CLAIMS

1. An isolated nucleic acid molecule encoding a chimeric antigen receptor (CAR), wherein the CAR comprises an anti-BCMA binding domain, a transmembrane domain, and an intracellular signaling domain, wherein said anti-BCMA binding domain comprises:

(i) a heavy chain complementary determin

ing region 1 (HC CDR1) comprising the amino acid sequence of SEQ ID NO: 394, a heavy chain complementary determining region 2 (HC CDR2) comprising the amino acid sequence of SEQ ID NO: 434, a heavy chain complementary determining region 3 (HC CDR3) comprising the amino acid sequence of SEQ ID NO: 474, a light chain complementary determining region 1 (LC CDR1) comprising the amino acid sequence of SEQ ID NO: 514, a light chain complementary determining region 2 (LC CDR2) comprising the amino acid sequence of SEQ ID NO: 554, and a light chain complementary determining region 3 (LC CDR3) comprising the amino acid sequence of SEQ ID NO: 594;

(ii) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 634, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 674, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 714, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 754, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 794, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 834;

(iii) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 874, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 914, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 954, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 994, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 1034, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 1074;

(iv) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 396, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 436, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 476, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 516, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 556, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 596;

(v) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 636, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 676, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 716, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 756, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 796, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 836; or

(vi) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 876, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 916, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 956, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 996, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 1036, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 1076.

2. The isolated nucleic acid molecule of claim 1, which encodes a CAR comprising:

the amino acid sequence of SEQ ID NO: 94 or 96, or an amino acid sequence with 95-99% identity thereof.

3. The isolated nucleic acid molecule of claim 1 or 2, which encodes a CAR comprising:

the amino acid sequence of SEQ ID NO: 79 or 81, or an amino acid sequence with 95-99% identity thereof.

4. The isolated nucleic acid molecule of any of claims 1-3, which encodes a CAR comprising:

(i) the amino acid sequence of SEQ ID NO: 94 and the amino acid sequence of SEQ ID NO: 79, or

(ii) the amino acid sequence of SEQ ID NO: 96 and the amino acid sequence of SEQ ID NO: 81.

5. The isolated nucleic acid molecule of any of the preceding claims, wherein the encoded anti-BCMA binding domain comprises:

the amino acid sequence of SEQ ID NO: 49 or 51, or an amino acid sequence with 95-99% identity thereof.

6. The isolated nucleic acid molecule of any of the preceding claims, comprising the nucleotide sequence of SEQ ID NO: 64 or 66, or a sequence with 95-99% identity thereof.

7. The isolated nucleic acid molecule of any of the preceding claims, wherein:

(i) 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;

(ii) the encoded transmembrane domain comprises the amino acid sequence of SEQ ID NO: 6, an amino acid sequence comprising 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:6, or a sequence with 95-99% identity to an

amino acid sequence of SEQ ID NO:6; or (ii) the nucleic acid sequence encoding the transmembrane domain comprises a sequence of SEQ ID NO:17, or a sequence with 95-99% identify thereof.

8. The isolated nucleic acid molecule of any of the preceding claims, wherein the encoded anti-BCMA binding domain comprises the amino acid sequence of SEQ ID NO: 49 or 51.

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

10. The isolated nucleic acid molecule of claim 9, wherein:

(i) the encoded hinge region comprises the amino acid sequence of SEQ ID NO:2, or a sequence with 95-99% identity thereof; or (ii) the nucleic acid sequence encoding the hinge region comprises the nucleotide sequence of SEQ ID NO: 13, or a sequence with 95-99% identify thereof.

11. The isolated nucleic acid molecule of any of the preceding claims, wherein the encoded intracellular signaling domain comprises a costimulatory intracellular signaling domain, wherein the costimulatory intracellular signaling domain is a functional signaling domain obtained from a costimulatory molecule selected from the group consisting of MHC class I molecule, TNF receptor proteins, signaling lymphocytic activation molecules (SLAM proteins), activating NK cell receptors, BTLA, a Toll ligand receptor, OX40, CD2, CD7, CD27, CD28, CD30, CD40, CDS, ICAM-1, LFA-1 (CD11a/CD18), 4-1BB (CD137), B7-H3, CDS, ICAM-1, ICOS (CD278), GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, NKG2C, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, and a ligand that specifically binds with CD83.

12. The isolated nucleic acid molecule of any of the preceding claims, wherein the encoded intracellular signaling domain comprises a costimulatory domain, wherein the costimulatory domain comprises the amino acid sequence of SEQ ID NO:7, or 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:7, or a sequence with 95-99% identity to the amino acid sequence of SEQ ID NO:7.

13. The isolated nucleic acid molecule of any of the preceding claims, wherein the nucleic acid sequence encoding the intracellular signaling domain comprises the nucleotide sequence of SEQ ID NO:18, or a sequence with 95-99% identify thereof.

14. 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.

15. 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: 7 and/or the sequence of SEQ ID NO:9 or SEQ ID NO:10; or 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:7 and/or the amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10, or a sequence with 95-99% identity to the amino acid sequence of SEQ ID NO:7 and/or the amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10.

16. The isolated nucleic acid molecule of any of the preceding claims, wherein the encoded intracellular signaling domain comprises the sequence of SEQ ID NO:7 and the sequence of SEQ ID NO:9 or SEQ ID NO:10, wherein the sequences comprising the intracellular signaling domain are expressed in the same frame and as a single polypeptide chain.

17. The isolated nucleic acid molecule of any of the preceding claims, wherein the nucleic acid sequence encoding the intracellular signaling domain comprises the sequence of SEQ ID NO:18, or a sequence with 95-99% identify thereof, and/or the sequence of SEQ ID NO:20 or SEQ ID NO:21, or a sequence with 95-99% identity thereof.

18. The isolated nucleic acid molecule of any of the preceding claims, further comprising a leader sequence which encodes the amino acid sequence of SEQ ID NO: 1.

19. The isolated nucleic acid molecule of any of the preceding claims, which encodes a CAR comprising:

the amino acid sequence of SEQ ID NO: 109 or 111, or an amino acid sequence with 95-99% identity thereof,

with or without a leader sequence comprising the amino acid sequence of SEQ ID NO: 1.

20. The isolated nucleic acid molecule of any of the preceding claims, comprising the nucleotide sequence of SEQ ID NO: 124 or 126, or a nucleotide sequence with 95-99% identity thereof.

21. An isolated polypeptide molecule encoded by the nucleic acid molecule of any one of claims 1-20.

22. An isolated chimeric antigen receptor (CAR) polypeptide, wherein the CAR comprises a human anti-BCMA binding domain, a transmembrane domain, and an intracellular signaling domain comprising a costimulatory domain and/or a primary signaling domain, wherein said anti-BCMA binding domain comprises:

(i) a heavy chain complementary determining region 1 (HC CDR1) comprising the amino acid sequence of SEQ ID NO: 394, a heavy chain complementary determining region 2 (HC CDR2) comprising the amino acid sequence of SEQ ID NO: 434, a heavy chain complementary determining region 3 (HC CDR3) comprising the amino acid sequence of SEQ ID NO: 474, a light chain complementary determining region 1 (LC CDR1) comprising the amino acid sequence of SEQ ID NO: 514, a light chain complementary determining region 2 (LC CDR2) comprising the amino acid sequence of SEQ ID NO: 554, and a light chain complementary determining region 3 (LC CDR3) comprising the amino acid sequence of SEQ ID NO: 594;

(ii) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 634, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 674, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 714, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 754, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 794, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 834;

(iii) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 874, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 914, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 954, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 994, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 1034, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 1074;

(iv) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 396, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 436, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 476, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 516, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 556, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 596;

(v) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 636, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 676, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 716, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 756, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 796, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 836; or

(vi) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 876, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 916, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 956, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 996, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 1036, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 1076.

23. The isolated CAR polypeptide of claim 22, comprising:

the amino acid sequence of SEQ ID NO: 94 or 96, or an amino acid sequence with 95-99% identity thereof.

24. The isolated CAR polypeptide of claim 22 or 23, comprising:

the amino acid sequence of SEQ ID NO: 79 or 81, or an amino acid sequence with 95-99% identity thereof.

25. The isolated CAR polypeptide of any of claims 22-24, comprising:

(i) the amino acid sequence of SEQ ID NO: 94 and the amino acid sequence of SEQ ID NO: 79, or

(ii) the amino acid sequence of SEQ ID NO: 96 and the amino acid sequence of SEQ ID NO: 81.

26. The isolated CAR polypeptide of any of claims 22-25, comprising:

the amino acid sequence of SEQ ID NO: 49 or 51, or an amino acid sequence with 95-99% identify thereof.

27. The isolated CAR polypeptide of any of claims 22-26, wherein the transmembrane domain comprises a transmembrane domain from 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.

28. The isolated CAR polypeptide of any of claims 22-27, wherein

(i) the transmembrane domain comprises the amino acid sequence of SEQ ID NO: 6;

(ii) an amino acid sequence comprises 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: 6; or

(iii) a sequence with 95-99% identity to the amino acid sequence of SEQ ID NO: 6.

29. The isolated CAR polypeptide of any one of claims 22-28, wherein the anti-BCMA binding domain is connected to the transmembrane domain by a hinge region.

30. The isolated CAR polypeptide of claim 29, wherein the hinge region comprises SEQ ID NO:2 or SEQ ID NO:36, or a sequence with 95-99% identity thereof.

31. The isolated CAR polypeptide of any of claims 22-30, wherein the costimulatory domain is a costimulatory intracellular signaling domain, wherein the costimulatory intracellular signaling domain is a functional signaling domain obtained from a costimulatory molecule selected from the group consisting of MHC class I molecule, TNF receptor proteins, signaling lymphocytic activation molecules (SLAM proteins), activating NK cell receptors, BTLA, a Toll ligand receptor, OX40, CD2, CD7, CD27, CD28, CD30, CD40, CDS, ICAM-1, LFA-1 (CD11a/CD18), 4-1BB (CD137), B7-H3, CDS, ICAM-1, ICOS (CD278), GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, NKG2C, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, and a ligand that specifically binds with CD83.

32. The isolated CAR polypeptide of any of claims 22-31, wherein the costimulatory domain comprises the amino acid sequence of SEQ ID NO: 7, or 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: 7, or a sequence with 95-99% identity to the amino acid sequence of SEQ ID NO: 7.

33. The isolated CAR polypeptide of any of claims 22-32, wherein the intracellular signaling domain comprises a functional signaling domain of 4-1BB and/or a functional signaling domain of CD3 zeta.

34. The isolated CAR polypeptide of any of claims 22-33, wherein the intracellular signaling domain comprises the amino acid sequence of SEQ ID NO: 7 and/or the amino acid sequence of SEQ ID NO: 9 or SEQ ID NO: 10, or 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:7 and/or the amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10, or a sequence with 95-99% identity to the amino acid sequence of SEQ ID NO:7 and/or the amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10.

35. The isolated CAR polypeptide of any of claims 22-34, wherein the intracellular signaling domain comprises the amino acid sequence of SEQ ID NO: 7 and the amino acid sequence of SEQ ID NO: 9 or SEQ ID NO:10, wherein the sequences comprising the intracellular signaling domain are expressed in the same frame and as a single polypeptide chain.

36. The isolated CAR polypeptide of any of claims 22-35, further comprising a leader sequence which comprises the amino acid sequence of SEQ ID NO: 1.

37. The isolated CAR polypeptide of any of claims 22-36, comprising:

the amino acid sequence of SEQ ID NO: 109 or 111, or an amino acid sequence with 95-99% identity thereof,

with or without a leader sequence comprising the amino acid sequence of SEQ ID NO: 1.

38. A vector comprising a nucleic acid molecule encoding the CAR polypeptide of any of claims 22-37, wherein the vector is selected from the group consisting of a DNA vector, a RNA vector, a plasmid, a lentivirus vector, adenoviral vector, or a retrovirus vector.

39. The vector of claim 38, further comprising an EF-1 promoter comprising the sequence of SEQ ID NO: 11.

40. A cell, e.g., an immune effector cell, comprising the nucleic acid molecule of any of claims 1-20, the CAR polypeptide of any of claims 22-37, or the vector of claim 38 or 39.

41. A method of making a cell, e.g., an immune effector cell, comprising transducing an immune effector cell ex vivo with the vector of claim 38 or 39.

42. A method of generating a population of RNA-engineered cells comprising introducing an in vitro transcribed RNA or synthetic RNA into a cell ex vivo, wherein the RNA comprises a nucleic acid encoding the CAR polypeptide of any of claims 22-37.

43. A cell, e.g., a population of immune effector cells, comprising the nucleic acid molecule of any of claims 1-20, or the CAR polypeptide of any of claims 22-37 for use in providing an anti-tumor immunity in a mammal.

44. The cell for use according to claim 43, wherein the cell is an autologous T cell or an allogeneic T cell.

45. A cell, e.g., a population of immune effector cells, comprising the nucleic acid molecule of any of claims 1-20, or the CAR polypeptide of any of claims 22-37 for use in treating a mammal having a cancer or malignancy, or a precancerous condition chosen from one or more of a myelodysplasia, a myelodysplastic syndrome or a preleukemia.

46. The cell for use according to claim 45, wherein the mammal has a hematologic cancer.

47. The cell for use according to claim 45 or 46, wherein the mammal has an acute leukemia chosen from one or more of B-cell acute lymphoid leukemia (“BALL”), T-cell acute lymphoid leukemia (“TALL”), acute lymphoid leukemia (ALL); chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL); 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; a prostate cancer (e.g., castrate-resistant or therapy-resistant prostate cancer, or metastatic prostate cancer), pancreatic cancer, lung cancer; or a plasma cell proliferative disorder (e.g., asymptomatic myeloma (smoldering multiple myeloma or indolent myeloma), monoclonal gammapathy of undetermined significance (MGUS), Waldenstrom’s macroglobulinemia, plasmacytomas (e.g., plasma cell dyscrasia, solitary myeloma, solitary plasmacytoma, extramedullary plasmacytoma, and multiple plasmacytoma), systemic amyloid light chain amyloidosis, and POEMS syndrome (also known as Crow-Fukase syndrome, Takatsuki disease, and PEP syndrome)), or a combination thereof.

48. The cell for use according to any of claims 45-47, wherein the cell, e.g., the population of immune effector cells, is to be administered in combination with one or more of:

(i) an agent that increases the efficacy of the cell comprising the CAR nucleic acid or CAR polypeptide;

(ii) an agent that ameliorates one or more side effects associated with administration of the cell comprising the CAR nucleic acid or CAR polypeptide;

(iii) an agent that treats a cancer or malignancy, or a precancerous condition chosen from one or more of a myelodysplasia, a myelodysplastic syndrome or a preleukemia .

49. The cell for use according to any of claims 45-48, wherein the cell, e.g., a population of immune effector cells, is to be administered in combination with a PD-L1 inhibitor, e.g., an anti-PD-L1 antibody.

50. The isolated nucleic acid molecule of any of claims 1-20, the isolated CAR polypeptide of any of claims 22-37, the vector of claim 38 or 39, or the cell of claim 40 for use as a medicament.

51. The isolated nucleic acid molecule of any of claims 1-20, the isolated CAR polypeptide of any of claims 22-37, the vector of claim 38 or 39, or the cell of claim 40 for use in the treatment of a disease associated with over-expression of BCMA.

52. The cell, e.g., a population of immune effector cells, of claim 40, further expressing an inhibitory molecule that comprises:

a first polypeptide that comprises an inhibitory molecule, wherein the inhibitory molecule is chosen from PD1, PD-L1, CTLA4, TIM3, CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 or TGFR beta, or a portion of the extracellular domain thereof, and

a second polypeptide that comprises an intracellular signaling domain, wherein the intracellular signaling domain comprises a costimulatory intracellular signaling domain derived from 4-1BB, CD27 or CD28, or a primary signaling domain derived from CD3 zeta, or both.

53. The cell of claim 52, wherein the inhibitory molecule comprise a first polypeptide that comprises at least a portion of the extracellular domain of PD1 and a second polypeptide comprising a costimulatory intracellular signaling domain derived from CD28 and a primary signaling domain derived from CD3 zeta.

54. The cell for use according to claim 48, wherein the agent is an mTOR inhibitor and the subject is to be administered a low, immune enhancing, dose of an mTOR inhibitor, e.g., RAD001 or rapamycin.

55. The cell for use according to claim 54, wherein the mTOR inhibitor is to be administered for an amount of time sufficient to decrease the proportion of PD-1 positive T cells, increase the proportion of PD-1 negative T cells, or increase the ratio of PD-1 negative T cells/ PD-1 positive T cells, in the peripheral blood of the subject, or in a preparation of T cells isolated from the subject.

56. The cell for use according to any of claims 45-49, wherein the cell expressing a CAR molecule is to be administered in combination with a cell comprising a CD19 CAR molecule.

57. The cell for use according to claim 56, wherein the disease associated with BCMA is multiple myeloma.

58. The cell for use according to claim 57, wherein the multiple myeloma is CD19-negative mutltiple myeloma.

59. The cell for use according to any of claims 45-49 and 56-58, wherein the cell expressing a CAR molecule is to be administered to the subject by dose fractionation, e.g., one, two, three, or more separate administrations of a partial dose,

optionally wherein a first percentage of the total dose is to be administered on a first day of treatment, a second percentage of the total dose is to be administered on a subsequent (e.g., second, third, fourth, fifth, sixth, or seventh or later) day of treatment, and optionally, a third percentage (e.g., the remaining percentage) of the total dose is to be administered on a yet subsequent (e.g., third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, or later) day of treatment,

optionally wherein 10% of the total dose of cells is to be administered on the first day, 30% of the total dose of cells is to be administered on the second day, and the remaining 60% of the total dose of cells is to be administered on the third day of treatment, and

optionally wherein the total cell dose comprises 1 to 5 x 10^7 or 1 to 5 x 10^8 cells.

60. An isolated anti-BCMA antigen binding domain comprising:

(i) a heavy chain complementary determining region 1 (HC CDR1) comprising the amino acid sequence of SEQ ID NO: 394, a heavy chain complementary determining region 2 (HC CDR2) comprising the amino acid sequence of SEQ ID NO: 434, a heavy chain complementary determining

region 3 (HC CDR3) comprising the amino acid sequence of SEQ ID NO: 474, a light chain complementary determining region 1 (LC CDR1) comprising the amino acid sequence of SEQ ID NO: 514, a light chain complementary determining region 2 (LC CDR2) comprising the amino acid sequence of SEQ ID NO: 554, and a light chain complementary determining region 3 (LC CDR3) comprising the amino acid sequence of SEQ ID NO: 594;

(ii) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 634, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 674, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 714, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 754, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 794, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 834;

(iii) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 874, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 914, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 954, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 994, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 1034, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 1074;

(iv) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 396, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 436, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 476, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 516, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 556, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 596;

(v) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 636, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 676, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 716, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 756, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 796, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 836; or

(vi) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 876, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 916, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 956, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 996, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 1036, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 1076.

61. The isolated anti-BCMA antigen binding domain of claim 60, comprising the amino acid sequence of SEQ ID NO: 94 or 96, or an amino acid sequence with 95-99% identity thereof.

62. The isolated anti-BCMA antigen binding domain of claim 60 or 61, comprising the amino acid sequence of SEQ ID NO: 79 or 81, or an amino acid sequence with 95-99% identity thereof.

63. The isolated anti-BCMA antigen binding domain of any one of claims 60-62, comprising (i) the amino acid sequence of SEQ ID NO: 94 and the amino acid sequence of SEQ ID NO: 79, or (ii) the amino acid sequence of SEQ ID NO: 96 and the amino acid sequence of SEQ ID NO: 81.

64. The isolated anti-BCMA antigen binding domain of any one of claims 60-63, comprising the amino acid sequence of SEQ ID NO: 49 or 51, or an amino acid sequence with 95-99% identity thereof.

65. An isolated nucleic acid molecule encoding the anti-BCMA antigen binding domain of any one of claims 60-64.

66. A vector comprising the nucleic acid molecule of claim 65.

67. A pharmaceutical composition comprising the cell of claim 40, and a pharmaceutically acceptable carrier, diluent or excipient.