

WHAT IS CLAIMED IS:

1. A chimeric antigen receptor (CAR), comprising an extracellular antigen-binding domain that specifically binds to CD19, a transmembrane domain, and an intracellular signaling domain, wherein the extracellular antigen-binding domain comprises:

a) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 7 or a conservative modification thereof, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 8 or a conservative modification thereof, and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 9 or a conservative modification thereof; and ~~for~~

b) a light chain variable region comprising:

_____ i) a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 11 or a conservative modification thereof, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 12 or a conservative modification thereof, and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 13 or a conservative modification thereof;

_____ ii) a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 16 or a conservative modification thereof, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 12 or a conservative modification thereof, and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 17 or a conservative modification thereof;

_____ iii) a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 11 or a conservative modification thereof, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 20 or a conservative modification thereof, and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 21 or a conservative modification thereof;

_____ iv) a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 11 or a conservative modification thereof, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 12 or a conservative modification thereof, and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 57 or a conservative modification thereof;

_____ v) a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 11 or a conservative modification thereof, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 12 or a conservative modification thereof, and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 59 or a conservative modification thereof;

_____ vi) a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 16 or a conservative modification thereof, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 12 or a conservative modification thereof, and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 61 or a conservative modification thereof;

_____vii) a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 11 or a conservative modification thereof, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 12 or a conservative modification thereof, and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 63 or a conservative modification thereof; or

_____viii) a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 11 or a conservative modification thereof, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 65 or a conservative modification thereof, and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 66 or a conservative modification thereof.

2. The CAR of claim 1, wherein the extracellular antigen-binding domain comprises a single-chain variable fragment (scFv), a Fab, or a F(ab)₂.

~~3. The CAR of claim 2, wherein the extracellular antigen-binding domain comprises a scFv.~~

~~4. The CAR of claim 3, wherein the scFv is a human scFv.~~

~~5. The CAR of any one of claims 1-4, wherein the heavy chain variable region comprises a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 7, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 8, and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 9.~~

~~6. The CAR of any one of claims 1-5, wherein the light chain variable region comprises:~~

~~(a) a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 11, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 12, and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 13;~~

~~(b) a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 16, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 12, and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 17;~~

~~(c) a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 11, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 20, and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 21~~

~~_____ (d) a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 11, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 12, and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 57;~~

~~(e) a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 11, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 12, and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 59;~~

~~(f) a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 16, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 12, and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 61;~~

~~(g) a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 11, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 12, and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 63; or~~

~~(h) a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 11, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 65, and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 66.~~

~~7. The CAR of any one of claims 1-6, wherein the light chain variable region comprises:~~

~~(a) a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 11, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 12, and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 13;~~

~~(b) a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 16, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 12, and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 17; or~~

~~(c) a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 11, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 20, and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 21.~~

~~8.3. The CAR of any one of claims 1-7 claim 1 or 2, wherein:~~

~~(a) the heavy chain variable region comprises a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 7, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 8, and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 9; and the light chain variable region comprises a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 11, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 12, and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 13;~~

~~(b) the heavy chain variable region comprises a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 7, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 8, and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 9;~~

SEQ ID NO: 8, and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 9; and the light chain variable region comprises a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 11, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 65, and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 66.

9.4. The CAR of ~~any one of claims 1-8~~claim 3, wherein:

(a) the heavy chain variable region comprises a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 7, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 8, and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 9; and the light chain variable region comprises a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 11, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 12, and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 13;

(b) the heavy chain variable region comprises a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 7, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 8, and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 9; and the light chain variable region comprises a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 16, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 12, and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 17; or

(c) the heavy chain variable region comprises a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 7, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 8, and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 9; and the light chain variable region comprises a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 11, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 20, and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 21

10.5. The CAR of any one of claims 1-~~94~~, wherein the heavy chain variable region comprises an amino acid sequence that is at least ~~about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99%~~ identical ~~or homologous~~ to the amino acid sequence set forth in SEQ ID NO: 10.

11.6. The CAR of any one of claims 1-~~105~~, wherein the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 10.

12.7. The CAR of any one of claims 1-~~116~~, wherein the light chain variable region comprises an amino acid sequence that is at least about 80%, ~~about 81%, about 82%, about 83%, about~~

~~84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99%~~
identical ~~or homologous~~ to the amino acid sequence set forth in SEQ ID NO: 14, SEQ ID NO: 18, SEQ ID NO: 22, SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 62, SEQ ID NO: 64, or SEQ ID NO: 67.

13.8. The CAR of any one of claims 1-~~127~~, wherein the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 14, SEQ ID NO: 18, SEQ ID NO: 22, SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 62, SEQ ID NO: 64, or SEQ ID NO: 67.

14.9. The CAR of any one of claims 1-~~138~~, wherein the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 14, SEQ ID NO: 18, or SEQ ID NO: 22.

~~15.—The CAR of any one of claims 1-14, wherein the heavy chain variable region comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% identical or homologous to the amino acid sequence set forth in SEQ ID NO: 10; and (b) the light chain variable region comprises an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% identical or homologous to the amino acid sequence set forth in SEQ ID NO: 14, SEQ ID NO: 18, SEQ ID NO: 22, SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 62, SEQ ID NO: 64, or SEQ ID NO: 67.~~

16.10. The CAR of any one of claims 1-~~159~~, wherein the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 10; and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 14, SEQ ID NO: 18, SEQ ID NO: 22, SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 62, SEQ ID NO: 64, or SEQ ID NO: 67.

17.11. The CAR of any one of claims 1-~~1610~~, wherein the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 10; and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 14, SEQ ID NO: 18, or SEQ ID NO: 22.

18.12. The CAR of any one of claims 1-~~1711~~, wherein:

(a) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 10, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 14;

(b) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 10, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 18;

(c) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 10, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 22;

(d) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 10, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 58;

(e) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 10, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 60;

(f) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 10, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 62;

(g) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 10, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 64; or

(h) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 10, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 67.

~~19-13.~~ The CAR of any one of claims 1-~~18~~12, wherein:

(a) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 10, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 14;

(b) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 10, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 18; or

~~20.~~ (c) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 10, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO: 22.

~~21.14.~~ The CAR of any one of claims 1-~~20~~13, wherein the extracellular antigen-binding domain comprises a linker between the heavy chain variable region and the light chain variable region, optionally wherein the linker comprises the amino acid sequence set forth in SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, or SEQ ID NO: 4.

~~22.~~ The CAR of claim 21, wherein the linker consists of the amino acid sequence set forth in SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, or SEQ ID NO: 4.

~~23.~~ The CAR of any one of claims 1-22, wherein the heavy chain variable region and the light chain variable region are positioned from the N- to the C-terminus: V_L-V_H.

~~24.15.~~ The CAR of any one of claims 1-~~23~~14, wherein the extracellular antigen-binding domain comprises or is a scFv, which comprises ~~or consists of~~ the amino acid sequence set forth in SEQ ID NO: 15, SEQ ID NO: 19, or SEQ ID NO: 23.

~~25.16.~~ The CAR of any one of claims 1-~~24~~15, wherein the transmembrane domain comprises a CD8 polypeptide, a CD28 polypeptide, a CD3ζ polypeptide, a CD4 polypeptide, a 4-1BB polypeptide, an OX40 polypeptide, an ICOS polypeptide, a CTLA-4 polypeptide, a PD-1 polypeptide, a LAG-3 polypeptide, a 2B4 polypeptide, or a BTLA polypeptide.

~~26.~~ The CAR of claim 25, wherein the transmembrane domain comprises a CD28 polypeptide.

~~27.17.~~ The CAR of any one of claims 1-~~26~~16, wherein the intracellular signaling domain comprises a CD3ζ polypeptide or a modified CD3ζ polypeptide.

~~28.~~ The CAR of claim 27, wherein the CD3ζ polypeptide is a modified CD3ζ polypeptide.

~~29.18.~~ The CAR of claim ~~28~~17, wherein the modified CD3ζ polypeptide comprises a native ITAM1, an ITAM2 variant consisting of two loss-of-function mutations, and an ITAM3 consisting of two loss-of-function mutations.

~~30.19.~~ The CAR of claim ~~29~~17 or 18, wherein

- a) the native ITAM1 consists of the amino acid sequence set forth in SEQ ID NO: 31;
- b) the ITAM2 variant consists of the amino acid sequence set forth in SEQ ID NO: 37
- c) the ITAM3 variant consists of the amino acid sequence set forth in SEQ ID NO: 41.

~~31.~~ The CAR of claim 29, wherein the ITAM2 variant consists of the amino acid sequence set forth in SEQ ID NO: 37.

~~32. The CAR of claim 29, wherein the ITAM3 variant consists of the amino acid sequence set forth in SEQ ID NO: 41.~~

~~33.20.~~ The CAR of any one of claims ~~28-32~~17-19, wherein the modified CD3 ζ polypeptide ~~comprising comprises or consists of~~ the amino acid sequence set forth in SEQ ID NO: 43.

~~34.21.~~ The CAR of any one of claims 1-~~33~~20, wherein the intracellular signaling domain further comprises at least one co-stimulatory signaling region.

~~35.22.~~ The CAR of claim ~~34~~21, wherein the at least one co-stimulatory signaling region comprises a CD28 polypeptide, a 4-1BB polypeptide, an OX40 polypeptide, an ICOS polypeptide, a DAP-10 polypeptide, or a combination thereof.

~~36. The CAR of claim 35, wherein the at least one co-stimulatory signaling region comprises a CD28 polypeptide.~~

~~37. The CAR of any one of claims 1-36, wherein the CAR is expressed from a vector.~~

~~38. The CAR of claim 37, wherein the vector is a retroviral vector.~~

~~39.23.~~ A cell comprising the CAR of any one of claims 1-~~38~~22.

~~40.24.~~ The cell of claim ~~39~~23, wherein the cell is transduced with the CAR.

~~41.25.~~ The cell of claim ~~39 or claim 40~~23 or 24, wherein the CAR is constitutively expressed on the surface of the cell.

~~42.26.~~ The cell of any one of claims ~~39-41~~23-25, wherein the cell is an immunoresponsive cell.

~~43.27.~~ The cell of any one of claims ~~39-42~~23-26, wherein the cell is a cell of the lymphoid lineage or a cell of the myeloid lineage.

~~44.28.~~ The cell of any one of claims ~~39-43~~23-27, wherein the cell is selected from the group consisting of a T cell, a Natural Killer (NK) cell, a stem cell from which lymphoid cells may be differentiated, and a stem cell from which myeloid cells may be differentiated.

~~45.29.~~ The cell of any one of claims ~~39-44~~23-28, wherein the cell is a T cell.

~~46.30.~~ The cell of claim ~~38-28~~ or claim ~~45~~29, wherein the T cell is selected from the group consisting of helper T cells, cytotoxic T cells, memory T cells, regulatory T cells, tumor-

infiltrating lymphocyte (TIL), Natural Killer T cells, mucosal associated invariant T cells, and $\gamma\delta$ T cells.

~~47. The cell of any one of claims 39-44, wherein the cell is a NK cell.~~

~~48. The cell of claim 47, wherein the NK cell is derived from a stem cell.~~

~~49. The cell of claim 44 or 48, wherein the stem cell is a pluripotent stem cell.~~

~~50. The cell of claim 49, wherein the pluripotent stem cell is an embryoid stem cell or an induced pluripotent stem cell.~~

~~51.31.~~ A nucleic acid molecule encoding the CAR of any one of claims 1-~~3822~~.

~~52.32.~~ The nucleic acid molecule of claim ~~5131~~, further comprising a promoter that is operably linked to the CAR.

~~53.33.~~ The nucleic acid molecule of claim ~~5232~~, wherein the promoter is an endogenous promoter, ~~or an~~ exogenous promoter, or an inducible promoter.

~~54.34.~~ The nucleic acid molecule of claim ~~5333~~, wherein

a) the exogenous promoter is selected from the group consisting of an elongation factor (EF)-1 promoter, a cytomegalovirus immediate-early promoter (CMV) promoter, a simian virus 40 early promoter (SV40) promoter, a phosphoglycerate kinase (PGK) promoter, a metallothionein promoter, and Ubiquitin C promoter;

b) the inducible promoter is selected from the group consisting of a NFAT transcriptional response element (TRE) promoter, a CD69 promoter, a CD25 promoter, an IL-2 promoter, a 4-1BB promoter, a PD1 promoter, and a LAG3 promoter; and/or

c) the endogenous promoter is selected from a TCR alpha promoter, a TCR beta promoter, and a beta 2-microglobulin promoter.

~~55. The nucleic acid molecule of claim 51, wherein the promoter is an inducible promoter.~~

~~56. The nucleic acid molecule of claim 55, wherein the inducible promoter is selected from the group consisting of a NFAT transcriptional response element (TRE) promoter, a CD69 promoter, a CD25 promoter, an IL-2 promoter, a 4-1BB promoter, a PD1 promoter, and a LAG3 promoter.~~

~~57. The nucleic acid molecule of claim 53, wherein the promoter is an endogenous promoter.~~

~~58.—The nucleic acid molecule of claim 57, wherein the endogenous promoter is selected from a TCR-alpha promoter, a TCR-beta promoter, and a beta 2-microglobulin promoter.~~

~~59.35.~~ A vector comprising the nucleic acid molecule of any one of claims ~~51-58~~31-34.

~~60.—The vector of claim 59, wherein the vector is a retroviral vector.~~

~~61.36.~~ A cell expressing the nucleic acid molecule of any one of claims ~~51-58~~31-34.

~~62.37.~~ The cell of claim ~~61~~36, wherein the cell is a T cell or a Natural Killer (NK) cell.

~~63.38.~~ A composition comprising the cell of any one of claims ~~39-50~~23-30, ~~61~~36, and ~~62~~37.

~~64.39.~~ The composition of claim ~~63~~38, which is a pharmaceutical composition further comprising a pharmaceutically acceptable carrier.

~~65.40.~~ The composition of claim ~~63-38~~ or ~~claim-64~~39, comprising

~~_____ a) between about 1×10^6 and about 5×10^8 cells;~~

~~_____ b) between about 1×10^6 and about 1×10^8 cells;~~

~~_____ c) between about 1×10^6 and about 5×10^7 cells; or~~

~~_____ d) about 2.5×10^7 cells.~~

~~66.—The composition of claim 63 or claim 64, comprising between about 1×10^6 and about 1×10^8 cells.~~

~~67.—The composition of claim 63 or claim 64, comprising between about 1×10^6 and about 5×10^7 cells.~~

~~68.—The composition of any one of claims 63-67, comprising about 2.5×10^7 cells.~~

~~69.—A method of reducing tumor burden in a subject, comprising administering to the subject the cell of any one of claims 39-50, 61, and 62 or the composition of any one of claims 63-68.~~

~~70.—The method of claim 69, wherein the method reduces the number of tumor cells, reduces tumor size, and/or eradicates the tumor in the subject.~~

~~71.—A method of increasing or lengthening survival of a subject having a neoplasm, comprising administering to the subject the cell of any one of claims 39-50, 61, and 62 or the composition of any one of claims 63-68.~~

~~72.—A method of treating and/or preventing a neoplasm in a subject, comprising administering to the subject the cell of any one of claims 39-50, 61, and 62 or the composition of any one of claims 63-68.~~

~~73.—The method of any one of claims 69-72, wherein the tumor and/or neoplasm is associated with CD19.~~

~~74.—The method of any one of claims 69-73, wherein the tumor and/or neoplasm is a blood cancer.~~

~~75.—The method of claim 74, wherein the blood cancer is selected from the group consisting of multiple myeloma, leukemia, and lymphomas.~~

~~76.—The method of claim 75, wherein the leukemia is selected from the group consisting of acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute promyelocytic leukemia (APL), mixed-phenotype acute leukemia (MLL), hairy cell leukemia, and B-cell prolymphocytic leukemia.~~

~~77.—The method of claim 75, wherein the lymphoma is Hodgkin's lymphoma or non-Hodgkin's lymphoma.~~

~~78.—The method of any one of claims 69-73, wherein the tumor and/or neoplasm is a B-cell malignancy.~~

~~79.—The method of claim 78, wherein the B-cell malignancy is selected from the group consisting of B-cell non-Hodgkin lymphomas (NHL), B-cell Hodgkin's lymphomas, B-cell acute lymphocytic leukemia (ALL), B-cell chronic lymphocytic leukemia (CLL), multiple myeloma (MM), CLL with Richter's transformation, and CNS lymphoma.~~

~~80.—The method of any one of claims 69-79, wherein the tumor and/or neoplasm is B-cell lymphoma.~~

~~81.—The method of claim 80, wherein the B-cell lymphoma is relapsed or refractory (R/R) B-cell lymphoma.~~

~~82.—The method of any one of claims 69-81, wherein the subject is a human subject.~~

~~83.—The cell of any one of claims 39-50, 61, and 62 or the composition of any one of claims 63-68 for use in a therapy.~~

~~84.41. Use of the cell of any one of claims 39-50, 61, and 62 or the composition of any one of claims 63-68 in the manufacture of a medicament for use in reducing tumor burden in a subject, treating and/or preventing a neoplasm in a subject, and/or increasing or lengthening survival of a subject having a neoplasm.~~

~~85. The cell of any one of claims 39-50, 61, and 62 or the composition of any one of claims 63-68 for use in increasing or lengthening survival of a subject having a neoplasm.~~

~~86. The cell of any one of claims 39-50, 61, and 62 or the composition of any one of claims 63-68 for use in treating and/or preventing a neoplasm in a subject.~~

~~87.42. The cell or composition for use of any one of claims 84-86 claim 41, wherein the tumor and/or neoplasm is associated with CD19.~~

~~88.43. The cell or composition for use of any one of claims 84-87 claim 41 or 42, wherein the tumor and/or neoplasm is a blood cancer.~~

~~89.44. The cell or composition for use of claim 8843, wherein the blood cancer is selected from the group consisting of multiple myeloma, leukemia, and lymphomas, a B cell malignancy, and a B cell lymphoma.~~

~~90.45. The cell or composition for use of claim 8944, wherein~~

~~_____ a) the leukemia is selected from the group consisting of acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute promyelocytic leukemia (APL), mixed-phenotype acute leukemia (MLL), hairy cell leukemia, and B cell prolymphocytic leukemia;~~

~~_____ b) the lymphoma is Hodgkin's lymphoma or non-Hodgkin's lymphoma;~~

~~_____ c) the B cell malignancy is selected from the group consisting of B cell non-Hodgkin lymphomas (NHL), B cell Hodgkin's lymphomas, B cell acute lymphocytic leukemia (ALL), B cell chronic lymphocytic leukemia (CLL), multiple myeloma (MM), CLL with Richter's transformation, and CNS lymphoma; or~~

~~_____ d) the B cell lymphoma is relapsed or refractory (R/R) B cell lymphoma.~~

~~91. The cell or composition for use of claim 89, wherein the lymphoma is Hodgkin's lymphoma or non-Hodgkin's lymphoma.~~

~~92. The cell or composition for use of any one of claims 84-87, wherein the tumor and/or neoplasm is a B-cell malignancy.~~

~~93. The cell or composition for use of claim 92, wherein the B-cell malignancy is selected from the group consisting of B-cell non-Hodgkin lymphomas (NHL), B-cell Hodgkin's lymphomas, B-cell acute lymphocytic leukemia (ALL), B-cell chronic lymphocytic leukemia (CLL), multiple myeloma (MM), CLL with Richter's transformation, and CNS lymphoma.~~

~~94. The cell or composition for use of any one of claims 84-93, wherein the tumor and/or neoplasm is B-cell lymphoma.~~

~~95. The cell or composition for use of claim 94, wherein the B-cell lymphoma is relapsed or refractory (R/R) B-cell lymphoma.~~

~~96.46. The cell or composition for use of any one of claims 84-95~~41-45, wherein the subject is a human subject.

~~97.47. A method for producing a cell comprising the CAR of any one of claims 1-38~~22, comprising introducing into the cell a nucleic acid molecule that encodes the CAR of any one of claims 1-~~38~~22.

~~98.48. A kit for reducing tumor burden in a subject, treating and/or preventing a neoplasm in a subject, and/or increasing or lengthening survival of a subject having a neoplasm, comprising the cell of any one of claims 39-50, 61, and 62~~23-30, 36, and 37, optionally wherein the kit further comprises written instructions for using the cell for reducing tumor burden in a subject, treating and/or preventing a neoplasm in a subject, and/or increasing or lengthening survival of a subject having a neoplasm.

~~99. The kit of claim 98, wherein the kit further comprises written instructions for using the cell for reducing tumor burden in a subject, treating and/or preventing a neoplasm in a subject, and/or increasing or lengthening survival of a subject having a neoplasm.~~

~~49. The cell of any one of claims 23-30, 36, and 37 or the composition of any one of claims 38-40 for use in therapy.~~