BCMA-DIRECTED CHIMERIC ANTIGEN RECEPTOR T CELL COMPOSITIONS AND METHODS AND USES THEREOF

Cross-Reference to Related Applications

[0001] This application claims priority from U.S. provisional application No. 62/975,731 filed February 12, 2020, entitled "BCMA-DIRECTED CHIMERIC ANTIGEN RECEPTOR T CELL COMPOSITIONS AND METHODS AND USES THEREOF," the contents of which are incorporated by reference in their entirety.

Incorporation by Reference of Sequence Listing

[0002] The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled 735042023540SEQLIST.txt, created February 10, 2021, which is 184 kilobytes in size. The information in the electronic format of the Sequence Listing is incorporated by reference in its entirety.

Field

[0003] The present disclosure relates in some aspects to adoptive cell therapy involving the administration of compositions of cells for treating subjects with disease and conditions such as multiple myeloma (MM), and related methods, compositions, uses and articles of manufacture.

Background

[0004] Various immunotherapy and/or cell therapy methods are available for treating diseases and conditions. For example, adoptive cell therapies (including those involving the administration of cells expressing chimeric receptors specific for a disease or disorder of interest, such as chimeric antigen receptors (CARs) and/or other recombinant antigen receptors, as well as other adoptive immune cell and adoptive T cell therapies) can be beneficial in the treatment of cancer or other diseases or disorders. Improved approaches are needed. Provided are methods, uses and articles of manufacture that meet such needs.

Summary

[0005] In one example, provided herein is a method of treating a multiple myeloma (MM), the method comprising administering to a subject having or suspected of having a MM a composition comprising engineered T cells expressing a chimeric antigen receptor (CAR) that targets B cell maturation antigen

(BCMA), wherein: the composition comprises $CD4^+$ T cells expressing the CAR and $CD8^+$ T cells expressing the CAR; the composition comprises between at or about 5×10^6 CAR-expressing T cells and at or about 200×10^6 CAR-expressing T cells, inclusive; and at least or at least about 80% of the cells in the composition are $CD3^+$ cells.

[0006] In one example, provided herein is a method of treating a multiple myeloma (MM), the method comprising administering to a subject having or suspected of having a MM a composition comprising engineered T cells expressing a chimeric antigen receptor (CAR) that targets B cell maturation antigen (BCMA), wherein: the composition comprises $CD4^+$ T cells expressing the CAR and $CD8^+$ T cells expressing the CAR at a ratio between about 1:2.5 and about 5:1; the composition comprises between at or about 5×10^6 CAR-expressing T cells and at or about 200×10^6 CAR-expressing T cells, inclusive; and at least or at least about 90% of the cells in the composition are $CD3^+$ cells.

[0007] In one example, provided herein is a method of treating a multiple myeloma (MM), the method comprising administering to a subject having or suspected of having a MM a composition comprising engineered T cells expressing a chimeric antigen receptor (CAR) that targets B cell maturation antigen (BCMA), wherein: the composition comprises $CD8^+$ T cells expressing the CAR and $CD4^+$ T cells expressing the CAR; the composition comprises between at or about 5×10^6 CAR-expressing T cells and at or about 200×10^6 CAR-expressing T cells, inclusive; at least or at least about 80% of the cells in the composition are $CD3^+$ cells; and at least or at least about 80% of the CAR^+ T cells in the composition are of a naïve-like or central memory phenotype.

[0007a] In one aspect, the present dislcosure refers to use of a composition comprising engineered T cells expressing a chimeric antigen receptor (CAR) that targets B cell maturation antigen (BCMA), in the manufacture of a medicament for treating a multiple myeloma (MM) in a subject having a MM, wherein: the composition comprises $CD8^+$ T cells expressing the CAR and $CD4^+$ T cells expressing the CAR; the composition comprises between at or about 5 × 106 CAR-expressing T cells and at or about 80×10^6 CAR-expressing T cells, inclusive;at least or at least about 80% of the cells in the composition are $CD3^+$ cells; and at least or at least about 80% of the CAR^+ T cells in the composition are of a naïve-like or central memory phenotype.

[0008] In one example, provided herein is a method of treating a multiple myeloma (MM), the method comprising administering to a subject having or suspected of having a MM a composition comprising engineered T cells expressing a chimeric antigen receptor (CAR) that targets B cell maturation antigen (BCMA), wherein: the composition comprises $CD8^+$ T cells expressing the CAR and $CD4^+$ T cells expressing the CAR; the composition comprises between at or about 5×10^6 CAR-expressing T cells and at or about 200×10^6 CAR-expressing T cells, inclusive; at least or at least about 80% of the cells in the composition are $CD3^+$ cells; and at least or at least about 50% of the $CD4^+CAR^+$ T cells in the composition are $CD27^+CCR7^+$ and/or at least or at least about 50% of the $CD8^+CAR^+$ T cells in the composition are $CD27^+CCR7^+$.

[0008a] In one aspect, the present disclosure refers to use of a composition comprising engineered T cells expressing a chimeric antigen receptor (CAR) that targets B cell maturation antigen (BCMA), in the manufacture of a medicament for treating a multiple myeloma (MM) in a subject having a MM, wherein: the composition comprises $CD8^+$ T cells expressing the CAR and $CD4^+$ T cells expressing the CAR; the composition comprises between at or about 5×10^6 CAR-expressing T cells and at or about 100×10^6 CAR-expressing T cells, inclusive; at least or at least about 80% of the cells in the composition are $CD3^+$ cells; and at least or at least about 50% of the $CD4^+CAR^+$ T cells in the composition are $CD27^+CCR7^+$ and/or at least or at least about 50% of the $CD8^+CAR^+$ T cells in the composition are $CD27^+CCR7^+$.

[0009] In one example, provided herein is a method of treating a multiple myeloma (MM), the method comprising administering to a subject having or suspected of having a MM a composition comprising engineered T cells expressing a chimeric antigen receptor (CAR) that targets B cell maturation antigen (BCMA), wherein: the composition comprises $CD8^+$ T cells expressing the CAR and $CD4^+$ T cells expressing the CAR; the composition comprises between at or about 5×10^6 CAR-expressing T cells and at or about 200×10^6 CAR-expressing T cells, inclusive; at least or at least about 80% of the cells in the

composition are $CD3^+$ cells; and the fraction of integrated vector copy number (iVCN) to total VCN in the CAR^+ T cells in the composition, on average, is less than or less than about 0.9.

[0010] In one example, provided herein is a method of treating a multiple myeloma (MM), the method comprising administering to a subject having or suspected of having a MM a composition comprising engineered T cells expressing a chimeric antigen receptor (CAR) that targets B cell maturation antigen (BCMA), wherein: the composition comprises $CD8^+$ T cells expressing the CAR and $CD4^+$ T cells expressing the CAR; the composition comprises between at or about 5×10^6 CAR-expressing T cells and at or about 200×10^6 CAR-expressing T cells, inclusive; at least or at least about 80% of the cells in the composition are $CD3^+$ cells; and the integrated vector copy number (iVCN) of the CAR^+ T cells in the composition, on average, is between or between about 0.4 copies per diploid genome and 2.0 copies per diploid genome, inclusive.

[0011] In some of any examples, the composition comprises between at or about 50×10^6 CAR-expressing T cells and at or about 200×10^6 CAR-expressing T cells, inclusive. In some of any examples, the composition comprises between at or about 70×10^6 CAR-expressing T cells and at or about 200×10^6 CAR-expressing T cells, inclusive. In some of any examples, the composition comprises between at or about 80×10^6 CAR-expressing T cells and at or about 200×10^6 CAR-expressing T cells, inclusive. In some of any examples, the composition comprises between at or about 80×10^6 CAR-expressing T cells and at or about 160×10^6 CAR-expressing T cells, inclusive.

[0012] In one example, provided herein is a method of treating a multiple myeloma (MM), the method including administering to a subject having or suspected of having a MM a composition including engineered T cells expressing a chimeric antigen receptor (CAR) that targets B cell maturation antigen (BCMA), wherein the composition includes $CD4^+$ T cells expressing the CAR and $CD8^+$ T cells expressing the CAR; the composition includes between at or about 5×10^6 CAR-expressing T cells and at or about 40×10^6 CAR-expressing T cells, inclusive; and at least or at least about 80% of the cells in the composition are $CD3^+$ cells.

[0013] In one example, provided herein is a method of treating a multiple myeloma (MM), the method including administering to a subject having or suspected of having a MM a composition including engineered T cells expressing a chimeric antigen receptor (CAR) that targets B cell maturation antigen (BCMA), wherein the composition includes $CD4^+$ T cells expressing the CAR and $CD8^+$ T cells expressing the CAR at a ratio between about 1:2.5 and about 5:1; the composition includes between at or about 5×10^6 CAR-expressing T cells and at or about 80×10^6 CAR-expressing T cells, inclusive; at least or at least about 90% of the cells in the composition are $CD3^+$ cells.

[0014] In one example, provided herein is a method of treating a multiple myeloma (MM), the method including administering to a subject having or suspected of having a MM a composition including engineered T cells expressing a chimeric antigen receptor (CAR) that targets B cell maturation antigen

(BCMA), wherein the composition includes $CD4^+$ T cells expressing the CAR and $CD8^+$ T cells expressing the CAR; the composition includes between at or about 5×10^6 CAR-expressing T cells and at or about 10×10^6 CAR-expressing T cells, inclusive; and at least or at least about 80% of the cells in the composition are $CD3^+$ cells.

[0015] In one example, provided herein is a method of treating a multiple myeloma (MM), the method including administering to a subject having or suspected of having a MM a composition including engineered T cells expressing a chimeric antigen receptor (CAR) that targets B cell maturation antigen (BCMA), wherein the composition includes $CD8^+$ T cells expressing the CAR and $CD4^+$ T cells expressing the CAR; the composition includes between at or about 5×10^6 CAR-expressing T cells and at or about 80×10^6 CAR-expressing T cells, inclusive; at least or at least about 80% of the cells in the composition are $CD3^+$ cells; and at least or at least about 80% of the CAR^+ T cells in the composition are of a naïve-like or central memory phenotype.

[0016] In one example, provided herein is a method of treating a multiple myeloma (MM), the method including administering to a subject having or suspected of having a MM a composition including engineered T cells expressing a chimeric antigen receptor (CAR) that targets B cell maturation antigen (BCMA), wherein the composition includes $CD8^+$ T cells expressing the CAR and $CD4^+$ T cells expressing the CAR; the composition includes between at or about 5×10^6 CAR-expressing T cells and at or about 100×10^6 CAR-expressing T cells, inclusive; at least or at least about 80% of the cells in the composition are $CD3^+$ cells; and at least or at least about 50% of the $CD4^+CAR^+$ T cells in the composition are $CD27^+CCR7^+$ and/or at least or at least about 50% of the $CD8^+CAR^+$ T cells in the composition are $CD27^+CCR7^+$.

[0017] In one example, provided herein is a method of treating a multiple myeloma (MM), the method including administering to a subject having or suspected of having a MM a composition including engineered T cells expressing a chimeric antigen receptor (CAR) that targets B cell maturation antigen (BCMA), wherein the composition includes $CD8^+$ T cells expressing the CAR and $CD4^+$ T cells expressing the CAR; the composition includes between at or about 5×10^6 CAR-expressing T cells and at or about 20×10^6 CAR-expressing T cells, inclusive; at least or at least about 80% of the cells in the composition are $CD3^+$ cells; and at least or at least about 80% of the CAR^+ T cells in the composition are of a naïve-like or central memory phenotype.

[0018] In one example, provided herein is a method of treating a multiple myeloma (MM), the method including administering to a subject having or suspected of having a MM a composition including engineered T cells expressing a chimeric antigen receptor (CAR) that targets B cell maturation antigen (BCMA), wherein the composition includes $CD8^+$ T cells expressing the CAR and $CD4^+$ T cells expressing the CAR; the composition includes between at or about 5×10^6 CAR-expressing T cells and at or about 80×10^6 CAR-expressing T cells, inclusive; at least or at least about 80% of the cells in the

composition are $CD3^+$ cells; and the fraction of integrated vector copy number (iVCN) to total VCN in the CAR^+ T cells in the composition, on average, is less than or less than about 0.9.

[0019] In one example, provided herein is a method of treating a multiple myeloma (MM), the method including administering to a subject having or suspected of having a MM a composition including engineered T cells expressing a chimeric antigen receptor (CAR) that targets B cell maturation antigen (BCMA), wherein the composition includes $CD8^+$ T cells expressing the CAR and $CD4^+$ T cells expressing the CAR; the composition includes between at or about 5×10^6 CAR-expressing T cells and at or about 80×10^6 CAR-expressing T cells, inclusive; at least or at least about 80% of the cells in the composition are $CD3^+$ cells; and the integrated vector copy number (iVCN) of the CAR^+ T cells in the composition, on average, is between or between about 0.4 copies per diploid genome and 2.0 copies per diploid genome, inclusive.

[0020] In some of any examples, the composition comprises $CD4^+$ T cells expressing the CAR and $CD8^+$ T cells expressing the CAR at a ratio between about 1:2.5 and about 5:1. In some of any examples, the composition comprises between at or about 5×10^6 CAR-expressing T cells and at or about 80×10^6 CAR-expressing T cells, inclusive. In some of any examples, the composition comprises between at or about 5×10^6 CAR-expressing T cells and at or about 40×10^6 CAR-expressing T cells, inclusive. In some of any examples, the composition comprises between at or about 5×10^6 CAR-expressing T cells and at or about 20×10^6 CAR-expressing T cells, inclusive.

[0021] In some of any examples, the composition may include $CD4^+$ T cells expressing the CAR and $CD8^+$ T cells expressing the CAR at a ratio between about 1:2 and about 4:1, between about 1:1.5 and about 2:1, or at or at about 1:1. In some of any examples, the composition may include $CD4^+$ T cells expressing the CAR and $CD8^+$ T cells expressing the CAR at a ratio between about 5:1 and about 2:1, between about 4:1 and about 2:1, between about 3:1 and about 2:1, at or at about 5:1, at or at about 4:1, at or at about 3:1, or at or at about 2:1. In some of any examples, the composition may include between at or about 5×10^6 CAR-expressing T cells and at or about 10×10^6 CAR-expressing T cells, inclusive. In some of any examples, the composition may include between at or about 10×10^6 CAR-expressing T cells and at or about 20×10^6 CAR-expressing T cells, inclusive. In some of any examples, the composition may include at or about 20×10^6 CAR-expressing T cells. In some of any examples, the composition may include or about 30×10^6 CAR-expressing T cells. In some of any examples, the composition may include at or about 40×10^6 CAR-expressing T cells.In some of any examples, the composition may include at or about 10×10^6 CAR-expressing T cells. In some of any examples, the composition may include at or about 60×10^6 CAR-expressing T cells. In some of any examples, the composition may include at or about 80×10^6 CAR-expressing T cells. In some of any examples, the composition may include at or about 160×10^6 CAR-expressing T cells.

[0022] In some of any examples, at least or at least about 90% of the cells in the composition are $CD3^+$ cells.

[0023] In some of any examples, at least or at least about 91%, at least or at least about 92%, at least or at least about 93%, at least or at least about 94%, at least or at least about 95%, or at least or at least about 96% of the cells in the composition are $CD3^+$ cells. In some of any examples, between at or about 2% and at or about 30% of the CAR^+ T cells in the composition express a marker of apoptosis, optionally Annexin V or active Caspase 3. In some of any examples, between at or about 5% and at or about 10% of the CAR^+ T cells in the composition express a marker of apoptosis, optionally Annexin V or active Caspase 3. In some of any examples, between at or about 10% and at or about 15% of the CAR^+ T cells in the composition express a marker of apoptosis, optionally Annexin V or active Caspase 3. In some of any examples, between at or about 15% and at or about 20% of the CAR^+ T cells in the composition express a marker of apoptosis, optionally Annexin V or active Caspase 3. In some of any examples, between at or about 20% and at or about 30% of the CAR^+ T cells in the composition express a marker of apoptosis, optionally Annexin V or active Caspase 3. In some of any examples, at or about 5%, at or about 10%, at or about 15%, at or about 20%, at or about 25%, or at or about 30% of the CAR^+ T cells in the composition express a marker of apoptosis, optionally Annexin V or active Caspase 3. In some examples, the marker of apoptosis is Annexin V. In some examples, the marker of apoptosis is active Caspase 3.

[0024] In some of any examples, at least or at least about 80% of the CAR^+ T cells in the composition are of a naïve-like or central memory phenotype.

[0025] In some of any examples, between at or about 80% and at or about 85% of the CAR^+ T cells in the composition are of a naïve-like or central memory phenotype. In some of any examples, between at or about 85% and at or about 90% of the CAR^+ T cells in the composition are of a naïve-like or central memory phenotype. In some of any examples, between at or about 90% and at or about 95% of the CAR^+ T cells in the composition are of a naïve-like or central memory phenotype. In some of any examples, between at or about 95% and at or about 99% of the CAR^+ T cells in the composition are of a naïve-like or central memory phenotype. In some of any examples, at or about 85%, at or about 90%, at or about 95%, or at or about 99% of the CAR^+ T cells in the composition are of a naïve-like or central memory phenotype.

[0026] In some of any examples, the at least or at least about 80% of the CAR^+ T cells in the composition that are of a naïve-like or central memory phenotype are surface positive for a marker expressed on naïve-like or central memory T cells. In some of any examples, the marker expressed on naïve-like or central memory T cell is selected from the group consisting of CD45RA, CD27, CD28, and CCR7.

[0027] In some of any examples, the at least or at least about 80% of the CAR^+ T cells in the composition that are of a naïve-like or central memory phenotype have a phenotype selected from $CCR7^+CD45RA^+$, $CD27^+CCR7^+$, or $CD62L^-CCR7^+$. In some of any examples, between at or about 80% and at or about 85%, between at or about 85% and at or about 90%, between at or about 90% and at or about 95%, between at or about 95% and at or about 99% of the CAR^+ T cells in the composition are of a naïve-like or central memory phenotype selected from $CCR7^+CD45RA^+$, $CD27^+CCR7^+$, or $CD62L^-CCR7^+$. In some of any examples, at or about 80%, at or about 85%, at or about 90%, at or about 95%, or at or about 99% of the CAR^+ T cells in the composition are of a naïve-like or central memory phenotype selected from $CCR7^+CD45RA^+$, $CD27^+CCR7^+$, or $CD62L^-CCR7^+$. In some of any examples, at or about 80%, at or about 85%, at or about 90%, at or about 95%, or at or about 99% of the CAR^+ T cells in the composition are of a naïve-like or central memory phenotype that is $CD27^+CCR7^+$.

[0028] In some of any examples, at least or at least about 50% of the $CD4^+CAR^+$ T cells in the composition are of a naïve-like or central memory phenotype that is $CCR7^+CD45RA^+$ or $CCR7^+CD45RA^-$. In some of any examples, at least or at least about 60% of the $CD4^+CAR^+$ T cells in the composition are of a naïve –like or central memory phenotype that is $CCR7^+CD45RA^+$ or $CCR7^+CD45RA^-$. In some of any examples, at least or at least about 70% of the $CD4^+CAR^+$ T cells in the composition are of a naïve-like or central memory phenotype that is $CCR7^+CD45RA^+$ or $CCR7^+CD45RA^-$. In some of any examples, at least or at least about 80% of the $CD4^+CAR^+$ T cells in the composition are of a naïve-like or central memory phenotype that is $CCR7^+CD45RA^+$ or $CCR7^+CD45RA^-$. In some of any examples, at least or at least about 85% of the $CD4^+CAR^+$ T cells in the composition are of a naïve-like or central memory phenotype that is $CCR7^+CD45RA^+$ or $CCR7^+CD45RA^-$.

[0029] In some of any examples, at least or at least about 50% of the $CD4^+CAR^+$ T cells in the composition are of a naïve-like or central memory phenotype that is $CD27^+CCR7^+$. In some of any examples, at least or at least about 60% of the $CD4^+CAR^+$ T cells in the composition are of a naïve-like or central memory phenotype that is $CD27^+CCR7^+$. In some of any examples, at least or at least about 70% of the $CD4^+CAR^+$ T cells in the composition are of a naïve-like or central memory phenotype that is $CD27^+CCR7^+$. In some of any examples, at least or at least about 80% of the $CD4^+CAR^+$ T cells in the composition are of a naïve-like or central memory phenotype that is $CD27^+CCR7^+$. In some of any examples, at least or at least about 85% of the $CD4^+CAR^+$ T cells in the composition are of a naïve-like or central memory phenotype that is $CD27^+CCR7^+$.

[0030] In some of any examples, at least or at least about 50% of the $CD8^+CAR^+$ T cells in the composition are of a naïve-like or central memory phenotype that is $CCR7^+CD45RA^+$ or $CCR7^+CD45RA^-$. In some of any examples, at least or at least about 60% of the $CD8^+CAR^+$ T cells

in the composition are of a naïve-like or central memory phenotype that is $CCR7^+CD45RA^+$ or $CCR7^+CD45RA^-$. In some of any examples, at least or at least about 70% of the $CD8^+CAR^+$ T cells in the composition are of a naïve-like or central memory phenotype that is $CCR7^+CD45RA^+$ or $CCR7^+CD45RA^-$. In some of any examples, at least or at least about 80% of the $CD8^+CAR^+$ T cells in the composition are of a naïve-like or central memory phenotype that is $CCR7^+CD45RA^+$ or $CCR7^+CD45RA^-$. In some of any examples, at least or at least about 85% of the $CD8^+CAR^+$ T cells in the composition are of a naïve-like or central memory phenotype that is $CCR7^+CD45RA^+$ or $CCR7^+CD45RA^-$.

[0031] In some of any examples, at least or at least about 50% of the $CD8^+CAR^+$ T cells in the composition are of a naïve-like or central memory phenotype that is $CD27^+CCR7^+$. In some of any examples, at least or at least about 60% of the $CD8^+CAR^+$ T cells in the composition are of a naïve-like or central memory phenotype that is $CD27^+CCR7^+$. In some of any examples, at least or at least about 70% of the $CD8^+CAR^+$ T cells in the composition are of a naïve-like or central memory phenotype that is $CD27^+CCR7^+$. In some of any examples, at least or at least about 80% of the $CD8^+CAR^+$ T cells in the composition are of a naïve-like or central memory phenotype that is $CD27^+CCR7^+$. In some of any examples, at least or at least about 85% of the $CD8^+CAR^+$ T cells in the composition are of a naïve-like or central memory phenotype that is $CD27^+CCR7^+$.

[0032] In some of any examples, at least or at least about 80% of the CAR^+ T cells in the composition are surface positive for a marker expressed on naïve-like or central memory T cells. In some of any examples, the marker expressed on naïve-like or central memory T cell is selected from the group consisting of CD45RA, CD27, CD28, and CCR7. In some of any examples, at least or at least about 80% of the CAR^+ T cells in the composition are $CCR7^+CD45RA^+$, $CD27^+CCR7^+$, and/or $CD62L^-CCR7^+$. In some of any examples, between at or about 80% and at or about 85%, between at or about 85% and at or about 90%, between at or about 90% and at or about 95%, between at or about 95% and at or about 99% of the CAR^+ T cells in the composition are $CCR7^+CD45RA^+$, $CD27^+CCR7^+$, and/or $CD62L^-CCR7^+$. In some of any examples, at or about 80%, at or about 85%, at or about 90%, at or about 95%, or at or about 99% of the CAR^+ T cells in the composition are $CCR7^+CD45RA^+$, $CD27^+CCR7^+$, and/or $CD62L^-CCR7^+$. In some of any examples, at or about 80%, at or about 85%, at or about 90%, at or about 95%, or at or about 99% of the CAR^+ T cells in the composition are $CD27^+CCR7^+$. In some of any examples, at least or at least about 50% of the $CD4^+CAR^+$ T cells in the composition are $CCR7^+CD45RA^+$ or $CCR7^+CD45RA^-$. In some of any examples, at least or at least about 60% of the $CD4^+CAR^+$ T cells in the composition are $CCR7^+CD45RA^+$ or $CCR7^+CD45RA^-$.

[0033] In some of any examples, at least or at least about 70% of the $CD4^+CAR^+$ T cells in the composition are $CCR7^+CD45RA^+$ or $CCR7^+CD45RA^-$. In some of any examples, at least or at least about 80% of the $CD4^+CAR^+$ T cells in the composition are $CCR7^+CD45RA^+$ or $CCR7^+CD45RA^-$. In

some of any examples, at least or at least about 85% of the $CD4^+CAR^+$ T cells in the composition are $CCR7^+CD45RA^+$ or $CCR7^+CD45RA^-$. In some of any examples, at least or at least about 50% of the $CD4^+CAR^+$ T cells in the composition are $CD27^+CCR7^+$. In some of any examples, at least or at least about 60% of the $CD4^+CAR^+$ T cells in the composition are $CD27^+CCR7^+$. In some of any examples, at least or at least about 70% of the $CD4^+CAR^+$ T cells in the composition are $CD27^+CCR7^+$. In some of any examples, at least or at least about 80% of the $CD4^+CAR^+$ T cells in the composition are $CD27^+CCR7^+$. In some of any examples, at least or at least about 85% of the $CD4^+CAR^+$ T cells in the composition are $CD27^+CCR7^+$. In some of any examples, at least or at least about 50% of the $CD8^+CAR^+$ T cells in the composition are $CCR7^+CD45RA^+$ or $CCR7^+CD45RA^-$. In some of any examples, at least or at least about 60% of the $CD8^+CAR^+$ T cells in the composition are $CCR7^+CD45RA^+$ or $CCR7^+CD45RA^-$. In some of any examples, at least or at least about 70% of the $CD8^+CAR^+$ T cells in the composition are $CCR7^+CD45RA^+$ or $CCR7^+CD45RA^-$. In some of any examples, at least or at least about 80% of the $CD8^+CAR^+$ T cells in the composition are $CCR7^+CD45RA^+$ or $CCR7^+CD45RA^-$. In some of any examples, at least or at least about 85% of the $CD8^+CAR^+$ T cells in the composition are $CCR7^+CD45RA^+$ or $CCR7^+CD45RA^-$. In some of any examples, at least or at least about 50% of the $CD8^+CAR^+$ T cells in the composition are $CD27^+CCR7^+$. In some of any examples, at least or at least about 60% of the $CD8^+CAR^+$ T cells in the composition are $CD27^+CCR7^+$. In some of any examples, at least or at least about 70% of the $CD8^+CAR^+$ T cells in the composition are $CD27^+CCR7^+$. In some of any examples, at least or at least about 80% of the $CD8^+CAR^+$ T cells in the composition are $CD27^+CCR7^+$. In some of any examples, at least or at least about 85% of the $CD8^+CAR^+$ T cells in the composition are $CD27^+CCR7^+$.

[0034] In some of any examples, the fraction of integrated vector copy number (iVCN) to total VCN in the CAR^+ T cells in the composition, on average, is less than or less than about 0.9.

[0035] In some of any examples, the fraction of integrated vector copy number (iVCN) to total VCN in the CAR^+ T cells in the composition, on average, is between at or about 0.9 and at or about 0.8. In some of any examples, the fraction of integrated vector copy number (iVCN) to total VCN in the CAR^+ T cells in the composition, on average, is less than or less than about 0.8. In some of any examples, the fraction of integrated vector copy number (iVCN) to total VCN in the CAR^+ T cells in the composition, on average, is between at or about 0.8 and at or about 0.7. In some of any examples, the fraction of integrated vector copy number (iVCN) to total VCN in the CAR^+ T cells in the composition, on average, is between at or about 0.7 and at or about 0.6. In some of any examples, the fraction of integrated vector copy number (iVCN) to total VCN in the CAR^+ T cells in the composition, on average, is between at or about 0.6 and at or about 0.5. In some of any examples, the fraction of integrated vector copy number (iVCN) to total VCN in the CAR^+ T cells in the composition, on average, is between at or about 0.5 and at or about 0.4.

[0036] In some of any examples, the integrated vector copy number (iVCN) of the CAR^+ T cells in the composition, on average, is between or between about 0.4 copies per diploid genome and 2.0 copies per diploid genome, inclusive.

[0037] In some of any examples, the integrated vector copy number (iVCN) of the CAR^+ T cells in the composition, on average, is between or between about 0.8 copies per diploid genome and 2.0 copies per diploid genome, inclusive. In some of any examples, the integrated vector copy number (iVCN) of the CAR^+ T cells in the composition, on average, is between or between about 0.8 copies per diploid genome and 1.0 copies per diploid genome, inclusive. In some of any examples, the integrated vector copy number (iVCN) of the CAR^+ T cells in the composition, on average, is between or between about 1.0 copies per diploid genome and 1.5 copies per diploid genome, inclusive. In some of any examples, the integrated vector copy number (iVCN) of the CAR^+ T cells in the composition, on average, is between or between about 1.5 copies per diploid genome and 2.0 copies per diploid genome, inclusive.

[0038] In some of any examples, at or prior to the administration of the composition of engineered T cells, the subject has received at least 3 prior antimyeloma treatment regimens. In some of any examples, at or prior to the administration of the composition of engineered T cells, the subject has received three or more therapies, optionally four or more prior therapies, selected from among an autologous stem cell transplant (ASCT); an immunomodulatory agent; a proteasome inhibitor; and an anti-CD38 agent, unless the subject was not a candidate for or was contraindicated for one or more of the therapies. In some of any examples, at or prior to the administration of the composition of engineered T cells, the subject has received three or more therapies, optionally four or more prior therapies, optionally selected from among an autologous stem cell transplant (ASCT); an immunomodulatory agent and a proteasome inhibitor, either alone or in combination; and an anti-CD38 agent. In some of any examples, at or prior to the administration of the composition of engineered T cells, the subject has received all three of the following therapies including autologous stem cell transplant (ASCT); a regimen including an immunomodulatory agent and a proteasome inhibitor; and an anti-CD38 agent.

[0039] In some of any examples, at or prior to the administration of the composition comprising engineered T cells, the subject has received all three of the following antimyeloma treatment regimens: autologous stem cell transplant (ASCT); an immunomodulatory agent and/or a proteasome inhibitor, either alone or in combination; and an anti-CD38 agent. In some of any examples, induction with or without bone marrow transplant and with or without maintenance therapy is considered one regimen for purpose of determining the number of prior antimyeloma treatment regimens.

[0040] In some of any examples, at or prior to the administration of the composition comprising engineered T cells, the subject is refractory to the last antimyeloma treatment regimen. In some of any examples, refractory myeloma is defined as documented progressive disease during or within 12

months, measured from the last dose, of completing treatment with the last anti-myeloma treatment regimen. In some of any examples, refractory myeloma is defined as documented progressive disease during or within 60 days, measured from the last dose, of completing treatment with the last anti-myeloma treatment regimen.

[0041] In some of any examples, the immunomodulatory agent is selected from among thalidomide, lenalidomide, and pomalidomide, either alone or in combination. In some of any examples, the proteasome inhibitor is selected from among bortezomib, carfilzomib, and ixazomib, either alone or in combination.

[0042] In some of any examples, the subject has undergone at least one complete cycle of treatment with the antimyeloma treatment regimen comprising the immunomodulatory agent and/or the proteasome inhibitor unless progressive disease was the best response to the antimyeloma treatment regimen. In some of any examples, the subject has undergone at least two consecutive cycles of treatment with the antimyeloma treatment regimen comprising the immunomodulatory agent and/or the proteasome inhibitor unless progressive disease was the best response to the antimyeloma treatment regimen.

[0043] In some of any examples, the anti-CD38 agent is an anti-CD38 antibody. In some of any examples, the anti-CD38 agent is or comprises daratumumab. In some of any examples, the anti-CD38 agent is used as part of a combination regimen or as a monotherapy.

[0044] In some of any examples, at the time of the administration of the composition comprising engineered T cells, the subject has not had an active or a history of plasma cell leukemia (PCL). In some of any examples, at the time of the administration, the subject has relapsed or has been refractory following at least 3 or at least 4 prior antimyeloma treatment regimen. In some of any examples, at the time of the administration, the subject has a time from diagnosis of multiple myeloma of approximately 4 years or between 2 and 15 years or between 2 and 12 years. In some of any examples, at the time of the administration, the subject has received about 10 or between 3 and 15 or between 4 and 15 prior antimyeloma treatment regimen. In some of any examples, at the time of the 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 the administration, the subject has had a prior autologous stem cell transplant. In some of any examples, at the time of the administration, the subject has not had a prior autologous stem cell transplant (ASCT) due to ineligibility for ASCT, optionally ineligibility due to age or other documented reasons. In some of any examples, at the time of the administration, the subject has IMWG high risk cytogenetics. In some of any examples, the subject does not have a central nervous system involvement of MM, plasma cell leukemia, Waldenstrom's macroglobulinemia, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) syndrome, and/or

clinically significant amyloidosis. In some of any examples, the subject has not received a prior CAR T cell or genetically-modified T cell therapy. In some of any examples, the subject has not received a prior BCMA-targeted therapy such as an anti-BCMA monoclonal antibody or bispecific antibody.

[0045] In some of any examples, the method further comprises obtaining a leukapheresis sample from the subject for manufacturing the composition comprising engineered T cells.

[0046] In some of any examples, the subject has not received a therapeutic dose of a corticosteroid, optionally within at or about 14 days prior to the time of leukapheresis. In some of any examples, the subject has not received an immunosuppressive therapy within 4 weeks of leukapheresis, optionally wherein the immunosuppressive therapy comprises a a calcineurin inhibitor, methotrexate or other chemotherapeutics, mycophenolate, rapamycin, immunosuppressive antibodies such as anti-TNF, anti-IL6, or anti-IL6R. In some of any examples, the subject has not received a autologous stem-cell transplant within at or about 6 months prior to the time of leukapheresis.

[0047] In some of any examples, the subject has not achieved complete remission (CR) in response to a prior therapy. In some of any examples, the subject has not achieved an objective response (partial response (PR) or better) in response to a prior therapy. In some of any examples, the subject is or has been identified as having an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1.

[0048] In some of any examples, the CAR may include an extracellular antigen-binding domain, including a variable heavy chain (V_H) including 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) including 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 including 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 including 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 including 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 including 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 including 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 including 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 including 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 including 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 including the amino acid sequence of SEQ ID NO: 116 and a V_L including the amino acid sequence of SEQ ID NO: 119; and a spacer

including 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; optionally wherein the spacer is set forth in SEQ ID NO: 174; and a transmembrane domain, optionally a transmembrane domain from a human CD28; and an intracellular signaling region including a cytoplasmic signaling domain of a CD3-zeta (CD3ζ) chain and a costimulatory signaling region including an intracellular signaling domain of a T cell costimulatory molecule or a signaling portion thereof. In some examples, the spacer is the spacer set forth in SEQ ID NO:174.

[0049] In some of any examples, the V_H is or may include the amino acid sequence of SEQ ID NO: 116; and the V_L is or includes the amino acid sequence of SEQ ID NO: 119. In some of any examples, the extracellular antigen-binding domain may include 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 may include a linker including the amino acid sequence GGGGSGGGGSGGGGS (SEQ ID NO:1). In some of any examples, the V_H is carboxy-terminal to the V_L. In some of any examples, the scFv comprises a linker comprising the amino acid sequence SRGGGGSGGGGSGGGGSLEMA (SEQ ID NO:255)

[0050] In some of any examples, the extracellular antigen-binding domain may include 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 extracellular antigen-binding domain may include the amino acid sequence of SEQ ID NO: 114.

[0051] In some of any examples, a nucleic acid encoding the extracellular antigen-binding domain may include the sequence of nucleotides of SEQ ID NO:113; a sequence of nucleotides that has at least 90% sequence identity thereto; or a degenerate sequence of either of the preceding sequences. In some of any examples, the nucleic acid encoding the extracellular antigen-binding domain may include the sequence of nucleotides of SEQ ID NO:115. In some of any examples, the V_H is amino-terminal to the V_L.

[0052] In some of any examples, the cytoplasmic signaling domain is or may include 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. In some of any examples, the costimulatory signaling region may include an intracellular signaling domain of CD28, 4-1BB, or ICOS, or a signaling portion thereof. In some of any examples, the costimulatory signaling region may include an intracellular signaling domain of 4-1BB, optionally human 4-1BB. In some of any examples,the costimulatory signaling region is or may include 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. In some of any examples, the

costimulatory signaling region is between the transmembrane domain and the cytoplasmic signaling domain of a CD3-zeta (CD3ζ) chain.

[0053] In some of any examples, the transmembrane domain is or may include a transmembrane domain from human CD28. In some of any examples, the transmembrane domain is or may include 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.

[0054] In some of any examples, the CAR may include from its N to C terminus in order: the extracellular antigen-binding domain, the spacer, the transmembrane domain and the intracellular signaling region. In some of any examples, the CAR may include an extracellular antigen-binding domain, including a variable heavy chain (V_H) including 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) including 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 spacer including 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; a transmembrane domain from a human CD28; and an intracellular signaling region including a cytoplasmic signaling domain of a CD3-zeta (CD3ζ) chain and a costimulatory signaling region including an intracellular signaling domain of a 4-1BB.

[0055] In some of any examples, the CAR may include an extracellular antigen-binding domain, including 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; a spacer including 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; a transmembrane domain including 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 an intracellular signaling region including a cytoplasmic signaling including 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 including 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.

[0056] In some of any examples, the CAR may include an extracellular antigen-binding domain, including the sequence set forth in SEQ ID NO: 114; a spacer including the sequence set forth in SEQ ID NO: 174; a transmembrane domain including the sequence set forth in SEQ ID NO:138; and an intracellular signaling region including a cytoplasmic signaling including the sequence set forth in SEQ ID NO:143 and a costimulatory signaling region including the sequence set forth in SEQ ID NO:4. In some of any examples, the CAR may include an extracellular antigen-binding domain set forth in

SEQ ID NO: 114; a spacer set forth in SEQ ID NO: 174; a transmembrane domain set forth in SEQ ID NO:138; and an intracellular signaling region including a cytoplasmic signaling set forth in SEQ ID NO:143 and a costimulatory signaling region set forth in SEQ ID NO:4. In some of any examples, CAR may include the sequence set forth in SEQ ID NO:19. In some of any examples, the sequence of the CAR is set forth in SEQ ID NO:19.

[0057] 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. 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 is encoded by a polynucleotide sequence comprising the sequence set forth in SEQ ID NO: 13.

[0058] In some of any examples, the binding of the extracellular 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.

[0059] 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/m^2 body surface area of the subject, optionally at or about 30 mg/m^2, daily, for 2-4 days, and/or cyclophosphamide at or about 200-400 mg/m^2 body surface area of the subject, optionally at or about 300 mg/m^2, daily, for 2-4 days. 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/m^2 body surface area of the subject, optionally at or about 30 mg/m^2, daily, for 2-4 days. 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/m^2 body surface area of the subject, optionally at or about 300 mg/m^2, 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/m^2 body surface area of the subject, daily, and cyclophosphamide at or about 300 mg/m^2 body surface area of the subject, daily, each for 3 days.

[0060] 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 MM, 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.

[0061] 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. 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 timepoint is equal to or improved compared to the response or outcome determined at the designated timepoint.

[0062] In some of any examples, the response or outcome is or comprises or further comprises the absence of neurotoxicity, the absence of cytokine release syndrome (CRS), and/or the absence of macrophage activation syndrome/ hemophagocytic lymphohistiocytosis (MAS/HLH). 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 MM.

[0063] In some of any examples, the specified toxicity outcome is neurotoxicity, cytokine release syndrome (CRS), and/or macrophage activation syndrome/ hemophagocytic lymphohistiocytosis (MAS/HLH). 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 subjects in the cohort of subjects having the MM. 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 of subjects having the MM. In some of any examples, the specified toxicity outcome is cytokine release syndrome (CRS), optionally grade 3 or higher, or grade 4 or higher, cytokine release syndrome (CRS). In some of any examples, the CRS does not result in at least 15%, 20%, 25% or 30% of the subjects in the cohort of subjects having the MM. In some of any examples, the designatied timepoint is at or about or within 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 12 days, 13 days, 14 days or 15 days following initiation of administration. In some of any

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

[0064] In some of any embodimetns, the method does not result in any cytokine release syndrome (CRS) in 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 MM . In some of any embodiemtns, the method does not result in severe cytokine release syndrome (CRS) in at least at least at least 80%, at least 90%, or at least 95% of subjects in the cohort of subjects having the MM . In some of any examples, the method does not result in any neurotoxicity in 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 MM. In some of any embodimetns, the method does not result in severe neurotoxicity in at least at least at least 70%, at least 80%, at least 90%, or at least 95% of subjects in the cohort of subjects having the MM . In some of any examples, the method does not result in severe CRS and severe neurotoxicity in at least at least at least 70%, at least 80%, at least 90%, or at least 95% of subjects in the cohort of subjects having the MM. In some of any examples, the method does not result in severe CRS and severe neurotoxicity in at least 80%, at least 90%, or at least 95% of subjects in the cohort of subjects having the MM. In any of such example, the severe CRS is grade 3 or higher, grade 4 or higher or grade 5 CRS. In any of such examples, the severe neurotoxicity is grade 3 or higher, grade 4 or higher or grade 5 CRS.

[0065] In some of any embodiemtns, the administration of the composition is carried out on an outpatient basis, optionally unless or until the subject exhibits a sustained fever or a fever that is or has not been reduced or not reduced by more than 1ºC after treatment with an antipyretic. In some of any embodimetns, the administration of the composition is without admitting the subject to a hospital and/or without an overnight stay at a hospital, optionally unless or until the subject exhibits a sustained fever or a fever that is or has not been reduced or not reduced by more than 1ºC after treatment with an antipyretic. In some of any examples, the administration of the composition is without requiring admission to or an overnight stay at a hospital, optionally unless or until the subject exhibits a sustained fever or a fever that is or has not been reduced or not reduced by more than 1ºC after treatment with an antipyretic.

[0066] In some of any examples, the composition comprising engineered T cells is administered parenterally, optionally intravenously. In some of any examples, the subject is a human subject.

[0067] In some of any examples, the composition comprising engineered T cells is produced by a manufacturing process comprising: (i) exposing an input composition comprising primary T cells with a stimulatory reagent comprising an oligomeric particle reagent comprising a plurality of streptavidin mutein molecules under conditions to stimulate T cells, thereby generating a stimulated population, wherein: the oligomeric particle reagent comprises a first agent comprising an anti-CD3 antibody or antigen binding fragment thereof and a second agent comprising an anti-CD28 antibody or antigen

binding fragment thereof; (ii) introducing into T cells of the stimulated population, a heterologous polynucleotide encoding the CAR that targets BCMA, thereby generating a population of transformed cells; (iii) incubating the population of transformed cells for up to 96 hours; and (iv) harvesting T cells of the population of transformed cells, thereby producing a composition of engineered cells, wherein the harvesting is carried out at a time between 24 and 120 hours, inclusive, after the exposing to the stimulatory reagent is initiated. In some examples, the input composition autologous T cells selected from the subject, such as enriched by immunoaffinity-based selection for CD3 T cells or CD4 and CD8 T cells from a blood or apheresis (e.g. leukarephesis) sample from the subject.

[0068] In some of any examples, the composition may include engineered T cells is produced by a manufacturing process including exposing an input composition including primary T cells with a stimulatory reagent including an oligomeric particle reagent including a plurality of avidin, streptavidin, avidin mutein, or streptavidin mutein molecules under conditions to stimulate T cells, thereby generating a stimulated population, wherein the stimulatory reagent is capable of activating one or more intracellular signaling domains of one or more components of a TCR complex and one or more intracellular signaling domains of one or more costimulatory molecules. In some of any examples, the manufacturing process may further include introducing into T cells of the stimulated population, a heterologous polynucleotide encoding the CAR that targets BCMA, thereby generating a population of transformed cells. In some of any examples, the manufacturing process may further include incubating the population of transformed cells for up to 96 hours. In some of any examples, the incubating is carried out in basal media lacking one or more recombinant cytokines.

[0069] In some of any examples, the oligomeric particle reagent comprises a first agent comprising an anti-CD3 antibody or antigen binding fragment thereof and a second agent comprising an anti-CD28 antibody or antigen binding fragment thereof. In some of any examples, the anti-CD3 antibody or antigen binding fragment is a Fab and the anti-CD28 antibody or antigen binding fragment is a Fab. In some of any examples, the first agent and the second agent each comprise a streptavidin-binding peptide that reversibly binds the first agent and the second agent to the oligomeric particle reagent, optionally wherein the streptavidin-binding peptide comprises the sequence of amino acids set forth in any of SEQ ID NOS:266-270. In some of any examples, the streptavidin mutein molecule is a tetramer of a streptavidin mutein comprising amino acid residues Val44-Thr45-Ala46-Arg47 or Ile44-Gly45-Ala46-Arg47, optionally wherein the streptavidin mutein comprises the sequence set forth in any of SEQ ID NOS: 257, 272, 275, 277, 279, 273 or 276. In some of any examples, the oligomeric particle reagent comprises between 1,000 and 5,000 streptavidin mutein tetramers, inclusive. In some of any examples, the method further comprises, prior to harvesting the cells, adding biotin or a biotin analog after or during the incubation.

[0070] In some of any examples, the manufacturing process further includes harvesting T cells of the transformed population, thereby producing a composition of engineered cells. In some of any examples, the harvesting is carried out at a time between 24 and 120 hours, inclusive, after the exposing to the stimulatory reagent is initiated. In some of any examples, the harvesting is carried out at a time between 48 and 120 hours, inclusive, after the exposing to the stimulatory reagent is initiated. In some of any examples, the harvesting is carried out at a time when integrated vector is detected in the genome but prior to achieving a stable integrated vector copy number (iVCN) per diploid genome. In some of any examples, the harvesting is carried out at a time before the total number of viable cells at the harvesting is more than or more than about three times as the number of total viable cells of the stimulated population. In some of any examples, the harvesting is carried out at a time when the total number of viable cells at the harvesting is at or about three times, at or about two times, or the same or about the same as the number of total viable cells of the stimulated population. In some of any examples, the harvesting is carried out at a time when the percentage of $CD27^+CCR7^+$ cells is greater than or greater than about 50% among total T cells in the population, total $CD3^+$ T cells in the population, total $CD4^+$ T cells in the population, or total $CD8^+$ T cells, or of CAR-expressing cells thereof, in the population. In some of any examples, the harvesting is carried out at a time when the percentage of $CD45RA^+CCR7^+$ and $CD45RA^-CCR7^+$ cells is greater than or greater than about 60% among total T cells in the population, total $CD3^+$ T cells in the population, total $CD4^+$ T cells in the population, or total $CD8^+$ T cells, or of CAR-expressing cells thereof, in the population.

[0071] In some of any examples, the cells in the administered composition are produced by a manufacturing process to produce an output composition exhibiting a predetermined feature, wherein iterations of the manufacturing process produce a plurality of the output compositions, optionally from human biological samples, when carried out among a plurality of different individual subjects, in which the predetermined feature of the output composition among the plurality of output compositions is selected from 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%; 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%; 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%; 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%; 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%.

[0072] In some of any examples, the administered composition is produced by a manufacturing process 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 composition including genetically engineered cells does not contain residual beads from the manufacturing process.

[0073] In some of any examples, the MM is a relapsed and/or refractory multiple myeloma (r/r MM).

[0074] Also provided herein is an article of manufacture including a composition including genetically engineered cells expressing a chimeric antigen receptor (CAR) that targets BCMA, and instructions for administering the composition of the cells in accordance with the method of any of the methods provided herein.

[0074a] In one aspect, the present disclosure refers to an article of manufacture comprising a composition comprising genetically engineered cells expressing a chimeric antigen receptor (CAR) that targets BCMA, and instructions for administering the composition of the cells in accordance with the method disclosed herein.

Brief Description of the Drawings

[0075] **FIG. 1** shows exemplary quantifications determined by flow cytometry of cell purity of T cell compositions produced from non-expanded engineering processes using different donor types (Reference, Patient). Cells were engineered to express an anti-BCMA CAR (BCMA) or were mock transduced (mock). Percentages of CD3+ cells of live CD45+ cells (left panel), percentages of NK cells

CLAIMS

1. Use of a composition comprising engineered T cells expressing a chimeric antigen receptor (CAR) that targets B cell maturation antigen (BCMA), in the manufacture of a medicament for treating a multiple myeloma (MM) in a subject having a MM, wherein:

the composition comprises $CD8^+$ T cells expressing the CAR and $CD4^+$ T cells expressing the CAR;

the composition comprises between at or about 5×10^6 CAR-expressing T cells and at or about 80×10^6 CAR-expressing T cells, inclusive;

at least or at least about 80% of the cells in the composition are $CD3^+$ cells; and

at least or at least about 80% of the CAR^+ T cells in the composition are of a naïve-like or central memory phenotype.

2. Use of a composition comprising engineered T cells expressing a chimeric antigen receptor (CAR) that targets B cell maturation antigen (BCMA), in the manufacture of a medicament for treating a multiple myeloma (MM) in a subject having a MM, wherein:

the composition comprises $CD8^+$ T cells expressing the CAR and $CD4^+$ T cells expressing the CAR;

the composition comprises between at or about 5×10^6 CAR-expressing T cells and at or about 100×10^6 CAR-expressing T cells, inclusive;

at least or at least about 80% of the cells in the composition are $CD3^+$ cells; and

at least or at least about 50% of the $CD4^+CAR^+$ T cells in the composition are $CD27^+CCR7^+$ and/or at least or at least about 50% of the $CD8^+CAR^+$ T cells in the composition are $CD27^+CCR7^+$.

3. The use of claim 1 or claim 2, wherein the composition comprises $CD4^+$ T cells expressing the CAR and $CD8^+$ T cells expressing the CAR at a ratio between about 1:2.5 and about 5:1.

4. The use of claim 2 or claim 3, wherein the composition comprises between at or about 5×10^6 CAR-expressing T cells and at or about 80×10^6 CAR-expressing T cells, inclusive, optionally wherein the composition comprises at or about 20×10^6 CAR-expressing T cells, at or about 30×10^6 CAR-expressing T cells, or at or about 40×10^6 CAR-expressing T cells.

5. The use of any of claims 1-4, wherein at least or at least about 90% of the cells in the composition are $CD3^+$ cells.

6. The use of any of claims 1-5, wherein between at or about 2% and at or about 30% of the CAR^+ T cells in the composition express a marker of apoptosis, optionally Annexin V or active Caspase 3.

7. The use of any of claims 2-6, wherein at least or at least about 80% of the CAR^+ T cells in the composition are of a naïve-like or central memory phenotype.

8. The use of any of claims 1 and 3-7, wherein the at least or at least about 80% of the CAR^+ T cells in the composition that are of a naïve-like or central memory phenotype are surface positive for a marker expressed on naïve-like or central memory T cells.

9. The use of claim 8, wherein the marker expressed on naïve-like or central memory T cell is selected from the group consisting of CD45RA, CD27, CD28, and CCR7.

10. The use of any of claims 1 and 3-9, wherein: the at least or at least about 80% of the CAR^+ T cells in the composition that are of a naïve-like or central memory phenotype have a phenotype selected from $CCR7^+CD45RA^+$, $CD27^+CCR7^+$, or $CD62L^-CCR7^+$;

wherein optionally at or about 80%, at or about 85%, at or about 90%, at or about 95%, or at or about 99% of the CAR^+ T cells in the composition are of a naïve-like or central memory phenotype that is $CD27^+CCR7^+$.

11. The use of any of claims 1-10, wherein: at least or at least about 50% of the $CD4^+CAR^+$ T cells in the composition are of a naïve-like or central memory phenotype that is $CCR7^+CD45RA^+$ or $CCR7^+CD45RA^-$;

at least or at least about 50% of the $CD4^+CAR^+$ T cells in the composition are of a naïve-like or central memory phenotype that is $CD27^+CCR7^+$;

at least or at least about 50% of the $CD8^+CAR^+$ T cells in the composition are of a naïve-like or central memory phenotype that is $CCR7^+CD45RA^+$ or $CCR7^+CD45RA^-$; and/or

at least or at least about 50% of the $CD8^+CAR^+$ T cells in the composition are of a naïve-like or central memory phenotype that is $CD27^+CCR7^+$.

12. The use of any of claims 1-11, wherein the fraction of integrated vector copy number (iVCN) to total VCN in the CAR^+ T cells in the composition, on average, is less than or less than about 0.9.

13. The use of any of claims 1-12, wherein the integrated vector copy number (iVCN) of the CAR^+ T cells in the composition, on average, is between or between about 0.4 copies per diploid genome and 2.0 copies per diploid genome, inclusive.

14. The use of any of claims 1-13, wherein the composition comprising engineered T cells is to be administered to the subject at a time in which at or prior to the administration, the subject has received at least 3 prior antimyeloma treatment regimens; optionally wherein the subject has received all three of the following antimyeloma treatment regimens: autologous stem cell transplant (ASCT); a regimen comprising an immunomodulatory agent and a proteasome inhibitor; and an anti-CD38 agent.

15. The use of claim 14, wherein: the administration of the composition comprising engineered T cells is to be administered to the subject at a time in which at or prior to the administration, the subject is refractory to the last antimyeloma treatment regimen, optionally wherein refractory myeloma is defined as documented progressive disease during or within 12 months, measured from the last dose, of completing treatment with the last anti-myeloma treatment regimen; and/or

prior to the administration of the composition comprising engineered T cells, the subject has received a lymphodepleting therapy comprising the administration of fludarabine at or about 20-40 mg/m^2 body surface area of the subject, optionally at or about 30 mg/m^2, daily, for 2-4 days, and/or cyclophosphamide at or about 200-400 mg/m^2 body surface area of the subject, optionally at or about 300 mg/m^2, daily, for 2-4 days.

16. The use of any of claims 1-15, wherein the subject has not received a prior CAR T cell or genetically-modified T cell therapy; optionally wherein the subject has not received a prior BCMA-targeted therapy such as an anti-BCMA monoclonal antibody or bispecific antibody.

17. The use of any of claims 1-16, wherein the composition comprising engineered T cells is manufactured from a leukapheresis sample from the subject.

18. The use of any one of claims 1-17, 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:

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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; optionally wherein the spacer is 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.

19. The use of claim 18, 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.

20. The use of claim 18 or claim 19, wherein the extracellular antigen-binding domain comprises an scFv, optionally wherein the V_H and the V_L are joined by a flexible linker.

21. The use of claim 20, wherein the scFv comprises a linker comprising the amino acid sequence GGGGSGGGGSGGGGS (SEQ ID NO:1).

22. The use of any of claims 18-21, 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; and/or

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, optionally wherein the costimulatory signaling region is between the transmembrane domain and the cytoplasmic signaling domain of a CD3-zeta (CD3ζ) chain.

23. The use of any of claims 18-22, wherein the costimulatory signaling region comprises an intracellular signaling domain of CD28, 4-1BB, or ICOS, or a signaling portion thereof, optionally wherein the costimulatory signaling region comprises an intracellular signaling domain of human 4-1BB.

24. The use of any of claims 18-23, 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.

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

26. The use of any of claims 1-25, 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;

(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.

27. The use of any of claims 1-26, wherein the CAR comprises the sequence set forth in SEQ ID NO:19.

28. The use of any of claims 1-27, wherein the composition is capable of achieving a specified response or outcome, optionally at a designated timepoint following 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 MM, wherein:

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);

the response or outcome is or comprises an OR; and/or

the response or outcome is or comprises a CR.

29. The use of claim 28, wherein the response or outcome is durable for greater than at or about 3, 6, 9 or 12 months; and/or 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.

30. The use of any of claims 1-29, wherein:

administration of the composition does not result in any cytokine release syndrome (CRS) in 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 MM; and/or

administration of the composition does not result in any neurotoxicity in at least 60% of subjects in the cohort of subjects having the MM; and/or

administration of the composition does not result in severe CRS and severe neurotoxicity in at least at least at least 70% of subjects in the cohort of subjects having the MM, optionally wherein the severe CRS is grade 3 or higher, grade 4 or higher or grade 5 CRS and the severe neurotoxicity is grade 3 or higher, grade 4 or higher or grade 5 CRS.

31. The use of any of claims 1-30, wherein the composition is to be administered to the subject on an outpatient basis and/or without admitting the subject to a hospital and/or without an overnight stay at a hospital and/or without requiring admission to or an overnight stay at a hospital, optionally unless or until the subject exhibits a sustained fever or a fever that is or has not been reduced or not reduced by more than 1ºC after treatment with an antipyretic.

32. The use of any of claims 1-31, wherein the composition comprising engineered T cells is to be administered parenterally, optionally intravenously.

33. The use of any of claims 1-32, wherein the subject is a human subject.

34. The use of any of claims 1-33, wherein the composition comprising engineered T cells is produced by a manufacturing process comprising:

(i) exposing an input composition comprising primary T cells, optionally an input composition comprising autologous T cells selected from the subject, with a stimulatory reagent comprising an oligomeric particle reagent comprising a plurality of streptavidin mutein molecules under conditions to stimulate T cells, thereby generating a stimulated population, wherein:

the oligomeric particle reagent comprises a first agent comprising an anti-CD3 antibody or antigen binding fragment thereof and a second agent comprising an anti-CD28 antibody or antigen binding fragment thereof, optionally wherein the anti-CD3 antibody or antigen binding fragment is a Fab and the anti-CD28 antibody or antigen binding fragment is a Fab;

(ii) introducing into T cells of the stimulated population, a heterologous polynucleotide encoding the CAR that targets BCMA, thereby generating a population of transformed cells;

(iii) incubating the population of transformed cells for up to 96 hours; and

(iv) harvesting T cells of the population of transformed cells, thereby producing a composition of engineered cells, wherein the harvesting is carried out at a time between 24 and 120 hours, inclusive, after the exposing to the stimulatory reagent is initiated.

35. The use of claim 34, wherein: the first agent and the second agent each comprise a streptavidin-binding peptide that reversibly binds the first agent and the second agent to the oligomeric particle reagent, optionally wherein the streptavidin-binding peptide comprises the sequence of amino acids set forth in any of SEQ ID NOS:266-270; and/or

the streptavidin mutein molecule is a tetramer of a streptavidin mutein comprising amino acid residues Val44-Thr45-Ala46-Arg47 or Ile44-Gly45-Ala46-Arg47, optionally wherein the streptavidin mutein comprises the sequence set forth in any of SEQ ID NOS: 257, 272, 275, 277, 279, 273 or 276.

36. The use of claim 34 or claim 35, wherein the oligomeric particle reagent comprises between 1,000 and 5,000 streptavidin mutein tetramers, inclusive.

37. The use of any of claims 34-36, wherein the method further comprises, prior to harvesting the cells, adding biotin or a biotin analog after or during the incubation .

38. The use of any of claims 34-37, wherein the harvesting is carried out:

(i) at a time between 48 and 120 hours, inclusive, after the exposing to the stimulatory reagent is initiated; and/or

(ii) at a time when integrated vector is detected in the genome but prior to achieving a stable integrated vector copy number (iVCN) per diploid genome; and/or

(iii) at a time before the total number of viable cells at the harvesting is more than or more than about three times the number of total viable cells of the stimulated population; or

(iv) at a time when the total number of viable cells at the harvesting is at or about three times, at or about two times, or the same or about the same as the number of total viable cells of the stimulated population; and/or

(v) at a time when the percentage of $CD27^+CCR7^+$ cells is greater than or greater than about 50% among total T cells in the population of transformed cells, total $CD3^+$ T cells in the population of transformed cells, total $CD4^+$ T cells in the population of transformed cells, or total $CD8^+$ T cells, or of CAR-expressing cells thereof, in the population of transformed cells; and/or

(vi) at a time when the percentage of $CD45RA^+CCR7^+$ and $CD45RA^-CCR7^+$ cells is greater than or greater than about 60% among total T cells in the population of transformed cells, total $CD3^+$ T cells in the population of transformed cells, total $CD4^+$ T cells in the population of transformed cells, or total $CD8^+$ T cells, or of CAR-expressing cells thereof, in the population of transformed cells.

39. The use of any of claims 1-38, wherein the cells in the composition are produced by a manufacturing process to produce an output composition (i) comprising engineered CD4+ T cells and engineered CD8+ T cells and (ii) exhibiting a predetermined feature, wherein iterations of the manufacturing process produce a plurality of the output compositions, optionally from human biological samples, when carried out among a plurality of different individual subjects, in which the predetermined feature of the output composition among the plurality of output compositions is selected from:

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%;

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%;

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%;

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%;

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%.

40. The use of any of claims 1-39, wherein the composition is produced by a manufacturing process 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.

41. The use of any of claims 1-40, wherein the MM is a relapsed and/or refractory multiple myeloma (r/r MM).

42. The use of any of claims 1-40, wherein at least or at least about 90%, at least or at least about 91%, at least or at least about 92%, at least or at least about 93%, at least or at least about 94%, at least or at least about 95%, or at least or at least about 96% of the cells in the composition are $CD3^+$ cells.

43. The use of claim 42, wherein:

the at least or at least about 80% of the CAR^+ T cells in the composition that are of a naïve-like or central memory phenotype have a phenotype selected from $CCR7^+CD45RA^+$, $CD27^+CCR7^+$, or $CD62L^-CCR7^+$;

between at or about 80% and at or about 85%, between at or about 85% and at or about 90%, between at or about 90% and at or about 95%, between at or about 95% and at or about 99% of the CAR^+ T cells in the composition are of a naïve-like or central memory phenotype selected from $CCR7^+CD45RA^+$, $CD27^+CCR7^+$, or $CD62L^-CCR7^+$;

at or about 80%, at or about 85%, at or about 90%, at or about 95%, or at or about 99% of the CAR^+ T cells in the composition are of a naïve-like or central memory phenotype selected from $CCR7^+CD45RA^+$, $CD27^+CCR7^+$, or $CD62L^-CCR7^+$; and/or

at or about 80%, at or about 85%, at or about 90%, at or about 95%, or at or about 99% of the CAR^+ T cells in the composition are of a naïve-like or central memory phenotype that is $CD27^+CCR7^+$.

44. The use of claim 42 or claim 43, wherein:

at least or at least about 50%, 60%, 70%, 80%, or 85% of the $CD4^+CAR^+$ T cells in the composition are of a naïve-like or central memory phenotype that is $CCR7^+CD45RA^+$ or $CCR7^+CD45RA^-$;

at least or at least about 50%, 60%, 70%, 80%, or 85% of the $CD4^+CAR^+$ T cells in the composition are of a naïve-like or central memory phenotype that is $CD27^+CCR7^+$;

at least or at least about 50%, 60%, 70%, 80%, or 85% of the $CD8^+CAR^+$ T cells in the composition are of a naïve-like or central memory phenotype that is $CCR7^+CD45RA^+$ or $CCR7^+CD45RA^-$; and/or

at least or at least about 50%, 60%, 70%, 80%, or 85% of the $CD8^+CAR^+$ T cells in the composition are of a naïve-like or central memory phenotype that is $CD27^+CCR7^+$.

45. The use of any one of claims 42-44, wherein the CAR comprises a transmembrane domain, optionally a transmembrane domain from a human CD28, 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.

46. The use of any one of claims 42-45, wherein the CAR comprises an scFv specific for BCMA, and wherein:

(i) the scFv comprises a variable heavy chain (V_H) region that is or comprises the amino acid sequence of SEQ ID NO: 116; and a variable light chain (V_L) region that is or comprises the amino acid sequence of SEQ ID NO: 119; and/or

(ii) the CAR comprises the sequence set forth in SEQ ID NO:19.

47. An article of manufacture comprising a composition comprising genetically engineered cells expressing a chimeric antigen receptor (CAR) that targets BCMA, and instructions for administering the composition of the cells in accordance with the method of any of claims 1-41.