

mg/m², daily, for 2-4 days.

[0005a] In one aspect, the present disclosure refers to a dose of engineered T cells comprising a chimeric antigen receptor (CAR) for use in the treatment of a subject having or suspect of having multiple myeloma (MM), the CAR comprising: (a) an extracellular antigen-binding domain, comprising: a variable heavy chain (V_H) comprising a heavy chain complementarity determining region 1 (CDR-H1), a heavy chain complementarity determining region 2 (CDR-H2) and a heavy chain complementarity determining region 3 (CDR-H3) contained within the sequence set forth in SEQ ID NO: 116 and a variable light chain (V_L) comprising a light chain complementarity determining region 1 (CDR-L1), a light chain complementarity determining region 2 (CDR-L2) and a light chain complementarity determining region 3 (CDR-L3) contained within the sequence set forth in SEQ ID NO: 119; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:97, 101 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:96, 100 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:95, 99 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:94, 98 and 102, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 104, 106 and 108, respectively; or a V_H comprising the amino acid sequence of SEQ ID NO: 116 and a V_L comprising the amino acid sequence of SEQ ID NO: 119; (b) a spacer comprising an IgG4/2 chimeric hinge or a modified IgG4 hinge; an IgG2/4 chimeric C_H2 region; and an IgG4 C_H3 region; or a spacer set forth in SEQ ID NO: 174; (c) a transmembrane domain; and (d) an intracellular signaling region comprising a cytoplasmic signaling domain of a CD3-zeta (CD3ζ) chain and a costimulatory signaling region comprising an intracellular signaling domain of a T cell costimulatory molecule or a signaling portion thereof; wherein, prior to the treatment, the subject has received a lymphodepleting therapy comprising the administration of fludarabine at or about 20-40 mg/m² body surface area of the subject.

[0005b] In another aspect, the present disclosure refers to the use of a dose of engineered T cells comprising a chimeric antigen receptor (CAR) in the manufacture of a medicament for the treatment of a subject having or suspected of having multiple myeloma (MM), wherein the CAR comprises: (a) an extracellular antigen-binding domain, comprising: a variable heavy chain (V_H) comprising a heavy chain complementarity determining region 1 (CDR-H1), a heavy chain complementarity determining region 2 (CDR-H2) and a heavy chain complementarity determining region 3 (CDR-H3) contained within the sequence set forth in SEQ ID NO: 116 and a variable light chain (V_L) comprising a light chain complementarity determining region 1 (CDR-L1), a light chain complementarity determining region 2

(CDR-L2) and a light chain complementarity determining region 3 (CDR-L3) contained within the sequence set forth in SEQ ID NO: 119; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:97, 101 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:96, 100 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:95, 99 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:94, 98 and 102, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 104, 106 and 108, respectively; or a V_H comprising the amino acid sequence of SEQ ID NO: 116 and a V_L comprising the amino acid sequence of SEQ ID NO: 119; (b) a spacer comprising an IgG4/2 chimeric hinge or a modified IgG4 hinge; an IgG2/4 chimeric C_H2 region; and an IgG4 C_H3 region; or a spacer set forth in SEQ ID NO: 174; (c) a transmembrane domain; and (d) an intracellular signaling region comprising a cytoplasmic signaling domain of a CD3-zeta (CD3ζ) chain and a costimulatory signaling region comprising an intracellular signaling domain of a T cell costimulatory molecule or a signaling portion thereof; wherein, prior to receiving the medicament, the subject has received a lymphodepleting therapy comprising the administration of fludarabine at or about 20-40 mg/m² body surface area of the subject.

[0006] Provided herein are methods of treating a subject having or suspected of having multiple myeloma (MM), the method comprising administering to the subject a dose of engineered T cells comprising a chimeric antigen receptor (CAR), the CAR including: (a) a variable heavy chain (V_H) comprising a heavy chain complementarity determining region 1 (CDR-H1), a heavy chain complementarity determining region 2 (CDR-H2) and a heavy chain complementarity determining region 3 (CDR-H3) contained within the sequence set forth in SEQ ID NO: 116 and a variable light chain (V_L) comprising a light chain complementarity determining region 1 (CDR-L1), a light chain complementarity determining region 2 (CDR-L2) and a light chain complementarity determining region 3 (CDR-L3) contained within the sequence set forth in SEQ ID NO: 119; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:97, 101 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:96, 100 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:95, 99 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:94, 98 and 102,

respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 104, 106 and 108, respectively; or a V_H comprising the amino acid sequence of SEQ ID NO: 116 and a V_L comprising the amino acid sequence of SEQ ID NO: 119; (b) a spacer comprising an IgG4/2 chimeric hinge or a modified IgG4 hinge; an IgG2/4 chimeric C_H2 region; and an IgG4 C_H3 region, which optionally is about 228 amino acids in length; or a spacer set forth in SEQ ID NO: 174; (c) a transmembrane domain, optionally a transmembrane domain from a human CD28; and (d) an intracellular signaling region that includes a cytoplasmic signaling domain of a CD3-zeta (CD3ζ) chain and a costimulatory signaling region that includes an intracellular signaling domain of a T cell costimulatory molecule or a signaling portion thereof; wherein at or prior to the administration of the dose of engineered T cells, the subject has received three or more therapies selected from among: autologous stem cell transplant (ASCT); an immunomodulatory agent; a proteasome inhibitor; and an anti-CD38 antibody; unless the subject was not a candidate for or was contraindicated for one or more of the therapies.

[0006a] In one aspect, the present disclosure refers to a dose of engineered T cells comprising a chimeric antigen receptor (CAR) for use in the treatment of a subject having or suspected of having multiple myeloma (MM), the CAR comprising: (a) an extracellular antigen-binding domain, comprising: a variable heavy chain (V_H) comprising a heavy chain complementarity determining region 1 (CDR-H1), a heavy chain complementarity determining region 2 (CDR-H2) and a heavy chain complementarity determining region 3 (CDR-H3) contained within the sequence set forth in SEQ ID NO: 116 and a variable light chain (V_L) comprising a light chain complementarity determining region 1 (CDR-L1), a light chain complementarity determining region 2 (CDR-L2) and a light chain complementarity determining region 3 (CDR-L3) contained within the sequence set forth in SEQ ID NO: 119; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:97, 101 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:96, 100 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:95, 99 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:94, 98 and 102, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 104, 106 and 108, respectively; or a V_H comprising the amino acid sequence of SEQ ID NO: 116 and a V_L comprising the amino acid sequence of SEQ ID NO: 119; (b) a spacer comprising an IgG4/2 chimeric hinge or a modified IgG4 hinge; an IgG2/4 chimeric C_H2 region; and an IgG4 C_H3 region; or a spacer set forth in SEQ ID NO: 174; (c) a transmembrane domain; and (d) an intracellular signaling region comprising a cytoplasmic signaling domain of a CD3-zeta (CD3ζ) chain

and a costimulatory signaling region comprising an intracellular signaling domain of a T cell costimulatory molecule or a signaling portion thereof; wherein at or prior to the treatment, the subject has received three or more therapies selected from among: autologous stem cell transplant (ASCT); an immunomodulatory agent; a proteasome inhibitor; and an anti-CD38 antibody; unless the subject was not a candidate for or was contraindicated for one or more of the therapies.

[0006b] In another aspect, the present disclosure refers to the use of a dose of engineered T cells comprising a chimeric antigen receptor (CAR) in the manufacture of a medicament for the treatment of a subject having or suspected of having multiple myeloma (MM), wherein the CAR comprises: (a) an extracellular antigen-binding domain, comprising: a variable heavy chain (V_H) comprising a heavy chain complementarity determining region 1 (CDR-H1), a heavy chain complementarity determining region 2 (CDR-H2) and a heavy chain complementarity determining region 3 (CDR-H3) contained within the sequence set forth in SEQ ID NO: 116 and a variable light chain (V_L) comprising a light chain complementarity determining region 1 (CDR-L1), a light chain complementarity determining region 2 (CDR-L2) and a light chain complementarity determining region 3 (CDR-L3) contained within the sequence set forth in SEQ ID NO: 119; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:97, 101 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:96, 100 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:95, 99 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:94, 98 and 102, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 104, 106 and 108, respectively; or a V_H comprising the amino acid sequence of SEQ ID NO: 116 and a V_L comprising the amino acid sequence of SEQ ID NO: 119; (b) a spacer comprising an IgG4/2 chimeric hinge or a modified IgG4 hinge; an IgG2/4 chimeric C_H2 region; and an IgG4 C_H3 region; or a spacer set forth in SEQ ID NO: 174; (c) a transmembrane domain; and (d) an intracellular signaling region comprising a cytoplasmic signaling domain of a CD3-zeta ($CD3\zeta$) chain and a costimulatory signaling region comprising an intracellular signaling domain of a T cell costimulatory molecule or a signaling portion thereof; wherein at or prior to receiving the medicament, the subject has received three or more therapies selected from among: autologous stem cell transplant (ASCT); an immunomodulatory agent; a proteasome inhibitor; and an anti-CD38 antibody; unless the subject was not a candidate for or was contraindicated for one or more of the therapies.

[0007] Provided herein are methods of treating a subject having or suspected of having multiple myeloma (MM), the method comprising administering to the subject a dose of engineered T cells comprising a chimeric antigen receptor (CAR), the CAR including: (a) a variable heavy chain (V_H) comprising a heavy chain complementarity determining region 1 (CDR-H1), a heavy chain complementarity determining region 2 (CDR-H2) and a heavy chain complementarity determining region

3 (CDR-H3) contained within the sequence set forth in SEQ ID NO: 116 and a variable light chain (V_L) comprising a light chain complementarity determining region 1 (CDR-L1), a light chain complementarity determining region 2 (CDR-L2) and a light chain complementarity determining region 3 (CDR-L3) contained within the sequence set forth in SEQ ID NO: 119; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:97, 101 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:96, 100 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:95, 99 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:94, 98 and 102, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 104, 106 and 108, respectively; or a V_H comprising the amino acid sequence of SEQ ID NO: 116 and a V_L comprising the amino acid sequence of SEQ ID NO: 119; (b) a spacer comprising an IgG4/2 chimeric hinge or a modified IgG4 hinge; an IgG2/4 chimeric C_H2 region; and an IgG4 C_H3 region, which optionally is about 228 amino acids in length; or a spacer set forth in SEQ ID NO: 174; (c) a transmembrane domain, optionally a transmembrane domain from a human CD28; and (d) an intracellular signaling region that includes a cytoplasmic signaling domain of a CD3-zeta ($CD3\zeta$) chain and a costimulatory signaling region that includes an intracellular signaling domain of a T cell costimulatory molecule or a signaling portion thereof; wherein at the administration of the dose of engineered T cells, the subject has not had active or history of plasma cell leukemia (PCL).

[0007a] In one aspect, the present disclosure refers to a dose of engineered T cells comprising a chimeric antigen receptor (CAR) for use in the treatment of a subject having or suspected of having multiple myeloma (MM), the CAR comprising: (a) an extracellular antigen-binding domain, comprising: a variable heavy chain (V_H) comprising a heavy chain complementarity determining region 1 (CDR-H1), a heavy chain complementarity determining region 2 (CDR-H2) and a heavy chain complementarity determining region 3 (CDR-H3) contained within the sequence set forth in SEQ ID NO: 116 and a variable light chain (V_L) comprising a light chain complementarity determining region 1 (CDR-L1), a light chain complementarity determining region 2 (CDR-L2) and a light chain complementarity determining region 3 (CDR-L3) contained within the sequence set forth in SEQ ID NO: 119; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:97, 101 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:96, 100 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:95, 99 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:94, 98 and 102, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 104, 106 and 108, respectively; or a V_H comprising the amino acid sequence of SEQ ID NO: 116 and a V_L comprising the amino acid sequence of SEQ ID NO: 119; (b) a spacer comprising an IgG4/2 chimeric hinge or a modified IgG4 hinge; an IgG2/4 chimeric C_H2 region; and an

IgG4 C_H3 region; or a spacer set forth in SEQ ID NO: 174; (c) a transmembrane domain; and (d) an intracellular signaling region comprising a cytoplasmic signaling domain of a CD3-zeta (CD3ζ) chain and a costimulatory signaling region comprising an intracellular signaling domain of a T cell costimulatory molecule or a signaling portion thereof; wherein at the time of treatment, the subject has not had an active or a history of plasma cell leukemia (PCL).

[0007b] In another aspect, the present disclosure refers to use of a dose of engineered T cells comprising a chimeric antigen receptor (CAR) in the manufacture of a medicament for the treatment of a subject having or suspected of having multiple myeloma (MM), wherein the CAR comprises: (a) an extracellular antigen-binding domain, comprising: a variable heavy chain (V_H) comprising a heavy chain complementarity determining region 1 (CDR-H1), a heavy chain complementarity determining region 2 (CDR-H2) and a heavy chain complementarity determining region 3 (CDR-H3) contained within the sequence set forth in SEQ ID NO: 116 and a variable light chain (V_L) comprising a light chain complementarity determining region 1 (CDR-L1), a light chain complementarity determining region 2 (CDR-L2) and a light chain complementarity determining region 3 (CDR-L3) contained within the sequence set forth in SEQ ID NO: 119; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:97, 101 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:96, 100 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:95, 99 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:94, 98 and 102, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 104, 106 and 108, respectively; or a V_H comprising the amino acid sequence of SEQ ID NO: 116 and a V_L comprising the amino acid sequence of SEQ ID NO: 119; (b) a spacer comprising an IgG4/2 chimeric hinge or a modified IgG4 hinge; an IgG2/4 chimeric C_H2 region; and an IgG4 C_H3 region; or a spacer set forth in SEQ ID NO: 174; (c) a transmembrane domain; and (d) an intracellular signaling region comprising a cytoplasmic signaling domain of a CD3-zeta (CD3ζ) chain and a costimulatory signaling region comprising an intracellular signaling domain of a T cell costimulatory molecule or a signaling portion thereof; wherein at the time of receiving the medicament, the subject has not had active or history of plasma cell leukemia (PCL).

[0008] Provided herein are methods of treating a subject having or suspected of having multiple myeloma (MM), the method comprising administering to the subject a dose of engineered T cells comprising a chimeric antigen receptor (CAR), the CAR including: (a) a variable heavy chain (V_H) comprising a heavy chain complementarity determining region 1 (CDR-H1), a heavy chain complementarity determining region 2 (CDR-H2) and a heavy chain complementarity determining region 3 (CDR-H3) contained within the sequence set forth in SEQ ID NO: 116 and a variable light chain (V_L) comprising a light chain complementarity determining region 1 (CDR-L1), a light chain complementarity determining region 2 (CDR-L2) and a light chain complementarity determining region 3 (CDR-L3) contained within the sequence set forth in SEQ ID NO: 119; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:97, 101 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:96, 100 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3

sequences set forth in SEQ ID NOS:95, 99 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:94, 98 and 102, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 104, 106 and 108, respectively; or a V_H comprising the amino acid sequence of SEQ ID NO: 116 and a V_L comprising the amino acid sequence of SEQ ID NO: 119; (b) a spacer comprising an IgG4/2 chimeric hinge or a modified IgG4 hinge; an IgG2/4 chimeric C_H2 region; and an IgG4 C_H3 region, which optionally is about 228 amino acids in length; or a spacer set forth in SEQ ID NO: 174; (c) a transmembrane domain, optionally a transmembrane domain from a human CD28; and (d) an intracellular signaling region that includes a cytoplasmic signaling domain of a CD3-zeta (CD3ζ) chain and a costimulatory signaling region that includes an intracellular signaling domain of a T cell costimulatory molecule or a signaling portion thereof; wherein the dose of engineered T cells comprises: between at or about 1 x 10⁷ CAR-expressing (CAR+) T cells and 2 x 10⁹ CAR-expressing T cells; a combination of CD4⁺ T cells and CD8⁺ T cells, at a defined ratio of CD4⁺ CAR-expressing T cells to CD8⁺ CAR-expressing T cells and/or of CD4⁺ T cells to CD8⁺ T cells, that is or is approximately 1:1 or is between approximately 1:3 and approximately 3:1; and less than 25%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2% or 1% of the CAR-expressing T cells in the dose express a marker of apoptosis, optionally Annexin V or active Caspase 3.

[0008a] In one aspect, the present disclosure refers to a dose of engineered T cells comprising a chimeric antigen receptor (CAR) for use in the treatment of a subject having or suspected of having multiple myeloma (MM), the CAR comprising: (a) an extracellular antigen-binding domain, comprising: a variable heavy chain (V_H) comprising a heavy chain complementarity determining region 1 (CDR-H1), a heavy chain complementarity determining region 2 (CDR-H2) and a heavy chain complementarity determining region 3 (CDR-H3) contained within the sequence set forth in SEQ ID NO: 116 and a variable light chain (V_L) comprising a light chain complementarity determining region 1 (CDR-L1), a light chain complementarity determining region 2 (CDR-L2) and a light chain complementarity determining region 3 (CDR-L3) contained within the sequence set forth in SEQ ID NO: 119; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:97, 101 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:96, 100 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:95, 99 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:94, 98 and 102, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 104, 106 and 108, respectively; or a V_H comprising the amino acid sequence of SEQ ID NO: 116 and a V_L comprising the amino acid sequence of SEQ ID NO: 119; (b) a spacer comprising an IgG4/2 chimeric hinge or a modified IgG4 hinge; an IgG2/4 chimeric C_H2 region; and an IgG4 C_H3 region; or a spacer set forth in SEQ ID NO: 174; (c) a transmembrane domain; and (d) an intracellular signaling region comprising a cytoplasmic signaling domain of a CD3-zeta (CD3ζ) chain and a costimulatory signaling region comprising an intracellular signaling domain of a T cell costimulatory molecule or a signaling portion thereof; wherein the dose of engineered T cells comprises: between at or about 1 x 10⁷ CAR-expressing (CAR+) T cells and at or about 2 x 10⁹ CAR+ T cells; a combination of CD4⁺ T cells and CD8⁺ T cells, at a defined ratio of CD4⁺ CAR+ T cells to CD8⁺ CAR+ T cells and/or of CD4⁺ T cells to CD8⁺ T cells, that is or is approximately 1:1 or is between at or approximately 1:3 and at or approximately 3:1; and less than 25%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2% or 1% of the CAR+ T cells in the dose express a marker of apoptosis.

[0008b] In another aspect, the present disclosure refers to the use of a dose of engineered T cells comprising a chimeric antigen receptor (CAR) in the manufacture of a medicament for treatment of a subject having or suspected of having multiple myeloma (MM), wherein the CAR comprises: (a) an extracellular antigen-binding domain, comprising: a variable heavy chain (V_H) comprising a heavy chain complementarity determining region 1 (CDR-H1), a heavy chain complementarity determining region 2 (CDR-H2) and a heavy chain complementarity determining region 3 (CDR-H3) contained within the

sequence set forth in SEQ ID NO: 116 and a variable light chain (V_L) comprising a light chain complementarity determining region 1 (CDR-L1), a light chain complementarity determining region 2 (CDR-L2) and a light chain complementarity determining region 3 (CDR-L3) contained within the sequence set forth in SEQ ID NO: 119; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:97, 101 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:96, 100 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:95, 99 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:94, 98 and 102, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 104, 106 and 108, respectively; or a V_H comprising the amino acid sequence of SEQ ID NO: 116 and a V_L comprising the amino acid sequence of SEQ ID NO: 119; (b) a spacer comprising an IgG4/2 chimeric hinge or a modified IgG4 hinge; an IgG2/4 chimeric C_H2 region; and an IgG4 C_H3 region; or a spacer set forth in SEQ ID NO: 174; (c) a transmembrane domain; and (d) an intracellular signaling region comprising a cytoplasmic signaling domain of a CD3-zeta ($CD3\zeta$) chain and a costimulatory signaling region comprising an intracellular signaling domain of a T cell costimulatory molecule or a signaling portion thereof; wherein the medicament is formulated for administration of: between at or about 1×10^7 CAR⁺ T cells and 2×10^9 CAR⁺ T cells; a combination of CD4⁺ T cells and CD8⁺ T cells, at a defined ratio of CD4⁺ CAR⁺ T cells to CD8⁺ CAR⁺ T cells and/or of CD4⁺ T cells to CD8⁺ T cells, that is or is approximately 1:1 or is between approximately 1:3 and approximately 3:1; and wherein less than 25%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2% or 1% of the CAR⁺ T cells in the dose express a marker of apoptosis.

[0009] In some of any examples, the extracellular antigen-binding domain of the CAR specifically binds to a B cell maturation antigen (BCMA).

[0010] In some of any examples, the V_H is or comprises the amino acid sequence of SEQ ID NO: 116; and the V_L is or comprises the amino acid sequence of SEQ ID NO: 119. In some of any examples, the extracellular antigen-binding domain comprises an scFv. In some of any examples, the V_H and the V_L are joined by a flexible linker. In some of any examples, the scFv comprises a linker comprising the amino acid sequence GGGGSGGGGSGGGGS (SEQ ID NO:1). In some of any examples, the V_H is amino-terminal to the V_L .

[0011] In some of any examples, the antigen-binding domain comprises the amino acid sequence of SEQ ID NO: 114 or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO: 114. In some of any examples, the antigen-binding domain comprises the amino acid sequence of SEQ ID NO: 114. In some of any examples, a nucleic acid encoding the antigen-binding domain comprises (a) the sequence of nucleotides of SEQ ID NO:113; (b) a sequence of nucleotides that has at least 90% sequence identity thereto; or (c) a degenerate sequence of (a) or (b). In some of any examples, the nucleic acid encoding the antigen-binding domain comprises the sequence of nucleotides of SEQ ID NO:115.

[0012] In some of any examples, the V_H is carboxy-terminal to the V_L .

[0013] In some of any examples, the cytoplasmic signaling domain is or comprises the sequence set forth in SEQ ID NO:143 or a sequence of amino acids that has at least 90% sequence identity to SEQ ID NO:143.

[0014] In some of any examples, the costimulatory signaling region comprises an intracellular signaling domain of CD28, 4-1BB, or ICOS, or a signaling portion thereof. In some of any examples, the costimulatory signaling region comprises an intracellular signaling domain of 4-1BB, optionally human 4-1BB. In some of any examples, the costimulatory signaling region is or comprises the sequence set forth in SEQ ID NO:4 or a sequence of amino acids that exhibits at least 90% sequence identity to the sequence set forth in SEQ ID NO: 4.

[0015] In some of any examples, the costimulatory signaling region is between the transmembrane domain and the cytoplasmic signaling domain of a CD3-zeta (CD3 ζ) chain.

[0016] In some of any examples, the transmembrane domain is or comprises a transmembrane domain from human CD28. In some of any examples, the transmembrane domain is or comprises the sequence set forth in SEQ ID NO:138 or a sequence of amino acids that exhibits at least 90% sequence identity to SEQ ID NO:138.

[0017] In some of any examples, the CAR includes from its N to C terminus in order: the antigen-binding domain, the spacer, the transmembrane domain and the intracellular signaling region.

[0018] In some of any examples, the CAR comprises (a) an extracellular antigen-binding domain, comprising: a variable heavy chain (V_H) comprising a heavy chain complementarity determining region 1 (CDR-H1), a heavy chain complementarity determining region 2 (CDR-H2) and a heavy chain complementarity determining region 3 (CDR-H3) contained within the sequence set forth in SEQ ID NO: 116 and a variable light chain (V_L) comprising a light chain complementarity determining region 1 (CDR-L1), a light chain complementarity determining region 2 (CDR-L2) and a light chain complementarity determining region 3 (CDR-L3) contained within the sequence set forth in SEQ ID NO: 119; (b) a spacer comprising a modified IgG4 hinge; an IgG2/4 chimeric C_H2 region; and an IgG4 C_H3 region, that is about 228 amino acids in length; (c) a transmembrane domain from a human CD28; and (d) an intracellular signaling region comprising a cytoplasmic signaling domain of a CD3-zeta (CD3 ζ) chain and a costimulatory signaling region comprising an intracellular signaling domain of a 4-1BB.

[0019] In some of any examples, the CAR comprises (a) an extracellular antigen-binding domain, comprising the sequence set forth in SEQ ID NO: 114 or a sequence of amino acids having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 114; (b) a spacer comprising the sequence set forth in SEQ ID NO: 174 or a sequence of amino acids that has at least 90% sequence identity to SEQ ID NO:174; (c) a transmembrane domain comprising the sequence set forth in SEQ ID NO:138 or a sequence of amino acids that has at least 90% sequence identity to SEQ ID NO:138; and (d) an intracellular signaling region comprising a cytoplasmic signaling comprising the sequence set forth in SEQ ID NO:143 or a sequence of amino acids that has at least 90% sequence identity to SEQ ID NO:143

and a costimulatory signaling region comprising the sequence set forth in SEQ ID NO:4 or a sequence of amino acids that has at least 90% sequence identity to the sequence set forth in SEQ ID NO: 4.

[0020] In some of any examples, the CAR comprises (a) an extracellular antigen-binding domain, comprising the sequence set forth in SEQ ID NO: 114; (b) a spacer comprising the sequence set forth in SEQ ID NO: 174; (c) a transmembrane domain comprising the sequence set forth in SEQ ID NO:138; and (d) an intracellular signaling region comprising a cytoplasmic signaling comprising the sequence set forth in SEQ ID NO:143 and a costimulatory signaling region comprising the sequence set forth in SEQ ID NO:4.

[0021] In some of any examples, the CAR comprises the sequence set forth in SEQ ID NO:19.

[0022] In some of any examples, the binding of the antigen-binding domain and/or the CAR or a measure indicative of function or activity of the CAR following exposure to cells expressing surface BCMA, is not reduced or blocked or is not substantially reduced or blocked in the presence of a soluble or shed form of BCMA. In some of any examples, the concentration or amount of the soluble or shed form of the BCMA corresponds to a concentration or amount present in serum or blood or plasma of the subject or of a multiple myeloma patient, or on average in a multiple myeloma patient population, or at a concentration or amount of the soluble or shed BCMA at which the binding or measure is reduced or blocked, or is substantially reduced or blocked, for cells expressing a reference anti-BCMA recombinant receptor, optionally a reference anti-BCMA CAR, in the same assay.

[0023] In some of any examples, the CAR is encoded by a polynucleotide sequence comprising the sequence set forth in SEQ ID NO: 13 or a sequence that exhibits at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto. In some of any examples, the CAR expressed by T cells in the provided method is encoded by a polynucleotide sequence comprising the sequence set forth in SEQ ID NO: 13.

[0024] In some of any examples, following expression of a polynucleotide encoding the CAR in a human cell, optionally a human T cell, the transcribed RNA, optionally messenger RNA (mRNA), from the polynucleotide, exhibits at least 70%, 75%, 80%, 85%, 90%, or 95% RNA homogeneity.

[0025] In some of any examples, the dose of engineered T cells comprises between at or about 1×10^7 CAR-expressing (CAR+) T cells and at or about 2×10^9 CAR-expressing T cells. In some of any examples, the dose of engineered T cells comprise between at or about 2.5×10^7 CAR-expressing T cells and at or about 1.2×10^9 CAR-expressing T cells, between at or about 5.0×10^7 CAR-expressing T cells and at or about 4.5×10^8 CAR-expressing T cells, or between at or about 1.5×10^8 CAR-expressing T cells and at or about 3.0×10^8 CAR-expressing T cells. In some of any examples, the dose of engineered T cells comprise at or about 2.5×10^7 , at or about 5.0×10^7 , at or about 1.5×10^8 , at or about 3.0×10^8 , at or about 4.5×10^8 , at or about 6.0×10^8 , at or about 8.0×10^8 or at or about 1.2×10^9 CAR-expressing T cells. In some of any examples, the dose of engineered T cells comprise at or about 5.0×10^7 , at or about 1.5×10^8 , at or about 3.0×10^8 or at or about 4.5×10^8 CAR-expressing T cells.

[0026] In some of any examples, the dose of engineered T cells is less than 1.5×10^8 cells or less than 1.5×10^8 CAR+ T cells or less than 3×10^8 CAR+ T cells or less than 4.5×10^8 CAR+ T cells. In some of any examples, the dose of engineered T cells is at or less than 1.5×10^8 cells or less than 1.5×10^8 CAR+ T cells. In some of any examples, the dose of engineered T cells is at or about 5×10^7 cells or CAR+ T cells. In some of any examples, the dose of engineered T cells is at or about 1.5×10^8 cells or CAR+ T cells. In some of any examples, the dose of engineered T cells is at or about 3×10^8 cells or CAR+ T cells. In some of any examples, the dose of engineered T cells is at or about 4.5×10^8 cells or CAR+ T cells. In some of any examples, the dose of engineered T cells is at or about 6×10^8 cells or CAR+ T cells.

[0027] In some of any examples, the dose of engineered T cells is less than 1.5×10^8 CAR+ T cells or less than 3×10^8 CAR+ T cells or less than 4.5×10^8 CAR+ T cells. In some of any examples, the dose of engineered T cells is at or less than 1.5×10^8 CAR+ T cells. In some of any examples, the dose of engineered T cells is at or about 5×10^7 CAR+ T cells. In some of any examples, the dose of engineered T cells is at or about 1.5×10^8 CAR+ T cells. In some of any examples, the dose of engineered T cells is at or about 3×10^8 CAR+ T cells. In some of any examples, the dose of engineered T cells is at or about 4.5×10^8 CAR+ T cells. In some of any examples, the dose of engineered T cells is at or about 6×10^8 CAR+ T cells.

[0028] In some of any examples, the dose of engineered T cells comprises a combination of CD4⁺ T cells and CD8⁺ T cells and/or a combination of CD4⁺ CAR-expressing T cells and CD8⁺ CAR-expressing T cells. In some examples, the ratio of CD4⁺ CAR-expressing T cells to CD8⁺ CAR-expressing T cells and/or of CD4⁺ T cells to CD8⁺ T cells, is or is approximately 1:1 or is between at or approximately 1:3 and at or approximately 3:1. In some examples, the ratio of CD4⁺ T cells to CD8⁺ T cells is or is approximately 1:1 or is between at or approximately 1:3 and at or approximately 3:1. In some examples, the dose of engineered T cells comprises CD3⁺ CAR-expressing T cells.

[0029] In some of any examples, less than at or about 25%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2% or 1% of the CAR-expressing T cells in the dose of engineered T cells express a marker of apoptosis, optionally Annexin V or active Caspase 3. In some of any examples, less than at or about 5%, 4%, 3%, 2% or 1% of the CAR-expressing T cells in the dose of engineered T cells express Annexin V or active Caspase 3.

[0030] In some of any examples, prior to the administration, the subject has received a lymphodepleting therapy comprising the administration of fludarabine at or about 20-40 mg/m² body surface area of the subject, optionally at or about 30 mg/m², daily, for 2-4 days, and/or cyclophosphamide at or about 200-400 mg/m² body surface area of the subject, optionally at or about 300 mg/m², daily, for 2-4 days. In some of any examples, the subject has received a lymphodepleting therapy comprising the administration of fludarabine at or about 30 mg/m² body surface area of the subject, daily, and cyclophosphamide at or about 300 mg/m² body surface area of the subject, daily, for 3 days.

[0031] In some of any examples, prior to the administration, the subject has received a lymphodepleting therapy comprising the administration of fludarabine at or about 20-40 mg/m² body surface area of the subject, optionally at or about 30 mg/m², daily, for 2-4 days.

[0032] In some of any examples, prior to the administration, the subject has received a lymphodepleting therapy comprising the administration of cyclophosphamide at or about 200-400 mg/m² body surface area of the subject, optionally at or about 300 mg/m², daily, for 2-4 days.

[0033] In some of any examples, the subject has or is suspected of having a relapsed or refractory multiple myeloma (R/R MM).

[0034] In some of any examples, at or prior to the administration of the dose of cells, the subject has received three or more prior therapies for the disease or disorder, optionally four or more prior therapies, optionally selected from among: autologous stem cell transplant (ASCT); an immunomodulatory agent; a proteasome inhibitor; and an anti-CD38 antibody. In some of any examples, the subject has relapsed or been refractory following the three or more prior therapies.

[0035] In some of any examples, at or prior to the administration of the dose of cells, the subject has received three or more prior therapies for the disease or disorder selected from among: autologous stem cell transplant (ASCT); an immunomodulatory agent or a proteasome inhibitor, or a combination thereof; and an anti-CD38 antibody. In some of any examples, the immunomodulatory agent is selected from among thalidomide, lenalidomide and pomalidomide. In some of any examples, the proteasome inhibitor is selected from among bortezomib, carfilzomib and ixazomib. In some of any examples, the anti-CD38 antibody is or comprises daratumumab.

[0036] In some of any examples, at the time of the administration of the dose of cells, and/or at the time of lymphodepleting chemotherapy or leukapheresis, the subject has not had active or history of plasma cell leukemia (PCL). In some of any examples, at the time of the administration of the dose of cells the subject has developed secondary plasma cell leukemia (PCL).

[0037] In some of any examples, at the time of administration, the subject: has relapsed or has been refractory following at least 3 or at least 4 prior therapies for multiple myeloma. In some of any examples, at the time of administration, the subject is an adult subject or is 25 or 35 years of age or older. In some of any examples, at the time of administration, the subject has a time from diagnosis of multiple myeloma of approximately 4 years or between 2 and 15 or 2 and 12 years. In some of any examples, at the time of administration, the subject has received about 10 or between 3 and 15 or between 4 and 15 prior regimens for multiple myeloma. In some of any examples, at the time of administration, the subject has been refractory to or not responded to bortezomib, carfilzomib, lenalidomide, pomalidomide and/or an anti-CD38 monoclonal antibody. In some of any examples, at the time of administration, the subject has had prior autologous stem cell transplant or has not had prior autologous stem cell transplant. In some of any examples, at the time of administration, the subject has IMWG high risk cytogenetics. In some of any examples, at the time of administration of the dose

of engineered T cells comprising a chimeric antigen receptor (CAR) the subject has relapsed or been refractory to at least 3 or at least 4 prior therapies that include bortezomib, carfilzomib, lenalidomide, pomalidomide and/or an anti-CD38 monoclonal antibody. In some of any examples, at the time of administration, the subject has had a prior autologous stem cell transplant.

[0038] In some of any examples, at the time of administration, the subject: has relapsed or been refractory following at least 3 or at least 4 prior therapies for multiple myeloma; is an adult subject or is 25 or 35 years of age or older; has a time from diagnosis of multiple myeloma of approximately 4 years or between 2 and 15 or 2 and 12 years; has received about 10 or between 3 and 15 or between 4 and 15 prior regimens for multiple myeloma; has been refractory to or not responded to bortezomib, carfilzomib, lenalidomide, pomalidomide and/or an anti-CD38 monoclonal antibody; has had prior autologous stem cell transplant or has not had prior autologous stem cell transplant; and/or has IMWG high risk cytogenetics.

[0039] In some of any examples, the method is capable of achieving a specified response or outcome, optionally at a designated timepoint following initiation of the administration, in at least one or in at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95% of subjects in a cohort of subjects having the disease or disorder of the subject, wherein: the response is selected from the group consisting of objective response (OR), complete response (CR), stringent complete response (sCR), very good partial response (VGPR), partial response (PR) and minimal response (MR); the response or outcome is or comprises an OR; and/or the response or outcome is or comprises a CR. In some of any examples, the cohort of subjects has at least the same number of prior therapies, prognosis or prognostic factor, sub-type, secondary involvement or other specified patient characteristic or characteristics, as the subject treated by the method.

[0040] In some of any examples, the method is capable of achieving a specified response or outcome, optionally at a designated timepoint following initiation of the administration, in at least one of or in at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95% of subjects in a cohort of subjects having the disease or disorder of the subject, optionally wherein the cohort of subjects has at least the same number of prior therapies, prognosis or prognostic factor, sub-type, secondary involvement or other specified patient characteristic or characteristics, as the subject treated by the method, wherein: the response is selected from the group consisting of objective response (OR), complete response (CR), stringent complete response (sCR), very good partial response (VGPR), partial response (PR) and minimal response (MR); the response or outcome is or comprises an OR; and/or the response or outcome is or comprises a CR.

[0041] In some examples, the designated timepoint is at or about 1, 2, 3, 6, 9, 12, 18, 24, 30 or 36 months following initiation of the administration, or within a range defined by any of the foregoing. In some examples, the designated timepoint is 4, 8, 12, 16, 20, 24, 28, 32, 36, 48 or 52 weeks months following initiation of the administration, or within a range defined by any of the foregoing. In some of

any examples, the designated timepoint is at or about 1 month following initiation of the administration. In some of any examples, the designated timepoint is at or about 3 months following initiation of the administration. In some of any examples, the designated timepoint is at or about 6 months following initiation of the administration. In some of any examples, the designated timepoint is at or about 9 months following initiation of the administration. In some of any examples, the designated timepoint is at or about 12 months following initiation of the administration.

[0042] In some of any examples, the response or outcome is an OR and is achieved in at least 40%, at least 50%, at least 60%, at least 70%, or at least 80% of subjects of the cohort. In some of any examples, the response or outcome is a VGPR, a CR or an sCR and is achieved in at least 30%, 35%, 40%, 45% or 50% of subjects of the cohort. In some of any examples, the response or outcome is or comprises a CR or an sCR and is achieved in at least 20%, 30%, or 40% of subjects of the cohort. In some of any examples, the response or outcome is or comprises an OR and is achieved in at least 50%, 60%, 70%, or 80% of subjects of the cohort. In some of any examples, the response or outcome is or comprises a VGPR, a CR or an sCR and is achieved in at least 40%, 45% or 50% of subjects of the cohort.

[0043] In some of any of the provided examples, the response or outcome is durable for greater than at or about 3, 6, 9 or 12 months. In some of any of the provided examples, the response or outcome determined at or about 3, 6, 9 or 12 months after the designated timepoint is equal to or improved compared to the response or outcome determined at the designated timepoint.

[0044] In some examples, subjects treated according to the provided methods, such as at a designated timepoint following the initiation of the administration, do not exhibit a response or outcome with any sign or symptom of neurotoxicity or CRS (absence of neurotoxicity or CRS). In some of any examples, the response or outcome comprises or further comprises the absence of neurotoxicity or the absence of cytokine release syndrome (CRS). In some of any examples, the response or outcome comprises or further comprises the absence of neurotoxicity, and is achieved in at least 40%, 50%, 60%, 70% or 80% of the subject in the cohort. In some of any examples, the response or outcome comprises or further comprises the absence of CRS, and is achieved in at least 10%, 15%, 20%, 25% or 30% of the subject in the cohort.

[0045] In some examples, subjects treated according to the provided methods, such as at a designated timepoint following the initiation of the administration, do not exhibit a response or outcome with grade 3 or higher or grade 4 or higher neurotoxicity (absence of grade 3 or higher or grade 4 or higher neurotoxicity). In some examples, subjects treated according to the provided methods, such as at a designated timepoint following the initiation of the administration, do not exhibit a response or outcome with grade 3 or higher or grade 4 or higher CRS (absence of grade 3 or higher or grade 4 or higher CRS). In some of any examples, the response or outcome comprises or further comprises the absence of grade 3 or higher, or grade 4 or higher, neurotoxicity, the absence of grade 3 or higher, or

grade 4 or higher, cytokine release syndrome (CRS). In some of any examples, the response or outcome comprises or further comprises the absence of grade 3 or higher neurotoxicity, and is achieved in at least 80%, 85%, 90% or 95% of the subjects in the cohort. In some of any examples, the response or outcome comprises or further comprises the absence of grade 3 or higher CRS, and is achieved in at least 80%, 85%, 90% or 95% of the subjects in the cohort.

[0046] In some of any examples, the method does not result in a specified toxicity outcome, optionally at a designated timepoint following initiation of the administration, in at least one of or in at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95% of subjects in the cohort of subjects having the disease or disorder.

[0047] In some of any examples, the specified toxicity outcome is neurotoxicity. In some of any examples, the specified toxicity outcome is neurotoxicity, and neurotoxicity does not result in at least 60%, 70% or 80% of the subject in the cohort. In some of any examples, the specified toxicity outcome is grade 3 or higher, or grade 4 or higher, neurotoxicity. In some of any examples, the specified toxicity outcome is grade 3 or higher neurotoxicity, and grade 3 or higher neurotoxicity does not result in in at least 80%, 85%, 90% or 95% of the subjects in the cohort.

[0048] In some of any examples, the specified toxicity outcome is cytokine release syndrome (CRS). In some of any examples, the specified toxicity outcome is CRS, and CRS does not result in at least 15%, 20%, 25% or 30% of the subject in the cohort. In some of any examples, the specified toxicity outcome is grade 3 or higher, or grade 4 or higher, cytokine release syndrome (CRS). In some of any examples, the specified toxicity outcome is grade 3 or higher CRS, and grade 3 or higher CRS does not result in achieved in at least 80%, 85%, 90% or 95% of the subjects in the cohort.

[0049] In some of any examples, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or greater than 95% of the cells in the dose are of a memory phenotype. In some of any examples, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or greater than 95% of the cells in the dose are of a central memory phenotype. In some of any examples, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or greater than 95% of the cells in the dose are CD27+, CD28+, CCR7+, CD45RA-, CD45RO+, CD62L+, CD3+, granzyme B-, and/or CD127+. In some of any examples, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or greater than 95% of the cells in the dose are CCR7+/CD45RA- or are CCR7+/CD45RO+.

[0050] In some of any examples, the cells in the administered dose are produced by a method to produce an output composition exhibiting a predetermined feature, wherein iterations of the method produce a plurality of the output compositions, optionally from human biological samples, when carried out among a plurality of different individual subjects. In some of any examples, the predetermined

feature of the output composition among the plurality of output compositions is the mean percentage of cells of a memory phenotype in the plurality of the output compositions is between about 40% and about 65%, between about 40% and about 45%, between about 45% and about 50%, between about 50% and about 55%, between about 55% and about 60%, or between about 60% and about 65%. In some of any examples, the predetermined feature of the output composition among the plurality of output compositions is the mean percentage of cells of a central memory phenotype in the plurality of the output compositions is between about 40% and about 65%, between about 40% and about 45%, between about 45% and about 50%, between about 50% and about 55%, between about 55% and about 60%, or between about 60% and about 65%. In some of any examples, the predetermined feature of the output composition among the plurality of output compositions is the mean percentage of cells that are CD27+, CD28+, CCR7+, CD45RA-, CD45RO+, CD62L+, CD3+, CD95+, granzyme B-, and/or CD127+ in the plurality of the output compositions is between about 40% and about 65%, between about 40% and about 45%, between about 45% and about 50%, between about 50% and about 55%, between about 55% and about 60%, or between about 60% and about 65%. In some of any examples, the predetermined feature of the output composition among the plurality of output compositions is the mean percentage of cells that are CCR7+/CD45RA- or CCR7+/CD45RO+ in the plurality of the output compositions is between about 40% and about 65%, between about 40% and about 45%, between about 45% and about 50%, between about 50% and about 55%, between about 55% and about 60%, or between about 60% and about 65%. In some of any examples, the predetermined feature of the output composition among the plurality of output compositions is the mean percentage of central memory CD4+ T cells in the engineered CD4+ T cells, optionally CAR+CD4+ T cells, of the plurality of the output compositions is between about 40% and about 65%, between about 40% and about 45%, between about 45% and about 50%, between about 50% and about 55%, between about 55% and about 60%, or between about 60% and about 65%. In some of any examples, the predetermined feature of the output composition among the plurality of output compositions is the mean percentage of central memory CD8+ T cells in the engineered CD8+ T cells, optionally CAR+CD8+ T cells, of the plurality of the output compositions is between about 40% and about 65%, between about 40% and about 45%, between about 45% and about 50%, between about 50% and about 55%, between about 55% and about 60%, or between about 60% and about 65%. In some of any examples, the predetermined feature of the output composition among the plurality of output compositions is the mean percentage of central memory T cells, optionally CD4+ central memory T cells and CD8+ central memory T cells, in the engineered T cells, optionally CAR+ T cells, of the plurality of the output compositions is between about 40% and about 65%, between about 40% and about 45%, between about 45% and about 50%, between about 50% and about 55%, between about 55% and about 60%, or between about 60% and about 65%.

[0051] In some of any examples, the administered dose is produced by a method to produce an output composition exhibiting a predetermined feature, optionally a threshold number of cells expressing

the CAR in the output composition, in at least about 80%, about 90%, about 95%, about 97%, about 99%, about 100%, or is 100% of the human biological samples in which it is carried out among a plurality of different individual subjects. In some of any examples, the plurality of different individual subject comprise subjects having a disease or condition. In some of any examples, the disease or condition is a cancer. In some of any examples, the cancer is a hematological cancer, optionally multiple myeloma. In some examples, the cancer is relapsed or refractory multiple myeloma (R/R MM).

[0052] In some of any examples, the dose of engineered T cells comprise at or about 5.0×10^7 , at or about 1.5×10^8 , at or about 3.0×10^8 or at or about 4.5×10^8 CAR-expressing T cells. In some of any examples, the dose of the engineered T cells comprise at or about 5.0×10^7 CAR-expressing T cells. In some of any examples, the dose of the engineered T cells comprise at or about 1.5×10^8 CAR-expressing T cells. In some of any examples, the dose of the engineered T cells comprise at or about 3×10^8 CAR-expressing T cells. In some of any examples, the dose of the engineered T cells comprise at or about 4.5×10^8 CAR-expressing T cells.

[0053] Also provided are the engineered T cell or a dose of engineered T cells administered in any of the provided methods or uses, or engineered T cells or a dose of engineered T cells for use in accordance with any of the methods provided herein. In some of any examples, wherein the engineered T cell or the dose of engineered T cells, following administration at a dose of engineered T cells is capable of achieving, optionally at a designated time following initiation of the administration, a specified response or outcome in at least one of, or in at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95% of subjects within a cohort of subjects or evaluable subjects thereof, wherein the cohort of subjects is a cohort having multiple myeloma. In any of the engineered T cells or dose of engineered T cells for use, the engineered T cells or dose of engineered T cells are administered in accordance with any of the methods provided herein.

[0054] Also provided are a dose of engineered T cells for use in or for use in accordance with any of the examples of the methods provided herein. In some of any examples, the dose of engineered T cells, following administration, is capable of achieving, optionally at a designated time following initiation of the administration, a specified response or outcome in at least one of, or in at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95% of subjects within a cohort of subjects or evaluable subjects thereof, wherein the cohort of subjects is a cohort having multiple myeloma. In any of the provided dose of engineered T cells for use, the dose of engineered T cells are administered in accordance with any of the methods provided herein.

[0055] Also provided are A dose of engineered T cells for use in or for use in accordance with any of the examples of the methods provided herein that comprises one or more engineered T cells comprising a chimeric antigen receptor (CAR) in a treatment regimen for a subject having or suspected

of having multiple myeloma (MM) comprising administering to the subject the dose of engineered T cells, wherein the CAR comprises: (a) an extracellular antigen-binding domain, comprising: a variable heavy chain (V_H) comprising a heavy chain complementarity determining region 1 (CDR-H1), a heavy chain complementarity determining region 2 (CDR-H2) and a heavy chain complementarity determining region 3 (CDR-H3) contained within the sequence set forth in SEQ ID NO: 116 and a variable light chain (V_L) comprising a light chain complementarity determining region 1 (CDR-L1), a light chain complementarity determining region 2 (CDR-L2) and a light chain complementarity determining region 3 (CDR-L3) contained within the sequence set forth in SEQ ID NO: 119; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:97, 101 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:96, 100 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:95, 99 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:94, 98 and 102, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 104, 106 and 108, respectively; or a V_H comprising the amino acid sequence of SEQ ID NO: 116 and a V_L comprising the amino acid sequence of SEQ ID NO: 119; (b) a spacer comprising an IgG4/2 chimeric hinge or a modified IgG4 hinge; an IgG2/4 chimeric C_H2 region; and an IgG4 C_H3 region, which optionally is about 228 amino acids in length; or a spacer set forth in SEQ ID NO: 174; (c) a transmembrane domain, optionally a transmembrane domain from a human CD28; and (d) an intracellular signaling region comprising a cytoplasmic signaling domain of a CD3-zeta (CD3ζ) chain and a costimulatory signaling region comprising an intracellular signaling domain of a T cell costimulatory molecule or a signaling portion thereof; and the dose of engineered T cells, following administration, is capable of achieving, optionally at a designated time following initiation of the administration, a specified response or outcome in at least one of, or in at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95% of subjects within a cohort of subjects or evaluable subjects thereof, wherein the cohort of subjects is a cohort having multiple myeloma.

[0056] In some of any examples, the CAR comprises (a) an extracellular antigen-binding domain, comprising: a variable heavy chain (V_H) comprising a heavy chain complementarity determining region 1 (CDR-H1), a heavy chain complementarity determining region 2 (CDR-H2) and a heavy chain complementarity determining region 3 (CDR-H3) contained within the sequence set forth in SEQ ID NO: 116 and a variable light chain (V_L) comprising a light chain complementarity determining region 1 (CDR-L1), a light chain complementarity determining region 2 (CDR-L2) and a light chain

complementarity determining region 3 (CDR-L3) contained within the sequence set forth in SEQ ID NO: 119; (b) a spacer comprising a modified IgG4 hinge; an IgG2/4 chimeric C_H2 region; and an IgG4 C_H3 region, that is about 228 amino acids in length; (c) a transmembrane domain from a human CD28; and (d) an intracellular signaling region comprising a cytoplasmic signaling domain of a CD3-zeta (CD3ζ) chain and a costimulatory signaling region comprising an intracellular signaling domain of a 4-1BB.

[0057] In some of any examples, the CAR comprises (a) an extracellular antigen-binding domain, comprising the sequence set forth in SEQ ID NO: 114 or a sequence of amino acids having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 114; (b) a spacer comprising the sequence set forth in SEQ ID NO: 174 or a sequence of amino acids that has at least 90% sequence identity to SEQ ID NO:174; (c) a transmembrane domain comprising the sequence set forth in SEQ ID NO:138 or a sequence of amino acids that has at least 90% sequence identity to SEQ ID NO:138; and (d) an intracellular signaling region comprising a cytoplasmic signaling comprising the sequence set forth in SEQ ID NO:143 or a sequence of amino acids that has at least 90% sequence identity to SEQ ID NO:143 and a costimulatory signaling region comprising the sequence set forth in SEQ ID NO:4 or a sequence of amino acids that has at least 90% sequence identity to the sequence set forth in SEQ ID NO: 4.

[0058] In some of any examples, the CAR comprises (a) an extracellular antigen-binding domain, comprising the sequence set forth in SEQ ID NO: 114; (b) a spacer comprising the sequence set forth in SEQ ID NO: 174; (c) a transmembrane domain comprising the sequence set forth in SEQ ID NO:138; and (d) an intracellular signaling region comprising a cytoplasmic signaling comprising the sequence set forth in SEQ ID NO:143 and a costimulatory signaling region comprising the sequence set forth in SEQ ID NO:4.

[0059] In some of any examples, the CAR comprises the sequence set forth in SEQ ID NO:19.

[0060] In some of any examples, the achievement of the response or outcome is at the designated time following initiation of administration, which is at or about 1, 2, 3, 6, 9, 12, 18, 24, 30 or 36 months following said initiation. In some of any examples, the achievement of the response or outcome is at the designated time following initiation of administration, which is at 1, 2, 3, 6, 9 or 12 months following said initiation. In some of any examples, the achievement of the response or outcome is at the designated time following initiation of administration, which is at 1 or 2 or 3 months following said initiation. In some of any examples, the achievement of the response or outcome is at the designated timepoint following initiation of administration, which is at or about 1 month following said initiation. In some of any examples, the achievement of the response or outcome is at the designated timepoint following initiation of administration, which is at or about 3 months following said initiation. In some of any examples, the achievement of the response or outcome is at the designated timepoint following initiation of administration, which is at or about 6 months following said initiation. In some of any examples, the achievement of the response or outcome is at the designated timepoint following initiation of administration, which is at or about 9 months following said initiation. In some of

any examples, the achievement of the response or outcome is at the designated timepoint following initiation of administration, which is at or about 12 months following said initiation.

[0061] In some of any examples, the cohort of subjects is subjects having relapsed or refractory multiple myeloma. In some of any examples, the cohort of subjects is subjects having relapsed or refractory multiple myeloma having been administered, and relapsed or been refractory following, at least 3 prior therapies for multiple myeloma, said prior therapies optionally including an autologous stem cell transplant (ASCT); an immunomodulatory agent; a proteasome inhibitor; and/or an anti-CD38 antibody. In some of any examples, the cohort of subjects is subjects having relapsed or refractory multiple myeloma having been administered, and relapsed or been refractory following, at least 3 prior therapies for multiple myeloma, said prior therapies optionally including an immunomodulatory agent; a proteasome inhibitor; and/or an anti-CD38 antibody and/or an autologous stem cell transplant. In some of any examples, the cohort of subjects is subjects has no active plasma cell leukemia (PCL) or no history of PCL at the time of said administration. In some of any examples, the cohort of subjects is subjects has developed secondary plasma cell leukemia (PCL) prior to administration of the cells. In some of any examples, the cohort of subjects is or includes subjects having relapsed or refractory multiple myeloma having been administered, and relapsed or been refractory following, at least 4 or an average of at least 10 prior therapies for multiple myeloma. In some of any examples, the cohort of subjects consists of or includes adult subjects. In some of any examples, the cohort of subjects has a median time from diagnosis of 4 years and/or a range of time from diagnosis from 2 to 12 years. In some of any examples, the cohort of subjects has received a median of 10 prior regimens or between 3 and 15 or 4 and 15 prior therapies for multiple myeloma. In some of any examples, the cohort of subjects includes subjects refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide and an anti-CD38 monoclonal antibody. In some of any examples, the cohort of subjects includes subjects having had prior autologous stem cell transplant. In some of any examples, the cohort of subjects includes subjects having IMWG high risk cytogenetics. In some of any examples, the at least 3 prior therapies comprise autologous stem cell transplant (ASCT); an immunomodulatory agent or a proteasome inhibitor, or a combination thereof; and an anti-CD38 antibody.

[0062] In some of any examples, the cohort of subjects is subjects having relapsed or refractory multiple myeloma; the cohort of subjects is subjects having relapsed or refractory multiple myeloma having been administered, and relapsed or been refractory following, at least 3 prior therapies for multiple myeloma, said prior therapies optionally including an autologous stem cell transplant (ASCT); an immunomodulatory agent; a proteasome inhibitor; and/or an anti-CD38 antibody; the cohort of subjects is subjects having relapsed or refractory multiple myeloma having been administered, and relapsed or been refractory following, at least 3 prior therapies for multiple myeloma, said prior therapies optionally including an immunomodulatory agent; a proteasome inhibitor; and/or an anti-CD38 antibody and/or an autologous stem cell transplant; and/or the cohort of subjects is subjects has no active plasma

cell leukemia (PCL) or no history of PCL at the time of said administration; the cohort of subjects is subjects has developed secondary plasma cell leukemia (PCL) prior to administration of the cells the cohort of subjects is or includes subjects having relapsed or refractory multiple myeloma having been administered, and relapsed or been refractory following, at least 4 or an average of at least 10 prior therapies for multiple myeloma; the cohort of subjects consists of or includes adult subjects; the cohort of subjects has a median time from diagnosis of 4 years and/or a range of time from diagnosis from 2 to 12 years; the cohort of subjects has received a median of 10 prior regimens or between 3 and 15 or 4 and 15 prior therapies for multiple myeloma; the cohort of subjects includes subjects refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide and an anti-CD38 monoclonal antibody; the cohort of subjects includes subjects having had prior autologous stem cell transplant; and/or the cohort of subjects includes subjects having IMWG high risk cytogenetics. In some of any examples, thee at least 3 prior therapies comprise autologous stem cell transplant (ASCT); an immunomodulatory agent or a proteasome inhibitor, or a combination thereof; and an anti-CD38 antibody.

[0063] In some of any examples, the immunomodulatory agent is selected from among thalidomide, lenalidomide and pomalidomide, the proteasome inhibitor is selected from among bortezomib, carfilzomib and ixazomib, and/or the anti-CD38 antibody is or comprises daratumumab.

[0064] In some of any examples, the response or outcome is selected from the group consisting of objective response (OR), complete response (CR), stringent complete response (sCR), very good partial response (VGPR), partial response (PR) and minimal response (MR), optionally based on the International Myeloma Working Group (IMWG) uniform response criteria; the response or outcome is or comprises an OR, optionally based on the International Myeloma Working Group (IMWG) uniform response criteria; or the response or outcome is or comprises a CR, optionally based on the International Myeloma Working Group (IMWG) uniform response criteria.

[0065] In some of any examples, the response or outcome is or comprises an OR. In some of any examples, the dose is capable of achieving the response or outcome in at least 40%, at least 50%, at least 60%, at least 70%, or at least 80% of subjects of the cohort.

[0066] In some of any examples, the response or outcome is or comprises a VGPR, a CR or an sCR. In some of any examples, the dose is capable of achieving the response or outcome in at least 30%, 35%, 40%, 45% or 50% of subjects of the cohort.

[0067] In some of any examples, the response or outcome is or comprises a CR or an sCR. In some of any examples, the dose is capable of achieving the response or outcome in at least 20%, 30%, or 40% of subjects of the cohort.

[0068] In some of any examples, the response or outcome is or comprises an OR and the dose is capable of achieving the response or outcome in at least 50%, 60%, 70%, or 80% of subjects of the cohort. In some of any examples, the response or outcome is or comprises a VGPR, a CR or an sCR, and the dose is capable of achieving the response or outcome in at least 40%, 45% or 50% of subjects of

the cohort. In some of any examples, the response or outcome is or comprises a CR or an sCR, and the dose is capable of achieving the response or outcome in at least 20%, 30%, or 40% of subjects of the cohort.

[0069] In some of any examples, the response or outcome is durable for greater than at or about 3, 6, 9 or 12 months. In some of any examples, the response or outcome determined at or about 3, 6, 9 or 12 months after the designated time is equal to or improved compared to the response or outcome determined at the designated time.

[0070] In some of any examples, the dose capable of achieving said response or outcome is less than 1.5×10^8 cells. In some of any examples, the dose capable of achieving said response or outcome is less than 1.5×10^8 CAR+ T cells. In some of any examples, the dose capable of achieving said response or outcome is less than 3×10^8 CAR+ T cells. In some of any examples, the dose capable of achieving said response or outcome is less than or less than 4.5×10^8 CAR+ T cells. In some of any examples, the dose capable of achieving said response or outcome is less than 1.5×10^8 cells; or the dose capable of achieving said response or outcome is less than 1.5×10^8 CAR+ T cells. In some of any examples, the dose capable of achieving said response or outcome is less than 1×10^8 cells. In some of any examples, the dose capable of achieving said response or outcome is less than 1×10^8 CAR+ T cells. In some of any examples, the dose capable of achieving said response or outcome is at or about 5×10^7 cells. In some of any examples, at or about 5×10^7 CAR+ T cells. In some of any examples, the dose capable of achieving said response or outcome is at or about 1.5×10^8 cells or CAR+ T cells. In some of any examples, the dose capable of achieving said response or outcome is at or about 3×10^8 cells or CAR+ T cells. In some of any examples, the dose capable of achieving said response or outcome is at or about 4.5×10^8 cells or CAR+ T cells. In some of any examples, the dose capable of achieving said response or outcome is at or about 6.0×10^8 cells or CAR+ T cells.

[0071] In some of any examples, the dose capable of achieving said response or outcome comprises a combination of CD4⁺ T cells and CD8⁺ T cells. In some of any examples, the dose capable of achieving said response or outcome comprises a combination of a combination of CD4⁺ CAR-expressing T cells and CD8⁺ CAR-expressing T cells. In some of any examples, the ratio of CD4⁺ CAR-expressing T cells to CD8⁺ CAR-expressing T cells and/or of CD4⁺ T cells to CD8⁺ T cells, is or is approximately 1:1 or is between at or approximately 1:3 and at or approximately 3:1. In some of any examples, the dose capable of achieving said response or outcome comprises CD3⁺ CAR-expressing T cells.

[0072] In some of any examples, the response or outcome comprises or further comprises the absence of neurotoxicity or the absence of cytokine release syndrome (CRS). In some of any examples, the response or outcome comprises or further comprises the absence of neurotoxicity, and is achieved in at least 40%, 50%, 60%, 70% or 80% of the subject in the cohort. In some of any

examples, the response or outcome comprises or further comprises the absence of CRS, and is achieved in at least 10%, 15%, 20%, 25% or 30% of the subject in the cohort. In some of any examples, the response or outcome comprises or further comprises the absence of grade 3 or higher, or grade 4 or higher, neurotoxicity, the absence of grade 3 or higher, or grade 4 or higher, cytokine release syndrome. In some of any examples, the response or outcome comprises or further comprises the absence of grade 3 or higher neurotoxicity, and is achieved in at least 80%, 85%, 90% or 95% of the subjects in the cohort. In some of any examples, the response or outcome comprises or further comprises the absence of grade 3 or higher CRS, and is achieved in at least 80%, 85%, 90% or 95% of the subjects in the cohort.

[0073] In some of any examples, administration of the dose of engineered T cell does not result in a specified toxicity outcome, optionally at a designated timepoint following initiation of the administration, in at least one of or in at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 90%, at least 70%, at least 80%, at least 90%, or at least 95% of subjects in the cohort of subjects having the disease or disorder.

[0074] In some of any examples, the specified toxicity outcome is neurotoxicity. In some of any examples, the specified toxicity outcome is neurotoxicity, and neurotoxicity does not result in at least 90%, 70% or 80% of the subject in the cohort. In some of any examples, the specified toxicity outcome is grade 3 or higher, or grade 4 or higher, neurotoxicity. In some of any examples, the specified toxicity outcome is grade 3 or higher neurotoxicity, and grade 3 or higher neurotoxicity does not result in at least 80%, 85%, 90% or 95% of the subjects in the cohort.

[0075] In some of any examples, the specified toxicity outcome is cytokine release syndrome (CRS). In some of any examples, the specified toxicity outcome is CRS, and CRS does not result in at least 15%, 20%, 25% or 30% of the subject in the cohort. In some of any examples, the specified toxicity outcome is grade 3 or higher, or grade 4 or higher, cytokine release syndrome (CRS). In some of any examples, the specified toxicity outcome is grade 3 or higher CRS, and grade 3 or higher CRS does not result in achieved in at least 80%, 85%, 90% or 95% of the subjects in the cohort.

[0076] In some of any examples, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or greater than 95% of the cells in the dose are of a memory phenotype. In some of any examples, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or greater than 95% of the cells in the dose are of a central memory phenotype. In some of any examples, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or greater than 95% of the cells in the dose are CD27+, CD28+, CCR7+, CD45RA-, CD45RO+, CD62L+, CD3+, granzyme B-, and/or CD127+. In some of any examples, wherein at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or greater than 95% of the cells in the dose are

CCR7+/CD45RA- or are CCR7+/CD45RO+.

[0077] In some of any examples, the dose of engineered T cells is produced by a method exhibiting a predetermined feature, wherein iterations of the method produce a plurality of output compositions, optionally from human biological samples in which the method is carried out among a plurality of different individual subjects. In some of any examples, the cells in the administered dose are produced by a method to produce an output composition exhibiting a predetermined feature, wherein iterations of the method produce a plurality of the output compositions, optionally from human biological samples, when carried out among a plurality of different individual subjects.

[0078] In some of any examples, the predetermined feature of the output composition among the plurality of output compositions includes the mean percentage of cells of a memory phenotype in the plurality of the output compositions is between about 40% and about 65%, between about 40% and about 45%, between about 45% and about 50%, between about 50% and about 55%, between about 55% and about 60%, or between about 60% and about 65%. In some of any examples, the predetermined feature of the output composition among the plurality of output compositions includes the mean percentage of cells of a central memory phenotype in the plurality of the output compositions is between about 40% and about 65%, between about 40% and about 45%, between about 45% and about 50%, between about 50% and about 55%, between about 55% and about 60%, or between about 60% and about 65%. In some of any examples, the predetermined feature of the output composition among the plurality of output compositions includes the mean percentage of cells that are CD27+, CD28+, CCR7+, CD45RA-, CD45RO+, CD62L+, CD3+, CD95+, granzyme B-, and/or CD127+ in the plurality of the output compositions is between about 40% and about 65%, between about 40% and about 45%, between about 45% and about 50%, between about 50% and about 55%, between about 55% and about 60%, or between about 60% and about 65%. In some of any examples, the predetermined feature of the output composition among the plurality of output compositions includes the mean percentage of cells that are CCR7+/CD45RA- or CCR7+/CD45RO+ in the plurality of the output compositions is between about 40% and about 65%, between about 40% and about 45%, between about 45% and about 50%, between about 50% and about 55%, between about 55% and about 60%, or between about 60% and about 65%; the mean percentage of central memory CD4+ T cells in the engineered CD4+ T cells, optionally CAR+CD4+ T cells, of the plurality of the output compositions is between about 40% and about 65%, between about 40% and about 45%, between about 45% and about 50%, between about 50% and about 55%, between about 55% and about 60%, or between about 60% and about 65%. In some of any examples, the predetermined feature of the output composition among the plurality of output compositions includes the mean percentage of central memory CD8+ T cells in the engineered CD8+ T cells, optionally CAR+CD8+ T cells, of the plurality of the output compositions is between about 40% and about 65%, between about 40% and about 45%, between about 45% and about 50%, between about 50% and about 55%, between about 55% and about 60%, or between about 60% and about 65%; and/or

the mean percentage of central memory T cells, optionally CD4⁺ central memory T cells and CD8⁺ central memory T cells, in the engineered T cells, optionally CAR⁺ T cells, of the plurality of the output compositions is between about 40% and about 65%, between about 40% and about 45%, between about 45% and about 50%, between about 50% and about 55%, between about 55% and about 60%, or between about 60% and about 65%.

[0079] In some of any examples, the dose is produced by a method to produce an output composition exhibiting a predetermined feature, optionally a threshold number of cells expressing the CAR in the output composition, in at least about 80%, about 90%, about 95%, about 97%, about 99%, about 100%, or is 100% of the human biological samples in which it is carried out among a plurality of different individual subjects.

[0080] In some of any examples, the plurality of different individual subject comprise subjects having a disease or condition. In some of any examples, the disease or condition is a cancer. In some of any examples, the cancer is a hematological cancer, optionally multiple myeloma. In particular examples, the disease or condition is a cancer that is multiple myeloma. In some of any examples, the disease or condition is a relapsed or refractory multiple myeloma (R/R MM).

[0081] Provided are uses of a dose of engineered T cells comprising a chimeric antigen receptor (CAR) in a treatment regimen for a subject having or suspected of having multiple myeloma (MM) comprising administering to the subject the dose of engineered T cells, wherein the CAR includes: (a) a variable heavy chain (V_H) comprising a heavy chain complementarity determining region 1 (CDR-H1), a heavy chain complementarity determining region 2 (CDR-H2) and a heavy chain complementarity determining region 3 (CDR-H3) contained within the sequence set forth in SEQ ID NO: 116 and a variable light chain (V_L) comprising a light chain complementarity determining region 1 (CDR-L1), a light chain complementarity determining region 2 (CDR-L2) and a light chain complementarity determining region 3 (CDR-L3) contained within the sequence set forth in SEQ ID NO: 119; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:97, 101 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:96, 100 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:95, 99 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:94, 98 and 102, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 104, 106 and 108, respectively; or a V_H comprising the amino acid sequence of SEQ ID NO: 116 and a V_L comprising the amino acid sequence of SEQ ID NO: 119; (b) a spacer comprising an IgG4/2 chimeric hinge or a modified IgG4 hinge; an IgG2/4 chimeric C_H2 region; and an

includes a cytoplasmic signaling domain of a CD3-zeta (CD3 ζ) chain and a costimulatory signaling region that includes an intracellular signaling domain of a T cell costimulatory molecule or a signaling portion thereof; wherein at the administration of the dose of engineered T cells, the subject has not had active or history of plasma cell leukemia (PCL).

[0088] Provided are uses of a dose of engineered T cells comprising a chimeric antigen receptor (CAR) for the manufacture of a medicament for the treatment for a subject having or suspected of having multiple myeloma (MM), wherein the CAR includes: (a) a variable heavy chain (V_H) comprising a heavy chain complementarity determining region 1 (CDR-H1), a heavy chain complementarity determining region 2 (CDR-H2) and a heavy chain complementarity determining region 3 (CDR-H3) contained within the sequence set forth in SEQ ID NO: 116 and a variable light chain (V_L) comprising a light chain complementarity determining region 1 (CDR-L1), a light chain complementarity determining region 2 (CDR-L2) and a light chain complementarity determining region 3 (CDR-L3) contained within the sequence set forth in SEQ ID NO: 119; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:97, 101 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:96, 100 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:95, 99 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 105, 107 and 108, respectively; a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:94, 98 and 102, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 104, 106 and 108, respectively; or a V_H comprising the amino acid sequence of SEQ ID NO: 116 and a V_L comprising the amino acid sequence of SEQ ID NO: 119; (b) a spacer comprising an IgG4/2 chimeric hinge or a modified IgG4 hinge; an IgG2/4 chimeric C_H2 region; and an IgG4 C_H3 region, which optionally is about 228 amino acids in length; or a spacer set forth in SEQ ID NO: 174; (c) a transmembrane domain, optionally a transmembrane domain from a human CD28; and (d) an intracellular signaling region that includes a cytoplasmic signaling domain of a CD3-zeta (CD3 ζ) chain and a costimulatory signaling region that includes an intracellular signaling domain of a T cell costimulatory molecule or a signaling portion thereof; wherein the dose of engineered T cells comprises: between at or about 1×10^7 CAR-expressing T cells and 2×10^9 CAR-expressing T cells; a combination of $CD4^+$ T cells and $CD8^+$ T cells, at a defined ratio of $CD4^+$ CAR-expressing T cells to $CD8^+$ CAR-expressing T cells and/or of $CD4^+$ T cells to $CD8^+$ T cells, that is or is approximately 1:1 or is between approximately 1:3 and approximately 3:1; and less than 25%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2% or 1% of the CAR-expressing T cells in the dose express a marker of apoptosis, optionally Annexin V or active Caspase 3.

[0089] In some of any examples, the extracellular antigen-binding domain specifically binds to a

B cell maturation antigen (BCMA). In some of any examples, the V_H is or comprises the amino acid sequence of SEQ ID NO: 116; and the V_L is or comprises the amino acid sequence of SEQ ID NO: 119.

[0090] In some of any examples, the CAR comprises (a) an extracellular antigen-binding domain, comprising: a variable heavy chain (V_H) comprising a heavy chain complementarity determining region 1 (CDR-H1), a heavy chain complementarity determining region 2 (CDR-H2) and a heavy chain complementarity determining region 3 (CDR-H3) contained within the sequence set forth in SEQ ID NO: 116 and a variable light chain (V_L) comprising a light chain complementarity determining region 1 (CDR-L1), a light chain complementarity determining region 2 (CDR-L2) and a light chain complementarity determining region 3 (CDR-L3) contained within the sequence set forth in SEQ ID NO: 119; (b) a spacer comprising a modified IgG4 hinge; an IgG2/4 chimeric C_H2 region; and an IgG4 C_H3 region, that is about 228 amino acids in length; (c) a transmembrane domain from a human CD28; and (d) an intracellular signaling region comprising a cytoplasmic signaling domain of a CD3-zeta (CD3ζ) chain and a costimulatory signaling region comprising an intracellular signaling domain of a 4-1BB.

[0091] In some of any examples, the CAR comprises (a) an extracellular antigen-binding domain, comprising the sequence set forth in SEQ ID NO: 114 or a sequence of amino acids having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 114; (b) a spacer comprising the sequence set forth in SEQ ID NO: 174 or a sequence of amino acids that has at least 90% sequence identity to SEQ ID NO:174; (c) a transmembrane domain comprising the sequence set forth in SEQ ID NO:138 or a sequence of amino acids that has at least 90% sequence identity to SEQ ID NO:138; and (d) an intracellular signaling region comprising a cytoplasmic signaling comprising the sequence set forth in SEQ ID NO:143 or a sequence of amino acids that has at least 90% sequence identity to SEQ ID NO:143 and a costimulatory signaling region comprising the sequence set forth in SEQ ID NO:4 or a sequence of amino acids that has at least 90% sequence identity to the sequence set forth in SEQ ID NO: 4.

[0092] In some of any examples, the CAR comprises (a) an extracellular antigen-binding domain, comprising the sequence set forth in SEQ ID NO: 114; (b) a spacer comprising the sequence set forth in SEQ ID NO: 174; (c) a transmembrane domain comprising the sequence set forth in SEQ ID NO:138; and (d) an intracellular signaling region comprising a cytoplasmic signaling comprising the sequence set forth in SEQ ID NO:143 and a costimulatory signaling region comprising the sequence set forth in SEQ ID NO:4.

[0093] In some of any examples, the CAR comprises the sequence set forth in SEQ ID NO:19.

[0094] In some of any examples, the dose of engineered T cells comprises between at or about 1 x 10⁷ CAR-expressing T cells and at or about 2 x 10⁹ CAR-expressing T cells. In some of any examples, the dose of engineered T cells comprise between at or about 2.5 x 10⁷ CAR-expressing T cells and at or about 1.2 x 10⁹ CAR-expressing T cells. In some of any examples, the dose of engineered T cells comprises between at or about 5.0 x 10⁷ CAR-expressing T cells and at or about 4.5 x 10⁸ CAR-expressing T cells. In some of any examples, the dose of engineered T cells comprises

between at or about 1.5×10^8 CAR-expressing (CAR+) T cells and at or about 3.0×10^8 CAR-expressing T cells. In some of any examples, the dose of engineered T cells comprise at or about 2.5×10^7 CAR-expressing (CAR+) T cells. In some of any examples, the dose of engineered T cells comprises at or about 5.0×10^7 CAR+ T cells. In some of any examples, the dose of engineered T cells comprises at or about 1.5×10^8 CAR+ T cells. In some of any examples, the dose of engineered T cells comprises at or about 3.0×10^8 CAR+ T cells. In some of any examples, the dose of engineered T cells comprises at or about 4.5×10^8 CAR+ T cells. In some of any examples, the dose of engineered T cells comprises at or about 6.0×10^8 CAR+ T cells. In some of any examples, the dose of engineered T cells comprises at or about 8.0×10^8 or at or about 1.2×10^9 CAR-expressing T (CAR+) cells. In some of any examples, the dose of engineered T cells comprise at or about 5.0×10^7 , at or about 1.5×10^8 , at or about 3.0×10^8 or at or about 4.5×10^8 CAR-expressing (CAR+) T cells.

[0095] In some of any examples, the dose of engineered T cells is less than 1.5×10^8 cells or less than 1.5×10^8 CAR+ T cells or less than 3×10^8 CAR+ T cells or less than 4.5×10^8 CAR+ T cells. In some of any examples, the dose of engineered T cells is at or less than 1.5×10^8 cells or less than 1.5×10^8 CAR+ T cells.

[0096] In some of any examples, the dose of engineered T cells is at or about 5×10^7 cells or CAR+ T cells. In some of any examples, the dose of engineered T cells is at or about 1.5×10^8 cells or CAR+ T cells. In some of any examples, the dose of engineered T cells is at or about 3×10^8 cells or CAR+ T cells. In some of any examples, the dose of engineered T cells is at or about 4.5×10^8 cells or CAR+ T cells. In some of any examples, the dose of engineered T cells is at or about 6×10^8 cells or CAR+ T cells.

[0097] In some of any examples, the dose of engineered T cells comprises a combination of CD4⁺ T cells and CD8⁺ T cells. In some of any examples, the dose of engineered T cells comprises a combination of CD4⁺ CAR-expressing T cells and CD8⁺ CAR-expressing T cells, In some of any examples, the ratio of CD4⁺ CAR-expressing T cells to CD8⁺ CAR-expressing T cells and/or of CD4⁺ T cells to CD8⁺ T cells is or is approximately 1:1 or is between at or approximately 1:3 and at or approximately 3:1. In some of any examples, the dose of engineered T cells comprises CD3⁺ CAR-expressing T cells.

[0098] In some of any examples, less than at or about 25%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2% or 1% of the CAR-expressing T cells in the dose of engineered T cells express a marker of apoptosis. In some of any examples, the marker is Annexin V or active Caspase 3. In some of any examples, less than at or about 5%, 4%, 3%, 2% or 1% of the CAR-expressing T cells in the dose of engineered T cells express Annexin V or active Caspase 3.

[0099] In some of any of the methods or uses provided herein, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or greater than 95% of the cells in the administered dose are of a memory phenotype. In some of any of the

methods or uses provided herein, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or greater than 95% of the cells in the administered dose are of a central memory phenotype. In some of any of the methods or uses provided herein, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or greater than 95% of the cells in the administered dose are CD27+, CD28+, CCR7+, CD45RA-, CD45RO+, CD62L+, CD3+, granzyme B-, and/or CD127+. In some of any of the methods or uses provided herein, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or greater than 95% of the cells in the administered dose are CCR7+/CD45RA- or are CCR7+/CD45RO+.

[0100] In some of any of the methods or uses provided herein, the cells in the administered dose are produced by a method that produces a plurality of output compositions, optionally from human biological samples in which the method is carried out among a plurality of different individual subjects. In some of any of the methods or uses provided herein, cells in the administered dose are produced by a method to produce an output composition exhibiting a predetermined feature, wherein iterations of the method produce a plurality of the output compositions, optionally from human biological samples, when carried out among a plurality of different individual subjects.

[0101] In some of any examples, the predetermined feature of the output composition among the plurality of output compositions includes the mean percentage of cells of a memory phenotype in the plurality of the output compositions includes the mean percentage of cells of a memory phenotype in the plurality of the output compositions is between about 40% and about 65%, between about 40% and about 45%, between about 45% and about 50%, between about 50% and about 55%, between about 55% and about 60%, or between about 60% and about 65%. In some of any examples, the predetermined feature of the output composition among the plurality of output compositions includes the mean percentage of cells of a central memory phenotype in the plurality of the output compositions is between about 40% and about 65%, between about 40% and about 45%, between about 45% and about 50%, between about 50% and about 55%, between about 55% and about 60%, or between about 60% and about 65%. In some of any examples, the predetermined feature of the output composition among the plurality of output compositions includes the mean percentage of cells that are CD27+, CD28+, CCR7+, CD45RA-, CD45RO+, CD62L+, CD3+, CD95+, granzyme B-, and/or CD127+ in the plurality of the output compositions is between about 40% and about 65%, between about 40% and about 45%, between about 45% and about 50%, between about 50% and about 55%, between about 55% and about 60%, or between about 60% and about 65%. In some of any examples, the predetermined feature of the output composition among the plurality of output compositions includes the mean percentage of cells that are CCR7+/CD45RA- or CCR7+/CD45RO+ in the plurality of the output compositions is between about 40% and about 65%, between about 40% and about 45%, between about 45% and about 50%, between about 50% and about 55%, between about 55% and about 60%, or between about 60% and about 65%. In

some of any examples, the predetermined feature of the output composition among the plurality of output compositions includes the mean percentage of central memory CD4⁺ T cells in the engineered CD4⁺ T cells, optionally CAR+CD4⁺ T cells, of the plurality of the output compositions is between about 40% and about 65%, between about 40% and about 45%, between about 45% and about 50%, between about 50% and about 55%, between about 55% and about 60%, or between about 60% and about 65%. In some of any examples, the predetermined feature of the output composition among the plurality of output compositions includes the mean percentage of central memory CD8⁺ T cells in the engineered CD8⁺ T cells, optionally CAR+CD8⁺ T cells, of the plurality of the output compositions is between about 40% and about 65%, between about 40% and about 45%, between about 45% and about 50%, between about 50% and about 55%, between about 55% and about 60%, or between about 60% and about 65%. In some of any examples, the predetermined feature of the output composition among the plurality of output compositions includes the mean percentage of central memory T cells, optionally CD4⁺ central memory T cells and CD8⁺ central memory T cells, in the engineered T cells, optionally CAR+ T cells, of the plurality of the output compositions is between about 40% and about 65%, between about 40% and about 45%, between about 45% and about 50%, between about 50% and about 55%, between about 55% and about 60%, or between about 60% and about 65%.

[0102] In some of any of the methods or uses provided herein, the administered dose is produced by a method to produce an output composition exhibiting a predetermined feature, optionally a threshold number of cells expressing the CAR in the output composition, in at least about 80%, about 90%, about 95%, about 97%, about 99%, about 100%, or is 100% of the human biological samples in which it is carried out among a plurality of different individual subjects. In some of any examples, the plurality of different individual subject comprise subjects having a disease or condition. In some of any examples, the disease or condition is a cancer. In some of any examples, the cancer is a hematological cancer, optionally multiple myeloma. In some examples, the cancer is relapsed or refractory multiple myeloma (R/R MM).

Brief Description of the Drawings

[0103] FIGS. 1A-1B depict results of an assay assessing RNA heterogeneity as assessed by agarose gel electrophoresis. **FIG. 1A** depicts the RNA heterogeneity of several anti-BCMA-CARs, containing a long spacer (LS) region, or a shorter CD28 spacer region. **FIG. 1B** depicts RNA heterogeneity of three different anti-BCMA CAR encoding sequences, containing the long spacer (LS) region, before and after coding sequence optimization and splice site elimination (O/SSE).

[0104] FIG. 2 depicts results of an assay assessing levels of BCMA-LS CAR expression on the surface of transduced T cells before (Non-SSE) and after (O/SSE) optimization and splice site elimination of the coding sequence.

[0105] FIG. 3 depicts the comparison of transduction efficiency of lentiviral vectors encoding

CLAIMS

WHAT IS CLAIMED:

1. A dose of engineered T cells comprising a chimeric antigen receptor (CAR) for use in the treatment of a subject having or suspected of having multiple myeloma (MM), the CAR comprising:
 - (a) an extracellular antigen-binding domain, comprising:
 - a variable heavy chain (V_H) comprising a heavy chain complementarity determining region 1 (CDR-H1), a heavy chain complementarity determining region 2 (CDR-H2) and a heavy chain complementarity determining region 3 (CDR-H3) contained within the sequence set forth in SEQ ID NO: 116 and a variable light chain (V_L) comprising a light chain complementarity determining region 1 (CDR-L1), a light chain complementarity determining region 2 (CDR-L2) and a light chain complementarity determining region 3 (CDR-L3) contained within the sequence set forth in SEQ ID NO: 119;
 - a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:97, 101 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively;
 - a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:96, 100 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively;
 - a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:95, 99 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 105, 107 and 108, respectively;
 - a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:94, 98 and 102, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 104, 106 and 108, respectively; or
 - a V_H comprising the amino acid sequence of SEQ ID NO: 116 and a V_L comprising the amino acid sequence of SEQ ID NO: 119;
 - (b) a spacer comprising an IgG4/2 chimeric hinge or a modified IgG4 hinge; an IgG2/4 chimeric C_H2 region; and an IgG4 C_H3 region; or a spacer set forth in SEQ ID NO: 174;
 - (c) a transmembrane domain; and
 - (d) an intracellular signaling region comprising a cytoplasmic signaling domain of a CD3-zeta ($CD3\zeta$) chain and a costimulatory signaling region comprising an intracellular signaling domain of a T cell costimulatory molecule or a signaling portion thereof;

wherein, prior to the treatment, the subject has received a lymphodepleting therapy comprising the

administration of fludarabine at or about 20-40 mg/m² body surface area of the subject.

2. A dose of engineered T cells comprising a chimeric antigen receptor (CAR) for use in the treatment of a subject having or suspected of having multiple myeloma (MM), the CAR comprising:

(a) an extracellular antigen-binding domain, comprising:

a variable heavy chain (V_H) comprising a heavy chain complementarity determining region 1 (CDR-H1), a heavy chain complementarity determining region 2 (CDR-H2) and a heavy chain complementarity determining region 3 (CDR-H3) contained within the sequence set forth in SEQ ID NO: 116 and a variable light chain (V_L) comprising a light chain complementarity determining region 1 (CDR-L1), a light chain complementarity determining region 2 (CDR-L2) and a light chain complementarity determining region 3 (CDR-L3) contained within the sequence set forth in SEQ ID NO: 119;

a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:97, 101 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively;

a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:96, 100 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively;

a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:95, 99 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 105, 107 and 108, respectively;

a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:94, 98 and 102, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 104, 106 and 108, respectively; or

a V_H comprising the amino acid sequence of SEQ ID NO: 116 and a V_L comprising the amino acid sequence of SEQ ID NO: 119;

(b) a spacer comprising an IgG4/2 chimeric hinge or a modified IgG4 hinge; an IgG2/4 chimeric C_H2 region; and an IgG4 C_H3 region; or a spacer set forth in SEQ ID NO: 174;

(c) a transmembrane domain; and

(d) an intracellular signaling region comprising a cytoplasmic signaling domain of a CD3-zeta (CD3ζ) chain and a costimulatory signaling region comprising an intracellular signaling domain of a T cell costimulatory molecule or a signaling portion thereof; wherein at or prior to the treatment, the subject has received three or more therapies selected from among:

autologous stem cell transplant (ASCT);

an immunomodulatory agent;
a proteasome inhibitor; and
an anti-CD38 antibody; unless the subject was not a candidate for or was contraindicated for one or more of the therapies.

3. A dose of engineered T cells comprising a chimeric antigen receptor (CAR) for use in the treatment of a subject having or suspected of having multiple myeloma (MM), the CAR comprising:

(a) an extracellular antigen-binding domain, comprising:

a variable heavy chain (V_H) comprising a heavy chain complementarity determining region 1 (CDR-H1), a heavy chain complementarity determining region 2 (CDR-H2) and a heavy chain complementarity determining region 3 (CDR-H3) contained within the sequence set forth in SEQ ID NO: 116 and a variable light chain (V_L) comprising a light chain complementarity determining region 1 (CDR-L1), a light chain complementarity determining region 2 (CDR-L2) and a light chain complementarity determining region 3 (CDR-L3) contained within the sequence set forth in SEQ ID NO: 119;

a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:97, 101 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively;

a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:96, 100 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively;

a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:95, 99 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 105, 107 and 108, respectively;

a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:94, 98 and 102, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 104, 106 and 108, respectively; or

a V_H comprising the amino acid sequence of SEQ ID NO: 116 and a V_L comprising the amino acid sequence of SEQ ID NO: 119;

(b) a spacer comprising an IgG4/2 chimeric hinge or a modified IgG4 hinge; an IgG2/4 chimeric C_H2 region; and an IgG4 C_H3 region; or a spacer set forth in SEQ ID NO: 174;

(c) a transmembrane domain; and

(d) an intracellular signaling region comprising a cytoplasmic signaling domain of a CD3-zeta ($CD3\zeta$) chain and a costimulatory signaling region comprising an intracellular signaling domain of a T cell

costimulatory molecule or a signaling portion thereof; wherein at the time of treatment, the subject has not had an active or a history of plasma cell leukemia (PCL).

4. A dose of engineered T cells comprising a chimeric antigen receptor (CAR) for use in the treatment of a subject having or suspected of having multiple myeloma (MM), the CAR comprising:

(a) an extracellular antigen-binding domain, comprising:

a variable heavy chain (V_H) comprising a heavy chain complementarity determining region 1 (CDR-H1), a heavy chain complementarity determining region 2 (CDR-H2) and a heavy chain complementarity determining region 3 (CDR-H3) contained within the sequence set forth in SEQ ID NO: 116 and a variable light chain (V_L) comprising a light chain complementarity determining region 1 (CDR-L1), a light chain complementarity determining region 2 (CDR-L2) and a light chain complementarity determining region 3 (CDR-L3) contained within the sequence set forth in SEQ ID NO: 119;

a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:97, 101 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively;

a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:96, 100 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively;

a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:95, 99 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 105, 107 and 108, respectively;

a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:94, 98 and 102, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 104, 106 and 108, respectively; or

a V_H comprising the amino acid sequence of SEQ ID NO: 116 and a V_L comprising the amino acid sequence of SEQ ID NO: 119;

(b) a spacer comprising an IgG4/2 chimeric hinge or a modified IgG4 hinge; an IgG2/4 chimeric C_H2 region; and an IgG4 C_H3 region; or a spacer set forth in SEQ ID NO: 174;

(c) a transmembrane domain; and

(d) an intracellular signaling region comprising a cytoplasmic signaling domain of a CD3-zeta ($CD3\zeta$) chain and a costimulatory signaling region comprising an intracellular signaling domain of a T cell costimulatory molecule or a signaling portion thereof; wherein the dose of engineered T cells comprises:

between at or about 1×10^7 CAR-expressing (CAR^+) T cells and at or about 2×10^9 CAR^+

T cells;

a combination of CD4⁺ T cells and CD8⁺ T cells, at a defined ratio of CD4⁺ CAR⁺ T cells to CD8⁺ CAR⁺ T cells and/or of CD4⁺ T cells to CD8⁺ T cells, that is or is approximately 1:1 or is between at or approximately 1:3 and at or approximately 3:1; and

less than 25%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2% or 1% of the CAR⁺ T cells in the dose express a marker of apoptosis.

5. The dose for use of any of claims 1-4, wherein the extracellular antigen-binding domain binds to a B cell maturation antigen (BCMA).

6. The dose for use of any of claims 1-5, wherein the V_H is or comprises the amino acid sequence of SEQ ID NO: 116; and the V_L is or comprises the amino acid sequence of SEQ ID NO: 119.

7. The dose for use of any of claims 1-6, wherein the extracellular antigen-binding domain comprises an scFv.

8. The dose for use of any of claims 1-7, wherein the V_H is carboxy-terminal to the V_L.

9. The dose for use of any of claims 1-8, wherein the extracellular antigen-binding domain comprises the amino acid sequence of SEQ ID NO: 114 or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO: 114.

10. The dose for use of any of claims 1-9, wherein a nucleic acid encoding the extracellular antigen-binding domain comprises (a) the sequence of nucleotides of SEQ ID NO:113; (b) a sequence of nucleotides that has at least 90% sequence identity thereto; or (c) a degenerate sequence of (a) or (b).

11. The dose for use of any of claims 1-10, wherein the nucleic acid encoding the extracellular antigen-binding domain comprises the sequence of nucleotides of SEQ ID NO:115.

12. The dose for use of any of claims 1-11, wherein the cytoplasmic signaling domain is or comprises the sequence set forth in SEQ ID NO:143 or a sequence of amino acids that has at least 90% sequence identity to SEQ ID NO:143.

13. The dose for use of any of claims 1-12, wherein the costimulatory signaling region comprises an intracellular signaling domain of CD28, 4-1BB, or ICOS, or a signaling portion thereof.

14. The dose for use of any of claims 1-13, wherein the costimulatory signaling region comprises an intracellular signaling domain of 4-1BB, optionally human 4-1BB.

15. The dose for use of any of claims 1-14, wherein the costimulatory signaling region is or comprises the sequence set forth in SEQ ID NO:4 or a sequence of amino acids that has at least 90% sequence identity to the sequence set forth in SEQ ID NO: 4.

16. The dose for use of any of claims 1-15, wherein the transmembrane domain is or comprises a transmembrane domain from human CD28.

17. The dose for use of any of claims 1-16, wherein the transmembrane domain is or comprises the sequence set forth in SEQ ID NO:138 or a sequence of amino acids that has at least 90% sequence identity to SEQ ID NO:138.

18. The dose for use of any of claims 1-17, wherein the CAR comprises from its N to C terminus in order: the extracellular antigen-binding domain, the spacer, the transmembrane domain and the intracellular signaling region.

19. The dose for use of any of claims 1-18, wherein the CAR comprises:

(a) an extracellular antigen-binding domain, comprising the sequence set forth in SEQ ID NO: 114 or a sequence of amino acids having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 114;

(b) a spacer comprising the sequence set forth in SEQ ID NO: 174 or a sequence of amino acids that has at least 90% sequence identity to SEQ ID NO:174;

(c) a transmembrane domain comprising the sequence set forth in SEQ ID NO:138 or a sequence of amino acids that has at least 90% sequence identity to SEQ ID NO:138; and

(d) an intracellular signaling region comprising a cytoplasmic signaling comprising the sequence set forth in SEQ ID NO:143 or a sequence of amino acids that has at least 90% sequence identity to SEQ ID NO:143 and a costimulatory signaling region comprising the sequence set forth in SEQ ID NO:4 or a sequence of amino acids that has at least 90% sequence identity to the sequence set forth in SEQ ID NO: 4.

20. The dose for use of any of claims 1-19, wherein the CAR comprises the sequence set forth in SEQ ID NO:19.

21. The dose for use of any of claims 1-20, wherein the dose of engineered T cells comprises between at or about 1×10^7 CAR⁺ T cells and at or about 2×10^9 CAR⁺ T cells, optionally wherein the dose of engineered T cells is at or about: 5×10^7 cells or CAR⁺ T cells;

1.5×10^8 cells or CAR⁺ T cells;

3×10^8 cells or CAR⁺ T cells;

4.5×10^8 cells or CAR⁺ T cells; or

6×10^8 cells or CAR⁺ T cells.

22. The dose for use of any of claims 1-21, wherein the dose of engineered T cells comprises a combination of CD4⁺ T cells and CD8⁺ T cells, optionally

wherein the ratio of CD4⁺ CAR⁺ T cells to CD8⁺ CAR⁺ T cells and/or of CD4⁺ T cells to CD8⁺ T cells is or is approximately 1:1 or is between at or approximately 1:3 and at or approximately 3:1.

23. The dose for use of any of claims 1-22, wherein prior to the treatment, the subject has received a lymphodepleting therapy comprising the administration of fludarabine at or about 20-40 mg/m² body surface area of the subject, optionally at or about 30 mg/m², daily, for 2-4 days, and/or cyclophosphamide at or about 200-400 mg/m² body surface area of the subject, optionally at or about 300 mg/m², daily, for 2-4 days.

24. The dose for use of any of claims 1-23, wherein the subject has or is suspected of having a relapsed or refractory multiple myeloma (R/R MM).

25. The dose for use of any of claims 1-24, wherein at or prior to the treatment, the subject has received three or more prior therapies for the disease or disorder, optionally four or more prior therapies, optionally selected from among:

autologous stem cell transplant (ASCT);

an immunomodulatory agent, optionally wherein the immunomodulatory agent is selected from among thalidomide, lenalidomide and pomalidomide;

a proteasome inhibitor, optionally wherein the proteasome inhibitor is selected from among bortezomib, carfilzomib and ixazomib; and

an anti-CD38 antibody, optionally wherein the anti-CD38 antibody is or comprises daratumumab.

26. The dose for use of any of claims 2 and 5-25, wherein the subject has relapsed or been refractory following the three or more prior therapies.

27. The dose for use of any of claims 1, 2, and 4-26, wherein at the treatment and/or at the time of the lymphodepleting chemotherapy, the subject has not had an active or a history of plasma cell leukemia (PCL).

28. The dose for use of any of claims 1-27, wherein at the time of the treatment, the subject:
has developed secondary plasma cell leukemia (PCL);
has relapsed or has been refractory following at least 3 or at least 4 prior therapies for multiple myeloma;
is an adult subject or is 25 or 35 years of age or older;
has a time from diagnosis of multiple myeloma of approximately 4 years or between 2 and 15 years or between 2 and 12 years;
has received about 10 or between 3 and 15 or between 4 and 15 prior regimens for multiple myeloma;
has been refractory to or not responded to bortezomib, carfilzomib, lenalidomide, pomalidomide and/or an anti-CD38 monoclonal antibody; has had prior autologous stem cell transplant or has not had prior autologous stem cell transplant; and/or
has IMWG high risk cytogenetics.

29. The dose for use of any of claims 1-28, wherein the treatment is capable of achieving a specified response or outcome and the response or outcome is or comprises an objective response (OR) and is achieved in at least 50%, 60%, 70%, or 80% of subjects of the cohort.

30. The dose for use of any of claims 1-29, wherein:
the response or outcome is or comprises or further comprises the absence of neurotoxicity or the absence of cytokine release syndrome (CRS); and/or
the treatment does not result in a specified toxicity outcome in at least one of or in at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or

at least 95% of subjects in the cohort of subjects having the disease or disorder, optionally wherein the specified toxicity outcome is neurotoxicity and/or cytokine release syndrome (CRS).

31. The dose for use of any of claims 1-30, wherein:

at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or greater than 95% of the cells in the dose are of a memory phenotype;

at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or greater than 95% of the cells in the dose are of a central memory phenotype;

at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or greater than 95% of the cells in the dose are CD27+, CD28+, CCR7+, CD45RA-, CD45RO+, CD62L+, CD3+, granzyme B-, and/or CD127+; and/or

at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or greater than 95% of the cells in the dose are CCR7+/CD45RA- or CCR7+/CD45RO+.

32. The dose for use of any of claims 1-31, wherein

the treatment is capable of achieving, optionally at a designated time following initiation of the treatment, a specified response or outcome in at least one of, or in at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95% of subjects within a cohort of subjects or evaluable subjects thereof, wherein the cohort of subjects is a cohort having multiple myeloma.

33. The dose for use of claim 32, wherein:

the cohort of subjects is subjects having relapsed or refractory multiple myeloma;

the cohort of subjects is subjects having relapsed or refractory multiple myeloma having been administered, and relapsed or has been refractory following, at least 3 prior therapies for multiple myeloma, said prior therapies optionally including an autologous stem cell transplant (ASCT); an immunomodulatory agent; a proteasome inhibitor; and/or an anti-CD38 antibody;

the cohort of subjects is subjects having relapsed or refractory multiple myeloma having been administered, and relapsed or has been refractory following, at least 3 prior therapies for multiple myeloma, said prior therapies optionally including an immunomodulatory agent; a proteasome inhibitor; and/or an anti-

CD38 antibody and/or an autologous stem cell transplant;

the cohort of subjects is subjects having no active plasma cell leukemia (PCL) or no history of PCL at the time of said administration;

the cohort of subjects is subjects having developed secondary plasma cell leukemia (PCL) prior to administration of the cells;

the cohort of subjects is or includes subjects having relapsed or refractory multiple myeloma having been administered, and relapsed or has been refractory following, at least 4 or an average of at least 10 prior therapies for multiple myeloma.

the cohort of subjects has received a median of 10 prior regimens or between 3 and 15 or 4 and 15 prior therapies for multiple myeloma;

the cohort of subjects includes subjects refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide and an anti-CD38 monoclonal antibody; and/or

the cohort of subjects includes subjects having had prior autologous stem cell transplant.

34. The dose for use of claim 32 or claim 33, wherein:

the cohort of subjects consists of or includes adult subjects;

the cohort of subjects has a median time from diagnosis of 4 years and/or a range of time from diagnosis from 2 to 12 years; and/or

the cohort of subjects includes subjects having IMWG high risk cytogenetics.

35. The dose for use of claim 33 or claim 34, wherein the at least 3 prior therapies comprise:

autologous stem cell transplant (ASCT);

an immunomodulatory agent or a proteasome inhibitor, or a combination thereof, optionally wherein the immunomodulatory agent is selected from among thalidomide, lenalidomide and pomalidomide and/or the proteasome inhibitor is selected from among bortezomib, carfilzomib and ixazomib; and

an anti-CD38 antibody, optionally wherein the anti-CD38 antibody is or comprises daratumumab.

36. The dose for use of any of claims 32-35, wherein the response or outcome is or comprises an OR and the dose is capable of achieving the response or outcome in at least 50%, 60%, 70%, or 80% of subjects of the cohort.

37. The dose for use of any of claims 32-36, wherein the dose capable of achieving said response or outcome comprises a combination of CD4⁺ T cells and CD8⁺ T cells and/or a combination of

CD4⁺ CAR⁺ T cells and CD8⁺ CAR⁺ T cells, optionally

wherein the ratio of CD4⁺ CAR⁺ T cells to CD8⁺ CAR⁺ T cells and/or of CD4⁺ T cells to CD8⁺ T cells, is or is approximately 1:1 or is between at or approximately 1:3 and at or approximately 3:1.

38. The dose for use of any of claims 32-37, wherein the treatment does not result in a specified toxicity outcome in at least one of or in at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 90%, at least 70%, at least 80%, at least 90%, or at least 95% of subjects in the cohort of subjects having the disease or disorder, optionally wherein the specified toxicity outcome is neurotoxicity or cytokine release syndrome (CRS).

39. The dose for use of any of claims 32-38, wherein the dose capable of achieving the response or outcome is at or about 5×10^7 cells or CAR⁺ T cells; at or about 1.5×10^8 cells or CAR⁺ T cells; at or about 3×10^8 cells or CAR⁺ T cells; at or about 4.5×10^8 cells or CAR⁺ T cells; or at or about 6.0×10^8 cells or CAR⁺ T cells.

40. The dose for use of any of claims 32-39, wherein:
at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or greater than 95% of the cells in the dose are of a memory phenotype

; at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or greater than 95% of the cells in the dose are of a central memory phenotype;

at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or greater than 95% of the cells in the dose are CD27⁺, CD28⁺, CCR7⁺, CD45RA⁻, CD45RO⁺, CD62L⁺, CD3⁺, granzyme B⁻, and/or CD127⁺; and/or

at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or greater than 95% of the cells in the dose are CCR7⁺/CD45RA⁻ or CCR7⁺/CD45RO⁺.

41. Use of a dose of engineered T cells comprising a chimeric antigen receptor (CAR) in the manufacture of a medicament for the treatment of a subject having or suspected of having multiple myeloma (MM), wherein the CAR comprises:

(a) an extracellular antigen-binding domain, comprising:

a variable heavy chain (V_H) comprising a heavy chain complementarity determining region 1 (CDR-H1), a heavy chain complementarity determining region 2 (CDR-H2) and a heavy chain complementarity determining region 3 (CDR-H3) contained within the sequence set forth in SEQ ID NO: 116 and a variable light chain (V_L) comprising a light chain complementarity determining region 1 (CDR-L1), a light chain complementarity determining region 2 (CDR-L2) and a light chain complementarity determining region 3 (CDR-L3) contained within the sequence set forth in SEQ ID NO: 119;

a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:97, 101 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively;

a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:96, 100 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively;

a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:95, 99 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 105, 107 and 108, respectively;

a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:94, 98 and 102, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 104, 106 and 108, respectively; or

a V_H comprising the amino acid sequence of SEQ ID NO: 116 and a V_L comprising the amino acid sequence of SEQ ID NO: 119;

(b) a spacer comprising an IgG4/2 chimeric hinge or a modified IgG4 hinge; an IgG2/4 chimeric C_{H2} region; and an IgG4 C_{H3} region; or a spacer set forth in SEQ ID NO: 174;

(c) a transmembrane domain; and

(d) an intracellular signaling region comprising a cytoplasmic signaling domain of a CD3-zeta ($CD3\zeta$) chain and a costimulatory signaling region comprising an intracellular signaling domain of a T cell costimulatory molecule or a signaling portion thereof;

wherein, prior to receiving the medicament, the subject has received a lymphodepleting therapy comprising the administration of fludarabine at or about 20–40 mg/m² body surface area of the subject.

42. Use of a dose of engineered T cells comprising a chimeric antigen receptor (CAR) in the manufacture of a medicament for the treatment of a subject having or suspected of having multiple myeloma (MM), wherein the CAR comprises:

(a) an extracellular antigen-binding domain, comprising:

a variable heavy chain (V_H) comprising a heavy chain complementarity determining region 1 (CDR-H1), a heavy chain complementarity determining region 2 (CDR-H2) and a heavy chain complementarity determining region 3 (CDR-H3) contained within the sequence set forth in SEQ ID NO: 116 and a variable light chain (V_L) comprising a light chain complementarity determining region 1 (CDR-L1), a light chain complementarity determining region 2 (CDR-L2) and a light chain complementarity determining region 3 (CDR-L3) contained within the sequence set forth in SEQ ID NO: 119;

a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:97, 101 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively;

a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:96, 100 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively;

a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:95, 99 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 105, 107 and 108, respectively;

a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:94, 98 and 102, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 104, 106 and 108, respectively; or

a V_H comprising the amino acid sequence of SEQ ID NO: 116 and a V_L comprising the amino acid sequence of SEQ ID NO: 119;

(b) a spacer comprising an IgG4/2 chimeric hinge or a modified IgG4 hinge; an IgG2/4 chimeric C_H2 region; and an IgG4 C_H3 region; or a spacer set forth in SEQ ID NO: 174;

(c) a transmembrane domain; and

(d) an intracellular signaling region comprising a cytoplasmic signaling domain of a CD3-zeta (CD3ζ) chain and a costimulatory signaling region comprising an intracellular signaling domain of a T cell costimulatory molecule or a signaling portion thereof; wherein at or prior to receiving the medicament, the subject has received three or more therapies selected from among:

autologous stem cell transplant (ASCT);

an immunomodulatory agent;

a proteasome inhibitor; and

an anti-CD38 antibody; unless the subject was not a candidate for or was contraindicated for one or more of the therapies.

43. Use of a dose of engineered T cells comprising a chimeric antigen receptor (CAR) in the manufacture of a medicament for the treatment of a subject having or suspected of having multiple myeloma (MM), wherein the CAR comprises:

(a) an extracellular antigen-binding domain, comprising:

a variable heavy chain (V_H) comprising a heavy chain complementarity determining region 1 (CDR-H1), a heavy chain complementarity determining region 2 (CDR-H2) and a heavy chain complementarity determining region 3 (CDR-H3) contained within the sequence set forth in SEQ ID NO: 116 and a variable light chain (V_L) comprising a light chain complementarity determining region 1 (CDR-L1), a light chain complementarity determining region 2 (CDR-L2) and a light chain complementarity determining region 3 (CDR-L3) contained within the sequence set forth in SEQ ID NO: 119;

a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:97, 101 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively;

a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:96, 100 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively;

a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:95, 99 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 105, 107 and 108, respectively;

a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:94, 98 and 102, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 104, 106 and 108, respectively; or

a V_H comprising the amino acid sequence of SEQ ID NO: 116 and a V_L comprising the amino acid sequence of SEQ ID NO: 119;

(b) a spacer comprising an IgG4/2 chimeric hinge or a modified IgG4 hinge; an IgG2/4 chimeric C_H2 region; and an IgG4 C_H3 region; or a spacer set forth in SEQ ID NO: 174;

(c) a transmembrane domain; and

(d) an intracellular signaling region comprising a cytoplasmic signaling domain of a CD3-zeta ($CD3\zeta$) chain and a costimulatory signaling region comprising an intracellular signaling domain of a T cell costimulatory molecule or a signaling portion thereof; wherein at the time of receiving the medicament, the subject has not had active or history of plasma cell leukemia (PCL).

44. Use of a dose of engineered T cells comprising a chimeric antigen receptor (CAR) in the

manufacture of a medicament for treatment of a subject having or suspected of having multiple myeloma (MM), wherein the CAR comprises:

(a) an extracellular antigen-binding domain, comprising:

a variable heavy chain (V_H) comprising a heavy chain complementarity determining region 1 (CDR-H1), a heavy chain complementarity determining region 2 (CDR-H2) and a heavy chain complementarity determining region 3 (CDR-H3) contained within the sequence set forth in SEQ ID NO: 116 and a variable light chain (V_L) comprising a light chain complementarity determining region 1 (CDR-L1), a light chain complementarity determining region 2 (CDR-L2) and a light chain complementarity determining region 3 (CDR-L3) contained within the sequence set forth in SEQ ID NO: 119;

a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:97, 101 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively;

a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:96, 100 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS:105, 107 and 108, respectively;

a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:95, 99 and 103, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 105, 107 and 108, respectively;

a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS:94, 98 and 102, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 104, 106 and 108, respectively; or

a V_H comprising the amino acid sequence of SEQ ID NO: 116 and a V_L comprising the amino acid sequence of SEQ ID NO: 119;

(b) a spacer comprising an IgG4/2 chimeric hinge or a modified IgG4 hinge; an IgG2/4 chimeric C_{H2} region; and an IgG4 C_{H3} region; or a spacer set forth in SEQ ID NO: 174;

(c) a transmembrane domain; and

(d) an intracellular signaling region comprising a cytoplasmic signaling domain of a CD3-zeta ($CD3\zeta$) chain and a costimulatory signaling region comprising an intracellular signaling domain of a T cell costimulatory molecule or a signaling portion thereof; wherein the medicament is formulated for administration of:

between at or about 1×10^7 CAR⁺ T cells and 2×10^9 CAR⁺ T cells;

a combination of CD4⁺ T cells and CD8⁺ T cells, at a defined ratio of CD4⁺ CAR⁺ T cells to CD8⁺ CAR⁺ T cells and/or of CD4⁺ T cells to CD8⁺ T cells, that is or is approximately 1:1 or is

between approximately 1:3 and approximately 3:1; and

wherein less than 25%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2% or 1% of the CAR⁺ T cells in the dose express a marker of apoptosis.

45. The use of any of claims 41-44, wherein the extracellular antigen-binding domain specifically binds to a B cell maturation antigen (BCMA).

46. The use of any of claims 41-45, wherein the V_H is or comprises the amino acid sequence of SEQ ID NO: 116; and the V_L is or comprises the amino acid sequence of SEQ ID NO: 119.

47. The use of any of claims 41-46, wherein the CAR comprises:

(a) an extracellular antigen-binding domain, comprising the sequence set forth in SEQ ID NO: 114 or a sequence of amino acids having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 114;

(b) a spacer comprising the sequence set forth in SEQ ID NO: 174 or a sequence of amino acids that has at least 90% sequence identity to SEQ ID NO:174;

(c) a transmembrane domain comprising the sequence set forth in SEQ ID NO:138 or a sequence of amino acids that has at least 90% sequence identity to SEQ ID NO:138; and

(d) an intracellular signaling region comprising a cytoplasmic signaling comprising the sequence set forth in SEQ ID NO:143 or a sequence of amino acids that has at least 90% sequence identity to SEQ ID NO:143 and a costimulatory signaling region comprising the sequence set forth in SEQ ID NO:4 or a sequence of amino acids that has at least 90% sequence identity to the sequence set forth in SEQ ID NO: 4.

48. The use of any of claims 41-47, wherein the CAR comprises the sequence set forth in SEQ ID NO:19.

49. The use of any of claims 41-48, wherein the medicament is formulated for administration of between at or about 1×10^7 CAR⁺ T cells and at or about 2×10^9 CAR⁺ T cells, optionally

wherein the medicament is formulated for administration of at or about 5×10^7 cells or CAR⁺ T cells, at or about 1.5×10^8 cells or CAR⁺ T cells, at or about 3×10^8 cells or CAR⁺ T cells, at or about 4.5×10^8 cells or CAR⁺ T cells, or at or about 6×10^8 cells or CAR⁺ T cells.

50. The use of any of claims 41-49, wherein the medicament is formulated for administration of a combination of CD4⁺ T cells and CD8⁺ T cells and/or a combination of CD4⁺ CAR⁺ T cells and CD8⁺ CAR⁺ T cells, optionally

wherein the ratio of CD4⁺ CAR⁺ T cells to CD8⁺ CAR⁺ T cells and/or of CD4⁺ T cells to CD8⁺ T cells is or is approximately 1:1 or is between at or approximately 1:3 and at or approximately 3:1.

51. The use of any of claims 41-51, wherein:

at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or greater than 95% of the cells in the dose are of a memory phenotype;

at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or greater than 95% of the cells in the dose are of a central memory phenotype;

at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or greater than 95% of the cells in the dose are CD27⁺, CD28⁺, CCR7⁺, CD45RA⁻, CD45RO⁺, CD62L⁺, CD3⁺, granzyme B⁻, and/or CD127⁺; and/or

at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or greater than 95% of the cells in the dose are CCR7⁺/CD45RA⁻ or CCR7⁺/CD45RO⁺.