

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, wherein the extracellular antigen-binding domain binds to a B cell maturation antigen (BCMA), comprising: a variable heavy chain (V_H) comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NO:97, 101 and 103, respectively, and a variable light chain (V_L) comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NO:105, 107 and 108, respectively; (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; (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, wherein the extracellular antigen-binding domain binds to a B cell maturation antigen (BCMA), comprising:

a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NO: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 NO:105, 107 and 108, respectively; (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; (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, wherein the extracellular antigen-binding domain binds to a B cell maturation antigen (BCMA), comprising: a variable heavy chain (V_H) comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NO:97, 101 and 103, respectively, and a variable light chain (V_L) comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NO:105, 107 and 108, respectively; (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; (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, wherein the extracellular antigen-binding domain binds to a B cell maturation antigen (BCMA), comprising: a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NO: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 NO:105, 107 and 108, respectively; (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; (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, wherein the extracellular antigen-binding domain binds to a B cell maturation antigen (BCMA), comprising: a variable heavy chain (V_H) comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NO:97, 101 and 103, respectively, and a variable light chain (V_L) comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NO:105, 107 and 108, respectively; (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; (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, wherein the extracellular antigen-binding domain binds to a B cell maturation antigen (BCMA), comprising: a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NO: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 NO:105, 107 and 108, respectively; (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; (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, wherein the extracellular antigen-binding domain binds to a B cell maturation antigen (BCMA), comprising: a variable heavy chain (V_H) comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NO:97, 101 and 103, respectively, and a variable light chain (V_L) comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NO:105, 107 and 108, respectively; (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; (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, wherein the extracellular antigen-binding domain binds to a B cell maturation antigen (BCMA), comprising:

a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NO: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 NO:105, 107 and 108, respectively; (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; (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 medicament is formulated for administration of: between at or about 1 x 10⁷ CAR⁺ T cells and 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 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.

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 suspect of having multiple myeloma (MM), the CAR comprising:
 - (a) an extracellular antigen-binding domain, wherein the extracellular antigen-binding domain binds to a B cell maturation antigen (BCMA), comprising:
 - a variable heavy chain (V_H) comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NO:97, 101 and 103, respectively, and a variable light chain (V_L) comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NO:105, 107 and 108, respectively;
 - (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;
 - (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, wherein the extracellular antigen-binding domain binds to a B cell maturation antigen (BCMA), comprising:
 - a variable heavy chain (V_H) comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NO:97, 101 and 103, respectively, and a variable light chain (V_L) comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NO:105, 107 and 108, respectively;
 - (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;
 - (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 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, wherein the extracellular antigen-binding domain binds to a B cell maturation antigen (BCMA), comprising: a variable heavy chain (V_H) comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NO:97, 101 and 103, respectively, and a variable light chain (V_L) comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NO:105, 107 and 108, respectively;

(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;

(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, wherein the extracellular antigen-binding domain binds to a B cell maturation antigen (BCMA), comprising: a variable heavy chain (V_H) comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NO:97, 101 and 103, respectively, and a variable light chain (V_L) comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NO:105, 107 and 108, respectively;

(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;

(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 spacer comprises the sequence set forth in SEQ ID NO: 174.

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; or (b) a sequence of nucleotides that has at least 90% sequence identity thereto.

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.

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.

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.

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;
- (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 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.

21. The dose for use of any of claims 1-20, wherein the CAR is encoded by a polynucleotide sequence comprising the sequence set forth in SEQ ID NO: 13.

22. The dose for use of any of claims 1-21, wherein the CAR comprises the sequence set forth in SEQ ID NO:19.

23. The dose for use of any of claims 1-22, 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 x 10^7 cells or CAR+ T cells;
- 1.5 x 10^8 cells or CAR+ T cells;
- 3 x 10^8 cells or CAR+ T cells;
- 4.5 x 10^8 cells or CAR+ T cells; or
- 6 x 10^8 cells or CAR+ T cells.

24. The dose for use of any of claims 1-23, 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.

25. The dose for use of any of claims 1-24, 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.

26. The dose for use of any of claims 1-25, wherein the subject has or is suspected of having a relapsed or refractory multiple myeloma (R/R MM).

27. The dose for use of any of claims 1-26, 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.

28. The dose for use of any of claims 2 and 5-27, wherein the subject has relapsed or been refractory following the three or more prior therapies.

29. The dose for use of any of claims 1, 2, and 4-28, 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).

30. The dose for use of any of claims 1-29, 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.

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

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

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

the treatment is capable of achieving 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.

34. The dose for use of claim 33, 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.

35. The dose for use of claim 33 or claim 34, 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.

36. The dose for use of claim 34 or claim 35, 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.

37. The dose for use of any of claims 33-36, 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.

38. The dose for use of any of claims 33-37, 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.

39. The dose for use of any of claims 33-38, 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).

40. The dose for use of any of claims 33-39, 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.

41. The dose for use of any of claims 33-40, 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⁺.

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, wherein the extracellular antigen-binding domain binds to a B cell maturation antigen (BCMA), comprising: a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NO: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 NO:105, 107 and 108, respectively;

(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;

(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.

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, wherein the extracellular antigen-binding domain binds to a B cell maturation antigen (BCMA), comprising: a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NO: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 NO:105, 107 and 108, respectively;

(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;

(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.

44. 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, wherein the extracellular antigen-binding domain binds to a B cell maturation antigen (BCMA), comprising: a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NO: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 NO:105, 107 and 108, respectively;

(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;

(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).

45. 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, wherein the extracellular antigen-binding domain binds to a B cell maturation antigen (BCMA), comprising: a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NO: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 NO:105, 107 and 108, respectively;

(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;

(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.

46. The use of any of claims 42-45, wherein the spacer comprises the sequence set forth in SEQ ID NO: 174.

47. The use of any of claims 42-46, 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.

48. The use of any of claims 42-47, 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.

49. The use of any of claims 42-48, wherein the CAR comprises the sequence set forth in SEQ ID NO:19.

50. The use of any of claims 42-49, 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.

51. The use of any of claims 42-50, 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.

52. The use of any of claims 42-51, 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⁺.