

What is claimed is:

1. A chimeric antigen receptor (CAR) comprising an extracellular antigen-binding domain, a transmembrane domain, and an intracellular signaling domain comprising a modified CD3 ζ polypeptide, wherein the modified CD3 ζ polypeptide lacks all or part of
5 immunoreceptor tyrosine-based activation motifs (ITAMs), wherein the ITAMs are ITAM1, ITAM2, and ITAM3.
2. The CAR of claim 1, wherein the modified CD3 ζ polypeptide lacks ITAM2 or a portion thereof.
3. The CAR of claim 2, wherein the modified CD3 ζ polypeptide further lacks
10 ITAM3 or a portion thereof.
4. The CAR of claim 2, wherein the modified CD3 ζ polypeptide further lacks ITAM1 or a portion thereof.
5. The CAR of claim 1, wherein the modified CD3 ζ polypeptide lacks ITAM1 or a portion thereof.
- 15 6. The CAR of claim 5, wherein the modified CD3 ζ polypeptide further lacks ITAM3 or a portion thereof.
7. The CAR of claim 1, wherein the modified CD3 ζ polypeptide lacks ITAM3 or a portion thereof.
8. The CAR of claim 1, wherein the modified CD3 ζ polypeptide comprises a
20 deletion of ITAM2 or a portion thereof.
9. The CAR of claim 8, wherein the modified CD3 ζ polypeptide further comprises a deletion of ITAM3 or a portion thereof.
10. The CAR of claim 8, wherein the modified CD3 ζ polypeptide further comprises a deletion of ITAM1 or a portion thereof.
- 25 11. The CAR of claim 1, wherein the modified CD3 ζ polypeptide comprises a deletion of ITAM1 or a portion thereof.

12. The CAR of claim 11, wherein the modified CD3 ζ polypeptide further comprises a deletion of ITAM3 or a portion thereof.
13. The CAR of claim 1, wherein the modified CD3 ζ polypeptide comprises a deletion of ITAM3 or a portion thereof.
- 5 14. The CAR of any one of claims 1-13, wherein the modified CD3 ζ polypeptide lacks all or part of basic-rich stretch (BRS) regions, wherein the BRS regions are BRS1, BRS2, and BRS3.
15. The CAR of claim 14, wherein the modified CD3 ζ polypeptide lacks BRS2 or a portion thereof.
- 10 16. The CAR of claim 15, wherein the modified CD3 ζ polypeptide further lacks BRS3 or a portion thereof.
17. The CAR of claim 16, wherein the modified CD3 ζ polypeptide further lacks BRS1 or a portion thereof.
18. The CAR of claim 14, wherein the modified CD3 ζ polypeptide lacks BRS1 or a
15 portion thereof.
19. The CAR of claim 18, wherein the modified CD3 ζ polypeptide further lacks BRS3 or a portion thereof.
20. The CAR of claim 14, wherein the modified CD3 ζ polypeptide lacks BRS3 or a portion thereof.
- 20 21. The CAR of claim 14, wherein the modified CD3 ζ polypeptide lacks BRS1 or portion thereof, BRS2 or portion thereof, and BRS3 or a portion thereof.
22. The CAR of claim 1, wherein the modified CD3 ζ polypeptide lacks ITAM2, ITAM3, BRS2, and BRS3.
23. The CAR of claim 14, wherein the modified CD3 ζ polypeptide comprises a
25 deletion of BRS2 or a portion thereof.
24. The CAR of claim 23, wherein the modified CD3 ζ polypeptide further comprises a deletion of BRS3 or a portion thereof.

25. The CAR of claim 24, wherein the modified CD3 ζ polypeptide further comprises a deletion of BRS1 or a portion thereof.
26. The CAR of claim 14, wherein the modified CD3 ζ polypeptide comprises a deletion of BRS1 or a portion thereof.
- 5 27. The CAR of claim 26, wherein the modified CD3 ζ polypeptide further comprises a deletion of BRS3 or a portion thereof.
28. The CAR of claim 14, wherein the modified CD3 ζ polypeptide comprises a deletion of BRS3 or a portion thereof.
29. The CAR of claim 14, wherein the modified CD3 ζ polypeptide comprises a
10 deletion of BRS1 or portion thereof, BRS2 or portion thereof, and BRS3 or a portion thereof.
30. The CAR of claim 1, wherein the modified CD3 ζ polypeptide comprises a deletion of ITAM2, ITAM3, BRS2, and BRS3.
31. The CAR of claim 1, wherein the CAR comprises the amino acid sequence set
15 forth in SEQ ID NO: 45 or SEQ ID NO: 47.
32. A chimeric antigen receptor (CAR) comprising an extracellular antigen-binding domain, a transmembrane domain, and an intracellular signaling domain comprising a modified CD3 ζ polypeptide, wherein the modified CD3 ζ polypeptide lacks all or part of basic-rich stretch (BRS) regions, wherein the BRS regions are BRS1, BRS2, and BRS3.
- 20 33. The CAR of claim 32, wherein the modified CD3 ζ polypeptide lacks BRS2 or a portion thereof.
34. The CAR of claim 33, wherein the modified CD3 ζ polypeptide further lacks BRS3 or a portion thereof.
35. The CAR of claim 34, wherein the modified CD3 ζ polypeptide further lacks
25 BRS1 or a portion thereof.
36. The CAR of claim 35, wherein the modified CD3 ζ polypeptide lacks BRS1 or a portion thereof.

37. The CAR of claim 36, wherein the modified CD3 ζ polypeptide further lacks BRS3 or a portion thereof.
38. The CAR of claim 37, wherein the modified CD3 ζ polypeptide lacks BRS3 or a portion thereof.
- 5 39. The CAR of claim 32, wherein the modified CD3 ζ polypeptide lacks BRS1 or portion thereof, BRS2 or portion thereof, and BRS3 or a portion thereof.
40. A chimeric antigen receptor (CAR) comprising an extracellular antigen-binding domain, a transmembrane domain, and an intracellular signaling domain comprising a modified CD3 ζ polypeptide, wherein the modified CD3 ζ polypeptide comprises a BRS
10 variant selected from a BRS1 variant, a BRS2 variant, and a BRS3 variant, wherein the BRS variant comprises one or more loss-of-function mutations.
41. The CAR of any one of claims 1-40, further comprising a hinge/spacer region, wherein the hinge/spacer region comprises a CD8 polypeptide, a CD28 polypeptide, a CD3 ζ polypeptide, a CD4 polypeptide, a 4-1BB polypeptide, an OX40 polypeptide, a
15 CD166 polypeptide, a CD166 polypeptide, a CD8a polypeptide, a CD8b polypeptide, an ICOS polypeptide, an ICAM-1 polypeptide, a CTLA-4 polypeptide, a CD27 polypeptide, a CD40/My88 peptide, a NKGD2 peptide, or a combination thereof.
42. The CAR of claim 41, wherein the hinge/spacer region comprises a CD166 polypeptide.
- 20 43. The CAR of claim 42, wherein the CD166 polypeptide has amino acids 489 to 527 of SEQ ID NO: 3.
44. A chimeric antigen receptor (CAR) comprising an extracellular antigen-binding domain, a hinge/spacer region, a transmembrane domain, and an intracellular signaling domain comprising a modified CD3 ζ polypeptide,
25 wherein the modified CD3 ζ polypeptide comprises one or more ITAM variant comprising one or more loss-of-function mutations, wherein each of the one or more ITAM variant is independently selected from the group consisting of an ITAM1 variant, an ITAM2 variant, and an ITAM3 variant, and
wherein the hinge/spacer region comprises a CD8 polypeptide, a CD28

polypeptide, a CD3 ζ polypeptide, a CD4 polypeptide, a 4-1BB polypeptide, an OX40 polypeptide, a CD166 polypeptide, a CD166 polypeptide, a CD8a polypeptide, a CD8b polypeptide, an ICOS polypeptide, an ICAM-1 polypeptide, a CTLA-4 polypeptide, a CD27 polypeptide, a CD40/My88 peptide, a NKGD2 peptide, or a combination thereof.

- 5 45. The method of claim 44, wherein the modified CD3 ζ polypeptide comprises an ITAM2 variant and an ITAM3 variant.
46. The method of claim 45, wherein the ITAM2 variant has the amino acid sequence set forth in SEQ ID NO: 29.
47. The method of claim 45 or 46, wherein the ITAM3 variant has the amino acid
10 sequence set forth in SEQ ID NO: 33.
48. The CAR of any one of claims 44-47, wherein the modified CD3 ζ polypeptide comprises or consists of amino acids 374 to 485 of SEQ ID NO: 43.
49. The CAR of any one of claims 44-48, wherein the CAR comprises the amino acid sequence set forth in SEQ ID NO: 43.
- 15 50. The method of any one of claims 45-49, wherein one or both of the ITAM2 variant and the ITAM3 variant comprise two loss-of-function mutations.
51. The method of any one of claims 44-50, wherein the one or more loss-of-function mutation is at a tyrosine amino acid residue.
52. The CAR any one of claims 1-51, wherein the transmembrane domain
20 comprises a CD8 polypeptide, a CD28 polypeptide, a CD3 ζ polypeptide, a CD4 polypeptide, a 4-1BB polypeptide, an OX40 polypeptide, a CD166 polypeptide, a CD166 polypeptide, a CD8a polypeptide, a CD8b polypeptide, an ICOS polypeptide, an ICAM-1 polypeptide, a CTLA-4 polypeptide, a CD27 polypeptide, a CD40/My88 peptide, a NKGD2 peptide, or a combination thereof.
- 25 53. The CAR of claim 52, wherein the transmembrane domain comprises a CD166 polypeptide.
54. The CAR of claim 53, wherein the CD166 polypeptide comprises amino acid 528 to 553 of SEQ ID NO: 3.

55. The CAR of any one of claims 44-54, wherein the transmembrane domain and the hinge/spacer region are derived from the same molecule.
56. The CAR of any one of claims 44-55, wherein the hinge/spacer region comprises a CD28 polypeptide and the transmembrane domain comprises a CD28 polypeptide.
- 5 57. The CAR of any one of claims 44-56, wherein the hinge/spacer region comprises a CD84 polypeptide and the transmembrane domain comprises a CD84 polypeptide.
58. The CAR of any one of claims 44-57, wherein the hinge/spacer region comprises a CD166 polypeptide and the transmembrane domain comprises a CD166 polypeptide.
59. The CAR of claim 58, wherein the CAR comprises amino acids 489 to 553 of
10 SEQ ID NO: 3.
60. The CAR of any one of claims 44-59, wherein the hinge/spacer region comprises a CD8a polypeptide and the transmembrane domain comprises a CD8a polypeptide.
61. The CAR of any one of claims 44-60, wherein the hinge/spacer region comprises a CD8b polypeptide and the transmembrane domain comprises a CD8b polypeptide.
- 15 62. The CAR of any one of claims 44-54, wherein the transmembrane domain and the hinge/spacer region are derived from different molecules.
63. The CAR of claim 62, wherein the hinge/spacer region comprises a CD28 polypeptide and the transmembrane domain comprises an ICOS polypeptide.
64. The CAR of any one of claims 1-63, wherein the intracellular signaling domain
20 further comprises a co-stimulatory signaling domain.
65. The CAR of claim 65, wherein the co-stimulatory signaling domain comprises a CD28 polypeptide.
66. An immunoresponsive cell comprising a CAR of any one of claims 1-65.
67. The immunoresponsive cell of claim 66, wherein the CAR is recombinantly
25 expressed.

68. The immunoresponsive cell of claim 66 or 67, wherein the CAR is expressed from a vector.
69. The immunoresponsive cell of any one of claims 66-68, wherein the CAR is placed at an endogenous gene locus of the immunoresponsive cell.
- 5 70. The immunoresponsive cell of claim 69, wherein the endogenous gene locus is a TRAC locus, a TRBC locus or a TRGC locus.
71. The immunoresponsive cell of claim 69 or 70, wherein the endogenous gene locus is a TRAC locus.
72. The immunoresponsive cell of any one of claims 69-71, wherein the placement of
10 the CAR disrupts or abolishes the endogenous expression of a TCR.
73. The immunoresponsive cell of any one of claims 66-72, wherein the cell is selected from the group consisting of a T cell, a Natural Killer (NK) cell, a cytotoxic T lymphocyte (CTL), a regulatory T cell, a Natural Killer T (NKT) cell, a myeloid cell, a human embryonic stem cell, and a pluripotent stem cell from which lymphoid cells may
15 be differentiated.
74. The immunoresponsive cell of any one of claims 66-73, wherein said immunoresponsive cell is autologous.
75. The immunoresponsive cell of any one of claims 66-74, wherein said antigen is a tumor antigen.
- 20 76. The immunoresponsive cell of claim 75, wherein the tumor antigen is selected from the group consisting of CD19, MUC16, MUC1, CAIX, CEA, CD8, CD7, CD10, CD20, CD22, CD30, CLL1, CD33, CD34, CD38, CD41, CD44, CD49f, CD56, CD74, CD133, CD138, EGP-2, EGP-40, EpCAM, erb-B2,3,4, FBP, Fetal acetylcholine receptor, folate receptor-a, GD2, GD3, HER-2, hTERT, IL-13R-a2, K-light chain, KDR,
25 LeY, L1 cell adhesion molecule, MAGE-A1, Mesothelin, ERBB2, MAGEA3, p53, MART1, GP100, Proteinase3 (PR1), Tyrosinase, Survivin, hTERT, EphA2, NKG2D ligands, NY-ES0-1, oncofetal antigen (h5T4), PSCA, PSMA, ROR1, TAG-72, VEGF-R2, WT-1, BCMA, CD123, CD44V6, NKCS1, EGF1R, EGFR-VIII, and CD99, CD70,

ADGRE2, CCR1, LILRB2, PRAME, CCR4, CD5, CD3, TRBC1, TRBC2, TIM-3, Integrin B7, ICAM-1, CD70, Tim3, CLEC12A and ERBB.

77. The immunoresponsive cell of claim 77, wherein said antigen is CD19.

78. A pharmaceutical composition comprising an effective amount of an
5 immunoresponsive cell of any one of claims 66-77 and a pharmaceutically acceptable excipient.

79. The pharmaceutical composition of claim 78, which is for treating a neoplasm.

80. A method of reducing tumor burden in a subject, the method comprising
administering to the subject an effective amount of the immunoresponsive cells of any
10 one of claims 66-77 or the pharmaceutical composition of claim 78 or 79.

81. A method of reducing tumor burden in a subject, the method comprising
administering to the subject an effective amount of immunoresponsive cells or a
pharmaceutical composition comprising thereof, wherein the immunoresponsive cells
comprises:

15 a chimeric antigen receptor (CAR) comprising an extracellular antigen-binding domain, a transmembrane domain, and an intracellular signaling domain comprising a modified CD3 ζ polypeptide, wherein the modified CD3 ζ polypeptide comprises one or more ITAM variant comprising one or more loss-of-function mutations, wherein each of the one or more ITAM variant is independently selected from the group consisting of an
20 ITAM1 variant, an ITAM2 variant, and an ITAM3 variant.

82. The method of claim 81 or 82, wherein the method reduces the number of tumor cells.

83. The method of any one of claims 81-83, wherein the method reduces tumor size.

84. The method of any one of claims 81-84, wherein the method eradicates the tumor
25 in the subject.

85. A method of treating or preventing a neoplasm, the method comprising
administering to the subject an effective amount of the immunoresponsive cells of any
one of claims 66-77 or the pharmaceutical composition of claim 78 or 79.

86. A method of treating or preventing a neoplasm, the method comprising administering to the subject an effective amount of immunoresponsive cells or a pharmaceutical composition comprising thereof, wherein the immunoresponsive cells comprises:

- 5 a chimeric antigen receptor (CAR) comprising an extracellular antigen-binding domain, a transmembrane domain, and an intracellular signaling domain comprising a modified CD3 ζ polypeptide, wherein the modified CD3 ζ polypeptide comprises one or more ITAM variant comprising one or more loss-of-function mutations, wherein each of the one or more ITAM variant is independently selected from the group consisting of an
10 ITAM1 variant, an ITAM2 variant, and an ITAM3 variant.

87. The method of any one of claims 80-86, wherein the neoplasm or tumor is selected from the group consisting of blood cancer, B cell leukemia, multiple myeloma, acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia, non-Hodgkin's lymphoma, and ovarian cancer.

- 15 88. The method of any one of claims 80-87, wherein the neoplasm is B cell leukemia, multiple myeloma, acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia, or non-Hodgkin's lymphoma, and the CAR binds to CD19.

89. The method of any one of claims 80-87, wherein the neoplasm is B cell leukemia, multiple myeloma, acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia,
20 or non-Hodgkin's lymphoma, and the CAR binds to BCMA, ADGRE2, MSLN, PSMA or combinations thereof.

90. A method of treating a subject having a relapse of a neoplasm, wherein the subject has a relapse of a disease, wherein the subject received treatment which leads to residual tumor cells, or the subject received an immunoresponsive cell comprising an
25 antigen recognizing receptor, wherein the antigen recognizing receptor comprises a 4-1BB costimulatory signal, the method comprising administering to the subject an effective amount of the immunoresponsive cells of any one of claims 66-77 or the pharmaceutical composition of claim 78 or 79.

91. A method of treating a subject having a relapse of a neoplasm, wherein the
30 subject has a relapse of a disease, wherein the subject received treatment which leads to residual tumor cells, or the subject received an immunoresponsive cell comprising an

antigen recognizing receptor, wherein the antigen recognizing receptor comprises a 4-1BB costimulatory signal, the method comprising administering to the subject an effective amount of immunoresponsive cells or a pharmaceutical composition comprising thereof, wherein the immunoresponsive cells comprises:

- 5 a chimeric antigen receptor (CAR) comprising an extracellular antigen-binding domain, a transmembrane domain, and an intracellular signaling domain comprising a modified CD3 ζ polypeptide, wherein the modified CD3 ζ polypeptide comprises one or more ITAM variant comprising one or more loss-of-function mutations, wherein each of the one or more ITAM variant is independently selected from the group consisting of an
- 10 ITAM1 variant, an ITAM2 variant, and an ITAM3 variant.

92. The method of claim 90 or 91, wherein the neoplasm is selected from the group consisting of blood cancer, B cell leukemia, multiple myeloma, acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia and non-Hodgkin's lymphoma.

93. The method of any one of claims 90-92, wherein the neoplasm is B cell leukemia,
- 15 multiple myeloma, acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia, or non-Hodgkin's lymphoma, and the CAR binds to CD19.

94. The method of claim 90-93, wherein the neoplasm is CD19+ ALL.

95. The method of claim 90-94, wherein the neoplasm comprises a tumor cell having a low density of a tumor specific antigen on the surface of the tumor cell.

- 20 96. The immunoresponsive cells of any one of claims 66-77 or the pharmaceutical composition of claim 78 or 79 for use in reducing tumor burden, treating or preventing a neoplasm, and/or treating a subject having a relapse of a neoplasm.

97. A chimeric antigen receptor (CAR) comprising an extracellular antigen-binding domain, a transmembrane domain, and an intracellular signaling domain comprising a
- 25 modified CD3 ζ polypeptide, wherein the modified CD3 ζ polypeptide comprises one or more ITAM variant comprising one or more loss-of-function mutations, wherein each of the one or more ITAM variant is independently selected from the group consisting of an ITAM1 variant, an ITAM2 variant, and an ITAM3 variant for use in reducing tumor
- 30 burden, treating or preventing a neoplasm, and/or treating a subject having a relapse of a neoplasm.

98. A method for producing an antigen-specific immunoresponsive cell, the method comprising introducing into an immunoresponsive cell a nucleic acid sequence encoding a CAR according to any one of claims 1-65.
99. The method of claim 98, wherein the nucleic acid sequence is comprised in a
5 vector.
100. The method of claim 99, wherein the vector is a retroviral vector.
101. An isolated nucleotide acid encoding the CAR of any one of claims 1-65.
102. The isolated nucleotide acid of claim 101, comprising the nucleotide sequence set forth in SEQ ID NO: 45 and SEQ ID NO: 47.
- 10 103. A nucleic acid composition comprising a CAR of any one of claims 1-65.
104. The nucleic acid composition of claim 103, wherein the nucleic acid sequences are comprised in a vector.
105. The nucleic acid composition of claim 104, where the vector is a retroviral vector.
- 15 106. A vector comprising the nucleic acid composition of any one of claims 103-105.
107. A kit comprising a CAR of any one of claims 1-65, an immunoresponsive cell of any one of claims 66-77, a pharmaceutical composition of claim 78 or 79, a nucleic acid composition of any one of claims 103-105, or a vector of claim 106.
108. The kit of claim 107, wherein the kit further comprises written instructions for
20 treating and/or preventing a neoplasm, a pathogen infection, an autoimmune disorder, or an allogeneic transplant.
109. An immunoresponsive cell comprising a) a first CAR comprising a first extracellular antigen-binding domain that binds to a first antigen, a first transmembrane domain, and a first intracellular signaling domain; and b) a second CAR comprising a
25 second extracellular antigen-binding domain that binds to a second antigen, a second transmembrane domain, and a second intracellular signaling domain, wherein the first CAR is a CAR of any one of claims 1-65 or the first intracellular signaling domain

comprises a modified CD3 ζ polypeptide that comprises one or more ITAM variant comprising one or more loss-of-function mutations, wherein each of the one or more ITAM variant is independently selected from the group consisting of an ITAM1 variant, an ITAM2 variant, and an ITAM3 variant.

- 5 110. The immunoresponsive cell of claim 109, wherein the second CAR is a CAR of any one of claims 1-65.

111. The immunoresponsive cell of claim 109, wherein the second intracellular signaling domain of the second CAR comprises a modified CD3 ζ polypeptide that comprises one or more ITAM variant comprising one or more loss-of-function
10 mutations, wherein each of the one or more ITAM variant is independently selected from the group consisting of an ITAM1 variant, an ITAM2 variant, and an ITAM3 variant.

112. The immunoresponsive cell of claim 109, wherein the second intracellular signaling domain of the second CAR comprises a modified CD3 ζ polypeptide that is the same as the modified CD3 ζ polypeptide comprised in the first intracellular signaling
15 domain of the first CAR.

113. The immunoresponsive cell of claim 109, wherein the second intracellular signaling domain of the second CAR comprises a modified CD3 ζ polypeptide that is different from the modified CD3 ζ polypeptide comprised in the first intracellular signaling domain of the first CAR.

- 20 114. The immunoresponsive cell of claim 109, wherein the second intracellular signaling domain of the second CAR comprises a native CD3 ζ polypeptide.

115. The immunoresponsive cell of any one of claims 109-113, wherein the first intracellular signaling domain of the first CAR is the same as the second intracellular signaling domain of the second CAR.

- 25 116. The immunoresponsive cell of any one of claims 109-114, wherein the first intracellular signaling domain of the first CAR is different from the second intracellular signaling domain of the second CAR.

117. The immunoresponsive cell of any one of claims 109-116, wherein the first antigen is different from the second antigen.

118. The immunoresponsive cell of any one of claims 109-117, wherein the first CAR further comprises a first hinge/spacer region.

119. The immunoresponsive cell of any one of claims 109-118, wherein the second CAR further comprises a second hinge/spacer region.

5 120. The immunoresponsive cell of any one of claims 109-119, wherein the first intracellular signaling domain comprises or has an ITAM2 variant and an ITAM3 variant, and the second intracellular signaling domain comprises or has a deletion of ITAM2 or a portion thereof and a deletion of ITAM3 or a portion thereof.

10 121. The immunoresponsive cell of any one of claims 109-119, wherein the first intracellular signaling domain comprises or has an ITAM2 variant and an ITAM3 variant, and the second intracellular signaling domain comprises or has an ITAM1 variant and an ITAM2 variant.

15 122. The immunoresponsive cell of any one of claims 109-121, further comprising a third CAR comprising a third extracellular antigen-binding domain that binds to a third antigen, a third transmembrane domain, and a third intracellular signaling domain.

20 123. The immunoresponsive cell of claim 122, wherein the first intracellular signaling domain comprises or has an ITAM2 variant and an ITAM3 variant, the second intracellular signaling domain comprises or has a deletion of ITAM2 or a portion thereof and a deletion of ITAM3 or a portion thereof, and the third intracellular signaling domain comprises or has an ITAM1 variant and an ITAM2 variant.

25 124. The immunoresponsive cell of claim 122, wherein the first intracellular signaling domain comprises or has a deletion of ITAM2 or a portion thereof and a deletion of ITAM3 or a portion thereof, the second intracellular signaling domain comprises or has a deletion of ITAM2 or a portion thereof and a deletion of ITAM3 or a portion thereof, and the third intracellular signaling domain comprises or has an ITAM1 variant and an ITAM2 variant.

125. The immunoresponsive cell of claim 122, wherein the first intracellular signaling domain comprises or has a deletion of ITAM2 or a portion thereof and a deletion of ITAM3 or a portion thereof, the second intracellular signaling domain comprises or has

an ITAM1 variant and an ITAM2 variant, and the third intracellular signaling domain comprises or has an ITAM1 variant and an ITAM2 variant.

126. The immunoresponsive cell of claim 122, wherein the first intracellular signaling domain comprises or has an ITAM1 variant and an ITAM2 variant, the second
5 intracellular signaling domain comprises or has an ITAM1 variant and an ITAM2 variant, and the third intracellular signaling domain comprises or has an ITAM1 variant and an ITAM2 variant.

127. A pharmaceutical composition comprising an effective amount of an
10 immunoresponsive cell of any one of claims 109-126 and a pharmaceutically acceptable excipient.

128. The immunoresponsive cells of any one of claims 109-126 or the pharmaceutical composition of claim 127 for use in reducing tumor burden, treating or preventing a neoplasm, and/or treating a subject having a relapse of a neoplasm.

129. A method of reducing tumor burden in a subject, the method comprising
15 administering to the subject an effective amount of the immunoresponsive cells of any one of claims 109-126 or the pharmaceutical composition of claim 127.

130. The method of claim 129, wherein the method reduces the number of tumor cells, reduces tumor size, and/or eradicates the tumor in the subject.

131. A method of treating or preventing a neoplasm, the method comprising
20 administering to the subject an effective amount of the immunoresponsive cells of any one of claims 109-126 or the pharmaceutical composition of claim 127.

132. The method of claim 131, wherein the neoplasm or tumor is selected from the group consisting of blood cancer, B cell leukemia, multiple myeloma, acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia, non-Hodgkin's
25 lymphoma, and ovarian cancer.

133. The method of claim 131 or 132, wherein the neoplasm is B cell leukemia, multiple myeloma, acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia, or non-Hodgkin's lymphoma, and the CAR binds to CD19.

134. The method of any one of claims 131-133, wherein the neoplasm is B cell leukemia, multiple myeloma, acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia, or non-Hodgkin's lymphoma, and the CAR binds to BCMA, ADGRE2, MSLN, PSMA or combinations thereof.
- 5 135. A method of treating a subject having a relapse of a neoplasm, wherein the subject has a relapse of a disease, wherein the subject received treatment which leads to residual tumor cells, or the subject received an immunoresponsive cell comprising an antigen recognizing receptor, wherein the antigen recognizing receptor comprises a 4-1BB costimulatory signal, the method comprising administering to the subject an
- 10 effective amount of the immunoresponsive cells of any one of claims 109-126 or the pharmaceutical composition of claim 127.
136. The method of claim 135, wherein the neoplasm is selected from the group consisting of blood cancer, B cell leukemia, multiple myeloma, acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia and non-Hodgkin's lymphoma.
- 15 137. The method of claim 135 or 136, wherein the neoplasm is B cell leukemia, multiple myeloma, acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia, or non-Hodgkin's lymphoma, and the CAR binds to CD19.
138. The method of claim 135-137, wherein the neoplasm is CD19+ ALL.
139. The method of claim 135-138, wherein the neoplasm comprises a tumor cell
- 20 having a low density of a tumor specific antigen on the surface of the tumor cell.