CLAIMS

1. An isolated nucleic acid molecule encoding a chimeric antigen receptor (CAR), wherein the CAR comprises an antibody or antibody fragment which includes a humanized anti-CD19 binding domain, a transmembrane domain, and an intracellular signaling domain comprising a stimulatory domain, and wherein said anti-CD19 binding domain comprises:
a light chain complementary determining region 1 (LC CDR1) comprising the amino acid sequence of SEQ ID NO: 25,
a light chain complementary determining region 2 (LC CDR2) comprising the amino acid sequence of SEQ ID NO: 26,
a light chain complementary determining region 3 (LC CDR3) comprising the amino acid sequence of SEQ ID NO: 27,
a heavy chain complementary determining region 1 (HC CDR1) comprising the amino acid sequence of SEQ ID NO: 19,
a heavy chain complementary determining region 2 (HC CDR2) comprising the amino acid sequence of any of SEQ ID NOS: 22, 21, or 23, and
a heavy chain complementary determining region 3 (HC CDR3) comprising the amino acid sequence of SEQ ID NO: 24.

2. The isolated nucleic acid molecule of claim 1, wherein the HC CDR2 comprises the amino acid sequence of SEQ ID NO: 21.

3. The isolated nucleic acid molecule of claim 1, wherein the HC CDR2 comprises the amino acid sequence of SEQ ID NO: 22.

4. The isolated nucleic acid molecule of claim 1, wherein the HC CDR2 comprises the amino acid sequence of SEQ ID NO: 23.

5. The isolated nucleic acid molecule of claim 1, which encodes any light chain variable region listed in SEQ ID NOs: 32, 31, or 33-42.

6. The isolated nucleic acid molecule of claim 1, which encodes any heavy chain variable region listed in SEQ ID NOs: 32, 31, or 33-42.

7. The isolated nucleic acid molecule of claim 1, which encodes any light chain variable region listed in SEQ ID NOs: 32, 31, or 33-42 and any heavy chain variable region listed SEQ ID NOs: 32, 31, or 33-42.

8. The isolated nucleic acid molecule of any of the preceding claims, wherein the CD19 binding domain is a scFv.

9. The isolated nucleic acid molecule of any of the preceding claims, wherein the light chain variable region comprises an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications of an amino acid sequence of a light chain variable region provided in SEQ ID NOs: 32, 31, or 33-42, or an amino acid sequence with at least 95% identity to an amino acid sequence provided in SEQ ID NOs: 32, 31, or 33-42.

10. The isolated nucleic acid molecule of any of the preceding claims, wherein the heavy chain variable region comprises an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications of an amino acid sequence of a heavy chain variable region provided in SEQ ID NOs: 32, 31, or 33-42, or an amino acid sequence with at least 95% identity to an amino acid sequence provided in SEQ ID NOs: 32, 31, or 33-42.

11. The isolated nucleic acid molecule of any of the preceding claims, wherein the anti-CD19 binding domain comprises an amino acid sequence selected from a group consisting of SEQ ID NO:2, SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, and SEQ ID NO:12, or an amino acid sequence with at least 95% identity thereof.

12. The isolated nucleic acid molecule of any of the preceding claims, wherein the nucleic acid sequence encoding the anti-CD19 binding domain comprises a nucleic acid sequence selected

from a group consisting of SEQ ID NO:62, SEQ ID NO:61, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:71 and SEQ ID NO:72, or a nucleic acid sequence with at least 95% identity thereof.

13. The isolated nucleic acid molecule of any of the preceding claims, which comprises a nucleic acid sequence selected from a group consisting of SEQ ID NO: 86, SEQ ID NO: 85, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID NO: 90, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 94, SEQ ID NO: 95, and SEQ ID NO: 96, or a nucleic acid sequence with at least 95% identity thereof.

14. The isolated nucleic acid molecule of any of the preceding claims, wherein the encoded CAR includes a transmembrane domain that comprises a transmembrane domain of a protein selected from the group consisting of the alpha, beta or zeta chain of the T-cell receptor, CD28, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137 and CD154.

15. The isolated nucleic acid molecule of any of the preceding claims, wherein the encoded transmembrane domain comprises the amino acid sequence of SEQ ID NO: 15, or comprises an amino acid sequence comprising at least one, two or three modifications but not more than 20, 10 or 5 modifications of the amino acid sequence of SEQ ID NO:15, or an amino acid sequence with at least 95% identity to the amino acid sequence of SEQ ID NO:15 or the nucleic acid sequence encoding the transmembrane domain comprises the amino acid sequence of SEQ ID NO:56, or a sequence with at least 95% identity thereof.

16. The isolated nucleic acid molecule of any of the preceding claims, wherein the encoded anti-CD19 binding domain is connected to the transmembrane domain by a hinge region.

17. The isolated nucleic acid molecule of claim 16, wherein the encoded hinge region comprises the amino acid sequence of SEQ ID NO:14, or an amino acid sequence with at least 95% identity

thereof or wherein the nucleic acid sequence encoding the hinge region comprises the nucleic acid sequence of SEQ ID NO: 55, or a nucleic acid sequence with at least 95% identity thereof.

18. The isolated nucleic acid molecule of any of the preceding claims, wherein the intracellular signaling domain comprises a costimulatory domain.

19. The isolated nucleic acid molecule of claim 18, wherein the costimulatory domain is a functional signaling domain obtained from a protein selected from the group consisting of OX40, CD2, CD27, CD28, CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), and 4-1BB (CD137).

20. The isolated nucleic acid molecule of claim 18 or 19, wherein the encoded costimulatory domain comprises the amino acid sequence of SEQ ID NO:16 or
an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of an amino acid sequence of SEQ ID NO:16, or an amino acid sequence with at least 95% identity to the amino acid sequence of SEQ ID NO:16 or
the nucleic acid sequence encoding the costimulatory domain comprises the nucleic acid sequence of SEQ ID NO:60, or a nucleic acid sequence with at least 95% identity thereof.

21. The isolated nucleic acid molecule of any of the preceding claims, wherein the intracellular signaling domain comprises a primary signaling domain.

22. The isolated nucleic acid molecule of any of the preceding claims, wherein the encoded intracellular signaling domain comprises a functional signaling domain of 4-1BB and/or a functional signaling domain of CD3 zeta.

23. The isolated nucleic acid molecule of any of the preceding claims, wherein the encoded intracellular signaling domain: (i) comprises the amino acid sequence of SEQ ID NO: 16 and/or the amino acid sequence of SEQ ID NO:17 or SEQ ID NO:43, or (ii) an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of the amino acid sequence of SEQ ID NO:16 and/or an amino acid sequence of SEQ ID NO:17 or

SEQ ID NO:43, or (iii) an amino acid sequence with at least 95% identity to the amino acid sequence of SEQ ID NO:16 and/or an amino acid sequence of SEQ ID NO:17 or SEQ ID NO:43.

24. The isolated nucleic acid molecule of any of the preceding claims, wherein the encoded intracellular signaling domain comprises the amino acid sequence of SEQ ID NO:16 and the amino acid sequence of SEQ ID NO:17 or SEQ ID NO:43, wherein the sequences comprising the intracellular signaling domain are expressed in the same frame and as a single polypeptide chain.

25. The isolated nucleic acid molecule of any of the preceding claims, wherein the nucleic acid sequence encoding the intracellular signaling domain comprises the nucleic acid sequence of SEQ ID NO:60, or a nucleic acid sequence with at least 95% identity thereof, and/or a nucleic acid sequence of SEQ ID NO:101 or SEQ ID NO:44, or a nucleic acid sequence with at least 95% identity thereof.

26. The isolated nucleic acid molecule of any of the preceding claims, further comprising a leader sequence.

27. The isolated nucleic acid molecule of claim 26, wherein the leader sequence encodes the amino acid sequence of SEQ ID NO: 13.

28. An isolated polypeptide molecule encoded by the nucleic acid molecule of any one of the preceding claims.

29. The isolated polypeptide of claim 28, comprising an amino acid sequence selected from the group consisting of SEQ ID NO:32, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, and SEQ ID NO:42.

30. An isolated chimeric antigen receptor (CAR) molecule comprising: (i) an antibody or antibody fragment which includes a humanized anti-CD19 binding domain, (ii) a transmembrane

domain, and (iii) an intracellular signaling domain, wherein the humanized anti-CD19 binding domain comprises:

a light chain complementary determining region 1 (LC CDR1) comprising the amino acid sequence of SEQ ID NO: 25,

a light chain complementary determining region 2 (LC CDR2) comprising the amino acid sequence of SEQ ID NO: 26,

a light chain complementary determining region 3 (LC CDR3) comprising the amino acid sequence of SEQ ID NO: 27,

a heavy chain complementary determining region 1 (HC CDR1) comprising the amino acid sequence of SEQ ID NO: 19,

a heavy chain complementary determining region 2 (HC CDR2) comprising the amino acid sequence of any of SEQ ID NOS: 22, 21, or 23, and

a heavy chain complementary determining region 3 (HC CDR3) comprising the amino acid sequence of SEQ ID NO: 24.

31. The isolated CAR molecule of claim 30, wherein the HC CDR2 comprises the amino acid sequence of SEQ ID NO: 21.

32. The isolated CAR molecule of claim 30, wherein the HC CDR2 comprises the amino acid sequence of SEQ ID NO: 22.

33. The isolated CAR molecule of claim 30, wherein the HC CDR2 comprises the amino acid sequence of SEQ ID NO: 23.

34. The isolated CAR molecule of any of claims 30-33, wherein the anti-CD19 binding domain is a scFv.

35. The isolated CAR molecule of any of claims 30-34, wherein the anti-CD19 binding domain comprises a light chain and a heavy chain of an amino acid sequence listed in SEQ ID NOs: 32, 31, or 33-42.

36. The isolated CAR molecule of any of claims 30-35, wherein the anti-CD19 binding domain comprises: (i) a light chain variable region listed in SEQ ID NOs: 32, 31, or 33-42, (ii) a light chain variable region comprising an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications of an amino acid sequence of a light chain variable region provided in SEQ ID NOs: 32, 31, or 33-42, or (iii) an amino acid sequence with at least 95% identity with a light chain variable region provided in SEQ ID NOs: 32, 31, or 33-42.

37. The isolated CAR molecule of any of claims 30-36, wherein the anti-CD19 binding domain comprises: (i) a heavy chain variable region listed in SEQ ID NOs: 32, 31, or 33-42, (ii) a heavy chain variable region comprising an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications of an amino acid sequence of a heavy chain variable region provided in SEQ ID NOs: 32, 31, or 33-42, or (iii) an amino acid sequence with at least 95% identity to a heavy chain variable region provided in SEQ ID NOs: 32, 31, or 33-42.

38. The isolated CAR molecule of any of claims 30-37, wherein the anti-CD19 binding domain comprises an amino acid sequence selected from a group consisting of SEQ ID NO:2, SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO: 4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11 and SEQ ID NO:12, or an amino acid sequence with at least 95% identity thereof.

39. The isolated CAR molecule of any of claims 30-38, further comprising a transmembrane domain of a protein selected from the group consisting of the alpha, beta or zeta chain of the T-cell receptor, CD28, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137 and CD154.

40. The isolated CAR molecule of claim 39, wherein the transmembrane domain comprises: (i) an amino acid sequence of SEQ ID NO: 15, (ii) an amino acid sequence having at least one, two

or three modifications but not more than 20, 10 or 5 modifications of the amino acid sequence of SEQ ID NO: 15, or (iii) a sequence with at least 95% identity to the amino acid sequence of SEQ ID NO: 15.

41. The isolated CAR molecule of any one of claims 30-40, wherein the humanized anti-CD19 binding domain is connected to the transmembrane domain by a hinge region.

42. The isolated CAR molecule of claim 41, wherein the encoded hinge region comprises the amino acid sequence of SEQ ID NO:14 or SEQ ID NO:102, or a sequence with at least 95% identity thereof.

43. The isolated CAR molecule of any of claims 30-42, wherein the intracellular signaling domain comprises a costimulatory domain.

44. The isolated CAR molecule of claim 43, wherein the costimulatory domain comprises a functional signaling domain of a protein selected from the group consisting of OX40, CD2, CD27, CD28, CDS, ICAM-1, LFA-1 (CD11a/CD18) and 4-1BB (CD137).

45. The isolated CAR molecule of claim 43 or 44, wherein the costimulatory domain comprises: (i) the amino acid sequence of SEQ ID NO: 16, (ii) an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of the amino acid sequence of SEQ ID NO: 16, or (iii) an amino acid sequence with at least 95% identity to the amino acid sequence of SEQ ID NO: 16.

46. The isolated CAR molecule of any one of claims 30-45, wherein the intracellular signaling domain comprises a primary signaling domain.

47. The isolated CAR molecule of claim 46, wherein the intracellular signaling domain comprises a functional signaling domain of 4-1BB and/or a functional signaling domain of CD3 zeta.

48. The isolated CAR molecule of claim 46 or 47, wherein the intracellular signaling domain comprises: (i) the amino acid sequence of SEQ ID NO: 16 and/or the amino acid sequence of SEQ ID NO:17, or the amino acid sequence of SEQ ID NO:43, or (ii) an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of the amino acid sequence of SEQ ID NO:16 and/or the amino acid sequence of SEQ ID NO:17 or SEQ ID NO:43, or an amino acid sequence with at least 95% identity to the amino acid sequence of SEQ ID NO:16 and/or the amino acid sequence of SEQ ID NO:17 or SEQ ID NO:43.

49. The isolated CAR molecule of any of claims 46-48, wherein the intracellular signaling domain comprises the amino acid sequence of SEQ ID NO: 16 and the amino acid sequence of SEQ ID NO: 17 or SEQ ID NO:43, wherein the sequences comprising the intracellular signaling domain are expressed in the same frame and as a single polypeptide chain.

50. The isolated CAR molecule of any of claims 30-49, further comprising a leader sequence.

51. The isolated CAR molecule of claim 50, wherein the leader sequence comprises the amino acid sequence of SEQ ID NO: 13, or a sequence with at least 95% identity to the amino acid sequence of SEQ ID NO:13.

52. A humanized anti-CD19 binding domain comprising:
a light chain complementary determining region 1 (LC CDR1) comprising the amino acid sequence of SEQ ID NO: 25,
a light chain complementary determining region 2 (LC CDR2) comprising the amino acid sequence of SEQ ID NO: 26,
a light chain complementary determining region 3 (LC CDR3) comprising the amino acid sequence of SEQ ID NO: 27,
a heavy chain complementary determining region 1 (HC CDR1) comprising the amino acid sequence of SEQ ID NO: 19,
a heavy chain complementary determining region 2 (HC CDR2) comprising the amino acid sequence of any of SEQ ID NOS: 22, 21, or 23, and

a heavy chain complementary determining region 3 (HC CDR3) comprising the amino acid sequence of SEQ ID NO: 24.

53. The humanized anti-CD19 binding domain of claim 52, wherein the HC CDR2 comprises the amino acid sequence of SEQ ID NO: 21.

54. The humanized anti-CD19 binding domain of claim 52, wherein the HC CDR2 comprises the amino acid sequence of SEQ ID NO: 22.

55. The humanized anti-CD19 binding domain of claim 52, wherein the HC CDR2 comprises the amino acid sequence of SEQ ID NO: 23.

56. The humanized anti-CD19 binding domain of any of claims 52-55, wherein the humanized anti-CD19 binding domain comprises (i) a scFv comprising a light chain variable region and a heavy chain variable region of an amino acid sequence of any of SEQ ID NOs: 32, 31, or 33-42, or (ii) a light chain variable region comprising an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications of an amino acid sequence of a light chain variable region provided, in any of SEQ ID NOs: 32, 31, or 33-42 or (iii) a sequence with at least 95% identity with an amino acid sequence in any of SEQ ID NOs: 32, 31, or 33-42; and/or a heavy chain variable region comprising an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications of an amino acid sequence of a heavy chain variable region provided any of SEQ ID NOs: 32, 31, or 33-42, or an amino acid sequence with at least 95% identity to an amino acid sequence in any of SEQ ID NOs: 32, 31, or 33-42.

57. A vector comprising a nucleic acid molecule encoding a CAR of any of claims 30-51.

58. The vector of claim 57, wherein the vector is selected from the group consisting of a DNA, a RNA, a plasmid, a lentivirus vector, adenoviral vector, or a retrovirus vector.

59. The vector of claim 57 or 58, further comprises a promoter.

60. The vector of claim 59, wherein the promoter is an EF-1 promoter.

61. The vector of claim 60, wherein the EF-1 promoter comprises the nucleic acid sequence of SEQ ID NO: 100.

62. The vector of any of claims 57-61, wherein the vector is an in vitro transcribed vector.

63. The vector of any of claims 57-62, wherein the nucleic acid sequence in the vector further comprises a poly(A) tail.

64. The vector of any of claims 57-63, wherein the nucleic acid sequence in the vector further comprises a 3'UTR.

65. A cell comprising the vector of any of claims 57-64.

66. A cell comprising a nucleic acid of any of claims 1-27.

67. A cell comprising a CAR molecule of any of claims 30-51.

68. The cell of any of claims 65-67, wherein the cell is a human T cell.

69. The cell of any of claims 65-67, wherein the T cell is a CD8+ T cell.

70. A cell of any of claims 65-69, further expressing an inhibitory molecule that comprises a first polypeptide that comprises at least a portion of an inhibitory molecule, associated with a second polypeptide that comprises a positive signal from an intracellular signaling domain.

71. The cell of claim 70, wherein the inhibitory molecule comprise first polypeptide that comprises at least a portion of PD1 and a second polypeptide comprising a costimulatory domain and primary signaling domain.

72. A method of making a cell comprising transducing a T cell with a vector of any of claims 57-64 or a nucleic acid of any of claims 1-27.

73. A method of generating a population of RNA-engineered cells comprising introducing an in vitro transcribed RNA or synthetic RNA into a cell, where the RNA comprises a nucleic acid encoding a CAR molecule of any of the claims 30-51.

74. A method of providing an anti-tumor immunity in a mammal comprising administering to the mammal an effective amount of a cell expressing a CAR molecule of any of claims 30-51.

75. The method of claim 74, wherein the cell is an autologous T cell.

76. The method of claim 74 or 75, wherein the cell is an allogeneic T cell.

77. The method of any of claims 74-75, wherein the mammal is a human.

78. A cell of any of claims 65-71, a nucleic acid of any of claims 1-27, or a CAR molecule of any of claims 30-51, for use in treating a disease associated with expression of CD19.

79. The cell, nucleic acid, or CAR molecule of claim 78, wherein the disease associated with CD19 expression is selected from a proliferative disease such as a cancer or malignancy or a precancerous condition such as a myelodysplasia, a myelodysplastic syndrome or a preleukemia, or is a non-cancer related indication associated with expression of CD19.

80. The cell, nucleic acid, or CAR molecule of claim 78 or 79, wherein the disease is a hematologic cancer selected from the group consisting of one or more acute leukemias including but not limited to B-cell acute lymphoid leukemia ("BALL"), T-cell acute lymphoid leukemia ("TALL"), acute lymphoid leukemia (ALL); one or more chronic leukemias including but not limited to chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL);

additional hematologic cancers or hematologic conditions including, but not limited to B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B cell lymphoma, follicular lymphoma, hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, Marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia, and "preleukemia" which are a diverse collection of hematological conditions united by ineffective production (or dysplasia) of myeloid blood cells, and to disease associated with CD19 expression include, but not limited to atypical and/or non-classical cancers, malignancies, precancerous conditions or proliferative diseases expressing CD19; and combinations thereof.

81. The cell of any of claims 78-80, which is administered in combination with an agent that increases the efficacy of a cell expressing a CAR molecule, an agent that ameliorates one or more side effects associated with administration of a cell expressing a CAR molecule, or an agent that treats the disease associated with CD19.

82. Use of a cell of any of claims 65-71, a nucleic acid of any of claims 1-27, or a CAR molecule of any of claims 30-51, for the manufacture of a medicament for treating a disease associated with expression of CD19.

83. The use of claim 82, wherein the disease associated with CD19 expression is selected from a proliferative disease such as a cancer or malignancy or a precancerous condition such as a myelodysplasia, a myelodysplastic syndrome or a preleukemia, or is a non-cancer related indication associated with expression of CD19.

84. The use of claim 82 or 83, wherein the disease is a hematologic cancer selected from the group consisting of one or more acute leukemias including but not limited to B-cell acute lymphoid leukemia ("BALL"), T-cell acute lymphoid leukemia ("TALL"), acute lymphoid leukemia (ALL); one or more chronic leukemias including but not limited to chronic

myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL); additional hematologic cancers or hematologic conditions including, but not limited to B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B cell lymphoma, follicular lymphoma, hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, Marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia, and "preleukemia" which are a diverse collection of hematological conditions united by ineffective production (or dysplasia) of myeloid blood cells, and to disease associated with CD19 expression include, but not limited to atypical and/or non-classical cancers, malignancies, precancerous conditions or proliferative diseases expressing CD19; and combinations thereof.

85. The use of any of claims 82-84, wherein the cell is administered in combination with an agent that increases the efficacy of a cell expressing a CAR molecule, an agent that ameliorates one or more side effects associated with administration of a cell expressing a CAR molecule, or an agent that treats the disease associated with CD19.

CLAIMS

1. An isolated nucleic acid molecule encoding a chimeric antigen receptor (CAR), wherein the CAR comprises an antibody or antibody fragment which includes a humanized anti-CD19 binding domain, a transmembrane domain, and an intracellular signaling domain comprising a stimulatory domain, and wherein said anti-CD19 binding domain comprises:
a light chain complementary determining region 1 (LC CDR1) comprising the amino acid sequence of SEQ ID NO: 25,
a light chain complementary determining region 2 (LC CDR2) comprising the amino acid sequence of SEQ ID NO: 26,
a light chain complementary determining region 3 (LC CDR3) comprising the amino acid sequence of SEQ ID NO: 27,
a heavy chain complementary determining region 1 (HC CDR1) comprising the amino acid sequence of SEQ ID NO: 19,
a heavy chain complementary determining region 2 (HC CDR2) comprising the amino acid sequence of any of SEQ ID NOS: 22, 21, or 23, and
a heavy chain complementary determining region 3 (HC CDR3) comprising the amino acid sequence of SEQ ID NO: 24.

2. The isolated nucleic acid molecule of claim 1, wherein the HC CDR2 comprises the amino acid sequence of SEQ ID NO: 21.

3. The isolated nucleic acid molecule of claim 1, wherein the HC CDR2 comprises the amino acid sequence of SEQ ID NO: 22.

4. The isolated nucleic acid molecule of claim 1, wherein the HC CDR2 comprises the amino acid sequence of SEQ ID NO: 23.

5. The isolated nucleic acid molecule of claim 1, which encodes any light chain variable region listed in SEQ ID NOs: 32, 31, or 33-42.

6. The isolated nucleic acid molecule of claim 1, which encodes any heavy chain variable region listed in SEQ ID NOs: 32, 31, or 33-42.

7. The isolated nucleic acid molecule of claim 1, which encodes any light chain variable region listed in SEQ ID NOs: 32, 31, or 33-42 and any heavy chain variable region listed SEQ ID NOs: 32, 31, or 33-42.

8. The isolated nucleic acid molecule of any of the preceding claims, wherein the CD19 binding domain is a scFv.

9. The isolated nucleic acid molecule of any of the preceding claims, wherein the light chain variable region comprises an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications of an amino acid sequence of a light chain variable region provided in SEQ ID NOs: 32, 31, or 33-42, or an amino acid sequence with at least 95% identity to an amino acid sequence provided in SEQ ID NOs: 32, 31, or 33-42.

10. The isolated nucleic acid molecule of any of the preceding claims, wherein the heavy chain variable region comprises an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications of an amino acid sequence of a heavy chain variable region provided in SEQ ID NOs: 32, 31, or 33-42, or an amino acid sequence with at least 95% identity to an amino acid sequence provided in SEQ ID NOs: 32, 31, or 33-42.

11. The isolated nucleic acid molecule of any of the preceding claims, wherein the anti-CD19 binding domain comprises an amino acid sequence selected from a group consisting of SEQ ID NO:2, SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, and SEQ ID NO:12, or an amino acid sequence with at least 95% identity thereof.

12. The isolated nucleic acid molecule of any of the preceding claims, wherein the nucleic acid sequence encoding the anti-CD19 binding domain comprises a nucleic acid sequence selected from a group consisting of SEQ ID NO:62, SEQ ID NO:61, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:71 and SEQ ID NO:72, or a nucleic acid sequence with at least 95% identity thereof.

13. The isolated nucleic acid molecule of any of the preceding claims, which comprises a nucleic acid sequence selected from a group consisting of SEQ ID NO: 86, SEQ ID NO: 85, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID NO: 90, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 93,

SEQ ID NO: 94, SEQ ID NO: 95, and SEQ ID NO: 96, or a nucleic acid sequence with at least 95% identity thereof.

14. The isolated nucleic acid molecule of any of the preceding claims, wherein the encoded CAR includes a transmembrane domain that comprises a transmembrane domain of a protein selected from the group consisting of the alpha, beta or zeta chain of the T-cell receptor, CD28, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137 and CD154 or the encoded CAR includes a transmembrane domain that comprises a transmembrane domain of the alpha chain of CD8.

15. The isolated nucleic acid molecule of any of the preceding claims, wherein the encoded transmembrane domain comprises the amino acid sequence of SEQ ID NO: 15, or comprises an amino acid sequence comprising at least one, two or three modifications but not more than 20, 10 or 5 modifications of the amino acid sequence of SEQ ID NO:15, or an amino acid sequence with at least 95% identity to the amino acid sequence of SEQ ID NO:15 or the nucleic acid sequence encoding the transmembrane domain comprises the amino acid sequence of SEQ ID NO:56, or a sequence with at least 95% identity thereof.

16. The isolated nucleic acid molecule of any of the preceding claims, wherein the encoded anti-CD19 binding domain is connected to the transmembrane domain by a hinge region, wherein the hinge region is optionally a CD8 alpha hinge.

17. The isolated nucleic acid molecule of claim 16, wherein the encoded hinge region comprises the amino acid sequence of SEQ ID NO:14, or an amino acid sequence with at least 95% identity thereof or wherein the nucleic acid sequence encoding the hinge region comprises the nucleic acid sequence of SEQ ID NO: 55, or a nucleic acid sequence with at least 95% identity thereof.

18. The isolated nucleic acid molecule of any of the preceding claims, wherein the intracellular signaling domain comprises a costimulatory domain.

19. The isolated nucleic acid molecule of claim 18, wherein the costimulatory domain is a functional signaling domain obtained from a protein selected from the group consisting of OX40, CD2, CD27, CD28, CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), and 4-1BB (CD137).

20. The isolated nucleic acid molecule of claim 18 or 19, wherein the encoded costimulatory domain comprises the amino acid sequence of SEQ ID NO:16 or
an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of an amino acid sequence of SEQ ID NO:16, or an amino acid sequence with at least 95% identity to the amino acid sequence of SEQ ID NO:16 or
the nucleic acid sequence encoding the costimulatory domain comprises the nucleic acid sequence of SEQ ID NO:60, or a nucleic acid sequence with at least 95% identity thereof.

21. The isolated nucleic acid molecule of any of the preceding claims, wherein the intracellular signaling domain comprises a primary signaling domain.

22. The isolated nucleic acid molecule of any of the preceding claims, wherein the encoded intracellular signaling domain comprises a functional signaling domain of 4-1BB and/or a functional signaling domain of CD3 zeta.

23. The isolated nucleic acid molecule of any of the preceding claims, wherein the encoded intracellular signaling domain: (i) comprises the amino acid sequence of SEQ ID NO: 16 and/or the amino acid sequence of SEQ ID NO:17 or SEQ ID NO:43, or (ii) an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of the amino acid sequence of SEQ ID NO:16 and/or an amino acid sequence of SEQ ID NO:17 or SEQ ID NO:43, or (iii) an amino acid sequence with at least 95% identity to the amino acid sequence of SEQ ID NO:16 and/or an amino acid sequence of SEQ ID NO:17 or SEQ ID NO:43.

24. The isolated nucleic acid molecule of any of the preceding claims, wherein the encoded intracellular signaling domain comprises the amino acid sequence of SEQ ID NO:16 and the amino acid sequence of SEQ ID NO:17 or SEQ ID NO:43, wherein the sequences comprising the intracellular signaling domain are expressed in the same frame and as a single polypeptide chain.

25. The isolated nucleic acid molecule of any of the preceding claims, wherein the nucleic acid sequence encoding the intracellular signaling domain comprises the nucleic acid sequence of SEQ ID NO:60, or a nucleic acid sequence with at least 95% identity thereof, and/or a nucleic acid sequence of SEQ ID NO:101 or SEQ ID NO:44, or a nucleic acid sequence with at least 95% identity thereof.

26. The isolated nucleic acid molecule of any of the preceding claims, further comprising a leader sequence.

27. The isolated nucleic acid molecule of claim 26, wherein the leader sequence encodes the amino acid sequence of SEQ ID NO: 13, or a sequence with at least 95% identity to the amino acid sequence of SEQ ID NO: 13.

28. An isolated polypeptide molecule encoded by the nucleic acid molecule of any one of the preceding claims.

29. The isolated polypeptide of claim 28, comprising an amino acid sequence selected from the group consisting of SEQ ID NO:32, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, and SEQ ID NO:42.

30. An isolated chimeric antigen receptor (CAR) molecule comprising: (i) an antibody or antibody fragment which includes a humanized anti-CD19 binding domain, (ii) a transmembrane domain, and (iii) an intracellular signaling domain, wherein the humanized anti-CD19 binding domain comprises:
a light chain complementary determining region 1 (LC CDR1) comprising the amino acid sequence of SEQ ID NO: 25,
a light chain complementary determining region 2 (LC CDR2) comprising the amino acid sequence of SEQ ID NO: 26,
a light chain complementary determining region 3 (LC CDR3) comprising the amino acid sequence of SEQ ID NO: 27,
a heavy chain complementary determining region 1 (HC CDR1) comprising the amino acid sequence of SEQ ID NO: 19,
a heavy chain complementary determining region 2 (HC CDR2) comprising the amino acid sequence of any of SEQ ID NOS: 22, 21, or 23, and
a heavy chain complementary determining region 3 (HC CDR3) comprising the amino acid sequence of SEQ ID NO: 24.

31. The isolated CAR molecule of claim 30, wherein the HC CDR2 comprises the amino acid sequence of SEQ ID NO: 21.

32. The isolated CAR molecule of claim 30, wherein the HC CDR2 comprises the amino acid sequence of SEQ ID NO: 22.

33. The isolated CAR molecule of claim 30, wherein the HC CDR2 comprises the amino acid sequence of SEQ ID NO: 23.

34. The isolated CAR molecule of any of claims 30-33, wherein the anti-CD19 binding domain is a scFv.

35. The isolated CAR molecule of any of claims 30-34, wherein the anti-CD19 binding domain comprises a light chain and a heavy chain of an amino acid sequence listed in SEQ ID NOs: 32, 31, or 33-42.

36. The isolated CAR molecule of any of claims 30-35, wherein the anti-CD19 binding domain comprises: (i) a light chain variable region listed in SEQ ID NOs: 32, 31, or 33-42, (ii) a light chain variable region comprising an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications of an amino acid sequence of a light chain variable region provided in SEQ ID NOs: 32, 31, or 33-42, or (iii) an amino acid sequence with at least 95% identity with a light chain variable region provided in SEQ ID NOs: 32, 31, or 33-42.

37. The isolated CAR molecule of any of claims 30-36, wherein the anti-CD19 binding domain comprises: (i) a heavy chain variable region listed in SEQ ID NOs: 32, 31, or 33-42, (ii) a heavy chain variable region comprising an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications of an amino acid sequence of a heavy chain variable region provided in SEQ ID NOs: 32, 31, or 33-42, or (iii) an amino acid sequence with at least 95% identity to a heavy chain variable region provided in SEQ ID NOs: 32, 31, or 33-42.

38. The isolated CAR molecule of any of claims 30-37, wherein the anti-CD19 binding domain comprises an amino acid sequence selected from a group consisting of SEQ ID NO:2, SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO: 4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11 and SEQ ID NO:12, or an amino acid sequence with at least 95% identity thereof, or

wherein the anti-CD19 binding domain comprises an amino acid sequence selected from a group consisting of SEQ ID NO:32, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, and SEQ ID NO:42, or an amino acid sequence with at least 95% identity thereof.

39. The isolated CAR molecule of any of claims 30-38, wherein the transmembrane domain comprises a transmembrane domain of a protein selected from the group consisting of the alpha, beta or zeta chain of the T-cell receptor, CD28, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137 and CD154, or

the transmembrane domain comprises a transmembrane domain of the alpha chain of CD8.

40. The isolated CAR molecule of claim 39, wherein the transmembrane domain comprises: (i) an amino acid sequence of SEQ ID NO: 15, (ii) an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of the amino acid sequence of SEQ ID NO: 15, or (iii) a sequence with at least 95% identity to the amino acid sequence of SEQ ID NO: 15.

41. The isolated CAR molecule of any one of claims 30-40, wherein the humanized anti-CD19 binding domain is connected to the transmembrane domain by a hinge region, wherein optionally the hinge region is a CD8 alpha hinge.

42. The isolated CAR molecule of claim 41, wherein the encoded hinge region comprises the amino acid sequence of SEQ ID NO:14 or SEQ ID NO:102, or a sequence with at least 95% identity thereof.

43. The isolated CAR molecule of any of claims 30-42, wherein the intracellular signaling domain comprises a costimulatory domain.

44. The isolated CAR molecule of claim 43, wherein the costimulatory domain comprises a functional signaling domain of a protein selected from the group consisting of OX40, CD2, CD27, CD28, CDS, ICAM-1, LFA-1 (CD11a/CD18) and 4-1BB (CD137).

45. The isolated CAR molecule of claim 43 or 44, wherein the costimulatory domain comprises: (i) the amino acid sequence of SEQ ID NO: 16, (ii) an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of the amino acid sequence of SEQ ID NO: 16, or (iii) an amino acid sequence with at least 95% identity to the amino acid sequence of SEQ ID NO: 16.

46. The isolated CAR molecule of any one of claims 30-45, wherein the intracellular signaling domain comprises a primary signaling domain.

47. The isolated CAR molecule of claim 46, wherein the intracellular signaling domain comprises a functional signaling domain of 4-1BB and/or a functional signaling domain of CD3 zeta.

48. The isolated CAR molecule of claim 46 or 47, wherein the intracellular signaling domain comprises: (i) the amino acid sequence of SEQ ID NO: 16 and/or the amino acid sequence of SEQ ID NO:17, or the amino acid sequence of SEQ ID NO:43, or (ii) an amino acid sequence having at least

one, two or three modifications but not more than 20, 10 or 5 modifications of the amino acid sequence of SEQ ID NO:16 and/or the amino acid sequence of SEQ ID NO:17 or SEQ ID NO:43, or an amino acid sequence with at least 95% identity to the amino acid sequence of SEQ ID NO:16 and/or the amino acid sequence of SEQ ID NO:17 or SEQ ID NO:43.

49. The isolated CAR molecule of any of claims 46-48, wherein the intracellular signaling domain comprises the amino acid sequence of SEQ ID NO: 16 and the amino acid sequence of SEQ ID NO: 17 or SEQ ID NO:43, wherein the sequences comprising the intracellular signaling domain are expressed in the same frame and as a single polypeptide chain.

50. The isolated CAR molecule of any of claims 30-49, further comprising a leader sequence.

51. The isolated CAR molecule of claim 50, wherein the leader sequence comprises the amino acid sequence of SEQ ID NO: 13, or a sequence with at least 95% identity to the amino acid sequence of SEQ ID NO:13.

52. A humanized anti-CD19 binding domain comprising:
a light chain complementary determining region 1 (LC CDR1) comprising the amino acid sequence of SEQ ID NO: 25,
a light chain complementary determining region 2 (LC CDR2) comprising the amino acid sequence of SEQ ID NO: 26,
a light chain complementary determining region 3 (LC CDR3) comprising the amino acid sequence of SEQ ID NO: 27,
a heavy chain complementary determining region 1 (HC CDR1) comprising the amino acid sequence of SEQ ID NO: 19,
a heavy chain complementary determining region 2 (HC CDR2) comprising the amino acid sequence of any of SEQ ID NOS: 22, 21, or 23, and
a heavy chain complementary determining region 3 (HC CDR3) comprising the amino acid sequence of SEQ ID NO: 24.

53. The humanized anti-CD19 binding domain of claim 52, wherein the HC CDR2 comprises the amino acid sequence of SEQ ID NO: 21.

54. The humanized anti-CD19 binding domain of claim 52, wherein the HC CDR2 comprises the amino acid sequence of SEQ ID NO: 22.

55. The humanized anti-CD19 binding domain of claim 52, wherein the HC CDR2 comprises the amino acid sequence of SEQ ID NO: 23.

56. The humanized anti-CD19 binding domain of any of claims 52-55, wherein the humanized anti-CD19 binding domain comprises (i) a scFv comprising a light chain variable region and a heavy chain variable region of an amino acid sequence of any of SEQ ID NOs: 32, 31, or 33-42, or (ii) a light chain variable region comprising an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications of an amino acid sequence of a light chain variable region provided, in any of SEQ ID NOs: 32, 31, or 33-42 or (iii) a sequence with at least 95% identity with an amino acid sequence in any of SEQ ID NOs: 32, 31, or 33-42; and/or a heavy chain variable region comprising an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications of an amino acid sequence of a heavy chain variable region provided any of SEQ ID NOs: 32, 31, or 33-42, or an amino acid sequence with at least 95% identity to an amino acid sequence in any of SEQ ID NOs: 32, 31, or 33-42.

57. A vector comprising a nucleic acid molecule encoding a CAR of any of claims 30-51.

58. The vector of claim 57, wherein the vector is selected from the group consisting of a DNA, a RNA, a plasmid, a viral vector, a lentivirus vector, adenoviral vector, or a retrovirus vector.

59. The vector of claim 57 or 58, further comprises a promoter.

60. The vector of claim 59, wherein the promoter is an EF-1 promoter.

61. The vector of claim 60, wherein the EF-1 promoter comprises the nucleic acid sequence of SEQ ID NO: 100.

62. The vector of any of claims 57-61, wherein the vector is an in vitro transcribed vector.

63. The vector of any of claims 57-62, wherein the nucleic acid sequence in the vector further comprises a poly(A) tail.

64. The vector of any of claims 57-63, wherein the nucleic acid sequence in the vector further comprises a 3'UTR.

65. A cell comprising the vector of any of claims 57-64.

66. A cell comprising a nucleic acid of any of claims 1-27.

67. A cell comprising a CAR molecule of any of claims 30-51.

68. The cell of any of claims 65-67, wherein the cell is a human T cell.

69. The cell of any of claims 65-67, wherein the T cell is a CD8+ T cell.

70. A cell of any of claims 65-69, further expressing an inhibitory molecule that comprises a first polypeptide that comprises at least a portion of an inhibitory molecule, associated with a second polypeptide that comprises a positive signal from an intracellular signaling domain.

71. The cell of claim 70, wherein the inhibitory molecule comprise first polypeptide that comprises at least a portion of PD1 and a second polypeptide comprising a costimulatory domain and primary signaling domain.

72. A method of making a cell comprising transducing a T cell with a vector of any of claims 57-64 or a nucleic acid of any of claims 1-27.

73. A method of generating a population of RNA-engineered cells comprising introducing an in vitro transcribed RNA or synthetic RNA into a cell, where the RNA comprises a nucleic acid encoding a CAR molecule of any of the claims 30-51.

74. A cell of any of claims 65-71, a nucleic acid of any of claims 1-27, or CAR molecule of any of claims 30-51, for use in providing an anti-tumor immunity.

75. The use of claim 74, wherein the cell is an autologous T cell.

76. The use of claim 74 or 75, wherein the cell is an allogeneic T cell.

77. The use of any of claims 74-75, wherein the anti-tumor immunity is provided in a human.

78. A cell of any of claims 65-71, a nucleic acid of any of claims 1-27, or a CAR molecule of any of claims 30-51, for use in treating a disease associated with expression of CD19.

79. The cell, nucleic acid, or CAR molecule of claim 78, wherein the disease associated with CD19 expression is selected from a proliferative disease such as a cancer or malignancy or a precancerous condition such as a myelodysplasia, a myelodysplastic syndrome or a preleukemia, or is a non-cancer related indication associated with expression of CD19.

80. The cell, nucleic acid, or CAR molecule of claim 78 or 79, wherein the disease is a hematologic cancer selected from the group consisting of one or more acute leukemias including but not limited to B-cell acute lymphoid leukemia ("BALL"), T-cell acute lymphoid leukemia ("TALL"), acute lymphoid leukemia (ALL); one or more chronic leukemias including but not limited to chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL); additional hematologic cancers or hematologic conditions including, but not limited to B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B cell lymphoma, follicular lymphoma, hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, Marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia, and preleukemia; and combinations thereof.

81. The cell of any of claims 78-80, which is administered in combination with an agent that increases the efficacy of a cell expressing a CAR molecule, an agent that ameliorates one or more side effects associated with administration of a cell expressing a CAR molecule, or an agent that treats the disease associated with CD19.

82. Use of a cell of any of claims 65-71, a nucleic acid of any of claims 1-27, or a CAR molecule of any of claims 30-51, for the manufacture of a medicament for treating a disease associated with expression of CD19.

83. The use of claim 82, wherein the disease associated with expression of CD19 is selected from a cancer, malignancy, precancerous condition, autoimmune disease, or inflammatory disorder.

84. The use of claim 82, wherein the disease associated with CD19 expression is selected from a proliferative disease such as a cancer or malignancy or a precancerous condition such as a myelodysplasia, a myelodysplastic syndrome or a preleukemia, or is a non-cancer related indication associated with expression of CD19.

85. The use of any of claims 82-84, wherein the disease is a hematologic cancer selected from the group consisting of one or more acute leukemias including but not limited to B-cell acute lymphoid leukemia ("BALL"), T-cell acute lymphoid leukemia ("TALL"), acute lymphoid leukemia (ALL); one or more chronic leukemias including but not limited to chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL); additional hematologic cancers or hematologic conditions including, but not limited to B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B cell lymphoma, follicular lymphoma, hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, Marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia, and preleukemia; and combinations thereof.

86. The use of any of claims 82-85, wherein the cell is administered in combination with a chemotherapeutic drug, immunosuppressive agent, therapy for CRS (cytokine release syndrome), or agent which inhibits an inhibitory molecule, wherein the inhibitory molecule is optionally chosen from PD1, PD-L1, CTLA4, TIM3, LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, and 2B4.

87. The use of any of claims 82-86, wherein:

the cells expressing a CAR molecule are administered at a dose of 10^4 to 10^9 cells/kg body weight, 10^5 to 10^6 cells/kg body weight, 1.4 x 10^7 to 1.1 x 10^9 cells per dose, up to 5 x10^7, 1 x 10^7 - 5 x 10^8, or 1 x 10^8 -5 x 10^8 cells per dose;

the use comprises one or more subsequent administrations the cell, nucleic acid, or CAR molecule; or

the use comprises more than one administration (e.g., 2, 3, or 4) administrations in a week, of the cell, nucleic acid, or CAR molecule.