaceutical composition comprising an antibody, or antigen-binding portion thereof, according to claims 1-6 and a pharmaceutically acceptable carrier.

CLAIMS

1. An isolated antibody, or antigen-binding portion thereof, wherein said antibody, or antigen-binding portion comprises:

(a) an H-CDR1 as set forth in SEQ ID NO:29;
(b) an H-CDR2 as set forth in SEQ ID NO:30;
(c) an H-CDR3 as set forth in SEQ ID NO:31;
(d) an L-CDR1 as set forth in SEQ ID NO:34;
(e) an L-CDR2 as set forth in SEQ ID NO:35; and
(f) an L-CDR3 as set forth in SEQ ID NO:36.

2. The antibody, or antigen-binding portion according to claim 1, wherein said antibody, or antigen-binding portion comprises a V_H region amino acid sequence as set forth in SEQ ID NO:43.

3. The antibody, or antigen-binding portion according to claim 1, wherein said antibody, or antigen-binding portion comprises a V_L region amino acid sequence as set forth in SEQ ID NO:45.

4. The antibody, or antigen-binding portion according to claim 1, comprising a V_H region amino acid sequence as set forth in SEQ ID NO:43 and a V_L region amino acid sequence as set forth in SEQ ID NO:45.

5. The isolated antibody, wherein said antibody comprises a heavy chain amino acid sequence as set forth in SEQ ID NO:44 and further comprises a light chain amino acid sequence set forth in SEQ ID NO:46, with the proviso that the C-terminal lysine residue of SEQ ID NO:44 is optionally absent.

6. The isolated antibody according to any of claims 1 to 5, wherein the antibody isotype is IgG2.

7. A pharmaceutical composition comprising an antibody or antigen-binding portion thereof according to any one of claims 1 to 6, and a pharmaceutically acceptable carrier.

8. An effective amount of an antibody or antigen-binding portion thereof according to any one of claims 1 to 6, or the pharmaceutical composition according to claim 7 for use in reducing tumor growth in a subject in need thereof.

9. The use of an effective amount of an antibody or antigen-binding portion thereof according to any one of claims 1 to 6, or the pharmaceutical composition according to claim 7 in the manufacture of a medicament for reducing tumor growth a subject in need thereof.

10. A therapeutically effective amount of an antibody or antigen-binding portion thereof according to any one of claims 1 to 6, or the pharmaceutical composition according to claim 7, for use in the treatment of cancer.

11. The use of a therapeutically effective amount of an antibody or antigen-binding portion thereof according to any one of claims 1 to 6, or the pharmaceutical composition according to claim 7 in the manufacture of a medicament for the treatment of cancer in a subject.

12. The antibody or antigen-binding portion thereof or the pharmaceutical composition according to claim 10 or the use according to claim 11, wherein said cancer is selected from the group consisting of colorectal cancer, non-Hodgkin's lymphoma, prostate cancer, and melanoma.

13. The antibody or antigen-binding portion thereof or the pharmaceutical composition according to claim 10 or the use according to claim 11, in combination with an immunotherapeutic agent.

14. The antibody or antigen-binding portion or the pharmaceutical composition, or the use according to claim 13, wherein said immunotherapeutic agent is rituximab.

15. An isolated nucleic acid molecule comprising a nucleotide sequence encoding a polypeptide that comprises one or more amino acid sequences selected from SEQ ID NO: 43, 44, 45 or 46.

16. An isolated nucleic acid comprising one or more nucleotide sequences selected from SEQ ID NO: 47, 48, 49, or 50.

17. A vector comprising an isolated nucleic acid according to claim 16.

18. A host cell comprising a vector according to claim 17.

19. A method of producing an antibody that comprises one or more amino acid sequences selected from SEQ ID NO: 43, 44, 45 or 46, the method comprising expressing the antibody in the host cell according to claim 18.

20. An antibody that comprises one or more amino acid sequences selected from SEQ ID NO: 43, 44, 45 or 46 when produced by the method according to claim 19.

21. An isolated antibody or a antigen-binding portion thereof wherein said antibody or antigen-binding portion binds human 4-1BB extracellular domain at an epitope comprising amino acid residues 115-156 of SEQ ID NO: 68.

22. The antibody or antigen-binding portion thereof according to claim 21, wherein said antibody or antigen-binding portion binds human 4-1BB with a K_D of 10 nM or less for the human 4-1BB extracellular domain as measured using a surface plasmon resonance assay.

23. The antibody or antigen-binding portion thereof according to claim 21 or claim 22,

comprising a V_H chain amino acid sequence selected from the group consisting of SEQ ID NO: 4, SEQ ID NO: 18, SEQ ID NO: 32, and SEQ ID NO: 43 and a V_L region amino acid sequence selected from the group consisting of SEQ ID NO: 9, SEQ ID NO: 23, SEQ ID NO: 37, SEQ ID NO: 45, SEQ ID NO: 51, SEQ ID NO: 56, SEQ ID NO: 60, and SEQ ID NO: 64.

24. A pharmaceutical composition comprising an antibody or antigen-binding portion thereof according to any one of claims 21 to 23, and a pharmaceutically acceptable carrier.

25. An effective amount of an antibody or antigen-binding portion thereof according to any one of claims 21 to 23, or the pharmaceutical composition according to claim 24 for use in reducing tumor growth in a subject in need thereof.

26. The use of an effective amount of an antibody or antigen-binding portion thereof according to any one of claims 21 to 23, or the pharmaceutical composition according to claim 24, in the manufacture of a medicament for reducing tumor growth in a subject in need thereof.

27. An effective amount of an antibody or antigen-binding portion thereof according to any one of claims 21 to 23, or the pharmaceutical composition according to claim 24 for use in reducing tumor cell metastasis in a subject in need thereof.

28. The use of an effective amount of an antibody or antigen-binding portion thereof according to any one of claims 21 to 23, or the pharmaceutical composition according to claim 24, in the manufacture of a medicament for reducing tumor cell metastasis in a subject.

29. An effective amount of an antibody or antigen-binding portion thereof according to any one of claims 21 to 23, or the pharmaceutical composition according to claim 24 for use in treating a disorder in a subject in need thereof.

30. The use of an effective amount of an antibody or antigen-binding portion thereof according to any one of claims 21 to 23, or the pharmaceutical composition according to claim 24, in the manufacture of a medicament for treating a disorder in a subject in need thereof.

31. The antibody or antigen-binding portion thereof according to claim 29, or the use according to claim 30, wherein said disorder is cancer.

32. The antibody or antigen-binding portion thereof or use according to claim 31, wherein said cancer is selected from the group consisting of colorectal cancer, non-Hodgkin's lymphoma, prostate cancer, or melanoma.

33. A combination therapy comprising an antibody or antigen-binding portion thereof according to any one of claims 21 to 23, and a pharmaceutically acceptable carrier in combination with an immunotherapeutic agent.

34. The combination therapy according to claim 33, wherein said immunotherapeutic agent is rituximab.

35. An isolated antibody or antigen-binding portion thereof wherein said antibody or antigen-binding portion binds human 4-1BB extracellular domain, and wherein said binding is abrogated by one or more mutations of SEQ ID NO: 68 selected from K115Q, C121R, R134Q, R154S, or V156A.

36. The antibody or antigen-binding portion thereof according to claim 35, wherein the one or more mutations of SEQ ID NO: 68 comprise K11Q, C121R, R134Q, R154S, and V156A.

37. A pharmaceutical composition comprising an antibody or antigen-binding portion thereof according to claim 35 or claim 36, and a pharmaceutically acceptable carrier.

38. An effective amount of an antibody or antigen-binding portion thereof according to claim 35 or claim 36, or the pharmaceutical composition according to claim 36 for use in reducing tumor growth in a subject in need thereof.

39. The use of an effective amount of an antibody or antigen-binding portion thereof according to claim 35 or claim 36, or the pharmaceutical composition according to claim 36 in the manufacture of a medicament for reducing tumor growth in a subject.

40. An effective amount of an antibody or antigen-binding portion thereof according to claim 35 or claim 36, or the pharmaceutical composition according to claim 36 for use in the treatment of cancer in a subject.

41. The use of an effective amount of an antibody or antigen-binding portion thereof according to claim 35 or claim 36, or the pharmaceutical composition according to claim 36 in the manufacture of a medicament for the treatment of cancer in a subject.

42. The antibody or antigen-binding portion or the pharmaceutical composition according to claim 40 or the use according to claim 41, wherein said cancer is selected from the group consisting of colorectal cancer, non-Hodgkin's lymphoma, prostate cancer, and melanoma.

43. The antibody or antigen-binding portion or the pharmaceutical composition according to claim 40 or the use according to claim 41, or the antibody or antigen-binding portion or the pharmaceutical composition or use according to claim 42, further comprising administering an immunotherapeutic agent.

44. The antibody or antigen-binding portion or the pharmaceutical composition or the use according to claim 43 wherein said immunotherapeutic agent is rituximab.

45. A human monoclonal antibody or antigen-binding portion thereof that binds to 4-1BB.

46. The antibody or antigen-binding portion thereof according to claim 45, wherein said 4-1BB is human.

47. The antibody or antigen-binding portion thereof according to claim 45 or claim 46, wherein said antibody or antigen-binding portion thereof has at least one property selected from the group consisting of:

(a) cross-competes for binding to 4-1BB with an antibody selected from the group consisting of MOR-6032, MOR-7361, MOR-7480, MOR-7480.1, MOR-7480.2, MOR-7483, MOR-7483.1 and MOR-7483.2;
(b) binds to the same epitope of 4-1BB as an antibody selected from the group consisting of MOR-6032, MOR-7361, MOR-7480, MOR-7480.1, MOR-7480.2, MOR-7483, MOR-7483.1 and MOR-7483.2;
(c) binds to the same antigen as that bound by an antibody selected from the group consisting of MOR-6032, MOR-7361, MOR-7480, MOR-7480.1, MOR-7480.2, MOR-7483, MOR-7483.1 and MOR-7483.2;
(d) binds to 4-1BB with substantially the same K_D as an antibody selected from the group consisting of MOR-6032, MOR-7361, MOR-7480, MOR-7480.1, MOR-7480.2, MOR-7483, MOR-7483.1 and MOR-7483.2;
(e) binds to 4-1BB with substantially the same EC50 as an antibody selected from the group consisting of MOR-6032, MOR-7361, MOR-7480, MOR-7480.1, MOR-7480.2, MOR-7483, MOR-7483.1 and MOR-7483.2;
(f) binds to 4-1BB with substantially the same IC50 as an antibody selected from the group consisting of MOR-6032, MOR-7361, MOR-7480, MOR-7480.1, MOR-7480.2, MOR-7483, MOR-7483.1 and MOR-7483.2;
(g) binds human 4-1BB and comprises a heavy chain variable region that is the product of, or derived from, a human V_H 3-23 gene, V_H 1-69 gene or V_H 5; and
(h) binds human 4-1BB and comprises a light chain variable region that is the product of, or derived from, a human V_L λ3 or λ1-13 gene.

48. The antibody or antigen-binding portion thereof according to claim 47, wherein

the antibody or antigen-binding portion thereof has one or more of the following properties or characteristics:

(a) specifically binds to human 4-1BB;
(b) binds to human and cynomolgus 4-1BB;
(c) binds to human 4-1BB or cynomolgus 4-1BB but not rat or mouse 4-1BB;
(d) is an IgG; and
(e) is a human antibody or antigen-binding portion thereof or a humanized antibody or antigen-binding portion thereof.

49. The antibody or antigen-binding portion thereof according to claim 47 or claim 48, wherein the antibody or antigen-binding portion thereof has all of said properties.

50. The antibody or antigen-binding portion thereof according to any one of claims 45 to 49 comprising a V_H region amino acid sequence selected from the group consisting of SEQ ID NO: 4, SEQ ID NO: 18, SEQ ID NO: 32, and SEQ ID NO: 43; and a V_L region amino acid sequence selected from the group consisting of SEQ ID NO: 9, SEQ ID NO: 23, SEQ ID NO: 37, SEQ ID NO: 45, SEQ ID NO: 51, SEQ ID NO: 56, SEQ ID NO: 60, and SEQ ID NO: 64.

51. The antibody or antigen-binding portion thereof according to claim 50, wherein said V_H region amino acid sequence is SEQ ID NO: 43 and said V_L region amino acid sequence is SEQ ID NO: 45.

52. The antibody or antigen-binding portion thereof according to any one of claims 45 to 49, comprising a V_H region comprising:

(a) a CDR1 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 15, and SEQ ID NO: 29;
(b) a CDR2 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 16, and SEQ ID NO: 30; and

(c) a CDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 17, and SEQ ID NO: 31;

and a V_L region comprising

(d) a CDR1 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 6, SEQ ID NO: 20, and SEQ ID NO: 34;

(e) a CDR2 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 7, SEQ ID NO: 21, and SEQ ID NO: 35; and

(f) a CDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 8, SEQ ID NO: 22, SEQ ID NO: 36, and SEQ ID NO: 55.

53. The antibody or antigen-binding portion thereof according to claim 52, wherein said V_H region comprises:

(a) a CDR1 domain comprising the amino acid sequence SEQ ID NO: 29;

(b) a CDR2 domain comprising the amino acid sequence SEQ ID NO: 30; and

(c) a CDR3 domain comprising the amino acid sequence SEQ ID NO: 31;

and said V_L region comprises

(d) a CDR1 domain comprising the amino acid sequence SEQ ID NO: 34;

(e) a CDR2 domain comprising the amino acid sequence SEQ ID NO: 35; and

(f) a CDR3 domain comprising the amino acid sequence SEQ ID NO: 36.

54. An isolated antibody, or antigen-binding portion thereof, wherein said antibody, or antigen-binding portion comprises:

(a) an H-CDR1 as set forth in SEQ ID NO:29;

(b) an H-CDR2 as set forth in SEQ ID NO:30;

(c) an H-CDR3 as set forth in SEQ ID NO:31;

(d) an L-CDR1 as set forth in SEQ ID NO:34;

(e) an L-CDR2 as set forth in SEQ ID NO:35; and

(f) an L-CDR3 as set forth in SEQ ID NO:36.

55. The antibody, or antigen-binding portion according to claim 54, wherein said antibody, or antigen-binding portion comprises a V_H region amino acid sequence as set forth in SEQ ID NO:43.

56. The antibody, or antigen-binding portion according to claim 54, wherein said antibody, or antigen-binding portion comprises a V_L region amino acid sequence as set forth in SEQ ID NO:45.

57. The antibody, or antigen-binding portion according to claim 54, comprising a V_H region amino acid sequence as set forth in SEQ ID NO:43 and a V_L region amino acid sequence as set forth in SEQ ID NO:45.

58. An isolated antibody, wherein said antibody comprises a heavy chain amino acid sequence as set forth in SEQ ID NO:44 and further comprises a light chain amino acid sequence set forth in SEQ ID NO:46.

59. The isolated antibody according to claim 58, wherein the C-terminal lysine residue of SEQ ID NO:44 is absent.

60. The isolated antibody according to any one of claims 54 to 59, which is an IgG2.

61. A pharmaceutical composition comprising an antibody, or antigen-binding portion thereof, according to any one of claims 54 to 60, and a pharmaceutically acceptable carrier.

62. The use of the antibody or antigen-binding portion thereof according to any of claims 54 to 60 or the pharmaceutical composition according to claim 61, in the manufacture of a medicament for reducing tumor growth.

63. The antibody or antigen-binding portion thereof according to any one of claims 54 to 60 or the pharmaceutical composition according to claim 61, for use in reducing

tumor growth.

64. The use of the antibody or antigen-binding portion thereof according to any of claims 54 to 60 or the pharmaceutical composition according to claim 61, in the manufacture of a medicament for the treatment of cancer.

65. The antibody or antigen-binding portion thereof according to any one of claims 54 to 60 or the pharmaceutical composition according to claim 61, for use in the treatment of cancer.

66. The use according to claim 64 or the antibody or antigen-binding portion thereof or the pharmaceutical composition according to claim 65, wherein said cancer is selected from the group consisting of colorectal cancer, non-Hodgkin's lymphoma, prostate cancer, and melanoma.

67. The use, according to claim 64, or an antibody or antigen-binding portion thereof or the pharmaceutical composition according to claim 65, in combination with an immunotherapeutic agent.

68. The use, or an antibody or antigen-binding portion thereof or the pharmaceutical composition according to claim 67, wherein said immunotherapeutic agent is rituximab.

69. An isolated nucleic acid molecule comprising a nucleotide sequence encoding a polypeptide that comprises one or more amino acid sequences selected from SEQ ID NO: 43, 44, 45 or 46.

70. An isolated nucleic acid comprising one or more nucleotide sequences selected from SEQ ID NO: 47, 48, 49 or 50.

71. A vector comprising an isolated nucleic acid according to claim 70.

72. A host cell comprising a vector according to claim 71.

73. A method for producing an antibody that comprises one or more amino acid sequences selected from SEQ ID NO: 43, 44, 45 or 46, comprising expressing the antibody in a host cell according to claim 71.

74. An isolated antibody or an antigen-binding portion thereof wherein said antibody or antigen-binding portion binds human 4-1BB extracellular domain at an epitope located within amino acid residues 115-156 of SEQ ID NO: 68.

75. The antibody or antigen-binding portion thereof according to claim 74, wherein said antibody or antigen-binding portion binds human 4-1BB with a K_D of 10 nM or less for the human 4-1BB extracellular domain as measured using a surface plasmon resonance assay.

76. The antibody or antigen-binding portion thereof according to claim 74 or claim 75, comprising a V_H region amino acid sequence selected from the group consisting of SEQ ID NO: 4, SEQ ID NO: 18, SEQ ID NO: 32, and SEQ ID NO: 43; and a V_L region amino acid sequence selected from the group consisting of SEQ ID NO: 9, SEQ ID NO: 23, SEQ ID NO: 37, SEQ ID NO: 45, SEQ ID NO: 51, SEQ ID NO: 56, SEQ ID NO: 60, and SEQ ID NO: 64.

77. The antibody or antigen-binding portion thereof according to claim 76, wherein said V_H region amino acid sequence is SEQ ID NO: 43 and said V_L region amino acid sequence is SEQ ID NO: 45.

78. A pharmaceutical composition comprising an antibody or antigen-binding portion thereof according to any one of claims 74 to 77, and a pharmaceutically acceptable carrier.

79. The use of the antibody or antigen-binding portion thereof according to any one

of claims 74 to 77, or the pharmaceutical composition according to claim 78, in the manufacture of a medicament for reducing tumor cell metastasis.

80. The antibody or antigen-binding portion thereof according to any one of claims 74 to 77, or the pharmaceutical composition according to claim 78, for use in reducing tumor cell metastasis.

81. The use of the antibody or antigen-binding portion thereof according to any one of claims 74 to 77, or the pharmaceutical composition according to claim 78, in the manufacture of a medicament for the treatment of a disorder.

82. The antibody or antigen-binding portion thereof according to any one of claims 74 to 77, or the pharmaceutical composition according to claim 78, for use in the treatment of a disorder.

83. The use according to claim 81 or antibody or antigen-binding portion thereof or the pharmaceutical composition according to claim 82, wherein said disorder is cancer.

84. The use, or antibody or antigen-binding portion thereof or the pharmaceutical composition according to claim 83, wherein said cancer is selected from the group consisting of colorectal cancer, non-Hodgkin's lymphoma, prostate cancer, and melanoma.

85. The use, or antibody or antigen-binding portion thereof or the pharmaceutical composition according to claim 83 or claim 84, in combination with an immuno-therapeutic agent.

86. The use, or antibody or antigen-binding portion thereof or the pharmaceutical composition according to claim 85, wherein said immunotherapeutic agent is rituximab.

87. The use of the antibody or antigen-binding portion thereof according to any one

of claims 74 to 77, or the pharmaceutical composition according to claim 78, in the manufacture of a medicament for reducing tumor growth.

88. The antibody or antigen-binding portion thereof according to any one of claims 74 to 77, or the pharmaceutical composition according to claim 78, for use in reducing tumor growth.

89. An isolated antibody or an antigen-binding portion thereof wherein said antibody or antigen-binding portion binds human 4-1BB extracellular domain, and wherein said binding is abrogated by one or more mutations of SEQ ID NO: 68 selected from K115Q, C121R, R134Q, R154S, or V156A.

90. The antibody or antigen-binding portion thereof according to claim 89, wherein the one or more mutations of SEQ ID NO: 68 comprise K115Q, C121R, R134Q, R154S, and V156A.

91. A pharmaceutical composition comprising an antibody or antigen-binding portion thereof according to claim 89 or claim 90, and a pharmaceutically acceptable carrier.

92. The use of the antibody or antigen-binding portion thereof according to claim 89 or claim 90, or the pharmaceutical composition according to claim 91, in the manufacture of a medicament for reducing tumor growth.

93. The antibody or antigen-binding portion thereof according to claim 89 or claim 90, or the pharmaceutical composition according to claim 91, for use in reducing tumor growth.

94. The use of the antibody or antigen-binding portion thereof according to claim 89 or claim 90, or the pharmaceutical composition according to claim 91, in the manufacture of a medicament for the treatment of cancer.

95. The antibody or antigen-binding portion thereof according to claim 89 or claim 90, or the pharmaceutical composition according to claim 91, for use in the treatment of cancer.

96. The use according to claim 94, or the antibody or antigen-binding portion thereof or the pharmaceutical composition according to claim 95, wherein said cancer is selected from the group consisting of lung cancers, alveolar cell carcinoma, bronchial adenoma, chondromatous hamartoma, sarcoma, bone cancers, Ewing's sarcoma, reticulum cell sarcoma, brain cancers, gliomas, anaplastic astrocytomas, astrocytomas, oligodendrogliomas, medulloblastomas, chordoma, Schwannomas, ependymomas, meningiomas, pituitary adenoma, pinealoma, osteomas, hemangioblastomas, craniopharyngiomas, chordomas, germinomas, teratomas, dermoid cysts, angiomas, cancers in the digestive system, leiomyoma, epidermoid carcinoma, adenocarcinoma, leiomyosarcoma, stomach adenocarcinomas, intestinal lipomas, intestinal neurofibromas, intestinal fibromas, polyps in the large intestine, colorectal cancers, liver cancers, hepatocellular adenomas, hemangioma, hepatocellular carcinoma, fibrolamellar carcinoma, cholangio-carcinoma, hepatoblastoma angiosarcoma, kidney cancers, kidney adenocarcinoma, renal cell carcinoma, hypernephroma, transitional cell carcinoma of the renal pelvis, bladder cancers, hematological cancers, acute lymphocytic (lymphoblastic) leukemia, acute myeloid (myelocytic, myelogenous, myeloblastic, myelomonocytic) leukemia, chronic lymphocytic leukemia, Sezary syndrome, hairy cell leukemia, chronic myelocytic (myeloid, myelogenous, granulocytic) leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, B cell lymphoma, mycosis fungoides, myeloproliferative disorders, poly-cythemia vera, myelofibrosis, thrombocythemia, chronic myelocytic leukemia, skin cancers, basal cell carcinoma, squamous cell carcinoma, melanoma, Kaposi's sarcoma, Paget's disease, head and neck cancers, eye-related cancers, retinoblastoma, intra-ocular melanocarcinoma, male reproductive system cancers, benign prostatic hyper-plasia, prostate cancer, testicular cancers, seminoma, teratoma, embryonal carcinoma, choriocarcinoma, breast cancer, female reproductive system cancers, uterine cancer, endometrial carcinoma, cervical cancer, cervical carcinoma, cancer of the ovaries, ovarian carcinoma, vulvar carcinoma,

vaginal carcinoma, fallopian tube cancer, hydatidiform mole, thyroid cancer, papillary cancer, follicular cancer, anaplastic cancer, medullary cancer, pheochromocytomas, non-cancerous growths of the parathyroid glands, pancreatic cancers, leukemias, and myelomas.

97. The use according to claim 94 or claim 96, or the antibody or antigen-binding portion thereof or the pharmaceutical composition according to claim 95 or claim 96, wherein said cancer is selected from the group consisting of colorectal cancer, hematological cancers, prostate cancer, and melanoma.

98. The use, or the antibody or antigen-binding portion thereof or the pharmaceutical composition according to claim 97, wherein said hematological cancer is selected from the group consisting of leukemias, myelomas, non-Hodgkin's lymphomas and Hodgkin's lymphomas.

99. The use according to claim 94 or 96-98, or the antibody or antigen-binding portion thereof or the pharmaceutical composition according to claim 95 or 95-98, in combination with an immunotherapeutic agent.

100. The use, or the antibody or antigen-binding portion thereof or the pharmaceutical composition according to claim 99, wherein said immunotherapeutic agent is rituximab.

101. An isolated antibody, wherein said antibody comprises a V_H and a V_L region wherein the V_H region amino acid sequence comprises the amino acid sequence set forth in SEQ ID NO: 43 and the V_L region amino acid sequence comprises the amino acid sequence set forth in SEQ ID NO: 45, wherein the antibody isotype is IgG1.

102. The antibody according to claim 101, wherein said antibody comprises the human IgG1 constant domain amino acid sequence comprising the amino acid sequence set forth in SEQ ID NO: 69.

103. The antibody according to claim 102, wherein the C-terminal lysine residue of SEQ ID NO: 69 is absent.

104. A pharmaceutical composition comprising an antibody according to any one of claims 101 to 103, and a pharmaceutically acceptable carrier.

105. The use of the antibody or antigen-binding portion thereof according to any one of claims 101 to 103, or the pharmaceutical composition according to claim 104, in the manufacture of a medicament for reducing tumor growth.

106. The antibody or antigen-binding portion thereof according to any one of claims 101 to 103, or the pharmaceutical composition according to claim 104, for use in reducing tumor growth.

107. The use of the antibody or antigen-binding portion thereof according to any one of claims 99 to 101, or the pharmaceutical composition according to claim 102, in the manufacture of a medicament for the treatment of cancer.

108. The antibody or antigen-binding portion thereof according to any one of claims 99 to 100, or the pharmaceutical composition according to claim 101, for use in the treatment of cancer.

109. The use according to claim 107, or the antibody or antigen-binding portion thereof or the pharmaceutical composition according to claim 108, wherein said cancer is selected from the group consisting of colorectal cancer, non-Hodgkin's lymphoma, prostate cancer, and melanoma.

110. The use according to claim 107 or claim 109, or the antibody or antigen-binding portion thereof or the pharmaceutical composition according to claim 108 or 109, in combination with an immunotherapeutic agent.

111. The use, or the antibody or antigen-binding portion thereof or the pharmaceutical composition according to claim 110, wherein said immunotherapeutic agent is rituximab.