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(54) Titre : RECEPTEUR D'ANTIGENE CHIMERIQUE CIBLANT LE BCMA ET SES UTILISATIONS
(54) Title: BCMA-TARGETING CHIMERIC ANTIGEN RECEPTOR, AND USES THEREOF

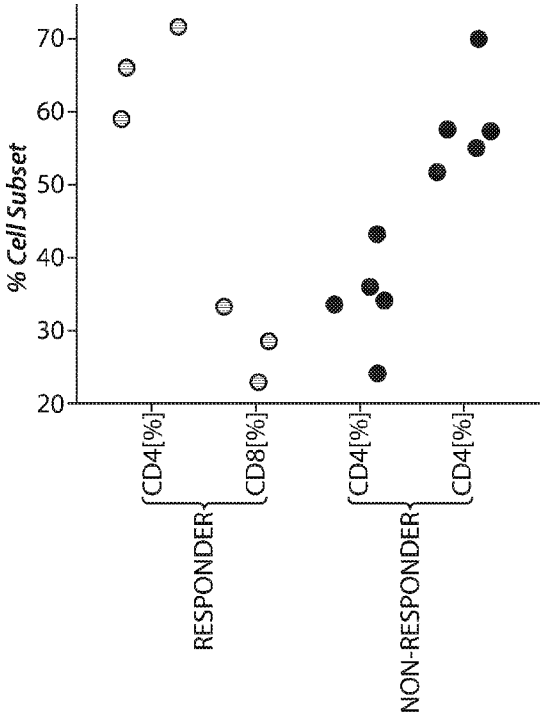


FIG. 1A

(57) Abrégé/Abstract:
The invention provides compositions and methods for treating diseases associated with expression of BCMA. The invention also relates to a method of administering a BCMA-targeting chimeric antigen receptor (CAR) therapy and an additional therapeutic agent.

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(54) Title: BCMA-TARGETING CHIMERIC ANTIGEN RECEPTOR, AND USES THEREOF

(57) Abstract: The invention provides compositions and methods for treating diseases associated with expression of BCMA. The invention also relates to a method of administering a BCMA-targeting chimeric antigen receptor (CAR) therapy and an additional therapeutic agent.

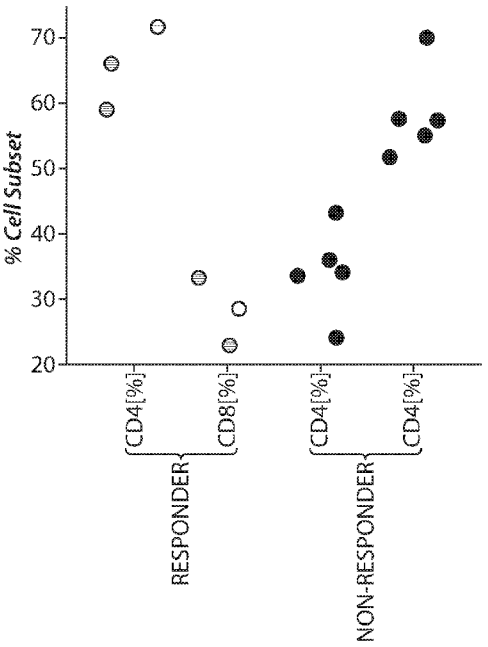


FIG. 1A

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CONTENANT LES PAGES 1 À 253

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JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 253

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NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

BCMA-TARGETING CHIMERIC ANTIGEN RECEPTOR, AND USES THEREOF

RELATED APPLICATIONS

This application claims priority to U.S. Serial No. 62/593,043 filed November 30, 2017, and U.S. Serial No. 62/752,010 filed October 29, 2018, the contents of each of which are incorporated herein by reference in their entirety.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on November 28, 2018, is named N2067-7137WO_SL.txt and is 1,411,518 bytes in size.

FIELD OF THE INVENTION

The present invention relates generally to the use of cells engineered to express a chimeric antigen receptor targeting B-cell maturation antigen protein (BCMA), optionally in combination with an additional therapeutic agent, to treat a disease associated with the expression of BCMA. The invention further describes prognostic biomarkers for BCMA-targeted therapies.

BACKGROUND OF THE INVENTION

BCMA is a tumor necrosis family receptor (TNFR) member expressed on cells of the B-cell lineage. BCMA expression is the highest on terminally differentiated B cells that assume the long lived plasma cell fate, including plasma cells, plasmablasts and a subpopulation of activated B cells and memory B cells. BCMA is involved in mediating the survival of plasma cells for maintaining long-term humoral immunity. The expression of BCMA has been recently linked to a number of cancers, autoimmune disorders, and infectious diseases. Cancers with increased expression of BCMA include some hematological cancers, such as multiple myeloma (MM), Hodgkin's and non-Hodgkin's lymphoma, diffuse large B-cell lymphoma (DLBCL), various leukemias (e.g., chronic lymphocytic leukaemia (CLL)), and glioblastoma.

Given the ongoing need for improved strategies for targeting diseases such as cancer, new compositions and methods for improving therapeutic agents that target BCMA, e.g., anti-BCMA chimeric antigen receptor (CAR) therapies, are highly desirable.

SUMMARY OF THE INVENTION

The disclosure features, at least in part, a method of treating a disease or disorder associated with expression of B-cell maturation antigen (BCMA, also known as TNFRSF17, BCM, or CD269). In certain embodiments, the disorder is a cancer, e.g., a hematological cancer. In some embodiments, the disclosure features a BCMA CAR-expressing cell therapy, e.g., as a monotherapy or in a combination therapy with an additional therapeutic agent. In some embodiments, the BCMA CAR-expressing cell therapy is a cell (e.g., a population of cells) that expresses a CAR molecule that binds BCMA. In some embodiments, the combination therapy maintains or has better clinical effectiveness as compared to either therapy alone. In one embodiment, the BCMA CAR-expressing cell therapy and the additional therapeutic agent are present in a single dose form, or as two or more dose forms. In one embodiment, provided herein is a composition comprising a BCMA CAR-expressing cell therapy and an additional therapeutic agent for use as a medicament. In one embodiment, provided herein is a composition comprising a BCMA CAR-expressing cell therapy and an additional therapeutic agent for use in the treatment of a disease associated with expression of BCMA. In one aspect, provided herein is a kit comprising a BCMA CAR-expressing cell therapy and an additional therapeutic agent. In some embodiments, the disclosure additional features methods of evaluating or predicting a subject's responsiveness to a BCMA CAR-expressing cell therapy, or methods of evaluating or predicting the potency of a BCMA CAR-expressing cell therapy in a subject. In some embodiments, a BCMA-targeting CAR therapy is manufactured or administered based on the acquisition of a level of a biomarker from a patient sample.

In one aspect, this invention features methods of predicting *in vivo* expansion of BCMA CAR T cells in a subject. In another aspect, featured herein are methods of predicting a subject's responsiveness to BCMA CAR T cells. In some embodiments, a higher CD4+:CD8+ T cell ratio in a leukapheresis product isolated from the subject can be used to predict greater *in vivo* expansion of BCMA CAR T cells in the subject and/or greater clinical responses of the subject to the BCMA CAR T cells. In some embodiments, a lower CD4+:CD8+ T cell ratio in a leukapheresis product isolated from the subject can be used to predict weaker *in vivo* expansion of BCMA CAR T cells in the subject and/or weaker clinical responses of the subject to the BCMA CAR T cells. In some embodiments, a higher CD4+:CD8+ T cell ratio in a seed culture at the start of the manufacturing of the BCMA CAR T cells (e.g., in a leukapheresis product after monocytes are removed) can be used to predict greater *in vivo* expansion of BCMA CAR T cells in the subject and/or greater clinical responses of the subject to the BCMA CAR T cells. In some embodiments, a lower CD4+:CD8+ T cell ratio in a seed culture at the start of the manufacturing of the BCMA CAR T cells (e.g., in a leukapheresis product after monocytes are removed) can be used to predict weaker *in vivo* expansion of BCMA CAR T cells in the subject and/or weaker clinical responses of the subject to the BCMA CAR T cells. In some embodiments, a

higher CD4+:CD8+ T cell ratio in the subject's peripheral blood and/or bone marrow prior to the administration of the BCMA CAR T cells can be used to predict greater *in vivo* expansion of BCMA CAR T cells in the subject. In some embodiments, a lower CD4+:CD8+ T cell ratio in the subject's peripheral blood and/or bone marrow prior to the administration of the BCMA CAR T cells can be used to predict weaker *in vivo* expansion of BCMA CAR T cells in the subject.

In some embodiments, a higher frequency of CD8+ T cells with an "early-memory" phenotype (e.g., a higher frequency of CD45RO-CD27+CD8+ T cells) in a leukapheresis product isolated from the subject can be used to predict greater *in vivo* expansion of BCMA CAR T cells in the subject and/or greater clinical responses of the subject to the BCMA CAR T cells. In some embodiments, a lower frequency of CD8+ T cells with an "early-memory" phenotype (e.g., a lower frequency of CD45RO-CD27+CD8+ T cells) in a leukapheresis product isolated from the subject can be used to predict weaker *in vivo* expansion of BCMA CAR T cells in the subject and/or weaker clinical responses of the subject to the BCMA CAR T cells.

In some embodiments, greater *in vitro* expansion of seeded cells from the subject during manufacturing of the BCMA CAR T cells can be used to predict greater *in vivo* expansion of BCMA CAR T cells in the subject. In some embodiments, weaker *in vitro* expansion of seeded cells from the subject during manufacturing of the BCMA CAR T cells can be used to predict weaker *in vivo* expansion of BCMA CAR T cells in the subject.

In one aspect, provided herein is a method of evaluating or predicting a subject's responsiveness to a BCMA CAR-expressing cell therapy, wherein the subject has a disease associated with the expression of BCMA, comprising:

acquiring a value for one, two, three, four, five, or all of:

(i) the level or activity of CD4+ immune effector cells (e.g., CD4+ T cells) relative to the level or activity of CD8+ immune effector cells (e.g., CD8+ T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample), in a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or in the subject's peripheral blood and/or bone marrow prior to the administration of the BCMA CAR-expressing cell therapy,

(ii) the level or activity of CD8+ Tscm (stem cell memory T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(iii) the level or activity of HLADR-CD95+CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of

the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(iv) the level or activity of CD45RO-CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(v) the level or activity of CCR7+CD45RO-CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or

(vi) the proliferation of seeded cells from the subject during manufacturing of the BCMA CAR-expressing cell therapy, e.g., as measured by population doublings by day 9 (PDL9), wherein:

(a) an increase in the value of one, two, three, four, five, or all of (i)-(vi), as compared to a reference value, e.g., a non-responder reference value, is indicative or predictive of increased responsiveness of the subject to the BCMA CAR-expressing cell therapy; or

(b) a decrease in the value of one, two, three, four, five, or all of (i)-(vi), as compared to a reference value, e.g., a responder reference value, is indicative or predictive of decreased responsiveness of the subject to the BCMA CAR-expressing cell therapy,

thereby evaluating or predicting the subject's responsiveness to the BCMA CAR-expressing cell therapy.

In some embodiments, the method comprises acquiring a value for the level or activity of CD4+ immune effector cells (e.g., CD4+ T cells) relative to the level or activity of CD8+ immune effector cells (e.g., CD8+ T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample), in a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or in the subject's peripheral blood and/or bone marrow prior to the administration of the BCMA CAR-expressing cell therapy. In some embodiments, the method comprises acquiring a value for the level or activity of CD8+ Tscm (stem cell memory T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)). In some embodiments, the method comprises acquiring a value for the level or activity of HLADR-CD95+CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)). In some embodiments, the method comprises acquiring a value for the level or activity of

CD45RO-CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)). In some embodiments, the method comprises acquiring a value for the level or activity of CCR7+CD45RO-CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)). In some embodiments, the method comprises acquiring a value for the proliferation of seeded cells from the subject during manufacturing of the BCMA CAR-expressing cell therapy, e.g., population doublings by day 9 (PDL9).

In some embodiments, the increase in the value of one, two, three, four, five, or all of (i)-(vi), as compared to a reference value, e.g., a non-responder reference value, is indicative or predictive of increased responsiveness of the subject to the BCMA CAR-expressing cell therapy. In some embodiments, the decrease in the value of one, two, three, four, five, or all of (i)-(vi), as compared to a reference value, e.g., a responder reference value, is indicative or predictive of decreased responsiveness of the subject to the BCMA CAR-expressing cell therapy.

In some embodiments, the increase in the value of one, two, three, four, five, or all of (i)-(vi), as compared to a reference value, e.g., a non-responder reference value, is indicative or predictive of one, two, three, or all of:

(a) increased responsiveness of the subject to the BCMA CAR-expressing cell therapy;

(b) the subject as a responder of the BCMA CAR-expressing cell therapy;

(c) the subject as suitable for the BCMA CAR-expressing cell therapy; or

(d) increased expansion of the BCMA CAR-expressing cell therapy in the subject, e.g., as measured by an assay disclosed herein, e.g., as measured by the copy number of CAR transgenes per µg DNA using qPCR.

In some embodiments, the increase in the value of one, two, three, four, five, or all of (i)-(vi), as compared to a reference value, e.g., a non-responder reference value, is indicative or predictive of increased responsiveness of the subject to the BCMA CAR-expressing cell therapy. In some embodiments, the increase in the value of one, two, three, four, five, or all of (i)-(vi), as compared to a reference value, e.g., a non-responder reference value, is indicative or predictive of the subject as a responder of the BCMA CAR-expressing cell therapy. In some embodiments, the increase in the value of one, two, three, four, five, or all of (i)-(vi), as compared to a reference value, e.g., a non-responder reference value, is indicative or predictive of the subject as suitable for the BCMA CAR-expressing cell therapy. In some embodiments, the increase in the value of one, two, three, four, five, or all of (i)-(vi), as compared to a reference value, e.g., a non-responder reference value, is indicative or predictive of

increased expansion of the BCMA CAR-expressing cell therapy in the subject, e.g., as measured by an assay disclosed herein, e.g., as measured by the copy number of CAR transgenes per µg DNA using qPCR.

In some embodiments, the decrease in the value of one, two, three, four, five, or all of (i)-(vi), as compared to a reference value, e.g., a responder reference value, is indicative or predictive of one, two, or all of:

(a) decreased responsiveness of the subject to the BCMA CAR-expressing cell therapy;

(b) the subject as a non-responder of the BCMA CAR-expressing cell therapy; or

(c) decreased expansion of the BCMA CAR-expressing cell therapy in the subject, e.g., as measured by an assay disclosed herein, e.g., as measured by the copy number of CAR transgenes per µg DNA using qPCR.

In some embodiments, the decrease in the value of one, two, three, four, five, or all of (i)-(vi), as compared to a reference value, e.g., a responder reference value, is indicative or predictive of decreased responsiveness of the subject to the BCMA CAR-expressing cell therapy. In some embodiments, the decrease in the value of one, two, three, four, five, or all of (i)-(vi), as compared to a reference value, e.g., a responder reference value, is indicative or predictive of the subject as a non-responder of the BCMA CAR-expressing cell therapy. In some embodiments, the decrease in the value of one, two, three, four, five, or all of (i)-(vi), as compared to a reference value, e.g., a responder reference value, is indicative or predictive of decreased expansion of the BCMA CAR-expressing cell therapy in the subject, e.g., as measured by an assay disclosed herein, e.g., as measured by the copy number of CAR transgenes per µg DNA using qPCR.

In some embodiments, the value for the level or activity of CD4+ immune effector cells (e.g., CD4+ T cells) relative to the level or activity of CD8+ immune effector cells (e.g., CD8+ T cells) comprises a ratio of the amount of CD4+ immune effector cells (e.g., CD4+ T cells) to the amount of CD8+ immune effector cells (e.g., CD8+ T cells), e.g., as measured by an assay disclosed herein, e.g., flow cytometry. In some embodiments,

In some embodiments, the ratio being:

(1) greater than or equal to 1 (e.g., between 1 and 5, e.g., between 1 and 3.5); or

(2) greater than or equal to 1.6 (e.g., between 1.6 and 5, e.g., between 1.6 and 3.5),

is indicative or predictive of one, two, three, or all of:

(a) increased responsiveness of the subject to the BCMA CAR-expressing cell therapy;

(b) the subject as a responder of the BCMA CAR-expressing cell therapy;

(c) the subject as suitable for the BCMA CAR-expressing cell therapy; or

(d) increased expansion of the BCMA CAR-expressing cell therapy in the subject, e.g., as measured by an assay disclosed herein, e.g., as measured by the copy number of CAR transgenes per µg DNA using qPCR.

In some embodiments, the ratio being less than 1 (e.g., between 0.001 and 1) is indicative or predictive of one, two, or all of:

(a) decreased responsiveness of the subject to the BCMA CAR-expressing cell therapy;

(b) the subject as a non-responder of the BCMA CAR-expressing cell therapy; or

(c) decreased expansion of the BCMA CAR-expressing cell therapy in the subject, e.g., as measured by an assay disclosed herein, e.g., as measured by the copy number of CAR transgenes per µg DNA using qPCR.

In some embodiments, the value for the level or activity of CD8+ Tscm (stem cell memory T cells) comprises the percentage of CD8+ Tscm (stem cell memory T cells) among CD8+ T cells, e.g., as measured by an assay disclosed herein, e.g., flow cytometry.

In some embodiments, the value for the level or activity of HLADR-CD95+CD27+CD8+ cells comprises the percentage of HLADR-CD95+CD27+CD8+ cells among CD8+ T cells, e.g., as measured by an assay disclosed herein, e.g., flow cytometry.

In some embodiments, the percentage of HLADR-CD95+CD27+CD8+ cells among CD8+ T cells being greater than or equal to 25% (e.g., between 30% and 90%, e.g., between 35% and 85%, e.g., between 40% and 80%, e.g., between 45% and 75%, e.g., between 50% and 75%) is indicative or predictive of one, two, three, or all of:

(a) increased responsiveness of the subject to the BCMA CAR-expressing cell therapy;

(b) the subject as a responder of the BCMA CAR-expressing cell therapy;

(c) the subject as suitable for the BCMA CAR-expressing cell therapy; or

(d) increased expansion of the BCMA CAR-expressing cell therapy in the subject, e.g., as measured by an assay disclosed herein, e.g., as measured by the copy number of CAR transgenes per µg DNA using qPCR.

In some embodiments, the percentage of HLADR-CD95+CD27+CD8+ cells among CD8+ T cells being less than 25% (e.g., between 0.1% and 25%, e.g., between 0.1% and 22%, e.g., between 0.1% and 20%, e.g., between 0.1% and 18%, e.g., between 0.1% and 15%)) is indicative or predictive of one, two, or all of:

(a) decreased responsiveness of the subject to the BCMA CAR-expressing cell therapy;

(b) the subject as a non-responder of the BCMA CAR-expressing cell therapy; or

(c) decreased expansion of the BCMA CAR-expressing cell therapy in the subject, e.g., as measured by an assay disclosed herein, e.g., as measured by the copy number of CAR transgenes per µg DNA using qPCR.

In some embodiments, the value for the level or activity of CD45RO-CD27+CD8+ cells comprises the percentage of CD45RO-CD27+CD8+ cells among CD8+ T cells, e.g., as measured by an assay disclosed herein, e.g., flow cytometry.

In some embodiments, the percentage of CD45RO-CD27+CD8+ cells among CD8+ T cells being greater than or equal to 20% (e.g., between 20% and 90%, e.g., between 20% and 80%, e.g., between 20% and 70%, e.g., between 20% and 60%) is indicative or predictive of one, two, three, or all of:

(a) increased responsiveness of the subject to the BCMA CAR-expressing cell therapy;

(b) the subject as a responder of the BCMA CAR-expressing cell therapy;

(c) the subject as suitable for the BCMA CAR-expressing cell therapy; or

(d) increased expansion of the BCMA CAR-expressing cell therapy in the subject, e.g., as measured by an assay disclosed herein, e.g., as measured by the copy number of CAR transgenes per µg DNA using qPCR.

In some embodiments, the percentage of CD45RO-CD27+CD8+ cells among CD8+ T cells being less than 20% (e.g., between 0.1% and 20%, e.g., between 0.1% and 18%, e.g., between 0.1% and 15%, e.g., between 0.1% and 12%, e.g., between 0.1% and 10%) is indicative or predictive of one, two, or all of:

(a) decreased responsiveness of the subject to the BCMA CAR-expressing cell therapy;

(b) the subject as a non-responder of the BCMA CAR-expressing cell therapy; or

(c) decreased expansion of the BCMA CAR-expressing cell therapy in the subject, e.g., as measured by an assay disclosed herein, e.g., as measured by the copy number of CAR transgenes per µg DNA using qPCR.

In some embodiments, the value for the level or activity of CCR7+CD45RO-CD27+CD8+ cells comprises the percentage of CCR7+CD45RO-CD27+CD8+ cells among CD8+ T cells, e.g., as measured by an assay disclosed herein, e.g., flow cytometry.

In some embodiments, the percentage of CCR7+CD45RO-CD27+CD8+ cells among CD8+ T cells being greater than or equal to 15% (e.g., between 15% and 90%, e.g., between 15% and 80%, e.g., between 15% and 70%, e.g., between 15% and 60%, e.g., between 15% and 50%) is indicative or predictive of one, two, three, or all of:

(a) increased responsiveness of the subject to the BCMA CAR-expressing cell therapy;

(b) the subject as a responder of the BCMA CAR-expressing cell therapy;

(c) the subject as suitable for the BCMA CAR-expressing cell therapy; or

(d) increased expansion of the BCMA CAR-expressing cell therapy in the subject, e.g., as measured by an assay disclosed herein, e.g., as measured by the copy number of CAR transgenes per µg DNA using qPCR.

In some embodiments, the percentage of CCR7+CD45RO-CD27+CD8+ cells among CD8+ T cells being less than 15% (e.g., between 0.1% and 15%, e.g., between 0.1% and 12%, e.g., between 0.1% and 10%, e.g., between 0.1% and 8%) is indicative or predictive of one, two, or all of:

(a) decreased responsiveness of the subject to the BCMA CAR-expressing cell therapy;

(b) the subject as a non-responder of the BCMA CAR-expressing cell therapy; or

(c) decreased expansion of the BCMA CAR-expressing cell therapy in the subject, e.g., as measured by an assay disclosed herein, e.g., as measured by the copy number of CAR transgenes per μg DNA using qPCR.

In some embodiments, the value for the proliferation of seeded cells from the subject during manufacturing of the BCMA CAR-expressing cell therapy comprises the fold expansion of seeded cells from the subject during manufacturing (e.g., total cell counts at the end of manufacturing relative to at the start of manufacturing) of the BCMA CAR-expressing cell therapy, e.g., as measured by an assay disclosed herein, e.g., as measured by cell counting.

In some embodiments, the method further comprises performing:

manufacturing the BCMA CAR-expressing cell therapy using cells (e.g., T cells) from the subject and administering the BCMA CAR-expressing cell therapy to the subject; or

administering, e.g., initiating administering or continuing administering, the BCMA CAR-expressing cell therapy to the subject, when:

(a) the subject was indicated or predicted to have increased responsiveness to the BCMA CAR-expressing cell therapy;

(b) the subject was indicated or predicted as a responder of the BCMA CAR-expressing cell therapy;

(c) the subject was indicated or predicted as suitable for the BCMA CAR-expressing cell therapy; or

(d) the BCMA CAR-expressing cell therapy was indicated or predicted to have increased expansion in the subject, e.g., as measured by an assay disclosed herein, e.g., as measured by the copy number of CAR transgenes per μg DNA using qPCR.

In some embodiments, the method further comprises performing one, two, three, four, five, six, seven, or all of:

administering an altered dosing regimen of the BCMA CAR-expressing cell therapy (e.g., a dosing regimen with a higher dose and/or more frequent administration than a reference dosing regimen) to the subject;

administering a second therapy (e.g., a second therapy that is not the BCMA CAR-expressing cell therapy) to the subject;

administering the BCMA CAR-expressing cell therapy and a second therapy to the subject;

discontinuing administration of the BCMA CAR-expressing cell therapy and optionally administering a second therapy to the subject;

modifying a manufacturing process of the BCMA CAR-expressing cell therapy, e.g., enriching for CD4+ immune effector cells (e.g., CD4+ T cells) relative to CD8+ immune effector cells (CD8+ T cells) prior to introducing a nucleic acid encoding a BCMA CAR, and administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject;

modifying a manufacturing process of the BCMA CAR-expressing cell therapy, e.g., enriching for CD8+ Tscm (e.g., HLADR-CD95+CD27+CD8+ cells, CD45RO-CD27+CD8+ cells, or CCR7+CD45RO-CD27+CD8+ cells) prior to introducing a nucleic acid encoding a BCMA CAR, and administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject;

modifying a manufacturing process of the BCMA CAR-expressing cell therapy, e.g., increasing the proliferation of seeded cells from the subject during the manufacturing of the BCMA CAR-expressing cell therapy, and administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject; or

administering a pretreatment to the subject, wherein the pretreatment increases the ratio of the amount of CD4+ immune effector cells (e.g., CD4+ T cells) to the amount of CD8+ immune effector cells (e.g., CD8+ T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample), in a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or in the subject's peripheral blood and/or bone marrow prior to the administration of the BCMA CAR-expressing cell therapy, e.g., the pretreatment increases the ratio to greater than or equal to 1.6 (e.g., between 1.6 and 5, e.g., between 1.6 and 3.5), manufacturing the BCMA CAR-expressing cell therapy using cells (e.g., T cells) from the subject, and administering the BCMA CAR-expressing cell therapy to the subject, when:

(a) the subject was indicated or predicted to have decreased responsiveness to the BCMA CAR-expressing cell therapy;

(b) the subject was indicated or predicted as a non-responder of the BCMA CAR-expressing cell therapy; or

(c) the BCMA CAR-expressing cell therapy was indicated or predicted to have decreased expansion in the subject, e.g., as measured by an assay disclosed herein, e.g., as measured by the copy number of CAR transgenes per μg DNA using qPCR.

In one aspect, disclosed herein is a method of treating a subject having a disease associated with the expression of BCMA, comprising:

responsive to an increased value for one, two, three, four, five, or all of:

(i) the level or activity of CD4+ immune effector cells (e.g., CD4+ T cells) relative to the level or activity of CD8+ immune effector cells (e.g., CD8+ T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample), in a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or in the subject's peripheral blood and/or bone marrow prior to the administration of the BCMA CAR-expressing cell therapy,

(ii) the level or activity of CD8+ Tscm (stem cell memory T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(iii) the level or activity of HLADR-CD95+CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(iv) the level or activity of CD45RO-CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(v) the level or activity of CCR7+CD45RO-CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or

(vi) the proliferation of seeded cells from the subject during manufacturing of a BCMA CAR-expressing cell therapy,

as compared to a reference value, e.g., a non-responder reference value, performing:

manufacturing a BCMA CAR-expressing cell therapy using cells (e.g., T cells) from the subject and administering the BCMA CAR-expressing cell therapy to the subject; or

administering, e.g., initiating administering or continuing administering, a BCMA CAR-expressing cell therapy to the subject,

thereby treating the subject having the disease associated with the expression of BCMA.

In some embodiments, the method comprises: responsive to an increased value for one, two, three, four, five, or all of (i)-(vi), identifying or predicting one, two, three, or all of:

(a) the subject as having increased responsiveness to the BCMA CAR-expressing cell therapy;

(b) the subject as a responder of the BCMA CAR-expressing cell therapy;

(c) the subject as suitable for the BCMA CAR-expressing cell therapy; or

(d) the BCMA CAR-expressing cell therapy as having increased expansion in the subject, e.g., as measured by an assay disclosed herein, e.g., as measured by the copy number of CAR transgenes per µg DNA using qPCR.

In one aspect, disclosed herein is a method of treating a subject having a disease associated with the expression of BCMA, comprising:

responsive to a decreased value for one, two, three, four, five, or all of:

(i) the level or activity of CD4+ immune effector cells (e.g., CD4+ T cells) relative to the level or activity of CD8+ immune effector cells (e.g., CD8+ T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample), in a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or in the subject's peripheral blood and/or bone marrow prior to the administration of the BCMA CAR-expressing cell therapy,

(ii) the level or activity of CD8+ Tscm (stem cell memory T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(iii) the level or activity of HLADR-CD95+CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(iv) the level or activity of CD45RO-CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(v) the level or activity of CCR7+CD45RO-CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or

(vi) the proliferation of seeded cells from the subject during manufacturing of a BCMA CAR-expressing cell therapy,

as compared to a reference value, e.g., a responder reference value, performing one, two, three, four, five, six, seven, or all of:

administering an altered dosing regimen of a BCMA CAR-expressing cell therapy (e.g., a dosing regimen with a higher dose and/or more frequent administration than a reference dosing regimen) to the subject;

administering a second therapy (e.g., a second therapy that is not a BCMA CAR-expressing cell therapy) to the subject;

administering a BCMA CAR-expressing cell therapy and a second therapy to the subject;

discontinuing administration of a BCMA CAR-expressing cell therapy and optionally administering a second therapy to the subject;

modifying a manufacturing process of a BCMA CAR-expressing cell therapy, e.g., enriching for CD4+ immune effector cells (e.g., CD4+ T cells) relative to CD8+ immune effector cells (CD8+ T cells) prior to introducing a nucleic acid encoding a BCMA CAR, and administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject;

modifying a manufacturing process of a BCMA CAR-expressing cell therapy, e.g., enriching for CD8+ Tscm (e.g., HLADR-CD95+CD27+CD8+ cells, CD45RO-CD27+CD8+ cells, or CCR7+CD45RO-CD27+CD8+ cells) prior to introducing a nucleic acid encoding a BCMA CAR, and administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject;

modifying a manufacturing process of the BCMA CAR-expressing cell therapy, e.g., increasing the proliferation of seeded cells from the subject during the manufacturing of the BCMA CAR-expressing cell therapy, and administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject; or

administering a pretreatment to the subject, wherein the pretreatment increases the ratio of the amount of CD4+ immune effector cells (e.g., CD4+ T cells) to the amount of CD8+ immune effector cells (e.g., CD8+ T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample), in a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or in the subject's peripheral blood and/or bone marrow prior to the administration of the BCMA CAR-expressing cell therapy, e.g., the pretreatment increases the ratio to greater than or equal to 1.6 (e.g., between 1.6 and 5, e.g., between 1.6 and 3.5), manufacturing the BCMA CAR-expressing cell therapy using cells (e.g., T cells) from the subject, and administering the BCMA CAR-expressing cell therapy to the subject,

thereby treating the subject having the disease associated with the expression of BCMA.

In some embodiments, the method comprises: response to a decreased value for one, two, three, four, five, or all of (i)-(vi), identifying or predicting one, two, or all of:

(a) the subject as having decreased responsiveness to the BCMA CAR-expressing cell therapy;

(b) the subject as a non-responder of the BCMA CAR-expressing cell therapy; or

(c) the BCMA CAR-expressing cell therapy as having decreased expansion in the subject, e.g., as measured by an assay disclosed herein, e.g., as measured by the copy number of CAR transgenes per µg DNA using qPCR.

In some embodiments, the value for the level or activity of CD4+ immune effector cells (e.g., CD4+ T cells) relative to the level or activity of CD8+ immune effector cells (e.g., CD8+ T cells) comprises a ratio of the amount of CD4+ immune effector cells (e.g., CD4+ T cells) to the amount of CD8+ immune effector cells (e.g., CD8+ T cells), e.g., as measured by an assay disclosed herein, e.g., flow cytometry.

In some embodiments, the method comprises:

responsive to the ratio being:

(1) greater than or equal to 1 (e.g., between 1 and 5, e.g., between 1 and 3.5); or

(2) greater than or equal to 1.6 (e.g., between 1.6 and 5, e.g., between 1.6 and 3.5), performing:

manufacturing a BCMA CAR-expressing cell therapy using cells (e.g., T cells) from the subject and administering the BCMA CAR-expressing cell therapy to the subject; or

administering, e.g., initiating administering or continuing administering, a BCMA CAR-expressing cell therapy to the subject.

In some embodiments, the method comprises:

responsive to the ratio being less than 1 (e.g., between 0.001 and 1), performing one, two, three, four, five, six, seven, or all of:

administering an altered dosing regimen of a BCMA CAR-expressing cell therapy (e.g., a dosing regimen with a higher dose and/or more frequent administration than a reference dosing regimen) to the subject;

administering a second therapy (e.g., a second therapy that is not a BCMA CAR-expressing cell therapy) to the subject;

administering a BCMA CAR-expressing cell therapy and a second therapy to the subject;

discontinuing administration of a BCMA CAR-expressing cell therapy and optionally administering a second therapy to the subject;

modifying a manufacturing process of a BCMA CAR-expressing cell therapy, e.g., enriching for CD4+ immune effector cells (e.g., CD4+ T cells) relative to CD8+ immune effector cells (CD8+ T cells) prior to introducing a nucleic acid encoding a BCMA CAR, and administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject;

modifying a manufacturing process of a BCMA CAR-expressing cell therapy, e.g., enriching for CD8+ Tscm (e.g., HLADR-CD95+CD27+CD8+ cells, CD45RO-CD27+CD8+ cells, or

CCR7+CD45RO-CD27+CD8+ cells) prior to introducing a nucleic acid encoding a BCMA CAR, and administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject;

modifying a manufacturing process of the BCMA CAR-expressing cell therapy, e.g., increasing the proliferation of seeded cells from the subject during the manufacturing of the BCMA CAR-expressing cell therapy, and administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject; or

administering a pretreatment to the subject, wherein the pretreatment increases the ratio of the amount of CD4+ immune effector cells (e.g., CD4+ T cells) to the amount of CD8+ immune effector cells (e.g., CD8+ T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample), in a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or in the subject's peripheral blood and/or bone marrow prior to the administration of the BCMA CAR-expressing cell therapy, e.g., the pretreatment increases the ratio to greater than or equal to 1.6 (e.g., between 1.6 and 5, e.g., between 1.6 and 3.5), manufacturing the BCMA CAR-expressing cell therapy using cells (e.g., T cells) from the subject, and administering the BCMA CAR-expressing cell therapy to the subject.

In some embodiments, the value for the level or activity of CD8+ Tscm (stem cell memory T cells) comprises the percentage of CD8+ Tscm (stem cell memory T cells) among CD8+ T cells, e.g., as measured by an assay disclosed herein, e.g., flow cytometry.

In some embodiments, the value for the level or activity of HLADR-CD95+CD27+CD8+ cells comprises the percentage of HLADR-CD95+CD27+CD8+ cells among CD8+ T cells, e.g., as measured by an assay disclosed herein, e.g., flow cytometry.

In some embodiments, the method comprises:

responsive to the percentage of HLADR-CD95+CD27+CD8+ cells among CD8+ T cells being greater than or equal to 25% (e.g., between 30% and 90%, e.g., between 35% and 85%, e.g., between 40% and 80%, e.g., between 45% and 75%, e.g., between 50% and 75%), performing:

manufacturing a BCMA CAR-expressing cell therapy using cells (e.g., T cells) from the subject and administering the BCMA CAR-expressing cell therapy to the subject; or

administering, e.g., initiating administering or continuing administering, a BCMA CAR-expressing cell therapy to the subject.

In some embodiments, the method comprises:

responsive to the percentage of HLADR-CD95+CD27+CD8+ cells among CD8+ T cells being less than 25% (e.g., between 0.1% and 25%, e.g., between 0.1% and 22%, e.g., between 0.1% and 20%,

e.g., between 0.1% and 18%, e.g., between 0.1% and 15%), performing one, two, three, four, five, six, seven, or all of:

administering an altered dosing regimen of a BCMA CAR-expressing cell therapy (e.g., a dosing regimen with a higher dose and/or more frequent administration than a reference dosing regimen) to the subject;

administering a second therapy (e.g., a second therapy that is not a BCMA CAR-expressing cell therapy) to the subject;

administering a BCMA CAR-expressing cell therapy and a second therapy to the subject;

discontinuing administration of a BCMA CAR-expressing cell therapy and optionally administering a second therapy to the subject;

modifying a manufacturing process of a BCMA CAR-expressing cell therapy, e.g., enriching for CD4+ immune effector cells (e.g., CD4+ T cells) relative to CD8+ immune effector cells (CD8+ T cells) prior to introducing a nucleic acid encoding a BCMA CAR, and administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject;

modifying a manufacturing process of a BCMA CAR-expressing cell therapy, e.g., enriching for CD8+ Tscm (e.g., HLADR-CD95+CD27+CD8+ cells, CD45RO-CD27+CD8+ cells, or CCR7+CD45RO-CD27+CD8+ cells) prior to introducing a nucleic acid encoding a BCMA CAR, and administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject;

modifying a manufacturing process of the BCMA CAR-expressing cell therapy, e.g., increasing the proliferation of seeded cells from the subject during the manufacturing of the BCMA CAR-expressing cell therapy, and administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject; or

administering a pretreatment to the subject, wherein the pretreatment increases the ratio of the amount of CD4+ immune effector cells (e.g., CD4+ T cells) to the amount of CD8+ immune effector cells (e.g., CD8+ T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample), in a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or in the subject's peripheral blood and/or bone marrow prior to the administration of the BCMA CAR-expressing cell therapy, e.g., the pretreatment increases the ratio to greater than or equal to 1.6 (e.g., between 1.6 and 5, e.g., between 1.6 and 3.5), manufacturing the BCMA CAR-expressing cell therapy using cells (e.g., T cells) from the subject, and administering the BCMA CAR-expressing cell therapy to the subject.

In some embodiments, the value for the level or activity of CD45RO-CD27+CD8+ cells comprises the percentage of CD45RO-CD27+CD8+ cells among CD8+ T cells, e.g., as measured by an assay disclosed herein, e.g., flow cytometry.

In some embodiments, the method comprises:

responsive to the percentage of CD45RO-CD27+CD8+ cells among CD8+ T cells being greater than or equal to 20% (e.g., between 20% and 90%, e.g., between 20% and 80%, e.g., between 20% and 70%, e.g., between 20% and 60%), performing:

manufacturing a BCMA CAR-expressing cell therapy using cells (e.g., T cells) from the subject and administering the BCMA CAR-expressing cell therapy to the subject; or

administering, e.g., initiating administering or continuing administering, a BCMA CAR-expressing cell therapy to the subject.

In some embodiments, the method comprises:

responsive to the percentage of CD45RO-CD27+CD8+ cells among CD8+ T cells being less than 20% (e.g., between 0.1% and 20%, e.g., between 0.1% and 18%, e.g., between 0.1% and 15%, e.g., between 0.1% and 12%, e.g., between 0.1% and 10%), performing one, two, three, four, five, six, seven, or all of:

administering an altered dosing regimen of a BCMA CAR-expressing cell therapy (e.g., a dosing regimen with a higher dose and/or more frequent administration than a reference dosing regimen) to the subject;

administering a second therapy (e.g., a second therapy that is not a BCMA CAR-expressing cell therapy) to the subject;

administering a BCMA CAR-expressing cell therapy and a second therapy to the subject;

discontinuing administration of a BCMA CAR-expressing cell therapy and optionally administering a second therapy to the subject;

modifying a manufacturing process of a BCMA CAR-expressing cell therapy, e.g., enriching for CD4+ immune effector cells (e.g., CD4+ T cells) relative to CD8+ immune effector cells (CD8+ T cells) prior to introducing a nucleic acid encoding a BCMA CAR, and administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject;

modifying a manufacturing process of a BCMA CAR-expressing cell therapy, e.g., enriching for CD8+ Tscm (e.g., HLADR-CD95+CD27+CD8+ cells, CD45RO-CD27+CD8+ cells, or CCR7+CD45RO-CD27+CD8+ cells) prior to introducing a nucleic acid encoding a BCMA CAR, and administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject;

modifying a manufacturing process of the BCMA CAR-expressing cell therapy, e.g., increasing the proliferation of seeded cells from the subject during the manufacturing of the BCMA CAR-

expressing cell therapy, and administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject; or

administering a pretreatment to the subject, wherein the pretreatment increases the ratio of the amount of CD4+ immune effector cells (e.g., CD4+ T cells) to the amount of CD8+ immune effector cells (e.g., CD8+ T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample), in a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or in the subject's peripheral blood and/or bone marrow prior to the administration of the BCMA CAR-expressing cell therapy, e.g., the pretreatment increases the ratio to greater than or equal to 1.6 (e.g., between 1.6 and 5, e.g., between 1.6 and 3.5), manufacturing the BCMA CAR-expressing cell therapy using cells (e.g., T cells) from the subject, and administering the BCMA CAR-expressing cell therapy to the subject.

In some embodiments, the value for the level or activity of CCR7+CD45RO-CD27+CD8+ cells comprises the percentage of CCR7+CD45RO-CD27+CD8+ cells among CD8+ T cells, e.g., as measured by an assay disclosed herein, e.g., flow cytometry.

In some embodiments, the method comprises:

responsive to the percentage of CCR7+CD45RO-CD27+CD8+ cells among CD8+ T cells being greater than or equal to 15% (e.g., between 15% and 90%, e.g., between 15% and 80%, e.g., between 15% and 70%, e.g., between 15% and 60%, e.g., between 15% and 50%), performing:

manufacturing a BCMA CAR-expressing cell therapy using cells (e.g., T cells) from the subject and administering the BCMA CAR-expressing cell therapy to the subject; or

administering, e.g., initiating administering or continuing administering, a BCMA CAR-expressing cell therapy to the subject.

In some embodiments, the method comprises:

responsive to the percentage of CCR7+CD45RO-CD27+CD8+ cells among CD8+ T cells being less than 15% (e.g., between 0.1% and 15%, e.g., between 0.1% and 12%, e.g., between 0.1% and 10%, e.g., between 0.1% and 8%), performing one, two, three, four, five, six, seven, or all of:

administering an altered dosing regimen of a BCMA CAR-expressing cell therapy (e.g., a dosing regimen with a higher dose and/or more frequent administration than a reference dosing regimen) to the subject;

administering a second therapy (e.g., a second therapy that is not a BCMA CAR-expressing cell therapy) to the subject;

administering a BCMA CAR-expressing cell therapy and a second therapy to the subject;

discontinuing administration of a BCMA CAR-expressing cell therapy and optionally administering a second therapy to the subject;

modifying a manufacturing process of a BCMA CAR-expressing cell therapy, e.g., enriching for CD4+ immune effector cells (e.g., CD4+ T cells) relative to CD8+ immune effector cells (CD8+ T cells) prior to introducing a nucleic acid encoding a BCMA CAR, and administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject;

modifying a manufacturing process of a BCMA CAR-expressing cell therapy, e.g., enriching for CD8+ Tscm (e.g., HLADR-CD95+CD27+CD8+ cells, CD45RO-CD27+CD8+ cells, or CCR7+CD45RO-CD27+CD8+ cells) prior to introducing a nucleic acid encoding a BCMA CAR, and administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject;

modifying a manufacturing process of the BCMA CAR-expressing cell therapy, e.g., increasing the proliferation of seeded cells from the subject during the manufacturing of the BCMA CAR-expressing cell therapy, and administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject; or

administering a pretreatment to the subject, wherein the pretreatment increases the ratio of the amount of CD4+ immune effector cells (e.g., CD4+ T cells) to the amount of CD8+ immune effector cells (e.g., CD8+ T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample), in a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or in the subject's peripheral blood and/or bone marrow prior to the administration of the BCMA CAR-expressing cell therapy, e.g., the pretreatment increases the ratio to greater than or equal to 1.6 (e.g., between 1.6 and 5, e.g., between 1.6 and 3.5), manufacturing the BCMA CAR-expressing cell therapy using cells (e.g., T cells) from the subject, and administering the BCMA CAR-expressing cell therapy to the subject.

In some embodiments, the value for the proliferation of seeded cells from the subject during manufacturing of the BCMA CAR-expressing cell therapy comprises the fold expansion of seeded cells from the subject during manufacturing (e.g., total cell counts at the end of manufacturing relative to at the start of manufacturing) of the BCMA CAR-expressing cell therapy, e.g., as measured by an assay disclosed herein, e.g., as measured by cell counting.

In one aspect, provided herein is a method of evaluating or predicting the potency of a BCMA CAR-expressing cell therapy in a subject, wherein the subject has a disease associated with the expression of BCMA and wherein the BCMA CAR-expressing cell therapy is manufactured using cells (e.g., T cells) from the subject, comprising:

acquiring a value for one, two, three, four, five, or all of:

(i) the level or activity of CD4+ immune effector cells (e.g., CD4+ T cells) relative to the level or activity of CD8+ immune effector cells (e.g., CD8+ T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample), in a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or in the subject's peripheral blood and/or bone marrow prior to the administration of the BCMA CAR-expressing cell therapy,

(ii) the level or activity of CD8+ Tscm (stem cell memory T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(iii) the level or activity of HLADR-CD95+CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(iv) the level or activity of CD45RO-CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(v) the level or activity of CCR7+CD45RO-CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or

(vi) the proliferation of seeded cells from the subject during manufacturing of the BCMA CAR-expressing cell therapy, e.g., as measured by population doublings by day 9 (PDL9), wherein:

(a) an increase in the value of one, two, three, four, five, or all of (i)-(vi), as compared to a reference value, e.g., a non-responder reference value, is indicative or predictive of increased potency of the BCMA CAR-expressing cell therapy in the subject; or

(b) a decrease in the value of one, two, three, four, five, or all of (i)-(vi), as compared to a reference value, e.g., a responder reference value, is indicative or predictive of decreased potency of the BCMA CAR-expressing cell therapy in the subject,

thereby evaluating or predicting the potency of the BCMA CAR-expressing cell therapy.

In some embodiments, the method comprises acquiring a value for the level or activity of CD4+ immune effector cells (e.g., CD4+ T cells) relative to the level or activity of CD8+ immune effector cells (e.g., CD8+ T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample), in a seed culture at the start of the manufacturing of the BCMA CAR-

expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or in the subject's peripheral blood and/or bone marrow prior to the administration of the BCMA CAR-expressing cell therapy. In some embodiments, the method comprises acquiring a value for the level or activity of CD8+ Tscm (stem cell memory T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)). In some embodiments, the method comprises acquiring a value for the level or activity of HLADR-CD95+CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)). In some embodiments, the method comprises acquiring a value for the level or activity of CD45RO-CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)). In some embodiments, the method comprises acquiring a value for the level or activity of CCR7+CD45RO-CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)). In some embodiments, the method comprises acquiring a value for the proliferation of seeded cells from the subject during manufacturing of the BCMA CAR-expressing cell therapy, e.g., population doublings by day 9 (PDL9).

In some embodiments, the increase in the value of one, two, three, four, five, or all of (i)-(vi), as compared to a reference value, e.g., a non-responder reference value, is indicative or predictive of increased expansion of the BCMA CAR-expressing cell therapy in the subject, e.g., as measured by an assay disclosed herein, e.g., as measured by the copy number of CAR transgenes per μg DNA using qPCR.

In some embodiments, the decrease in the value of one, two, three, four, five, or all of (i)-(vi), as compared to a reference value, e.g., a responder reference value, is indicative or predictive of decreased expansion of the BCMA CAR-expressing cell therapy in the subject, e.g., as measured by an assay disclosed herein, e.g., as measured by the copy number of CAR transgenes per μg DNA using qPCR.

In one aspect, disclosed herein is a method of manufacturing a BCMA CAR-expressing cell therapy, wherein the BCMA CAR-expressing cell therapy is manufactured using cells (e.g., T cells) from a subject, comprising:

acquiring a value for one, two, three, four, five, or all of:

(i) the level or activity of CD4+ immune effector cells (e.g., CD4+ T cells) relative to the level or activity of CD8+ immune effector cells (e.g., CD8+ T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample), in a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or in the subject's peripheral blood and/or bone marrow prior to the administration of the BCMA CAR-expressing cell therapy,

(ii) the level or activity of CD8+ Tscm (stem cell memory T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(iii) the level or activity of HLADR-CD95+CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(iv) the level or activity of CD45RO-CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(v) the level or activity of CCR7+CD45RO-CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or

(vi) the proliferation of seeded cells from the subject during manufacturing of the BCMA CAR-expressing cell therapy, e.g., as measured by population doublings by day 9 (PDL9), wherein:

responsive to an increase in the value of one, two, three, four, five, or all of (i)-(vi), as compared to a reference value, e.g., a non-responder reference value, manufacturing the BCMA CAR-expressing cell therapy using cells from the subject.

In some embodiments, the method comprises acquiring a value for the level or activity of CD4+ immune effector cells (e.g., CD4+ T cells) relative to the level or activity of CD8+ immune effector cells (e.g., CD8+ T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample), in a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or in the subject's peripheral blood and/or bone marrow prior to the administration of the BCMA CAR-expressing cell therapy. In some embodiments, the method comprises acquiring a value for the level or

activity of CD8+ Tscm (stem cell memory T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)). In some embodiments, the method comprises acquiring a value for the level or activity of HLADR-CD95+CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)). In some embodiments, the method comprises acquiring a value for the level or activity of CD45RO-CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)). In some embodiments, the method comprises acquiring a value for the level or activity of CCR7+CD45RO-CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)). In some embodiments, the method comprises acquiring a value for the proliferation of seeded cells from the subject during manufacturing of the BCMA CAR-expressing cell therapy, e.g., population doublings by day 9 (PDL9).

In one aspect, provided herein is a method of manufacturing a BCMA CAR-expressing cell therapy, wherein the BCMA CAR-expressing cell therapy is manufactured using cells (e.g., T cells) from a subject, comprising:

acquiring a value for one, two, three, four, five, or all of:

(i) the level or activity of CD4+ immune effector cells (e.g., CD4+ T cells) relative to the level or activity of CD8+ immune effector cells (e.g., CD8+ T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample), in a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or in the subject's peripheral blood and/or bone marrow prior to the administration of the BCMA CAR-expressing cell therapy,

(ii) the level or activity of CD8+ Tscm (stem cell memory T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(iii) the level or activity of HLADR-CD95+CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of

the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(iv) the level or activity of CD45RO-CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(v) the level or activity of CCR7+CD45RO-CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or

(vi) the proliferation of seeded cells from the subject during manufacturing of the BCMA CAR-expressing cell therapy, e.g., as measured by population doublings by day 9 (PDL9), wherein:

responsive to a decrease in the value of one, two, three, four, five, or all of (i)-(vi), as compared to a reference value, e.g., a responder reference value, performing one, two, three, or all of:

modifying a manufacturing process of the BCMA CAR-expressing cell therapy, e.g., enriching for CD4+ immune effector cells (e.g., CD4+ T cells) relative to CD8+ immune effector cells (CD8+ T cells) prior to introducing a nucleic acid encoding a BCMA CAR;

modifying a manufacturing process of the BCMA CAR-expressing cell therapy, e.g., enriching for CD8+ Tscm (e.g., HLADR-CD95+CD27+CD8+ cells, CD45RO-CD27+CD8+ cells, or CCR7+CD45RO-CD27+CD8+ cells) prior to introducing a nucleic acid encoding a BCMA CAR;

modifying a manufacturing process of the BCMA CAR-expressing cell therapy, e.g., increasing the proliferation of seeded cells from the subject during the manufacturing of the BCMA CAR-expressing cell therapy; or

administering a pretreatment to the subject, wherein the pretreatment increases the ratio of the amount of CD4+ immune effector cells (e.g., CD4+ T cells) to the amount of CD8+ immune effector cells (e.g., CD8+ T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample), in a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or in the subject's peripheral blood and/or bone marrow prior to the administration of the BCMA CAR-expressing cell therapy, e.g., the pretreatment increases the ratio to greater than or equal to 1.6 (e.g., between 1.6 and 5, e.g., between 1.6 and 3.5), and manufacturing the BCMA CAR-expressing cell therapy using cells (e.g., T cells) from the subject.

In some embodiments, the method comprises acquiring a value for the level or activity of CD4+ immune effector cells (e.g., CD4+ T cells) relative to the level or activity of CD8+ immune effector cells (e.g., CD8+ T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample

(e.g., a leukapheresis sample), in a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or in the subject's peripheral blood and/or bone marrow prior to the administration of the BCMA CAR-expressing cell therapy. In some embodiments, the method comprises acquiring a value for the level or activity of CD8+ Tscm (stem cell memory T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)). In some embodiments, the method comprises acquiring a value for the level or activity of HLADR-CD95+CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)). In some embodiments, the method comprises acquiring a value for the level or activity of CD45RO-CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)). In some embodiments, the method comprises acquiring a value for the level or activity of CCR7+CD45RO-CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)). In some embodiments, the method comprises acquiring a value for the proliferation of seeded cells from the subject during manufacturing of the BCMA CAR-expressing cell therapy, e.g., population doublings by day 9 (PDL9).

In some embodiments, the value for the level or activity of CD4+ immune effector cells (e.g., CD4+ T cells) relative to the level or activity of CD8+ immune effector cells (e.g., CD8+ T cells) comprises a ratio of the amount of CD4+ immune effector cells (e.g., CD4+ T cells) to the amount of CD8+ immune effector cells (e.g., CD8+ T cells), e.g., as measured by an assay disclosed herein, e.g., flow cytometry.

In some embodiments, the value for the level or activity of CD8+ Tscm (stem cell memory T cells) comprises the percentage of CD8+ Tscm (stem cell memory T cells) among CD8+ T cells, e.g., as measured by an assay disclosed herein, e.g., flow cytometry.

In some embodiments, the value for the level or activity of HLADR-CD95+CD27+CD8+ cells comprises the percentage of HLADR-CD95+CD27+CD8+ cells among CD8+ T cells, e.g., as measured by an assay disclosed herein, e.g., flow cytometry.

In some embodiments, the value for the level or activity of CD45RO-CD27+CD8+ cells comprises the percentage of CD45RO-CD27+CD8+ cells among CD8+ T cells, e.g., as measured by an assay disclosed herein, e.g., flow cytometry.

In some embodiments, the value for the level or activity of CCR7+CD45RO-CD27+CD8+ cells comprises the percentage of CCR7+CD45RO-CD27+CD8+ cells among CD8+ T cells, e.g., as measured by an assay disclosed herein, e.g., flow cytometry.

In some embodiments, the value for the proliferation of seeded cells from the subject during manufacturing of the BCMA CAR-expressing cell therapy comprises the fold expansion of seeded cells from the subject during manufacturing (e.g., total cell counts at the end of manufacturing relative to at the start of manufacturing) of the BCMA CAR-expressing cell therapy, e.g., as measured by an assay disclosed herein, e.g., as measured by cell counting.

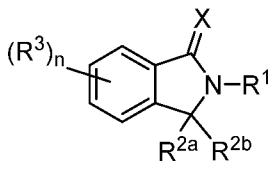
In certain embodiments of the foregoing aspects, the method comprises administering the BCMA CAR-expressing cell therapy to the subject in combination with one, two, or all of:

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

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

(3) an agent that treats the disease associated with the expression of BCMA.

In certain embodiments of the foregoing aspects, the method comprises administering the BCMA CAR-expressing cell therapy to the subject in combination with a compound of Formula (I) (COF1), wherein the COF1 is:



(I)

or a pharmaceutically acceptable salt, ester, hydrate, solvate, or tautomer thereof, wherein:

X is O or S;

R^1 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted by one or more R^4;

each of R^{2a} and R^{2b} is independently hydrogen or C_1-C_6 alkyl; or R^{2a} and R^{2b} together with the carbon atom to which they are attached form a carbonyl group or a thiocarbonyl group;

each of R^3 is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, halo, cyano, $-C(O)R^A$, $-C(O)OR^B$, $-OR^B$, $-N(R^C)(R^D)$, $-C(O)N(R^C)(R^D)$, $-N(R^C)C(O)R^A$, $-S(O)_xR^E$, -

$S(O)_xN(R^C)(R^D)$, or $-N(R^C)S(O)_xR^E$, wherein each alkyl, alkenyl, alkynyl, and heteroalkyl is independently and optionally substituted with one or more R^6;

each R^4 is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, halo, cyano, oxo, $-C(O)R^A$, $-C(O)OR^B$, $-OR^B$, $-N(R^C)(R^D)$, $-C(O)N(R^C)(R^D)$, $-N(R^C)C(O)R^A$, $-S(O)_xR^E$, $-S(O)_xN(R^C)(R^D)$, $-N(R^C)S(O)_xR^E$, carbocyclyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently and optionally substituted with one or more R^7;

each of R^A, R^B, R^C, R^D, and R^E is independently hydrogen or C_1-C_6 alkyl;

each R^6 is independently C_1-C_6 alkyl, oxo, cyano, $-OR^B$, $-N(R^C)(R^D)$, $-C(O)N(R^C)(R^D)$, $-N(R^C)C(O)R^A$, aryl, or heteroaryl, wherein each aryl and heteroaryl is independently and optionally substituted with one or more R^8;

each R^7 is independently halo, oxo, cyano, $-OR^B$, $-N(R^C)(R^D)$, $-C(O)N(R^C)(R^D)$, or $-N(R^C)C(O)R^A$;

each R^8 is independently C_1-C_6 alkyl, cyano, $-OR^B$, $-N(R^C)(R^D)$, $-C(O)N(R^C)(R^D)$, or $-N(R^C)C(O)R^A$;

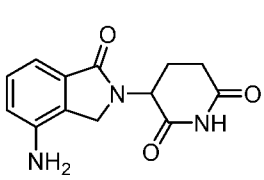
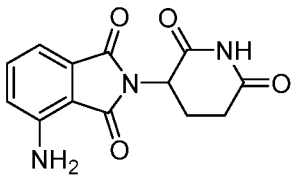
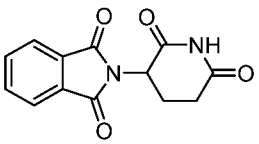
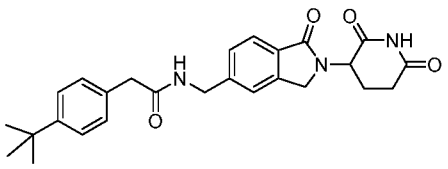
n is 0, 1, 2, 3 or 4; and

x is 0, 1, or 2, optionally wherein:

(1) the COF1 is an immunomodulatory imide drug (IMiD), or a pharmaceutically acceptable salt thereof;

(2) the COF1 is selected from the group consisting of lenalidomide, pomalidomide, thalidomide, and 2-(4-(tert-butyl)phenyl)-N-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)methyl)acetamide, or a pharmaceutically acceptable salt thereof;

(3) the COF1 is selected from the group consisting of:


,

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, and

, or a pharmaceutically acceptable salt thereof; or

(4) the COF1 is lenalidomide, or a pharmaceutically acceptable salt thereof.

In certain embodiments of the foregoing aspects, the method comprises administering the BCMA CAR-expressing cell therapy to the subject in combination with a kinase inhibitor, e.g., a BTK inhibitor, e.g., ibrutinib.

In certain embodiments of the foregoing aspects, the method comprises administering the BCMA CAR-expressing cell therapy to the subject in combination with a second CAR-expressing cell therapy.

In some embodiments, the second CAR-expressing cell therapy is a CD19 CAR-expressing cell therapy, e.g., a CD19 CAR-expressing cell therapy disclosed herein, e.g., CTL119 or CTL019. In some embodiments, the CD19 CAR-expressing cell therapy is administered after the administration of the BCMA CAR-expressing cell therapy, e.g., after CD19 expression is increased in the subject following the administration of the BCMA CAR-expressing cell therapy. In some embodiments, the CD19 CAR-expressing cell therapy comprises a cell (e.g., a population of cells) expressing a CD19 CAR. In some embodiments, the CD19 CAR comprises an amino acid sequence disclosed in Table 8, 9, or 10 (e.g., a CDR, scFv, or full-length amino acid sequence disclosed in Table 8, 9, or 10), or a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one, two, three or more substitutions, insertions or deletions, e.g., conserved substitutions.

In some embodiments, the second CAR-expressing cell therapy is a CD20 CAR-expressing cell therapy, e.g., a CD20 CAR-expressing cell therapy disclosed herein. In some embodiments, the CD20 CAR-expressing cell therapy is administered after the administration of the BCMA CAR-expressing cell therapy, e.g., after CD20 expression is increased in the subject following the administration of the BCMA CAR-expressing cell therapy. In some embodiments, the CD20 CAR-expressing cell therapy comprises a cell (e.g., a population of cells) expressing a CD20 CAR. In some embodiments, the CD20 CAR comprises an amino acid sequence disclosed in Table 11, 12, or 13 (e.g., a CDR, scFv, or full-length amino acid sequence disclosed in Table 11, 12, or 13), or a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one, two, three or more substitutions, insertions or deletions, e.g., conserved substitutions.

In some embodiments, the second CAR-expressing cell therapy is a CD22 CAR-expressing cell therapy, e.g., a CD22 CAR-expressing cell therapy disclosed herein. In some embodiments, the CD22 CAR-expressing cell therapy is administered after the administration of the BCMA CAR-expressing cell therapy, e.g., after CD22 expression is increased in the subject following the administration of the BCMA CAR-expressing cell therapy. In some embodiments, the CD22 CAR-expressing cell therapy comprises a cell (e.g., a population of cells) expressing a CD22 CAR. In some embodiments, the CD22 CAR comprises an amino acid sequence disclosed in Table 14 or 15 (e.g., a CDR, scFv, or full-length amino acid sequence disclosed in Table 14 or 15), or a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one, two, three or more substitutions, insertions or deletions, e.g., conserved substitutions.

In some embodiments, the second CAR-expressing cell therapy is a CAR-expressing cell therapy comprising a cell expressing a first CAR and a second CAR, wherein the first CAR is a BCMA

CAR (e.g., a BCMA CAR disclosed herein). In some embodiments, the second CAR is selected from the group consisting of a CD19 CAR (e.g., a CD19 CAR disclosed herein), a CD20 CAR (e.g., a CD20 CAR disclosed herein), and a CD22 CAR (e.g., a CD22 CAR disclosed herein). In some embodiments, the second CAR is a CD19 CAR (e.g., a CD19 CAR disclosed herein). In some embodiments, the CD19 CAR-expressing cell therapy comprises a cell (e.g., a population of cells) expressing a CD19 CAR. In some embodiments, the CD19 CAR comprises an amino acid sequence disclosed in Table 8, 9, or 10 (e.g., a CDR, scFv, or full-length amino acid sequence disclosed in Table 8, 9, or 10), or a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one, two, three or more substitutions, insertions or deletions, e.g., conserved substitutions. In some embodiments, the second CAR is a CD20 CAR (e.g., a CD20 CAR disclosed herein). In some embodiments, the CD20 CAR comprises an amino acid sequence disclosed in Table 11, 12, or 13 (e.g., a CDR, scFv, or full-length amino acid sequence disclosed in Table 11, 12, or 13), or a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one, two, three or more substitutions, insertions or deletions, e.g., conserved substitutions. In some embodiments, the second CAR is a CD22 CAR (e.g., a CD22 CAR disclosed herein). In some embodiments, the CD22 CAR comprises an amino acid sequence disclosed in Table 14 or 15 (e.g., a CDR, scFv, or full-length amino acid sequence disclosed in Table 14 or 15), or a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one, two, three or more substitutions, insertions or deletions, e.g., conserved substitutions.

In some embodiments, the second CAR-expressing cell therapy is a CAR-expressing cell therapy comprising a cell expressing a multispecific CAR, e.g., a bispecific CAR, that binds to a first antigen and a second antigen, wherein the first antigen is BCMA. In some embodiments, the second antigen is selected from the group consisting of CD19, CD20, and CD22. In some embodiments, the second antigen is CD19. In some embodiments, the second antigen is CD20. In some embodiments, the second antigen is CD22.

In certain embodiments of the foregoing aspects, the method comprises administering the BCMA CAR-expressing cell therapy to the subject in combination with a CD19 inhibitor, e.g., a CD19 inhibitor disclosed herein. In some embodiments, the CD19 inhibitor is administered after the administration of the BCMA CAR-expressing cell therapy, e.g., after CD19 expression is increased in the subject following the administration of the BCMA CAR-expressing cell therapy.

In certain embodiments of the foregoing aspects, the method comprises administering the BCMA CAR-expressing cell therapy to the subject in combination with a CD20 inhibitor, e.g., a CD20 inhibitor disclosed herein. In some embodiments, the CD20 inhibitor is a multispecific antibody molecule, e.g., a bispecific antibody molecule, that binds to CD20 and CD3, e.g., THG338. In some embodiments, the CD20 inhibitor is administered after the administration of the BCMA CAR-

expressing cell therapy, e.g., after CD20 expression is increased in the subject following the administration of the BCMA CAR-expressing cell therapy.

In certain embodiments of the foregoing aspects, the method comprises administering the BCMA CAR-expressing cell therapy to the subject in combination with a CD22 inhibitor, e.g., a CD22 inhibitor disclosed herein. In some embodiments, the CD22 inhibitor is administered after the administration of the BCMA CAR-expressing cell therapy, e.g., after CD22 expression is increased in the subject following the administration of the BCMA CAR-expressing cell therapy.

In certain embodiments of the foregoing aspects, the method comprises administering the BCMA CAR-expressing cell therapy to the subject in combination with a molecule that binds to Fc receptor like 2 (FCRL2) or Fc receptor like 5 (FCRL5). In some embodiments, the molecule is a CAR-expressing cell therapy comprising a cell expressing a CAR that binds to FCRL2 or FCRL5. In some embodiments, the molecule is a multispecific antibody molecule, e.g., a bispecific antibody molecule, that binds to a first antigen and a second antigen, wherein the first antigen is FCRL2 or FCRL5, optionally wherein the second antigen is CD3.

In certain embodiments of the foregoing aspects, the method comprises administering the BCMA CAR-expressing cell therapy to the subject in combination with an interleukin-15 (IL-15) polypeptide, an interleukin-15 receptor alpha (IL-15Ra) polypeptide, or a combination of both an IL-15 polypeptide and an IL-15Ra polypeptide, e.g., hetIL-15.

In certain embodiments of the foregoing aspects, the method comprises administering the BCMA CAR-expressing cell therapy to the subject in combination with an inhibitor of TGF beta.

In certain embodiments of the foregoing aspects, the method comprises administering the BCMA CAR-expressing cell therapy to the subject in combination with an EGFR inhibitor, e.g., an $EGFR^{mut}$-tyrosine kinase inhibitor (TKI). In some embodiments, the EGFR inhibitor is EGF816. In some embodiments, the EGFR inhibitor is (R,E)-N-(7-chloro-1-(1-(4-(dimethylamino)but-2-enoyl)azepan-3-yl)-1H-benzo[d]imidazol-2-yl)-2-methylisonicotinamide. In some embodiments, the EGFR inhibitor is compound A40 disclosed in Table 27.

In certain embodiments of the foregoing aspects, the method comprises administering the BCMA CAR-expressing cell therapy to the subject in combination with an adenosine A2AR antagonist. In some embodiments, the adenosine A2AR antagonist is selected from the group consisting of PBF509, CPI444, AZD4635, Vipadenant, GBV-2034, and AB928. In some embodiments, the adenosine A2AR antagonist is selected from the group consisting of 5-bromo-2,6-di-(1H-pyrazol-1-yl)pyrimidine-4-amine; (S)-7-(5-methylfuran-2-yl)-3-((6-(((tetrahydrofuran-3-yl)oxy)methyl)pyridin-2-yl)methyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-amine; (R)-7-(5-methylfuran-2-yl)-3-((6-(((tetrahydrofuran-3-yl)oxy)methyl)pyridin-2-yl)methyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-amine, or racemate thereof; 7-(5-methylfuran-2-yl)-3-((6-(((tetrahydrofuran-3-yl)oxy)methyl)pyridin-2-yl)methyl)-3H-

[1,2,3]triazolo[4,5-d]pyrimidin-5-amine; and 6-(2-chloro-6-methylpyridin-4-yl)-5-(4-fluorophenyl)-1,2,4-triazin-3-amine.

In certain embodiments of the foregoing aspects, the method comprises administering the BCMA CAR-expressing cell therapy to the subject in combination with an anti-CD73 antibody molecule, e.g., an anti-CD73 antibody molecule disclosed herein.

In certain embodiments of the foregoing aspects, the method comprises administering the BCMA CAR-expressing cell therapy to the subject in combination with a check point inhibitor. In some embodiments, the check point inhibitor is a PD-1 inhibitor. In some embodiments, the PD-1 inhibitor is selected from the group consisting of PDR001, Nivolumab, Pembrolizumab, Pidilizumab, MEDI0680, REGN2810, TSR-042, PF-06801591, and AMP-224. In some embodiments, the PD-1 inhibitor increases expansion of BCMA CAR-expressing cells in the subject, e.g. for at least 1, 2, 3, 4, or 5 weeks, e.g., for at least, 1, 2, 3, 4, 5, 10, 15, 20, 25, or 30-fold. In some embodiments, the BCMA CAR-expressing cells are administered to the subject prior to the administration of the PD-1 inhibitor. In some embodiments, the BCMA CAR-expressing cells do not expand or have minimal expansion (e.g., no more than 1, 2, 3, 4, 5, or 10-fold expansion) in the subject at the time the PD-1 inhibitor is administered. In some embodiments, the check point inhibitor is a PD-L1 inhibitor. In some embodiments, the PD-L1 inhibitor is selected from the group consisting of FAZ053, Atezolizumab, Avelumab, Durvalumab, and BMS-936559. In some embodiments, the PD-L1 inhibitor increases expansion of BCMA CAR-expressing cells in the subject, e.g. for at least 1, 2, 3, 4, or 5 weeks, e.g., for at least, 1, 2, 3, 4, 5, 10, 15, 20, 25, or 30-fold. In some embodiments, the BCMA CAR-expressing cells are administered to the subject prior to the administration of the PD-L1 inhibitor. In some embodiments, the BCMA CAR-expressing cells do not expand or have minimal expansion (e.g., no more than 1, 2, 3, 4, 5, or 10-fold expansion) in the subject at the time the PD-L1 inhibitor is administered. In some embodiments, the check point inhibitor is a LAG-3 inhibitor. In some embodiments, the LAG-3 inhibitor is selected from the group consisting of LAG525, BMS-986016, TSR-033, MK-4280 and REGN3767. In some embodiments, the check point inhibitor is a TIM-3 inhibitor. In some embodiments, the TIM-3 inhibitor is selected from the group consisting of MGB453, TSR-022, and LY3321367.

In certain embodiments of the foregoing aspects, the method comprises administering the BCMA CAR-expressing cell therapy to the subject in combination with an antibody molecule that binds to CD32B.

In certain embodiments of the foregoing aspects, the method comprises administering the BCMA CAR-expressing cell therapy to the subject in combination with an antibody molecule that binds to IL-17, e.g., an antagonistic antibody molecule that binds to IL-17, e.g., CJM112.

In certain embodiments of the foregoing aspects, the method comprises administering the BCMA CAR-expressing cell therapy to the subject in combination with an antibody molecule that binds to IL-1 beta.

In certain embodiments of the foregoing aspects, the method comprises administering the BCMA CAR-expressing cell therapy to the subject in combination with an inhibitor of indoleamine 2,3-dioxygenase (IDO) and/or tryptophan 2,3-dioxygenase (TDO), e.g., an IDO1 inhibitor. In some embodiments, the inhibitor of IDO and/or TDO is INCB24360, indoximod, NLG919, epacadostat, NLG919, or F001287. In some embodiments, the inhibitor of IDO and/or TDO is (4E)-4-[(3-chloro-4-fluoroanilino)-nitrosomethylidene]-1,2,5-oxadiazol-3-amine, 1-methyl-D-tryptophan, α-cyclohexyl-5H-Imidazo[5,1-a]isoindole-5-ethanol, or the D isomer of 1-methyl-tryptophan.

In one aspect, disclosed herein is a method of treating a subject having a disease associated with the expression of BCMA, comprising administering a BCMA CAR-expressing cell therapy and a second therapy to the subject. In some embodiments, the second therapy is a CD19 CAR-expressing cell therapy, e.g., a CD19 CAR-expressing cell therapy disclosed herein, e.g., CTL119 or CTL019. In some embodiments, the CD19 CAR-expressing cell therapy is administered after the administration of the BCMA CAR-expressing cell therapy, e.g., after CD19 expression is increased in the subject following the administration of the BCMA CAR-expressing cell therapy. In some embodiments, the CD19 CAR-expressing cell therapy comprises a cell (e.g., a population of cells) expressing a CD19 CAR. In some embodiments, the CD19 CAR comprises an amino acid sequence disclosed in Table 8, 9, or 10 (e.g., a CDR, scFv, or full-length amino acid sequence disclosed in Table 8, 9, or 10), or a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one, two, three or more substitutions, insertions or deletions, e.g., conserved substitutions.

In some embodiments, the second therapy is a CD20 CAR-expressing cell therapy, e.g., a CD20 CAR-expressing cell therapy disclosed herein. In some embodiments, the CD20 CAR-expressing cell therapy is administered after the administration of the BCMA CAR-expressing cell therapy, e.g., after CD20 expression is increased in the subject following the administration of the BCMA CAR-expressing cell therapy. In some embodiments, the CD20 CAR-expressing cell therapy comprises a cell (e.g., a population of cells) expressing a CD20 CAR. In some embodiments, the CD20 CAR comprises an amino acid sequence disclosed in Table 11, 12, or 13 (e.g., a CDR, scFv, or full-length amino acid sequence disclosed in Table 11, 12, or 13), or a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one, two, three or more substitutions, insertions or deletions, e.g., conserved substitutions.

In some embodiments, the second therapy is a CD22 CAR-expressing cell therapy, e.g., a CD22 CAR-expressing cell therapy disclosed herein. In some embodiments, the CD22 CAR-expressing cell

therapy is administered after the administration of the BCMA CAR-expressing cell therapy, e.g., after CD22 expression is increased in the subject following the administration of the BCMA CAR-expressing cell therapy. In some embodiments, the CD22 CAR-expressing cell therapy comprises a cell (e.g., a population of cells) expressing a CD22 CAR. In some embodiments, the CD22 CAR comprises an amino acid sequence disclosed in Table 14 or 15 (e.g., a CDR, scFv, or full-length amino acid sequence disclosed in Table 14 or 15), or a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one, two, three or more substitutions, insertions or deletions, e.g., conserved substitutions.

In some embodiments, the second therapy is a CAR-expressing cell therapy comprising a cell expressing a first CAR and a second CAR, wherein the first CAR is a BCMA CAR (e.g., a BCMA CAR disclosed herein). In some embodiments, the second CAR is selected from the group consisting of a CD19 CAR (e.g., a CD19 CAR disclosed herein), a CD20 CAR (e.g., a CD20 CAR disclosed herein), and a CD22 CAR (e.g., a CD22 CAR disclosed herein). In some embodiments, the second CAR is a CD19 CAR (e.g., a CD19 CAR disclosed herein). In some embodiments, the CD19 CAR-expressing cell therapy comprises a cell (e.g., a population of cells) expressing a CD19 CAR. In some embodiments, the CD19 CAR comprises an amino acid sequence disclosed in Table 8, 9, or 10 (e.g., a CDR, scFv, or full-length amino acid sequence disclosed in Table 8, 9, or 10), or a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one, two, three or more substitutions, insertions or deletions, e.g., conserved substitutions. In some embodiments, the second CAR is a CD20 CAR (e.g., a CD20 CAR disclosed herein). In some embodiments, the CD20 CAR comprises an amino acid sequence disclosed in Table 11, 12, or 13 (e.g., a CDR, scFv, or full-length amino acid sequence disclosed in Table 11, 12, or 13), or a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one, two, three or more substitutions, insertions or deletions, e.g., conserved substitutions. In some embodiments, the second CAR is a CD22 CAR (e.g., a CD22 CAR disclosed herein). In some embodiments, the CD22 CAR comprises an amino acid sequence disclosed in Table 14 or 15 (e.g., a CDR, scFv, or full-length amino acid sequence disclosed in Table 14 or 15), or a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one, two, three or more substitutions, insertions or deletions, e.g., conserved substitutions.

In some embodiments, the second therapy is a CAR-expressing cell therapy comprising a cell expressing a multispecific CAR, e.g., a bispecific CAR that binds to a first antigen and a second antigen, wherein the first antigen is BCMA. In some embodiments, the second antigen is selected from the group consisting of CD19, CD20, and CD22. In some embodiments, the second antigen is CD19. In some embodiments, the second antigen is CD20. In some embodiments, the second antigen is CD22.

In one aspect, disclosed herein is a method of treating a subject having a disease associated with the expression of BCMA, comprising administering a BCMA CAR-expressing cell therapy and a

second therapy to the subject. In some embodiments, the second therapy is a CD19 inhibitor, e.g., a CD19 inhibitor disclosed herein. In some embodiments, the CD19 inhibitor is administered after the administration of the BCMA CAR-expressing cell therapy, e.g., after CD19 expression is increased in the subject following the administration of the BCMA CAR-expressing cell therapy.

In some embodiments, the second therapy is a CD20 inhibitor, e.g., a CD20 inhibitor disclosed herein. In some embodiments, the CD20 inhibitor is a multispecific antibody molecule, e.g., a bispecific antibody molecule, that binds to CD20 and CD3, e.g., THG338. In some embodiments, the CD20 inhibitor is administered after the administration of the BCMA CAR-expressing cell therapy, e.g., after CD20 expression is increased in the subject following the administration of the BCMA CAR-expressing cell therapy.

In some embodiments, the second therapy is a CD22 inhibitor, e.g., a CD22 inhibitor disclosed herein. In some embodiments, the CD22 inhibitor is administered after the administration of the BCMA CAR-expressing cell therapy, e.g., after CD22 expression is increased in the subject following the administration of the BCMA CAR-expressing cell therapy.

In one aspect, disclosed herein is a method of treating a subject having a disease associated with the expression of BCMA, comprising administering a BCMA CAR-expressing cell therapy and a second therapy to the subject, wherein the second therapy is a molecule that binds to Fc receptor like 2 (FCRL2) or Fc receptor like 5 (FCRL5). In some embodiments, the molecule is a CAR-expressing cell therapy comprising a cell expressing a CAR that binds to FCRL2 or FCRL5. In some embodiments, the molecule is a multispecific antibody molecule, e.g., a bispecific antibody molecule, that binds to a first antigen and a second antigen, wherein the first antigen is FCRL2 or FCRL5, optionally wherein the second antigen is CD3.

In one aspect, disclosed herein is a method of treating a subject having a disease associated with the expression of BCMA, comprising administering a BCMA CAR-expressing cell therapy and a second therapy to the subject, wherein the second therapy is an inhibitor of TGF beta.

In one aspect, disclosed herein is a method of treating a subject having a disease associated with the expression of BCMA, comprising administering a BCMA CAR-expressing cell therapy and a second therapy to the subject, wherein the second therapy is an EGFR inhibitor, e.g., an $EGFR^{mut}$-tyrosine kinase inhibitor (TKI). In some embodiments, the EGFR inhibitor is EGF816. In some embodiments, the EGFR inhibitor is (R,E)-N-(7-chloro-1-(1-(4-(dimethylamino)but-2-enoyl)azepan-3-yl)-1H-benzo[d]imidazol-2-yl)-2-methylisonicotinamide. In some embodiments, the EGFR inhibitor is compound A40 disclosed in Table 27.

In one aspect, disclosed herein is a method of treating a subject having a disease associated with the expression of BCMA, comprising administering a BCMA CAR-expressing cell therapy and a second therapy to the subject, wherein the second therapy is an adenosine A2AR antagonist. In some

embodiments, the adenosine A2AR antagonist is selected from the group consisting of PBF509, CPI444, AZD4635, Vipadenant, GBV-2034, and AB928. In some embodiments, the adenosine A2AR antagonist is selected from the group consisting of 5-bromo-2,6-di-(1H-pyrazol-1-yl)pyrimidine-4-amine; (S)-7-(5-methylfuran-2-yl)-3-((6-(((tetrahydrofuran-3-yl)oxy)methyl)pyridin-2-yl)methyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-amine; (R)-7-(5-methylfuran-2-yl)-3-((6-(((tetrahydrofuran-3-yl)oxy)methyl)pyridin-2-yl)methyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-amine, or racemate thereof; 7-(5-methylfuran-2-yl)-3-((6-(((tetrahydrofuran-3-yl)oxy)methyl)pyridin-2-yl)methyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-amine; and 6-(2-chloro-6-methylpyridin-4-yl)-5-(4-fluorophenyl)-1,2,4-triazin-3-amine.

In one aspect, disclosed herein is a method of treating a subject having a disease associated with the expression of BCMA, comprising administering a BCMA CAR-expressing cell therapy and a second therapy to the subject, wherein the second therapy is an anti-CD73 antibody molecule, e.g., an anti-CD73 antibody molecule disclosed herein.

In one aspect, disclosed herein is a method of treating a subject having a disease associated with the expression of BCMA, comprising administering a BCMA CAR-expressing cell therapy and a second therapy to the subject, wherein the second therapy is a check point inhibitor. In some embodiments, the check point inhibitor is a PD-1 inhibitor. In some embodiments, the PD-1 inhibitor is selected from the group consisting of PDR001, Nivolumab, Pembrolizumab, Pidilizumab, MEDI0680, REGN2810, TSR-042, PF-06801591, and AMP-224. In some embodiments, the PD-1 inhibitor is administered after the administration of the BCMA CAR-expressing cell therapy, e.g., after the expression of PD-1 or PD-L1 is increased in the subject following the administration of the BCMA CAR-expressing cell therapy. In some embodiments, the PD-1 inhibitor increases expansion of BCMA CAR-expressing cells in the subject, e.g. for at least 1, 2, 3, 4, or 5 weeks, e.g., for at least, 1, 2, 3, 4, 5, 10, 15, 20, 25, or 30-fold. In some embodiments, the BCMA CAR-expressing cells are administered to the subject prior to the administration of the PD-1 inhibitor. In some embodiments, the BCMA CAR-expressing cells do not expand or have minimal expansion (e.g., no more than 1, 2, 3, 4, 5, or 10-fold expansion) in the subject at the time the PD-1 inhibitor is administered. In some embodiments, the check point inhibitor is a PD-L1 inhibitor. In some embodiments, the PD-L1 inhibitor is selected from the group consisting of FAZ053, Atezolizumab, Avelumab, Durvalumab, and BMS-936559. In some embodiments, the PD-L1 inhibitor is administered after the administration of the BCMA CAR-expressing cell therapy, e.g., after the expression of PD-1 or PD-L1 is increased in the subject following the administration of the BCMA CAR-expressing cell therapy. In some embodiments, the PD-L1 inhibitor increases expansion of BCMA CAR-expressing cells in the subject, e.g. for at least 1, 2, 3, 4, or 5 weeks, e.g., for at least, 1, 2, 3, 4, 5, 10, 15, 20, 25, or 30-fold. In some embodiments, the BCMA CAR-expressing cells are administered to the subject prior to the administration of the PD-L1 inhibitor.

In some embodiments, the BCMA CAR-expressing cells do not expand or have minimal expansion (e.g., no more than 1, 2, 3, 4, 5, or 10-fold expansion) in the subject at the time the PD-L1 inhibitor is administered. In some embodiments, the check point inhibitor is a LAG-3 inhibitor. In some embodiments, the LAG-3 inhibitor is selected from the group consisting of LAG525, BMS-986016, TSR-033, MK-4280 and REGN3767. In some embodiments, the LAG-3 inhibitor is administered after the administration of the BCMA CAR-expressing cell therapy, e.g., after the expression of LAG-3 is increased in the subject following the administration of the BCMA CAR-expressing cell therapy. In some embodiments, the check point inhibitor is a TIM-3 inhibitor. In some embodiments, the TIM-3 inhibitor is selected from the group consisting of MGB453, TSR-022, and LY3321367. In some embodiments, the TIM-3 inhibitor is administered after the administration of the BCMA CAR-expressing cell therapy, e.g., after the expression of TIM-3 is increased in the subject following the administration of the BCMA CAR-expressing cell therapy.

In one aspect, disclosed herein is a method of treating a subject having a disease associated with the expression of BCMA, comprising administering a BCMA CAR-expressing cell therapy and a second therapy to the subject, wherein the second therapy is an antibody molecule that binds to CD32B.

In one aspect, disclosed herein is a method of treating a subject having a disease associated with the expression of BCMA, comprising administering a BCMA CAR-expressing cell therapy and a second therapy to the subject, wherein the second therapy is an antibody molecule that binds to IL-17, e.g., an antagonistic antibody molecule that binds to IL-17, e.g., CJM112.

In one aspect, disclosed herein is a method of treating a subject having a disease associated with the expression of BCMA, comprising administering a BCMA CAR-expressing cell therapy and a second therapy to the subject, wherein the second therapy is an antibody molecule that binds to IL-1 beta.

In one aspect, disclosed herein is a method of treating a subject having a disease associated with the expression of BCMA, comprising administering a BCMA CAR-expressing cell therapy and a second therapy to the subject, wherein the second therapy is an inhibitor of indoleamine 2,3-dioxygenase (IDO) and/or tryptophan 2,3-dioxygenase (TDO), e.g., an IDO1 inhibitor. In some embodiments, the inhibitor of IDO and/or TDO is INCB24360, indoximod, NLG919, epacadostat, NLG919, or F001287. In some embodiments, the inhibitor of IDO and/or TDO is (4E)-4-[(3-chloro-4-fluoroanilino)-nitrosomethylidene]-1,2,5-oxadiazol-3-amine, 1-methyl-D-tryptophan, α-cyclohexyl-5H-Imidazo[5,1-a]isoindole-5-ethanol, or the D isomer of 1-methyl-tryptophan. In some embodiments, the inhibitor of IDO and/or TDO is administered after the administration of the BCMA CAR-expressing cell therapy, e.g., after IDO and/or TDO expression is increased in the subject following the administration of the BCMA CAR-expressing cell therapy.

In certain embodiments for the foregoing aspects, the second therapy is administered prior to, concurrently with, or subsequent to the administration of the BCMA CAR-expressing cell therapy.

In one aspect, disclosed herein is a method of treating a subject having a disease associated with the expression of BCMA, wherein the subject has received or is receiving a BCMA CAR-expressing cell therapy, comprising:

responsive to an increase in a value of the level or activity of an antigen in the subject, e.g., in a sample from the subject (e.g., a biopsy sample, e.g., a bone marrow biopsy sample), at at least one time point after the subject began receiving the BCMA CAR-expressing cell therapy, relative to a reference value, wherein the reference value is:

(i) the level or activity of the antigen in the subject, e.g., in a sample from the subject (e.g., a biopsy sample, e.g., a bone marrow biopsy sample), prior to the at least one time point (e.g., the level or activity of the antigen in the subject before the subject began receiving the BCMA CAR-expressing cell therapy, or the level or activity of the antigen in the subject after the subject began receiving the BCMA CAR-expressing cell therapy but prior to the at least one time point);

(ii) the level or activity of the antigen in a different subject having the disease associated with the expression of BCMA; or

(iii) an average level or activity of the antigen in a population of subjects having the disease associated with the expression of BCMA,

administering an inhibitor of the antigen to the subject, wherein:

(1) the antigen is CD19 and the inhibitor of the antigen is a CD19 inhibitor, optionally wherein the CD19 inhibitor is:

(a) a CD19 CAR-expressing cell therapy, e.g., a CD19 CAR-expressing cell therapy disclosed herein, e.g., CTL119 or CTL019;

(b) a CAR-expressing cell therapy comprising a cell expressing a first CAR and a second CAR, wherein the first CAR is a BCMA CAR (e.g., a BCMA CAR disclosed herein) and the second CAR is a CD19 CAR (e.g., a CD19 CAR disclosed herein); or

(c) a CAR-expressing cell therapy comprising a cell expressing a multispecific CAR, e.g., a bispecific CAR, that binds to BCMA and CD19,

(2) the antigen is CD20 and the inhibitor of the antigen is a CD20 inhibitor, optionally wherein the CD20 inhibitor is:

(d) a CD20 CAR-expressing cell therapy, e.g., a CD20 CAR-expressing cell therapy disclosed herein;

(e) a CAR-expressing cell therapy comprising a cell expressing a first CAR and a second CAR, wherein the first CAR is a BCMA CAR (e.g., a BCMA CAR disclosed herein) and the second CAR is a CD20 CAR (e.g., a CD20 CAR disclosed herein);

(f) a CAR-expressing cell therapy comprising a cell expressing a multispecific CAR, e.g., a bispecific CAR, that binds to BCMA and CD20; or

(g) a multispecific antibody molecule, e.g., a bispecific antibody molecule, that binds to CD20 and CD3, e.g., THG338,

(3) the antigen is CD22 and the inhibitor of the antigen is a CD22 inhibitor, optionally wherein the CD22 inhibitor is:

(h) a CD22 CAR-expressing cell therapy, e.g., a CD22 CAR-expressing cell therapy disclosed herein;

(i) a CAR-expressing cell therapy comprising a cell expressing a first CAR and a second CAR, wherein the first CAR is a BCMA CAR (e.g., a BCMA CAR disclosed herein) and the second CAR is a CD22 CAR (e.g., a CD22 CAR disclosed herein); or

(j) a CAR-expressing cell therapy comprising a cell expressing a multispecific CAR, e.g., a bispecific CAR, that binds to BCMA and CD22,

(4) the antigen is PD1 or PD-L1 and the inhibitor of the antigen is an anti-PD1 antibody molecule or an anti-PD-L1 antibody molecule, optionally wherein the inhibitor of the antigen is:

(k) PDR001, Nivolumab, Pembrolizumab, Pidilizumab, MEDI0680, REGN2810, TSR-042, PF-06801591, or AMP-224; or

(l) FAZ053, Atezolizumab, Avelumab, Durvalumab, or BMS-936559,

(5) the antigen is IDO or TDO and the inhibitor of the antigen is an inhibitor of IDO and/or TDO, optionally wherein the inhibitor of IDO and/or TDO is:

(m) INCB24360, indoximod, NLG919, epacadostat, NLG919, or F001287; or

(n) (4E)-4-[(3-chloro-4-fluoroanilino)-nitrosomethylidene]-1,2,5-oxadiazol-3-amine, 1-methyl-D-tryptophan, α-cyclohexyl-5H-Imidazo[5,1-a]isoindole-5-ethanol, or the D isomer of 1-methyl-tryptophan, or

(6) the antigen is TGF-beta and the inhibitor of the antigen is a TGF beta inhibitor.

In one aspect, disclosed herein is a method of treating a subject having a disease associated with the expression of BCMA, wherein the subject has received or is receiving a BCMA CAR-expressing cell therapy, comprising:

acquiring a value of the level or activity of an antigen in the subject, e.g., in a sample from the subject (e.g., a biopsy sample, e.g., a bone marrow biopsy sample), at at least one time point after the subject began receiving the BCMA CAR-expressing cell therapy,

responsive to an increase in the value relative to a reference value, wherein the reference value is:

(i) the level or activity of the antigen in the subject, e.g., in a sample from the subject (e.g., a biopsy sample, e.g., a bone marrow biopsy sample), prior to the at least one time point (e.g., the level or activity of the antigen in the subject before the subject began receiving the BCMA CAR-expressing cell therapy, or the level or activity of the antigen in the subject after the subject began receiving the BCMA CAR-expressing cell therapy but prior to the at least one time point);

(ii) the level or activity of the antigen in a different subject having the disease associated with the expression of BCMA; or

(iii) an average level or activity of the antigen in a population of subjects having the disease associated with the expression of BCMA,

administering an inhibitor of the antigen to the subject, wherein:

(1) the antigen is CD19 and the inhibitor of the antigen is a CD19 inhibitor, optionally wherein the CD19 inhibitor is:

(a) a CD19 CAR-expressing cell therapy, e.g., a CD19 CAR-expressing cell therapy disclosed herein, e.g., CTL119 or CTL019;

(b) a CAR-expressing cell therapy comprising a cell expressing a first CAR and a second CAR, wherein the first CAR is a BCMA CAR (e.g., a BCMA CAR disclosed herein) and the second CAR is a CD19 CAR (e.g., a CD19 CAR disclosed herein); or

(c) a CAR-expressing cell therapy comprising a cell expressing a multispecific CAR, e.g., a bispecific CAR, that binds to BCMA and CD19,

(2) the antigen is CD20 and the inhibitor of the antigen is a CD20 inhibitor, optionally wherein the CD20 inhibitor is:

(d) a CD20 CAR-expressing cell therapy, e.g., a CD20 CAR-expressing cell therapy disclosed herein;

(e) a CAR-expressing cell therapy comprising a cell expressing a first CAR and a second CAR, wherein the first CAR is a BCMA CAR (e.g., a BCMA CAR disclosed herein) and the second CAR is a CD20 CAR (e.g., a CD20 CAR disclosed herein);

(f) a CAR-expressing cell therapy comprising a cell expressing a multispecific CAR, e.g., a bispecific CAR, that binds to BCMA and CD20; or

(g) a multispecific antibody molecule, e.g., a bispecific antibody molecule, that binds to CD20 and CD3, e.g., THG338,

(3) the antigen is CD22 and the inhibitor of the antigen is a CD22 inhibitor, optionally wherein the CD22 inhibitor is:

(h) a CD22 CAR-expressing cell therapy, e.g., a CD22 CAR-expressing cell therapy disclosed herein;

(i) a CAR-expressing cell therapy comprising a cell expressing a first CAR and a second CAR, wherein the first CAR is a BCMA CAR (e.g., a BCMA CAR disclosed herein) and the second CAR is a CD22 CAR (e.g., a CD22 CAR disclosed herein); or

(j) a CAR-expressing cell therapy comprising a cell expressing a multispecific CAR, e.g., a bispecific CAR, that binds to BCMA and CD22,

(4) the antigen is PD1 or PD-L1 and the inhibitor of the antigen is an anti-PD1 antibody molecule or an anti-PD-L1 antibody molecule, optionally wherein the inhibitor of the antigen is:

(k) PDR001, Nivolumab, Pembrolizumab, Pidilizumab, MEDI0680, REGN2810, TSR-042, PF-06801591, or AMP-224; or

(l) FAZ053, Atezolizumab, Avelumab, Durvalumab, or BMS-936559,

(5) the antigen is IDO or TDO and the inhibitor of the antigen is an inhibitor of IDO and/or TDO, optionally wherein the inhibitor of IDO and/or TDO is:

(m) INCB24360, indoximod, NLG919, epacadostat, NLG919, or F001287; or

(n) (4E)-4-[(3-chloro-4-fluoroanilino)-nitrosomethylidene]-1,2,5-oxadiazol-3-amine, 1-methyl-D-tryptophan, α-cyclohexyl-5H-Imidazo[5,1-a]isoindole-5-ethanol, or the D isomer of 1-methyl-tryptophan, or

(6) the antigen is TGF-beta and the inhibitor of the antigen is a TGF beta inhibitor.

In one aspect, disclosed herein is a method of treating a subject having a disease associated with the expression of BCMA, comprising:

administering a BCMA CAR-expressing cell therapy to the subject,

responsive to an increase in a value of the level or activity of an antigen in the subject, e.g., in a sample from the subject (e.g., a biopsy sample, e.g., a bone marrow biopsy sample), at at least one time point after the subject began receiving the BCMA CAR-expressing cell therapy, relative to a reference value, wherein the reference value is:

(i) the level or activity of the antigen in the subject, e.g., in a sample from the subject (e.g., a biopsy sample, e.g., a bone marrow biopsy sample), prior to the at least one time point (e.g., the level or activity of the antigen in the subject before the subject began receiving the BCMA CAR-expressing cell therapy, or the level or activity of the antigen in the subject after the subject began receiving the BCMA CAR-expressing cell therapy but prior to the at least one time point);

(ii) the level or activity of the antigen in a different subject having the disease associated with the expression of BCMA; or

(iii) an average level or activity of the antigen in a population of subjects having the disease associated with the expression of BCMA,

administering an inhibitor of the antigen to the subject, wherein:

(1) the antigen is CD19 and the inhibitor of the antigen is a CD19 inhibitor, optionally wherein the CD19 inhibitor is:

(a) a CD19 CAR-expressing cell therapy, e.g., a CD19 CAR-expressing cell therapy disclosed herein, e.g., CTL119 or CTL019;

(b) a CAR-expressing cell therapy comprising a cell expressing a first CAR and a second CAR, wherein the first CAR is a BCMA CAR (e.g., a BCMA CAR disclosed herein) and the second CAR is a CD19 CAR (e.g., a CD19 CAR disclosed herein); or

(c) a CAR-expressing cell therapy comprising a cell expressing a multispecific CAR, e.g., a bispecific CAR, that binds to BCMA and CD19,

(2) the antigen is CD20 and the inhibitor of the antigen is a CD20 inhibitor, optionally wherein the CD20 inhibitor is:

(d) a CD20 CAR-expressing cell therapy, e.g., a CD20 CAR-expressing cell therapy disclosed herein;

(e) a CAR-expressing cell therapy comprising a cell expressing a first CAR and a second CAR, wherein the first CAR is a BCMA CAR (e.g., a BCMA CAR disclosed herein) and the second CAR is a CD20 CAR (e.g., a CD20 CAR disclosed herein);

(f) a CAR-expressing cell therapy comprising a cell expressing a multispecific CAR, e.g., a bispecific CAR, that binds to BCMA and CD20; or

(g) a multispecific antibody molecule, e.g., a bispecific antibody molecule, that binds to CD20 and CD3, e.g., THG338,

(3) the antigen is CD22 and the inhibitor of the antigen is a CD22 inhibitor, optionally wherein the CD22 inhibitor is:

(h) a CD22 CAR-expressing cell therapy, e.g., a CD22 CAR-expressing cell therapy disclosed herein;

(i) a CAR-expressing cell therapy comprising a cell expressing a first CAR and a second CAR, wherein the first CAR is a BCMA CAR (e.g., a BCMA CAR disclosed herein) and the second CAR is a CD22 CAR (e.g., a CD22 CAR disclosed herein); or

(j) a CAR-expressing cell therapy comprising a cell expressing a multispecific CAR, e.g., a bispecific CAR, that binds to BCMA and CD22,

(4) the antigen is PD1 or PD-L1 and the inhibitor of the antigen is an anti-PD1 antibody molecule or an anti-PD-L1 antibody molecule, optionally wherein the inhibitor of the antigen is:

(k) PDR001, Nivolumab, Pembrolizumab, Pidilizumab, MEDI0680, REGN2810, TSR-042, PF-06801591, or AMP-224; or

(l) FAZ053, Atezolizumab, Avelumab, Durvalumab, or BMS-936559,

(5) the antigen is IDO or TDO and the inhibitor of the antigen is an inhibitor of IDO and/or TDO, optionally wherein the inhibitor of IDO and/or TDO is:

(m) INCB24360, indoximod, NLG919, epacadostat, NLG919, or F001287; or

(n) (4E)-4-[(3-chloro-4-fluoroanilino)-nitrosomethylidene]-1,2,5-oxadiazol-3-amine, 1-methyl-D-tryptophan, α-cyclohexyl-5H-Imidazo[5,1-a]isoindole-5-ethanol, or the D isomer of 1-methyl-tryptophan, or

(6) the antigen is TGF-beta and the inhibitor of the antigen is a TGF beta inhibitor.

In one aspect, disclosed herein is method of treating a subject having a disease associated with the expression of BCMA, comprising:

administering a BCMA CAR-expressing cell therapy to the subject,

acquiring a value of the level or activity of an antigen in the subject, e.g., in a sample from the subject (e.g., a biopsy sample, e.g., a bone marrow biopsy sample), at at least one time point after the subject began receiving the BCMA CAR-expressing cell therapy,

responsive to an increase in the value relative to a reference value, wherein the reference value is:

(i) the level or activity of the antigen in the subject, e.g., in a sample from the subject (e.g., a biopsy sample, e.g., a bone marrow biopsy sample), prior to the at least one time point (e.g., the level or activity of the antigen in the subject before the subject began receiving the BCMA CAR-expressing cell therapy, or the level or activity of the antigen in the subject after the subject began receiving the BCMA CAR-expressing cell therapy but prior to the at least one time point);

(ii) the level or activity of the antigen in a different subject having the disease associated with the expression of BCMA; or

(iii) an average level or activity of the antigen in a population of subjects having the disease associated with the expression of BCMA,

administering an inhibitor of the antigen to the subject, wherein:

(1) the antigen is CD19 and the inhibitor of the antigen is a CD19 inhibitor, optionally wherein the CD19 inhibitor is:

(a) a CD19 CAR-expressing cell therapy, e.g., a CD19 CAR-expressing cell therapy disclosed herein, e.g., CTL119 or CTL019;

(b) a CAR-expressing cell therapy comprising a cell expressing a first CAR and a second CAR, wherein the first CAR is a BCMA CAR (e.g., a BCMA CAR disclosed herein) and the second CAR is a CD19 CAR (e.g., a CD19 CAR disclosed herein); or

(c) a CAR-expressing cell therapy comprising a cell expressing a multispecific CAR, e.g., a bispecific CAR, that binds to BCMA and CD19,

(2) the antigen is CD20 and the inhibitor of the antigen is a CD20 inhibitor, optionally wherein the CD20 inhibitor is:

(d) a CD20 CAR-expressing cell therapy, e.g., a CD20 CAR-expressing cell therapy disclosed herein;

(e) a CAR-expressing cell therapy comprising a cell expressing a first CAR and a second CAR, wherein the first CAR is a BCMA CAR (e.g., a BCMA CAR disclosed herein) and the second CAR is a CD20 CAR (e.g., a CD20 CAR disclosed herein);

(f) a CAR-expressing cell therapy comprising a cell expressing a multispecific CAR, e.g., a bispecific CAR, that binds to BCMA and CD20; or

(g) a multispecific antibody molecule, e.g., a bispecific antibody molecule, that binds to CD20 and CD3, e.g., THG338,

(3) the antigen is CD22 and the inhibitor of the antigen is a CD22 inhibitor, optionally wherein the CD22 inhibitor is:

(h) a CD22 CAR-expressing cell therapy, e.g., a CD22 CAR-expressing cell therapy disclosed herein;

(i) a CAR-expressing cell therapy comprising a cell expressing a first CAR and a second CAR, wherein the first CAR is a BCMA CAR (e.g., a BCMA CAR disclosed herein) and the second CAR is a CD22 CAR (e.g., a CD22 CAR disclosed herein); or

(j) a CAR-expressing cell therapy comprising a cell expressing a multispecific CAR, e.g., a bispecific CAR, that binds to BCMA and CD22,

(4) the antigen is PD1 or PD-L1 and the inhibitor of the antigen is an anti-PD1 antibody molecule or an anti-PD-L1 antibody molecule, optionally wherein the inhibitor of the antigen is:

(k) PDR001, Nivolumab, Pembrolizumab, Pidilizumab, MEDI0680, REGN2810, TSR-042, PF-06801591, or AMP-224; or

(l) FAZ053, Atezolizumab, Avelumab, Durvalumab, or BMS-936559,

(5) the antigen is IDO or TDO and the inhibitor of the antigen is an inhibitor of IDO and/or TDO, optionally wherein the inhibitor of IDO and/or TDO is:

(m) INCB24360, indoximod, NLG919, epacadostat, NLG919, or F001287; or

(n) (4E)-4-[(3-chloro-4-fluoroanilino)-nitrosomethylidene]-1,2,5-oxadiazol-3-amine, 1-methyl-D-tryptophan, α-cyclohexyl-5H-Imidazo[5,1-a]isoindole-5-ethanol, or the D isomer of 1-methyl-tryptophan, or

(6) the antigen is TGF-beta and the inhibitor of the antigen is a TGF beta inhibitor.

In certain embodiments of the foregoing aspects, the value of the level or activity of the antigen comprises the expression level of the antigen in the subject, e.g., in a sample from the subject (e.g., a biopsy sample, e.g., a bone marrow biopsy sample), as measured by an assay described herein, e.g., immunohistochemistry.

In some embodiments, the at least one time point is 5, 10, 15, 20, 25, 28, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, or 90 days after the subject began receiving the BCMA CAR-expressing cell therapy.

In some embodiments, the subject experiences a decrease in BCMA expression after the subject began receiving the BCMA CAR-expressing cell therapy.

In certain embodiments of the foregoing aspects, the BCMA CAR-expressing cell therapy comprises a cell expressing a BCAM CAR. In some embodiments, the BCMA CAR comprises one or more of (e.g., all three of) heavy chain complementary determining region 1 (HCDR1), HCDR2, and HCDR3 listed in Table 3 or 5 and/or one or more of (e.g., all three of) light chain complementary determining region 1 (LCDR1), LCDR2, and LCDR3 listed in Table 4 or 5, or a sequence with 95-99% identify thereof. In some embodiments, the BCMA CAR comprises a heavy chain variable region (VH) listed in Table 2 or 5 and/or a light chain variable region (VL) listed in Table 2 or 5, or a sequence with 95-99% identify thereof. In some embodiments, the BCMA CAR comprises a BCMA scFv domain amino acid sequence listed in Table 2 or 5 (e.g., SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 135, SEQ ID NO: 136, SEQ ID NO: 137, SEQ ID NO: 138, SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, SEQ ID NO: 143, SEQ ID NO: 144, SEQ ID NO: 145, SEQ ID NO: 146, SEQ ID NO: 147, SEQ ID NO: 148, and SEQ ID NO: 149), or a sequence with 95-99% identify thereof. In some embodiments, the BCMA CAR comprises a full-length BCMA CAR amino acid sequence listed in Table 2 or 5 (e.g., residues 22-483 of SEQ ID NO: 109, residues 22-490 of SEQ ID NO: 99, residues 22-488 of SEQ ID NO: 100, residues 22-487 of SEQ ID NO: 101, residues 22-493 of SEQ ID NO: 102, residues 22-490 of SEQ ID NO: 103, residues 22-491 of SEQ ID NO: 104, residues 22-482 of SEQ ID NO: 105, residues 22-483 of SEQ ID NO: 106, residues 22-485 of SEQ ID NO: 107, residues 22-483 of SEQ ID NO: 108, residues 22-490 of SEQ ID NO: 110,

residues 22-483 of SEQ ID NO: 111, residues 22-484 of SEQ ID NO: 112, residues 22-485 of SEQ ID NO: 113, residues 22-487 of SEQ ID NO: 213, residues 23-489 of SEQ ID NO: 214, residues 22-490 of SEQ ID NO: 215, residues 22-484 of SEQ ID NO: 216, residues 22-485 of SEQ ID NO: 217, residues 22-489 of SEQ ID NO: 218, residues 22-497 of SEQ ID NO: 219, residues 22-492 of SEQ ID NO: 220, residues 22-490 of SEQ ID NO: 221, residues 22-485 of SEQ ID NO: 222, residues 22-492 of SEQ ID NO: 223, residues 22-492 of SEQ ID NO: 224, residues 22-483 of SEQ ID NO: 225, residues 22-490 of SEQ ID NO: 226, residues 22-485 of SEQ ID NO: 227, residues 22-486 of SEQ ID NO: 228, residues 22-492 of SEQ ID NO: 229, residues 22-488 of SEQ ID NO: 230, residues 22-488 of SEQ ID NO: 231, residues 22-495 of SEQ ID NO: 232, residues 22-490 of SEQ ID NO: 233), or a sequence with 95-99% identify thereof. In some embodiments, the BCMA CAR is encoded by a nucleic acid sequence listed in Table 2 or 5 (e.g., SEQ ID NO: 54, SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 150, SEQ ID NO: 151, SEQ ID NO: 152, SEQ ID NO: 153, SEQ ID NO: 154, SEQ ID NO: 155, SEQ ID NO: 156, SEQ ID NO: 157, SEQ ID NO: 158, SEQ ID NO: 159, SEQ ID NO: 160, SEQ ID NO: 161, SEQ ID NO: 162, SEQ ID NO: 163, SEQ ID NO: 164, SEQ ID NO: 165, SEQ ID NO: 166, SEQ ID NO: 167, SEQ ID NO: 168, SEQ ID NO: 169, SEQ ID NO: 170), or a sequence with 95-99% identify thereof.

In certain embodiments of the foregoing aspects, the disease associated with the expression of BCMA is cancer, optionally wherein the cancer is a hematological cancer. In some embodiments, the disease associated with the expression of BCMA is an acute leukemia chosen from one or more of B-cell acute lymphoid leukemia ("BALL"), T-cell acute lymphoid leukemia ("TALL"), acute lymphoid leukemia (ALL); chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL); B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B cell lymphoma, follicular lymphoma, hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, Marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia; a prostate cancer (e.g., castrate-resistant or therapy-resistant prostate cancer, or metastatic prostate cancer), pancreatic cancer, lung cancer; or a plasma cell proliferative disorder (e.g., asymptomatic myeloma (smoldering multiple myeloma or indolent myeloma), monoclonal gammapathy of undetermined significance (MGUS), Waldenstrom's macroglobulinemia, plasmacytomas (e.g., plasma cell dyscrasia, solitary myeloma, solitary plasmacytoma, extramedullary plasmacytoma, and multiple plasmacytoma), systemic amyloid light chain amyloidosis, and POEMS syndrome (also known

as Crow-Fukase syndrome, Takatsuki disease, and PEP syndrome)), or a combination thereof. In some embodiments, the disease associated with the expression of BCMA is ALL, CLL, DLBCL, or multiple myeloma. In some embodiments, the subject is a human patient.

The materials, methods, and examples are illustrative only and not intended to be limiting.

Headings, sub-headings or numbered or lettered elements, e.g., (a), (b), (i) etc, are presented merely for ease of reading. The use of headings or numbered or lettered elements in this document does not require the steps or elements be performed in alphabetical order or that the steps or elements are necessarily discrete from one another.

All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety.

Other features, objects, and advantages of the invention will be apparent from the description and drawings, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

FIGs.1A and 1B are a pair of graphs showing the percentage of CD4+ or CD8+ T cells among CD3+ T cells (FIG. 1A) and the CD4:CD8 T cell ratio (FIG. 1B) in apheresis samples acquired from multiple myeloma patients who were later determined to be Responders (R, $N_R = 3$) or Non-Responders (NR, $N_{NR} = 5$) to treatment with an infusion of CART-BCMA. These data demonstrate that Responders had a higher percentage of CD4+ T cells and a lower percentage of CD8+ T cells (and thus a higher CD4:CD8 ratio) in their apheresis sample than Non-Responders did. A CD4:CD8 ratio greater than about 1.6 was found to be predictive of response to CART-BCMA.

FIGs. 2A, 2B, and 2C are graphs showing that the percentage of HLADR-CD95+CD27+CD8+ T cells (FIG. 2A), CD45RO-CD27+CD8+ T cells (FIG. 2B), or CCR7+CD45RO-CD27+CD8+ T cells (FIG. 2C) among CD8+ T cells is higher in apheresis samples acquired from multiple myeloma patients who were later determined to be Responders (R, $N_R = 3$) to CART-BCMA as compared to Non-Responders (NR, $N_{NR} = 5$). P-values are shown for each graph.

FIG. 3 is a series of images showing CD138+ cell localization as determined by immunohistochemistry (IHC) in bone marrow core biopsies acquired prior to administration ("Pre"), and on Day 28 and Day 90 ("3 month") post-infusion of CART-BCMA from Patient 13, Patient 14, Patient 15, Patient 16, and Patient 17. Patient outcomes to treatment with CART-BCMA are provided

in the Examples and are referred to herein as follows: Progressive disease (PD); Stable disease (SD); Minor response (MR); Partial regression (PR); and Very good partial regression (VGPR). Pretreatment, Day 28, and Day 90 samples acquired from Patient 13 had 1%, 0%, and 0% CD138+ MM cell infiltration, respectively. Pretreatment and Day 28 samples acquired from Patient 14 had 80% and 90% CD138+ MM cell infiltration, respectively. Pretreatment, Day 28, and Day 90 samples acquired from Patient 15 had 95%, 5%, and 10% CD138+ MM cell infiltration, respectively. Pretreatment, Day 28, and Day 90 samples acquired from Patient 16 had 50%, 5%, and 75% CD138+ MM cell infiltration, respectively. Pretreatment, Day 28, and Day 90 samples acquired from Patient 17 had 50%, 5%, and 75% CD138+ MM cell infiltration, respectively.

FIG. 4 is a series of images showing BCMA protein expression as determined by IHC in bone marrow core biopsies acquired prior to administration ("Pre"), and on Day 28 and Day 90 ("3 month") post-infusion of CART-BCMA from Patient 13, Patient 14, Patient 15, Patient 16, and Patient 17.

FIG. 5 is a series of images showing a comparison between BCMA protein expression as determined by IHC to BCMA mRNA levels as determined by in situ hybridization (ISH) in bone marrow core biopsies acquired prior to administration of CART-BCMA from Patient 13, Patient 14, Patient 15, Patient 16, and Patient 17.

FIGs. 6A, 6B, and 6C are a series of images showing BCMA protein expression as determined by IHC, BCMA mRNA levels as determined by ISH, and CART-BCMA mRNA levels as determined by ISH in bone marrow core biopsies acquired from Patient 15 (FIG. 6A), Patient 16 (FIG. 6B), and Patient 17 (FIG. 6C), prior to administration ("Pre"), and on Day 28 and Day 90 ("3 month") post-infusion of CART-BCMA.

FIGs. 7A, 7B, and 7C are a series of images showing IDO1, IFN-γ, and TGFβ mRNA levels as determined by ISH in bone marrow core biopsies acquired from Patient 15 (FIG. 7A), Patient 16 (FIG. 7B), and Patient 17 (FIG. 7C), prior to administration ("Pre"), and on Day 28 and Day 90 ("3 month") post-infusion of CART-BCMA. FIGs. 7D and 7E are a series of images showing CAR, IFN-γ, and IDO1 mRNA levels as determined by ISH in biopsies acquired from Patient 19 (FIG. 7D) and Patient 20 (FIG. 7E), prior to administration ("Pre"), and on Day 10 and Day 28 post-infusion of CART-BCMA.

FIGs. 8A, 8B, and 8C are a series of images showing PD-L1, PD1, CD3, and FoxP3 protein expression as determined by IHC in bone marrow core biopsies acquired from Patient 15 (FIG. 8A), Patient 16 (FIG. 8B), and Patient 17 (FIG. 8C), prior to administration ("Pre"), and on Day 28 and Day 90 ("3 month") post-infusion of CART-BCMA. FIGs. 8D and 8E are a series of images showing PD1, PD-L1, and FoxP3 protein expression as determined by IHC in biopsies acquired from Patient 19 (FIG. 8D) and Patient 20 (FIG. 8E), prior to administration ("Pre"), and on Day 10 and Day 28 post-infusion of CART-BCMA.

FIG. 9 is a series of images showing CD19 protein expression as determined by IHC in bone marrow core biopsies acquired prior to administration ("Pre"), and on Day 28 and Day 90 ("3 month") post-infusion of CART-BCMA from Patient 13, Patient 14, Patient 15, Patient 16, and Patient 17.

FIG. 10 is a series of images showing CD20 protein expression as determined by IHC in bone marrow core biopsies acquired prior to administration ("Pre"), and on Day 28 and Day 90 ("3 month") post-infusion of CART-BCMA from Patient 13, Patient 14, Patient 15, Patient 16, and Patient 17.

FIGs. 11A and 11B are a series of spectrally unmixed pseudo fluorescent microscopy images showing that BCMA positive cells and CD19 positive cells are separate populations in bone marrow core biopsies acquired from Patient 15 prior to administration ("pre") and on Day 90 ("3M") post-infusion of CAR-BCMA.

FIGs. 12A and 12B are a series of spectrally unmixed pseudo fluorescent microscopy images showing that CD19+ $CD34^{dim}$ cell population was present in the pretreatment bone marrow core biopsies acquired from Patient 15 and Patient 17, respectively.

FIG. 13 is a series of spectrally unmixed pseudo fluorescent microscopy images showing that the CD19 population was variably CD138+ and CD138- in the pretreatment bone marrow core biopsies acquired from Patient 15.

FIG. 14 is a graph comparing the level of tumor burden in a KMS11 tumor model following implant and administration of PBS, untransduced T cells ("UTD"), or T cells transduced with either a tool CAR ("J6MO"), BCMA-4, BCMA-9, BCMA-10 ("MCM998"), BCMA-13, or BCMA-15. BCMA-10 demonstrated the most potent anti-tumor activity.

FIG. 15 is a diagram showing the design of a clinical trial (NCT Number: NCT02546167; UPCC 14415) to assess the safety and feasibility of infusion of autologous T cells expressing CART-BCMA in adult patients with multiple myeloma.

FIG. 16A is a table showing MM patient disease characteristics. FIG. 16B is a table showing the presence of baseline lymphopenia due to disease and prior therapies in MM patients.

FIGs. 17A, 17B, and 17C are graphs showing patient response for Cohort 1, Cohort 2, and Cohort 3, respectively.

FIGs. 18A and 18B are a series of graphs showing expansion of CART-BCMA evaluated by flow cytometry in Cohort 1 patients and Cohort 2/3 patients, respectively.

FIGs. 19A and 19B are a series of graphs showing expansion of CART-BCMA evaluated by PCR in Cohort 1 patients and Cohort 2/3 patients, respectively. The plots show the number of detected CART genes per µg of DNA isolated from patient's blood (y-axis) at the respective day post CART infusion (x-axis).

FIGs. 20A and 20B are graphs showing that BCMA expansion may correlate with clinical outcomes.

FIG. 21A, 21B, 21C, and 21D are graphs showing the fraction of CAR-positive (CAR+) CD4/CD8 cells at various time points post-infusion in Responders compared to Non-Responders.

FIG. 22 is a series of graphs showing the changes in level of cytokine expression at various time points post infusion of CART-BCMA. The y-axis in each graph shows fold change from Day 0. The x-axis in each graph shows days post-infusion of CART-BCMA.

FIGs. 23A and 23B are graphs showing the change in IL-6 expression at various time points post infusion of CART-BCMA. The y-axis in each graph shows fold change from Day 0. The x-axis in each graph shows days post-infusion of CART-BCMA.

FIGs. 24A and 24B are graphs showing the change in IFN-γ expression at various time points post infusion of CART-BCMA. The y-axis in each graph shows fold change from Day 0. The x-axis in each graph shows days post-infusion of CART-BCMA.

FIGs. 25A and 25B are graphs showing the serum level of BCMA in 14 normal donors (FIG. 25A) and 12 myeloma patients (FIG. 25B).

FIGs. 26A, 26B, 26C, and 26D are graphs showing serum BCMA level at various time points post infusion of CART-BCMA. The y-axis in FIGs. 26A and 26B shows peripheral blood (PB) serum BCMA levels. The y-axis in FIGs. 26C and 26D shows PB serum BCMA level fold change from baseline. The x-axis in each graph shows days post-infusion of CART-BCMA.

FIGs. 27A, 27B, and 27C are graphs showing data collected from three multiple myeloma patients who received CART-BCMA treatment. The y-axis on the left shows the percentage of CD4+ or CD8+ CART cells. The y-axis on the right shows the level of serum BCMA (ng/mL) or the number of CART copies (BBz) per μg DNA, as evaluated by qPCR.

FIGs. 28A and 28B are graphs showing CD4+ T cell subsets of normal donors (FIG. 28A) and multiple myeloma (MM) patients (FIG. 28B). FIGs. 28C and 28D are graphs showing CD8+ T cell subsets of normal donors (FIG. 28C) and MM patients (FIG. 28D). FIGs. 28E and 28F are graphs showing CD4+ and CD8+ T cell subsets, respectively, in apheresis samples acquired from MM patients (dots with slashes represent non-responders and white dots represent responders).

FIG. 29 is a series of graphs showing T cell differentiation in apheresis samples acquired from MM patients. The x-axis shows CD45RO expression and the y-axis shows CCR7 expression. Signal in the top left quadrant indicates naïve cell phenotype; signal in top right quadrant indicates central memory (T_{CM}) phenotype; signal in bottom right quadrant indicates effector memory (T_{EM}) phenotype; and signal in bottom left quadrant indicates T_{EMRA}. CR stands for complete response. PD stands for progressive disease. VGPR stands for very good partial response.

FIGs. 30A and 30B are a pair of graphs showing CD4+ and CD8+ T cell subsets in apheresis samples acquired from MM patients (dots with slashes represent non-responders and white dots represent responders).

FIG. 31 is a graph showing treatment schema.

FIGs. 32A, 32B, and 32C are a set of graphs showing clinical outcomes. FIG. 32A is a Swimmer's plot showing best response and progression-free survival (PFS) for each subject. Arrow indicates ongoing response. FIG. 32B is a pair of PET/CT scan images for subject 03 showing resolution of extramedullary disease and malignant pleural effusion post-treatment. FIG. 32C is a Kaplan-Meier plot showing overall survival for Cohort 1. MR=minimal response; MRD=minimal residual disease; PR=partial response; PD=progressive disease; sCR=stringent complete response; SD=stable disease.

FIGs. 33A, 33B, and 33C are a set of graphs showing CART-BCMA expansion and persistence. FIG. 33A is a set of graphs depicting CART-BCMA cell levels over time in peripheral blood for each subject, as measured by flow cytometry (%CAR+ within CD3+ T cells, ▲, left axis) and quantitative PCR for CAR sequence (■, right axis). See FIG. 38 for representative flow cytometry plots. FIG. 33B is a graph showing that peak CART-BCMA levels by qPCR correlate with response: median 102507 vs. 4187 copies/µg DNA for ≥PR vs. <PR, respectively (p=0.016, Mann-Whitney). FIG. 33C is a graph showing that AUC-28 (area under the curve for CART-BCMA levels by qPCR during first 28 days after infusion) correlates with response: median 885181 vs. 26183 (copies)x(days)/µg DNA for ≥PR vs. <PR, respectively (p=0.016, Mann-Whitney).

FIG. 34 is a set of graphs showing soluble BCMA (sBCMA), BAFF, APRIL levels and B cell frequency after CART-BCMA infusions. Peripheral blood serum levels of sBCMA, BAFF, and APRIL (ng/ml, left axis) were measured by ELISA pre- and post-CART-BCMA infusions for each subject as indicated above. Subjects with deepest clinical responses (01 (sCR), 03 (VGPR), 15 (VGPR)) had greatest declines in sBCMA and reciprocal increases in BAFF and APRIL. Peripheral blood B cell frequency (%CD19+ of CD45+CD14- gate, right axis) was assessed by flow cytometry at indicated time points.

FIG. 35 is a set of histograms showing BCMA expression by flow cytometry on gated MM cells in marrow aspirates for each subject, before and after CART-BCMA infusions. Hatched histograms show BCMA; filled histograms show FMO (fluorescence minus one) control. Post-infusion time point is Day 28, unless specified. Percentage of cells expressing BCMA as well as mean BCMA fluorescence intensity (MFI) for each subject are listed in Table 37. Note decreased BCMA expression for subject 03 at relapse (D164). See FIG. 42 for representative gating.

FIGs. 36A, 36B, 36C, and 36D are a set of graphs showing predictors of in vivo CART-BCMA expansion. The ratio of CD4+ to CD8+ T cells (CD4/CD8 ratio) within the apheresis product immediately after collection (FIG. 36A) and within the seed culture at start of manufacturing (i.e. following elutriation step to reduce monocyte contamination) (FIG. 36B) was determined by flow cytometry. In vitro fold expansion (FIG. 36C) was calculated from total cell counts at start and end of

manufacturing. The proportion of CD8+ T cells within the apheresis product with a CD45RO-CD27+ phenotype was assessed by flow cytometry (FIG. 36D). The CD4/CD8 ratio and frequency of CD45RO-CD27+CD8+ T cells pre-manufacturing, and degree of in vitro expansion were associated with peak in vivo CART-BCMA expansion post-infusion (Spearman correlation r and p-value shown).

FIG. 37 is a CONSORT diagram showing subject enrollment.

FIG. 38 is a set of graphs showing representative gating and staining for CART-BCMA cells. Staining is shown for peripheral blood from subject 01, day +7 after first CART-BCMA infusion. Cells are gated by forward and side scatter, then singlets, then CD45+CD14- leukocytes, then T cells (CD3+CD19-). CART-BCMA+ cells were identified using biotinylated recombinant human BCMA-Fc and streptavidin-PE. Negative control was an FMO (fluorescence minus one) tube (lacking biotinylated BCMA-Fc) with streptavidin-PE. The % of CD3+ T cells expressing CART-BCMA was calculated by subtracting CAR+ cells in FMO tube from CAR+ cells in tube with biotinylated BCMA-FC (i.e. in this example 34.7 – 0.9 = 33.8). Activation status of CART-BCMA+ cells was identified by staining for HLA-DR (bottom right panel). The % of CAR+ cells that were activated at each time point was calculated by dividing %HLA-DR+ by (%HLA-DR+ plus %HLA-DR-) (i.e. in this example 32.9/(32.9 + 1.5) = 95.6%).

FIG. 39 is a set of graphs showing absolute number of CART-BCMA+ T cells for each subject. Absolute # of CD3+CAR+ cells per µl of blood was estimated from the absolute lymphocyte count (ALC, reported from the clinical complete blood count (CBC) differential) and the CART-BCMA flow cytometry results (FIG. 38), using the following formula: (ALC) (%CD45+CD14-)(%CD3+CD19-)(%CAR+)/10000. For example, for subject 01 at day+7, ALC was 0.08 x 10^3 cells/µl. Estimated absolute # of circulating CAR+ T cells at this time point is (0.08)(48.3)(72.1)(33.8)/10000 = 0.019 x 10^3 cells/µl.

FIG. 40 is a set of graphs showing serum cytokine changes after CART-BCMA treatment. Levels of 30 peripheral blood cytokines were assessed at multiple time points by Luminex assay. Changes in selected cytokines over first 28 days are depicted. Subjects with deepest responses (01, 03, 15) had greatest fold-increase in cytokines, typically at or just before peak CART-BCMA expansion.

FIGs. 41A and 41B are a pair of graphs showing baseline soluble BCMA (sBCMA) levels, peak expansion, and response. Peripheral blood serum levels of sBCMA were measured by ELISA pre-treatment. FIG. 41A is a graph showing that baseline sBCMA levels did not correlate significantly with peak expansion of CART-BCMA by qPCR (Spearman correlation r=0.43, p=0.25). FIG. 41B is a graph showing that baseline levels of sBCMA were not significantly associated with response (p=0.56, Mann-Whitney test).

FIG. 42 is a set of graphs showing representative gating for myeloma cells and BCMA staining. Bone marrow aspirate cells were gated by forward and side scatter, then by singlets, then on CD3-

CD14- cells. Myeloma cells were identified by gating first on $CD38^{hi}$ cells, then by gating on clonal plasma cells using CD19, CD56, and kappa/lambda staining. In this example, myeloma cells are CD19-CD56+kappa+. The % BCMA + was determined using an FMO tube lacking anti-BCMA antibody.

FIGs. 43A and 43B are a pair of graphs showing baseline BCMA expression on MM cells, peak expansion, and response. BCMA mean fluorescence intensity (MFI) on myeloma cells pre-treatment did not correlate with peak CART-BCMA expansion by qPCR (Spearman correlation r=0.45, p=0.27) (FIG. 43A), nor was it significantly associated with response (p=0.25, Mann-Whitney test) (FIG. 43B). One subject (07) did not have a pre-treatment sample available.

FIGs. 44A and 44B are a set of graphs showing BCMA expression on B cell malignancy cell lines. FIG. 44A is a set of histograms showing the surface expression of BCMA on each cell line. Hatched histograms indicate staining with PE-labeled anti-BCMA antibody and filled histograms show the respective isotype control staining. In FIG. 44B, expression was quantified and the antibody binding capacity (ABC) plotted for each cell line tested.

FIG. 45A is a graph showing % CD27+CD45RO-CD8+ cells in the post-induction cohort and the relapsed/refractory cohort. FIG. 45B is a graph showing CD4/CD8 ratio in the post-induction cohort and the relapsed/refractory cohort. FIG. 45C is a graph showing in vitro population doublings by Day 9 in the post-induction cohort and the relapsed/refractory cohort.

FIG. 46 is a graph showing treatment schema. BM asp/Bx = bone marrow aspirate and biopsy; Cytoxan = cyclophosphamide; D = day; Lenti = lentivirus; Wk = week.

FIGs. 47A-47C are a panel of swimmer's plots showing best response and progression-free survival (PFS) for each subject in Cohort 1 (1-5 x 10^8 CART-BCMA cells alone) (FIG. 47A), Cohort 2 (Cyclophosphamide (Cy) + 1-5 x 10^7 CART-BCMA cells) (FIG. 47B), and Cohort 3 (Cy + 1-5 x 10^8 CART-BCMA cells) (FIG. 47C). Arrow indicates ongoing response. FIG. 47D is a graph showing overall survival (OS) based on cohort, Kaplan-Meier plot. MR=minimal response; MRD=minimal residual disease; PR=partial response; PD=progressive disease; sCR=stringent complete response; SD=stable disease.

FIGs. 48A-48D are graphs showing CART-BCMA expansion and persistence. FIGs. 48A-48C are graphs showing CART-BCMA cell levels over time in peripheral blood for each cohort, as measured by quantitative PCR for CAR sequence. FIG. 48D is a graph showing peak CART-BCMA levels by qPCR for each subject (except subj. 34, for whom peak data not available). Median peak CART-BCMA levels (grey bars) were not significantly different between cohorts (Mann-Whitney).

FIGs. 49A-49I are graphs showing serum cytokines associated with CRS severity and neurotoxicity. Serum cytokine concentrations in pg/ml through day 28 were measured by Luminex assay. FIGs. 49A-49E: The median peak fold increase over baseline for each cytokine was compared between subjects with no cytokine release syndrome (CRS), grade 1 CRS, or grade 2 CRS not receiving

tocilizumab (CRS gr 0-2) and those with grade 3-4 CRS or grade 2 CRS receiving tocilizumab (CRS Gr 3-4 or Gr 2 + toci). The cytokines most significantly associated with CRS severity were IL-6 (FIG. 49A), IFN-γ (FIG. 49B), IL-2Rα (FIG. 49C), MIP-1α (FIG. 49D), and IL-15 (FIG. 49E). FIGs. 49F-49I: Median peak fold increase over baseline for each cytokine was compared between subjects with no neurotoxicity (No Ntx) and those with any grade of neurotoxicity (Any Ntx). The cytokines most significantly associated with neurotoxicity were IL-6 (FIG. 49F), IFN-γ (FIG. 49G), IL-1RA (FIG. 49H), and MIP-1α (FIG. 49I). Stars depict subjects with grade 3-4 neurotoxicity. Exact p-value by Mann-Whitney test is shown. Horizontal lines depict medians. IFN-γ = interferon gamma; IL-1RA = interleukin 1 receptor antagonist; IL-2Rα = interleukin 2 receptor alpha; IL-6 = interleukin 6; IL-15 = interleukin 15. MIP-1α = macrophage inflammatory protein 1 alpha.

FIGs. 50A-50D are graphs showing soluble BCMA (sBCMA), BAFF, and APRIL concentration, and BCMA expression on MM cells pre- and post-CART-BCMA infusions. FIG. 50A: Baseline peripheral blood serum concentration of sBCMA and APRIL for subjects (sub) were significantly increased and decreased, respectively, compared to a panel of healthy donors (HD, n=6) ($p=0.017$, and <0.001, respectively, Mann-Whitney). Baseline BAFF concentrations were not significantly different. Median concentrations are depicted. FIG. 50B: Serial sBCMA concentrations decline after CART-BCMA infusions more significantly in hematologic responders (PR/VGPR/CR/sCR) than non-responders (MR/SD/PD). Mean concentration (ng/ml) + SEM are depicted. *$p<0.05$ by unpaired t-test. FIG. 50C: Representative examples of BCMA expression on MM cells by flow cytometry. See FIG. 42 for gating strategy. FMO=fluorescence minus one. FIG. 50D: BCMA mean fluorescence intensity (MFI) on MM cells over time in 18 subjects with evaluable serial bone marrow aspirates. Median MFI was significantly different between pre-treatment (pre-tx) and day 28 (D28) for responders (4000 vs. 944, $p=0.02$, paired t-test) but not for non-responders (2704 vs. 2140, $p=0.19$). Median MFI was not significantly different between pre-tx and day 90 (D90) for responders (4000 vs.2022, $p=0.26$). *Subj. 15 had no detectable MM cells at D28. #Subj. 03 had no detectable MM cells at D45 (D28 not done) and too few MM cells to characterize at D90. D164 marrow is depicted at D90 time-point.

FIGs. 51A-51I are graphs showing predictors of *in vivo* CART-BCMA expansion and response. Peak blood CART-BCMA expansion, as measured by qPCR (FIG. 51A), as well as total CART-BCMA expansion over first 28 days (calculated as area under the curve (AUC)) (FIG. 51B), were both associated with clinical response. Greater peak CART-BCMA expansion (FIG. 51C) and response (FIG. 51D) were also associated with more severe CRS, defined as grade 3/4 or grade 2 requiring tocilizumab. A higher ratio of CD4+ to CD8+ T cells (CD4/CD8 ratio) within the leukopheresis product, as determined by flow cytometry, also correlated with both peak expansion (FIG. 51E) and response (FIG. 51F), while i*n vitro* proliferation, measured as fold increase of seeded cells during

manufacturing, correlated only with peak expansion (FIG. 51G), but not response (p=0.54, Mann-Whitney test, data not shown). FIGs. 51H-I: A higher proportion of CD8+ T cells within the leukopheresis product with a CD45RO-CD27+ phenotype was significantly associated with peak CART-BCMA expansion (FIG. 51H), and to a lesser degree, response (FIG. 51I). For FIGs. 51A, 51B, 51C, 51F, and 51I, analysis was by Mann-Whitney test; lines represent median values. For FIG. 51D, analysis was by Fisher's exact test. For FIGs. 51E, 51G, and 51H, analysis was by Spearman correlation.

FIG. 52 is a CONSORT diagram showing subject enrollment. ALC = absolute lymphocyte count.

FIGs. 53A-53D are graphs showing additional clinical outcomes for treated subjects. FIG. 53A: Duration of response (DOR) for all subjects with partial response (PR) or better. FIG. 53B: Overall survival (OS) for all subjects. FIG. 53C: Progression-free survival (PFS) by cohort. FIG. 53D: PFS for all subjects. Curves derived by Kaplan-Meier method.

FIGs. 54A-54C are graphs showing expansion of CART-BCMA cells for Cohort 1 (FIG. 54A), Cohort 2 (FIG. 54B) or Cohort 3 (FIG. 54C). The frequency of CAR+ T cells within all peripheral blood CD3+ T cells, as measured by flow cytometry, is depicted for each subject.

FIG. 55 is a panel of graphs showing serum cytokine changes after CART-BCMA treatment. Concentrations (pg/ml) of peripheral blood cytokines were assessed at multiple time-points by Luminex assay. The peak fold increase over baseline for the most frequently elevated cytokines over first 28 days post-infusion are shown, based on cohort.

FIGs. 56A-56L are graphs showing that peak CART-BCMA expansion is not associated with baseline clinical characteristics, baseline BCMA expression or sBCMA concentration. Peak CART-BCMA level (copies/µg genomic DNA) by qPCR was not significantly associated with age at enrollment (above or below median) (FIG. 56A); years from diagnosis (above or below median) (FIG. 56B); presence of del17p by FISH or TP53 mutation by sequencing (FIG. 56C); number (#) of therapeutic lines (above or below median) (FIG. 56D); being penta-refractory to 2 proteasome inhibitors (PIs), 2 immunomodulatory drugs (IMiDs) and daratumumab (dara) (FIG. 56E); receiving therapy just prior to leukapheresis that contained an IMiD (FIG. 56F), a PI (FIG. 56G), dara (FIG. 56H), or cyclophosphamide (Cytoxan) (FIG. 56I); percentage of pre-treatment bone marrow plasma cells (%BM PC) (FIG. 56J); baseline BCMA mean fluorescence intensity (MFI) on BM PC (FIG. 56K); or baseline serum soluble BCMA (sBCMA) concentration (FIG. 56L). For FIGs. 56A-56I, analysis by Mann-Whitney test; line represents median value. For FIGs. 56J-56L, analysis by Spearman correlation.

FIGs. 57A-57L are graphs showing that response is not associated with baseline clinical characteristics, baseline BCMA expression or sBCMA concentration. Clinical response (≥ partial response (PR)) was not significantly associated with age at enrollment (FIG. 57A); years from diagnosis

(FIG. 57B); presence of del17p by FISH or TP53 mutation by sequencing (FIG. 57C); number (#) of therapeutic lines (FIG. 57D); being penta-refractory to 2 proteasome inhibitors (PIs), 2 immunomodulatory drugs (IMiDs) and daratumumab (dara) (FIG. 57E); receiving a regimen just prior to leukapheresis that contained an IMiD, a PI, dara, or cyclophosphamide (Cytoxan) (FIGs. 57F-57I); percentage of pre-treatment bone marrow plasma cells (%BM PC) (FIG. 57J); baseline BCMA mean fluorescence intensity (MFI) on BM PC (FIG. 57K); or baseline serum soluble BCMA (sBCMA) concentration (FIG. 57L). For FIGs. 57C, 57E-57I, analysis by Fisher Exact test. For FIGs. 57A, 57B, 57D, 57J-57L, analysis by Mann-Whitney test; line represents median value.

DESCRIPTION

Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains.

As used herein, the term "BCMA" refers to B-cell maturation antigen. BCMA (also known as TNFRSF17, BCM or CD269) is a member of the tumor necrosis receptor (TNFR) family and is predominantly expressed on terminally differentiated B cells, e.g., memory B cells, and plasma cells. Its ligand is called B-cell activator of the TNF family (BAFF) and a proliferation inducing ligand (APRIL). BCMA is involved in mediating the survival of plasma cells for mataining long-term humoral immunity. The gene for BCMA is encoded on chromosome 16 producing a primary mRNA transcript of 994 nucleotides in length (NCBI accession NM_001192.2) that encodes a protein of 184 amino acids (NP_001183.2). A second antisense transcript derived from the BCMA locus has been described, which may play a role in regulating BCMA expression. (Laabi Y. et al., Nucleic Acids Res., 1994, 22:1147-1154). Additional transcript variants have been described with unknown significance (Smirnova AS et al. Mol Immunol., 2008, 45(4):1179-1183. A second isoform, also known as TV4, has been identified (Uniprot identifier Q02223-2). As used herein, "BCMA" includes proteins comprising mutations, e.g., point mutations, fragments, insertions, deletions and splice variants of full length wild-type BCMA.

As used herein, the term "CD19" refers to the Cluster of Differentiation 19 protein, which is an antigenic determinant detectable on leukemia precursor cells. The human and murine amino acid and nucleic acid sequences can be found in a public database, such as GenBank, UniProt and Swiss-Prot. For example, the amino acid sequence of human CD19 can be found as UniProt/Swiss-Prot Accession No. P15391 and the nucleotide sequence encoding of the human CD19 can be found at Accession No. NM_001178098. As used herein, "CD19" includes proteins comprising mutations, e.g., point mutations, fragments, insertions, deletions and splice variants of full length wild-type CD19. CD19 is expressed on

most B lineage cancers, including, e.g., acute lymphoblastic leukemia, chronic lymphocyte leukemia and non-Hodgkin lymphoma. Other cells with express CD19 are provided below in the definition of "disease associated with expression of CD19." It is also an early marker of B cell progenitors. See, e.g., Nicholson et al. Mol. Immun. 34 (16-17): 1157-1165 (1997). In one aspect the antigen-binding portion of the CART recognizes and binds an antigen within the extracellular domain of the CD19 protein. In one aspect, the CD19 protein is expressed on a cancer cell.

The term "a" and "an" refers to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

The term "about" when referring to a measurable value such as an amount, a temporal duration, and the like, is meant to encompass variations of ±20% or in some instances ±10%, or in some instances ±5%, or in some instances ±1%, or in some instances ±0.1% from the specified value, as such variations are appropriate to perform the disclosed methods.

The term "Chimeric Antigen Receptor" or alternatively a "CAR" refers to a recombinant polypeptide construct comprising at least an extracellular antigen binding domain, a transmembrane domain and a cytoplasmic signaling domain (also referred to herein as "an intracellular signaling domain") comprising a functional signaling domain derived from a stimulatory molecule as defined below. In some embodiments, the domains in the CAR polypeptide construct are in the same polypeptide chain, e.g., comprise a chimeric fusion protein. In some embodiments, the domains in the CAR polypeptide construct are not contiguous with each other, e.g., are in different polypeptide chains, e.g., as provided in an RCAR as described herein.

In one aspect, the stimulatory molecule of the CAR is the zeta chain associated with the T cell receptor complex. In one aspect, the cytoplasmic signaling domain comprises a primary signaling domain (e.g., a primary signaling domain of CD3-zeta). In one aspect, the cytoplasmic signaling domain further comprises one or more functional signaling domains derived from at least one costimulatory molecule as defined below. In one aspect, the costimulatory molecule is chosen from 4 1BB (i.e., CD137), CD27, ICOS, and/or CD28. In one aspect, the CAR comprises a chimeric fusion protein comprising an extracellular antigen recognition domain, a transmembrane domain and an intracellular signaling domain comprising a functional signaling domain derived from a stimulatory molecule. In one aspect, the CAR comprises a chimeric fusion protein comprising an extracellular antigen recognition domain, a transmembrane domain and an intracellular signaling domain comprising a functional signaling domain derived from a co-stimulatory molecule and a functional signaling domain derived from a stimulatory molecule. In one aspect, the CAR comprises a chimeric fusion protein comprising an extracellular antigen recognition domain, a transmembrane domain and an

intracellular signaling domain comprising two functional signaling domains derived from one or more co-stimulatory molecule(s) and a functional signaling domain derived from a stimulatory molecule. In one aspect, the CAR comprises a chimeric fusion protein comprising an extracellular antigen recognition domain, a transmembrane domain and an intracellular signaling domain comprising at least two functional signaling domains derived from one or more co-stimulatory molecule(s) and a functional signaling domain derived from a stimulatory molecule. In one aspect the CAR comprises an optional leader sequence at the amino-terminus (N-ter) of the CAR fusion protein. In one aspect, the CAR further comprises a leader sequence at the N-terminus of the extracellular antigen recognition domain, wherein the leader sequence is optionally cleaved from the antigen recognition domain (e.g., an scFv) during cellular processing and localization of the CAR to the cellular membrane.

A CAR that comprises an antigen binding domain (e.g., an scFv, a single domain antibody, or TCR (e.g., a TCR alpha binding domain or TCR beta binding domain)) that targets a specific tumor marker X, wherein X can be a tumor marker as described herein, is also referred to as XCAR. For example, a CAR that comprises an antigen binding domain that targets BCMA is referred to as BCMACAR. The CAR can be expressed in any cell, e.g., an immune effector cell as described herein (e.g., a T cell or an NK cell).

The term "signaling domain" refers to the functional portion of a protein which acts by transmitting information within the cell to regulate cellular activity via defined signaling pathways by generating second messengers or functioning as effectors by responding to such messengers.

The term "antibody," as used herein, refers to a protein, or polypeptide sequence derived from an immunoglobulin molecule, which specifically binds with an antigen. Antibodies can be polyclonal or monoclonal, multiple or single chain, or intact immunoglobulins, and may be derived from natural sources or from recombinant sources. Antibodies can be tetramers of immunoglobulin molecules.

The term "antibody fragment" refers to at least one portion of an intact antibody, or recombinant variants thereof, and refers to the antigen binding domain, e.g., an antigenic determining variable region of an intact antibody, that is sufficient to confer recognition and specific binding of the antibody fragment to a target, such as an antigen. Examples of antibody fragments include, but are not limited to, Fab, Fab', F(ab')2, and Fv fragments, scFv antibody fragments, linear antibodies, single domain antibodies such as sdAb (either VL or VH), camelid VHH domains, and multi-specific molecules formed from antibody fragments such as a bivalent fragment comprising two or more, e.g., two, Fab fragments linked by a disulfide brudge at the hinge region, or two or more, e.g., two isolated CDR or other epitope binding fragments of an antibody linked. An antibody fragment can also be incorporated into single domain antibodies, maxibodies, minibodies, nanobodies, intrabodies, diabodies,

triabodies, tetrabodies, v-NAR and bis-scFv (see, e.g., Hollinger and Hudson, Nature Biotechnology 23:1126-1136, 2005). Antibody fragments can also be grafted into scaffolds based on polypeptides such as a fibronectin type III (Fn3) (see U.S. Patent No.: 6,703,199, which describes fibronectin polypeptide minibodies).

The term "scFv" refers to a fusion protein comprising at least one antibody fragment comprising a variable region of a light chain and at least one antibody fragment comprising a variable region of a heavy chain, wherein the light and heavy chain variable regions are contiguously linked via a short flexible polypeptide linker, and capable of being expressed as a single chain polypeptide, and wherein the scFv retains the specificity of the intact antibody from which it is derived. Unless specified, as used herein an scFv may have the VL and VH variable regions in either order, e.g., with respect to the N-terminal and C-terminal ends of the polypeptide, the scFv may comprise VL-linker-VH or may comprise VH-linker-VL.

The terms "complementarity determining region" or "CDR," as used herein, refer to the sequences of amino acids within antibody variable regions which confer antigen specificity and binding affinity. For example, in general, there are three CDRs in each heavy chain variable region (e.g., HCDR1, HCDR2, and HCDR3) and three CDRs in each light chain variable region (LCDR1, LCDR2, and LCDR3). The precise amino acid sequence boundaries of a given CDR can be determined using any of a number of well-known schemes, including those described by Kabat et al. (1991), "Sequences of Proteins of Immunological Interest," 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD ("Kabat" numbering scheme), Al-Lazikani et al., (1997) JMB 273,927-948 ("Chothia" numbering scheme), or a combination thereof. Under the Kabat numbering scheme, in some embodiments, the CDR amino acid residues in the heavy chain variable domain (VH) are numbered 31-35 (HCDR1), 50-65 (HCDR2), and 95-102 (HCDR3); and the CDR amino acid residues in the light chain variable domain (VL) are numbered 24-34 (LCDR1), 50-56 (LCDR2), and 89-97 (LCDR3). Under the Chothia numbering scheme, in some embodiments, the CDR amino acids in the VH are numbered 26-32 (HCDR1), 52-56 (HCDR2), and 95-102 (HCDR3); and the CDR amino acid residues in the VL are numbered 26-32 (LCDR1), 50-52 (LCDR2), and 91-96 (LCDR3). In a combined Kabat and Chothia numbering scheme, in some embodiments, the CDRs correspond to the amino acid residues that are part of a Kabat CDR, a Chothia CDR, or both. For instance, in some embodiments, the CDRs correspond to amino acid residues 26-35 (HCDR1), 50-65 (HCDR2), and 95-102 (HCDR3) in a VH, e.g., a mammalian VH, e.g., a human VH; and amino acid residues 24-34 (LCDR1), 50-56 (LCDR2), and 89-97 (LCDR3) in a VL, e.g., a mammalian VL, e.g., a human VL.

The portion of the CAR composition of the invention comprising an antibody or antibody fragment thereof may exist in a variety of forms, for example, where the antigen binding domain is

expressed as part of a polypeptide chain including, for example, a single domain antibody fragment (sdAb), a single chain antibody (scFv), or e.g., a humanized antibody (Harlow et al., 1999, In: Using Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory Press, NY; Harlow et al., 1989, In: Antibodies: A Laboratory Manual, Cold Spring Harbor, New York; Houston et al., 1988, Proc. Natl. Acad. Sci. USA 85:5879-5883; Bird et al., 1988, Science 242:423-426). In one aspect, the antigen binding domain of a CAR composition of the invention comprises an antibody fragment. In a further aspect, the CAR comprises an antibody fragment that comprises an scFv.

As used herein, the term “binding domain” or "antibody molecule" (also referred to herein as “anti-target (e.g., BCMA) binding domain”) refers to a protein, e.g., an immunoglobulin chain or fragment thereof, comprising at least one immunoglobulin variable domain sequence. The term “binding domain” or “antibody molecule” encompasses antibodies and antibody fragments. In an embodiment, an antibody molecule is a multispecific antibody molecule, e.g., it comprises a plurality of immunoglobulin variable domain sequences, wherein a first immunoglobulin variable domain sequence of the plurality has binding specificity for a first epitope and a second immunoglobulin variable domain sequence of the plurality has binding specificity for a second epitope. In an embodiment, a multispecific antibody molecule is a bispecific antibody molecule. A bispecific antibody has specificity for no more than two antigens. A bispecific antibody molecule is characterized by a first immunoglobulin variable domain sequence which has binding specificity for a first epitope and a second immunoglobulin variable domain sequence that has binding specificity for a second epitope. The term “antibody heavy chain,” refers to the larger of the two types of polypeptide chains present in antibody molecules in their naturally occurring conformations, and which normally determines the class to which the antibody belongs.

The term “antibody light chain,” refers to the smaller of the two types of polypeptide chains present in antibody molecules in their naturally occurring conformations. Kappa (κ) and lambda (λ) light chains refer to the two major antibody light chain isotypes.

The term “recombinant antibody” refers to an antibody which is generated using recombinant DNA technology, such as, for example, an antibody expressed by a bacteriophage or yeast expression system. The term should also be construed to mean an antibody which has been generated by the synthesis of a DNA molecule encoding the antibody and which DNA molecule expresses an antibody protein, or an amino acid sequence specifying the antibody, wherein the DNA or amino acid sequence has been obtained using recombinant DNA or amino acid sequence technology which is available and well known in the art.

The term "antigen" or "Ag" refers to a molecule that provokes an immune response. This immune response may involve either antibody production, or the activation of specific immunologically-competent cells, or both. The skilled artisan will understand that any macromolecule, including virtually all proteins or peptides, can serve as an antigen. Furthermore, antigens can be derived from recombinant or genomic DNA. A skilled artisan will understand that any DNA, which comprises a nucleotide sequences or a partial nucleotide sequence encoding a protein that elicits an immune response therefore encodes an "antigen" as that term is used herein. Furthermore, one skilled in the art will understand that an antigen need not be encoded solely by a full length nucleotide sequence of a gene. It is readily apparent that the present invention includes, but is not limited to, the use of partial nucleotide sequences of more than one gene and that these nucleotide sequences are arranged in various combinations to encode polypeptides that elicit the desired immune response. Moreover, a skilled artisan will understand that an antigen need not be encoded by a "gene" at all. It is readily apparent that an antigen can be generated synthesized or can be derived from a biological sample, or might be macromolecule besides a polypeptide. Such a biological sample can include, but is not limited to a tissue sample, a tumor sample, a cell or a fluid with other biological components.

The term "anti-tumor effect" refers to a biological effect which can be manifested by various means, including but not limited to, e.g., a decrease in tumor volume, a decrease in the number of tumor cells, a decrease in the number of metastases, an increase in life expectancy, decrease in tumor cell proliferation, decrease in tumor cell survival, or amelioration of various physiological symptoms associated with the cancerous condition. An "anti-tumor effect" can also be manifested by the ability of the peptides, polynucleotides, cells and antibodies of the invention in prevention of the occurrence of tumor in the first place.

The term "anti-cancer effect" refers to a biological effect which can be manifested by various means, including but not limited to, e.g., a decrease in tumor volume, a decrease in the number of cancer cells, a decrease in the number of metastases, an increase in life expectancy, decrease in cancer cell proliferation, decrease in cancer cell survival, or amelioration of various physiological symptoms associated with the cancerous condition. An "anti-cancer effect" can also be manifested by the ability of the peptides, polynucleotides, cells and antibodies in prevention of the occurrence of cancer in the first place. The term "anti-tumor effect" refers to a biological effect which can be manifested by various means, including but not limited to, e.g., a decrease in tumor volume, a decrease in the number of tumor cells, a decrease in tumor cell proliferation, or a decrease in tumor cell survival. The term "autologous" refers to any material derived from the same individual to whom it is later to be re-introduced into the individual.

The term "allogeneic" refers to any material derived from a different animal of the same species as the individual to whom the material is introduced. Two or more individuals are said to be allogeneic to one another when the genes at one or more loci are not identical. In some aspects, allogeneic material from individuals of the same species may be sufficiently unlike genetically to interact antigenically.

The term "xenogeneic" refers to a graft derived from an animal of a different species.

The term "apheresis" as used herein refers to the art-recognized extracorporeal process by which the blood of a donor or patient is removed from the donor or patient and passed through an apparatus that separates out selected particular constituent(s) and returns the remainder to the circulation of the donor or patient, e.g., by retransfusion. Thus, in the context of "an apheresis sample" refers to a sample obtained using apheresis.

The term "combination" refers to either a fixed combination in one dosage unit form, or a combined administration where a compound of the present invention and a combination partner (e.g. another drug as explained below, also referred to as "therapeutic agent" or "co-agent") may be administered independently at the same time or separately within time intervals, especially where these time intervals allow that the combination partners show a cooperative, e.g. synergistic effect. The single components may be packaged in a kit or separately. One or both of the components (e.g., powders or liquids) may be reconstituted or diluted to a desired dose prior to administration. The terms "co-administration" or "combined administration" or the like as utilized herein are meant to encompass administration of the selected combination partner to a single subject in need thereof (e.g. a patient), and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time. The term "pharmaceutical combination" as used herein means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, e.g. a compound of the present invention and a combination partner, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, e.g. a compound of the present invention and a combination partner, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the two compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of three or more active ingredients.

The term "cancer" refers to a disease characterized by the rapid and uncontrolled growth of aberrant cells. Cancer cells can spread locally or through the bloodstream and lymphatic system to other parts of the body. Examples of various cancers are described herein and include but are not limited to,

breast cancer, prostate cancer, ovarian cancer, cervical cancer, skin cancer, pancreatic cancer, colorectal cancer, renal cancer, liver cancer, brain cancer, lymphoma, leukemia, lung cancer and the like. Preferred cancers treated by the methods described herein include multiple myeloma, Hodgkin's lymphoma or non-Hodgkin's lymphoma.

The terms "tumor" and "cancer" are used interchangeably herein, e.g., both terms encompass solid and liquid, e.g., diffuse or circulating, tumors. As used herein, the term "cancer" or "tumor" includes premalignant, as well as malignant cancers and tumors.

"Derived from" as that term is used herein, indicates a relationship between a first and a second molecule. It generally refers to structural similarity between the first molecule and a second molecule and does not connotate or include a process or source limitation on a first molecule that is derived from a second molecule. For example, in the case of an intracellular signaling domain that is derived from a CD3zeta molecule, the intracellular signaling domain retains sufficient CD3zeta structure such that is has the required function, namely, the ability to generate a signal under the appropriate conditions. It does not connotate or include a limitation to a particular process of producing the intracellular signaling domain, e.g., it does not mean that, to provide the intracellular signaling domain, one must start with a CD3zeta sequence and delete unwanted sequence, or impose mutations, to arrive at the intracellular signaling domain.

The phrase "disease associated with expression of BCMA" includes, but is not limited to, a disease associated with a cell which expresses BCMA (e.g., wild-type or mutant BCMA) or condition associated with a cell which expresses BCMA (e.g., wild-type or mutant BCMA) including, e.g., proliferative diseases such as a cancer or malignancy or a precancerous condition such as a myelodysplasia, a myelodysplastic syndrome or a preleukemia; or a noncancer related indication associated with a cell which expresses BCMA (e.g., wild-type or mutant BCMA). For the avoidance of doubt, a disease associated with expression of BCMA may include a condition associated with a cell which does not presently express BCMA, e.g., because BCMA expression has been downregulated, e.g., due to treatment with a molecule targeting BCMA, e.g., a BCMA inhibitor described herein, but which at one time expressed BCMA. In one aspect, a cancer associated with expression of BCMA (e.g., wild-type or mutant BCMA) is a hematological cancer. In one aspect, the hematological cancer is a leukemia or a lymphoma. In one aspect, a cancer associated with expression of BCMA (e.g., wild-type or mutant BCMA) is a malignancy of differentiated plasma B cells. In one aspect, a cancer associated with expression of BCMA(e.g., wild-type or mutant BCMA) includes cancers and malignancies including, but not limited to, e.g., one or more acute leukemias including but not limited to, e.g., B-cell acute Lymphoid Leukemia ("BALL"), T-cell acute Lymphoid Leukemia ("TALL"), acute lymphoid leukemia (ALL); one or more chronic leukemias including but not limited to, e.g., chronic myelogenous

leukemia (CML), Chronic Lymphoid Leukemia (CLL). Additional cancers or hematologic conditions associated with expression of BMCA (e.g., wild-type or mutant BCMA) comprise, but are not limited to, e.g., B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B cell lymphoma, Follicular lymphoma, Hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, Marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia, and "preleukemia" which are a diverse collection of hematological conditions united by ineffective production (or dysplasia) of myeloid blood cells, and the like. In some embodiments, the cancer is multiple myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, or glioblastoma. In embodiments, a disease associated with expression of BCMA includes a plasma cell proliferative disorder, e.g., asymptomatic myeloma (smoldering multiple myeloma or indolent myeloma), monoclonal gammapathy of undetermined significance (MGUS), Waldenstrom's macroglobulinemia, plasmacytomas (e.g., plasma cell dyscrasia, solitary myeloma, solitary plasmacytoma, extramedullary plasmacytoma, and multiple plasmacytoma), systemic amyloid light chain amyloidosis, and POEMS syndrome (also known as Crow-Fukase syndrome, Takatsuki disease, and PEP syndrome). Further diseases associated with expression of BCMA (e.g., wild-type or mutant BCMA) expression include, but not limited to, e.g., atypical and/or non-classical cancers, malignancies, precancerous conditions or proliferative diseases associated with expression of BCMA (e.g., wild-type or mutant BCMA), e.g., a cancer described herein, e.g., a prostate cancer (e.g., castrate-resistant or therapy-resistant prostate cancer, or metastatic prostate cancer), pancreatic cancer, or lung cancer.

Non-cancer related conditions that are associated with BCMA (e.g., wild-type or mutant BCMA) include viral infections; e.g., HIV, fungal infections, e.g., C. neoformans; autoimmune disease; e.g. rheumatoid arthritis, system lupus erythematosus (SLE or lupus), pemphigus vulgaris, and Sjogren's syndrome; inflammatory bowel disease, ulcerative colitis; transplant-related allospecific immunity disorders related to mucosal immunity; and unwanted immune responses towards biologics (e.g., Factor VIII) where humoral immunity is important. In embodiments, a non-cancer related indication associated with expression of BCMA includes but is not limited to, e.g., autoimmune disease, (e.g., lupus), inflammatory disorders (allergy and asthma) and transplantation. In some embodiments, the tumor antigen-expressing cell expresses, or at any time expressed, mRNA encoding the tumor antigen. In an embodiment, the tumor antigen -expressing cell produces the tumor antigen protein (e.g., wild-type or mutant), and the tumor antigen protein may be present at normal levels or reduced levels. In an embodiment, the tumor antigen -expressing cell produced detectable levels of a tumor antigen protein at one point, and subsequently produced substantially no detectable tumor antigen protein.

The term "conservative sequence modifications" refers to amino acid modifications that do not significantly affect or alter the binding characteristics of the antibody or antibody fragment containing the amino acid sequence. Such conservative modifications include amino acid substitutions, additions and deletions. Modifications can be introduced into an antibody or antibody fragment of the invention by standard techniques known in the art, such as site-directed mutagenesis and PCR-mediated mutagenesis. Conservative substitutions are ones in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine, tryptophan), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Thus, one or more amino acid residues within a CAR of the invention can be replaced with other amino acid residues from the same side chain family and the altered CAR can be tested using the functional assays described herein.

The term "stimulation," refers to a primary response induced by binding of a stimulatory molecule (e.g., a TCR/CD3 complex) with its cognate ligand thereby mediating a signal transduction event, such as, but not limited to, signal transduction via the TCR/CD3 complex. Stimulation can mediate altered expression of certain molecules, such as downregulation of TGF-β, and/or reorganization of cytoskeletal structures, and the like.

The term "stimulatory molecule," refers to a molecule expressed by a T cell that provides the primary cytoplasmic signaling sequence(s) that regulate primary activation of the TCR complex in a stimulatory way for at least some aspect of the T cell signaling pathway. In some embodiments, the ITAM-containing domain within the CAR recapitulates the signaling of the primary TCR independently of endogenous TCR complexes. In one aspect, the primary signal is initiated by, for instance, binding of a TCR/CD3 complex with an MHC molecule loaded with peptide, and which leads to mediation of a T cell response, including, but not limited to, proliferation, activation, differentiation, and the like. A primary cytoplasmic signaling sequence (also referred to as a "primary signaling domain") that acts in a stimulatory manner may contain a signaling motif which is known as immunoreceptor tyrosine-based activation motif or ITAM. Examples of an ITAM containing primary cytoplasmic signaling sequence that is of particular use in the invention includes, but is not limited to, those derived from TCR zeta, FcR gamma, FcR beta, CD3 gamma, CD3 delta , CD3 epsilon, CD5, CD22, CD79a, CD79b, CD278 (also known as "ICOS") , FcεRI and CD66d, DAP10 and DAP12. In a specific CAR of the invention, the intracellular signaling domain in any one or more CARS of the invention comprises an intracellular

signaling sequence, e.g., a primary signaling sequence of CD3-zeta. The term "antigen presenting cell" or "APC" refers to an immune system cell such as an accessory cell (e.g., a B-cell, a dendritic cell, and the like) that displays a foreign antigen complexed with major histocompatibility complexes (MHC's) on its surface. T-cells may recognize these complexes using their T-cell receptors (TCRs). APCs process antigens and present them to T-cells.

An "intracellular signaling domain," as the term is used herein, refers to an intracellular portion of a molecule. In embodiments, the intracellular signal domain transduces the effector function signal and directs the cell to perform a specialized function. While the entire intracellular signaling domain can be employed, in many cases it is not necessary to use the entire chain. To the extent that a truncated portion of the intracellular signaling domain is used, such truncated portion may be used in place of the intact chain as long as it transduces the effector function signal. The term intracellular signaling domain is thus meant to include any truncated portion of the intracellular signaling domain sufficient to transduce the effector function signal.

The intracellular signaling domain generates a signal that promotes an immune effector function of the CAR containing cell, e.g., a CART cell. Examples of immune effector function, e.g., in a CART cell, include cytolytic activity and helper activity, including the secretion of cytokines.

In an embodiment, the intracellular signaling domain can comprise a primary intracellular signaling domain. Exemplary primary intracellular signaling domains include those derived from the molecules responsible for primary stimulation, or antigen dependent simulation. In an embodiment, the intracellular signaling domain can comprise a costimulatory intracellular domain. Exemplary costimulatory intracellular signaling domains include those derived from molecules responsible for costimulatory signals, or antigen independent stimulation. For example, in the case of a CART, a primary intracellular signaling domain can comprise a cytoplasmic sequence of a T cell receptor, and a costimulatory intracellular signaling domain can comprise cytoplasmic sequence from co-receptor or costimulatory molecule.

A primary intracellular signaling domain can comprise a signaling motif which is known as an immunoreceptor tyrosine-based activation motif or ITAM. Examples of ITAM containing primary cytoplasmic signaling sequences include, but are not limited to, those derived from CD3 zeta, FcR gamma, FcR beta, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, CD278 (also known as "ICOS"), FcεRI, CD66d, DAP10 and DAP12.

The term "zeta" or alternatively "zeta chain", "CD3-zeta" or "TCR-zeta" refers to CD247. Swiss-Prot accession number P20963 provides exemplary human CD3 zeta amino acid sequences. A "zeta stimulatory domain" or alternatively a "CD3-zeta stimulatory domain" or a "TCR-zeta stimulatory

domain" refers to a stimulatory domain of CD3-zeta or a variant thereof (e.g., a molecule having mutations, e.g., point mutations, fragments, insertions, or deletions). In one embodiment, the cytoplasmic domain of zeta comprises residues 52 through 164 of GenBank Acc. No. BAG36664.1 or a variant thereof (e.g., a molecule having mutations, e.g., point mutations, fragments, insertions, or deletions). In one embodiment, the "zeta stimulatory domain" or a "CD3-zeta stimulatory domain" is the sequence provided as SEQ ID NO: 1027 or 1030 or a variant thereof (e.g., a molecule having mutations, e.g., point mutations, fragments, insertions, or deletions).

The term "costimulatory molecule" refers to the cognate binding partner on a T cell that specifically binds with a costimulatory ligand, thereby mediating a costimulatory response by the T cell, such as, but not limited to, proliferation. Costimulatory molecules are cell surface molecules other than antigen receptors or their ligands that are required for an efficient immune response. Costimulatory molecules include, but are not limited to an MHC class I molecule, TNF receptor proteins, Immunoglobulin-like proteins, cytokine receptors, integrins, signaling lymphocytic activation molecules (SLAM proteins), activating NK cell receptors, BTLA, Toll ligand receptor, OX40, CD2, CD7, CD27, CD28, CD30, CD40, CDS, ICAM-1, LFA-1 (CD11a/CD18), 4-1BB (CD137), B7-H3, CDS, ICAM-1, ICOS (CD278), GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, NKG2C, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, and a ligand that specifically binds with CD83.

A costimulatory intracellular signaling domain refers to the intracellular portion of a costimulatory molecule.

The intracellular signaling domain can comprise the entire intracellular portion, or the entire native intracellular signaling domain, of the molecule from which it is derived, or a functional fragment thereof.

The term "4-1BB" refers to CD137 or Tumor necrosis factor receptor superfamily member 9. Swiss-Prot accession number P20963 provides exemplary human 4-1BB amino acid sequences. A "4-1BB costimulatory domain" refers to a costimulatory domain of 4-1BB, or a variant thereof (e.g., a molecule having mutations, e.g., point mutations, fragments, insertions, or deletions). In one

embodiment, the "4-1BB costimulatory domain" is the sequence provided as SEQ ID NO: 1022 or a variant thereof (e.g., a molecule having mutations, e.g., point mutations, fragments, insertions, or deletions).

"Immune effector cell," as that term is used herein, refers to a cell that is involved in an immune response, e.g., in the promotion of an immune effector response. Examples of immune effector cells include T cells, e.g., alpha/beta T cells and gamma/delta T cells, B cells, natural killer (NK) cells, natural killer T (NKT) cells, mast cells, and myeloic-derived phagocytes.

"Immune effector function or immune effector response," as that term is used herein, refers to function or response, e.g., of an immune effector cell, that enhances or promotes an immune attack of a target cell. E.g., an immune effector function or response refers a property of a T or NK cell that promotes killing or the inhibition of growth or proliferation, of a target cell. In the case of a T cell, primary stimulation and co-stimulation are examples of immune effector function or response.

The term "effector function" refers to a specialized function of a cell. Effector function of a T cell, for example, may be cytolytic activity or helper activity including the secretion of cytokines.

The term "encoding" refers to the inherent property of specific sequences of nucleotides in a polynucleotide, such as a gene, a cDNA, or an mRNA, to serve as templates for synthesis of other polymers and macromolecules in biological processes having either a defined sequence of nucleotides (e.g., rRNA, tRNA and mRNA) or a defined sequence of amino acids and the biological properties resulting therefrom. Thus, a gene, cDNA, or RNA, encodes a protein if transcription and translation of mRNA corresponding to that gene produces the protein in a cell or other biological system. Both the coding strand, the nucleotide sequence of which is identical to the mRNA sequence and is usually provided in sequence listings, and the non-coding strand, used as the template for transcription of a gene or cDNA, can be referred to as encoding the protein or other product of that gene or cDNA.

Unless otherwise specified, a "nucleotide sequence encoding an amino acid sequence" includes all nucleotide sequences that are degenerate versions of each other and that encode the same amino acid sequence. The phrase nucleotide sequence that encodes a protein or a RNA may also include introns to the extent that the nucleotide sequence encoding the protein may in some version contain an intron(s).

The term "effective amount" or "therapeutically effective amount" are used interchangeably herein, and refer to an amount of a compound, formulation, material, or composition, as described herein effective to achieve a particular biological result.

The term "endogenous" refers to any material from or produced inside an organism, cell, tissue or system.

The term "exogenous" refers to any material introduced from or produced outside an organism, cell, tissue or system.

The term "expression" refers to the transcription and/or translation of a particular nucleotide sequence driven by a promoter.

The term "transfer vector" refers to a composition of matter which comprises an isolated nucleic acid and which can be used to deliver the isolated nucleic acid to the interior of a cell. Numerous vectors are known in the art including, but not limited to, linear polynucleotides, polynucleotides associated with ionic or amphiphilic compounds, plasmids, and viruses. Thus, the term "transfer vector" includes an autonomously replicating plasmid or a virus. The term should also be construed to further include non-plasmid and non-viral compounds which facilitate transfer of nucleic acid into cells, such as, for example, a polylysine compound, liposome, and the like. Examples of viral transfer vectors include, but are not limited to, adenoviral vectors, adeno-associated virus vectors, retroviral vectors, lentiviral vectors, and the like.

The term "expression vector" refers to a vector comprising a recombinant polynucleotide comprising expression control sequences operatively linked to a nucleotide sequence to be expressed. An expression vector comprises sufficient cis-acting elements for expression; other elements for expression can be supplied by the host cell or in an in vitro expression system. Expression vectors include all those known in the art, including cosmids, plasmids (e.g., naked or contained in liposomes) and viruses (e.g., lentiviruses, retroviruses, adenoviruses, and adeno-associated viruses) that incorporate the recombinant polynucleotide.

The term "lentivirus" refers to a genus of the Retroviridae family. Lentiviruses are unique among the retroviruses in being able to infect non-dividing cells; they can deliver a significant amount of genetic information into the DNA of the host cell, so they are one of the most efficient methods of a gene delivery vector. HIV, SIV, and FIV are all examples of lentiviruses.

The term "lentiviral vector" refers to a vector derived from at least a portion of a lentivirus genome, including especially a self-inactivating lentiviral vector as provided in Milone et al., Mol. Ther. 17(8): 1453–1464 (2009). Other examples of lentivirus vectors that may be used in the clinic, include but are not limited to, e.g., the LENTIVECTOR® gene delivery technology from Oxford BioMedica, the LENTIMAX™ vector system from Lentigen and the like. Nonclinical types of lentiviral vectors are also available and would be known to one skilled in the art.

The term "homologous" or "identity" refers to the subunit sequence identity between two polymeric molecules, e.g., between two nucleic acid molecules, such as, two DNA molecules or two RNA molecules, or between two polypeptide molecules. When a subunit position in both of the two

molecules is occupied by the same monomeric subunit; e.g., if a position in each of two DNA molecules is occupied by adenine, then they are homologous or identical at that position. The homology between two sequences is a direct function of the number of matching or homologous positions; e.g., if half (e.g., five positions in a polymer ten subunits in length) of the positions in two sequences are homologous, the two sequences are 50% homologous; if 90% of the positions (e.g., 9 of 10), are matched or homologous, the two sequences are 90% homologous.

"Humanized" forms of non-human (e.g., murine) antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', F(ab')2 or other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin. For the most part, humanized antibodies and antibody fragments thereof are human immunoglobulins (recipient antibody or antibody fragment) in which residues from a complementary-determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity, and capacity. In some instances, Fv framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, a humanized antibody/antibody fragment can comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. These modifications can further refine and optimize antibody or antibody fragment performance. In general, the humanized antibody or antibody fragment thereof will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or a significant portion of the FR regions are those of a human immunoglobulin sequence. The humanized antibody or antibody fragment can also comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see Jones et al., Nature, 321: 522-525, 1986; Reichmann et al., Nature, 332: 323-329, 1988; Presta, Curr. Op. Struct. Biol., 2: 593-596, 1992.

"Fully human" refers to an immunoglobulin, such as an antibody or antibody fragment, where the whole molecule is of human origin or consists of an amino acid sequence identical to a human form of the antibody or immunoglobulin.

The term "isolated" means altered or removed from the natural state. For example, a nucleic acid or a peptide naturally present in a living animal is not "isolated," but the same nucleic acid or peptide partially or completely separated from the coexisting materials of its natural state is "isolated." An isolated nucleic acid or protein can exist in substantially purified form, or can exist in a non-native environment such as, for example, a host cell.

In the context of the present invention, the following abbreviations for the commonly occurring nucleic acid bases are used. "A" refers to adenosine, "C" refers to cytosine, "G" refers to guanosine, "T" refers to thymidine, and "U" refers to uridine.

The term "operably linked" or "transcriptional control" refers to functional linkage between a regulatory sequence and a heterologous nucleic acid sequence resulting in expression of the latter. For example, a first nucleic acid sequence is operably linked with a second nucleic acid sequence when the first nucleic acid sequence is placed in a functional relationship with the second nucleic acid sequence. For instance, a promoter is operably linked to a coding sequence if the promoter affects the transcription or expression of the coding sequence. Operably linked DNA sequences can be contiguous with each other and, e.g., where necessary to join two protein coding regions, are in the same reading frame.

The term "parenteral" administration of an immunogenic composition includes, e.g., subcutaneous (s.c.), intravenous (i.v.), intramuscular (i.m.), or intrasternal injection, intratumoral, or infusion techniques.

The term "nucleic acid" or "polynucleotide" refers to deoxyribonucleic acids (DNA) or ribonucleic acids (RNA) and polymers thereof in either single- or double-stranded form. Unless specifically limited, the term encompasses nucleic acids containing known analogues of natural nucleotides that have similar binding properties as the reference nucleic acid and are metabolized in a manner similar to naturally occurring nucleotides. Unless otherwise indicated, a particular nucleic acid sequence also implicitly encompasses conservatively modified variants thereof (e.g., degenerate codon substitutions, e.g., conservative substitutions), alleles, orthologs, SNPs, and complementary sequences as well as the sequence explicitly indicated. Specifically, degenerate codon substitutions, e.g., conservative substitutions may be achieved by generating sequences in which the third position of one or more selected (or all) codons is substituted with mixed-base and/or deoxyinosine residues (Batzer et al., Nucleic Acid Res. 19:5081 (1991); Ohtsuka et al., J. Biol. Chem. 260:2605-2608 (1985); and Rossolini et al., Mol. Cell. Probes 8:91-98 (1994)).

The terms "peptide," "polypeptide," and "protein" are used interchangeably, and refer to a compound comprised of amino acid residues covalently linked by peptide bonds. A protein or peptide must contain at least two amino acids, and no limitation is placed on the maximum number of amino acids that can comprise a protein's or peptide's sequence. Polypeptides include any peptide or protein comprising two or more amino acids joined to each other by peptide bonds. As used herein, the term refers to both short chains, which also commonly are referred to in the art as peptides, oligopeptides and oligomers, for example, and to longer chains, which generally are referred to in the art as proteins, of which there are many types. "Polypeptides" include, for example, biologically active fragments,

substantially homologous polypeptides, oligopeptides, homodimers, heterodimers, variants of polypeptides, modified polypeptides, derivatives, analogs, fusion proteins, among others. A polypeptide includes a natural peptide, a recombinant peptide, or a combination thereof.

The term "promoter" refers to a DNA sequence recognized by the synthetic machinery of the cell, or introduced synthetic machinery, required to initiate the specific transcription of a polynucleotide sequence.

The term "promoter/regulatory sequence" refers to a nucleic acid sequence which is required for expression of a gene product operably linked to the promoter/regulatory sequence. In some instances, this sequence may be the core promoter sequence and in other instances, this sequence may also include an enhancer sequence and other regulatory elements which are required for expression of the gene product. The promoter/regulatory sequence may, for example, be one which expresses the gene product in a tissue specific manner.

The term "constitutive" promoter refers to a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a cell under most or all physiological conditions of the cell.

The term "inducible" promoter refers to a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a cell substantially only when an inducer which corresponds to the promoter is present in the cell.

The term "tissue-specific" promoter refers to a nucleotide sequence which, when operably linked with a polynucleotide encodes or specified by a gene, causes the gene product to be produced in a cell substantially only if the cell is a cell of the tissue type corresponding to the promoter.

The terms "cancer associated antigen" or "tumor antigen" interchangeably refers to a molecule (typically a protein, carbohydrate or lipid) that is expressed on the surface of a cancer cell, either entirely or as a fragment (e.g., MHC/peptide), and which is useful for the preferential targeting of a pharmacological agent to the cancer cell. In some embodiments, a tumor antigen is a marker expressed by both normal cells and cancer cells, e.g., a lineage marker, e.g., CD19 on B cells. In some embodiments, a tumor antigen is a cell surface molecule that is overexpressed in a cancer cell in comparison to a normal cell, for instance, 1-fold over expression, 2-fold overexpression, 3-fold overexpression or more in comparison to a normal cell. In some embodiments, a tumor antigen is a cell surface molecule that is inappropriately synthesized in the cancer cell, for instance, a molecule that contains deletions, additions or mutations in comparison to the molecule expressed on a normal cell. In some embodiments, a tumor antigen will be expressed exclusively on the cell surface of a cancer cell,

entirely or as a fragment (e.g., MHC/peptide), and not synthesized or expressed on the surface of a normal cell. In some embodiments, the CARs of the present invention includes CARs comprising an antigen binding domain (e.g., antibody or antibody fragment) that binds to a MHC presented peptide. Normally, peptides derived from endogenous proteins fill the pockets of Major histocompatibility complex (MHC) class I molecules, and are recognized by T cell receptors (TCRs) on CD8 + T lymphocytes. The MHC class I complexes are constitutively expressed by all nucleated cells. In cancer, virus-specific and/or tumor-specific peptide/MHC complexes represent a unique class of cell surface targets for immunotherapy. TCR-like antibodies targeting peptides derived from viral or tumor antigens in the context of human leukocyte antigen (HLA)-A1 or HLA-A2 have been described (see, e.g., Sastry et al., J Virol. 2011 85(5):1935-1942; Sergeeva et al., Blood, 2011 117(16):4262-4272; Verma et al., J Immunol 2010 184(4):2156-2165; Willemsen et al., Gene Ther 2001 8(21) :1601-1608 ; Dao et al., Sci Transl Med 2013 5(176) :176ra33 ; Tassev et al., Cancer Gene Ther 2012 19(2):84-100). For example, TCR-like antibody can be identified from screening a library, such as a human scFv phage displayed library.

The term "tumor-supporting antigen" or "cancer-supporting antigen" interchangeably refer to a molecule (typically a protein, carbohydrate or lipid) that is expressed on the surface of a cell that is, itself, not cancerous, but supports the cancer cells, e.g., by promoting their growth or survival e.g., resistance to immune cells. Exemplary cells of this type include stromal cells and myeloid-derived suppressor cells (MDSCs). The tumor-supporting antigen itself need not play a role in supporting the tumor cells so long as the antigen is present on a cell that supports cancer cells.

The term "flexible polypeptide linker" or "linker" as used in the context of an scFv refers to a peptide linker that consists of amino acids such as glycine and/or serine residues used alone or in combination, to link variable heavy and variable light chain regions together. In one embodiment, the flexible polypeptide linker is a Gly/Ser linker and comprises the amino acid sequence (Gly-Gly-Gly-Ser)n (SEQ ID NO: 1038), where n is a positive integer equal to or greater than 1. For example, n=1, n=2, n=3. n=4, n=5 and n=6, n=7, n=8, n=9 and n=10 In one embodiment, the flexible polypeptide linkers include, but are not limited to, (Gly4 Ser)4 (SEQ ID NO: 1039) or (Gly4 Ser)3 (SEQ ID NO: 1040). In another embodiment, the linkers include multiple repeats of (Gly2Ser), (GlySer) or (Gly3Ser) (SEQ ID NO: 1041). Also included within the scope of the invention are linkers described in WO2012/138475, incorporated herein by reference.

As used herein, a 5' cap (also termed an RNA cap, an RNA 7-methylguanosine cap or an RNA m7G cap) is a modified guanine nucleotide that has been added to the "front" or 5' end of a eukaryotic messenger RNA shortly after the start of transcription. The 5' cap consists of a terminal group which is linked to the first transcribed nucleotide. Its presence is critical for recognition by the ribosome and

protection from RNases. Cap addition is coupled to transcription, and occurs co-transcriptionally, such that each influences the other. Shortly after the start of transcription, the 5' end of the mRNA being synthesized is bound by a cap-synthesizing complex associated with RNA polymerase. This enzymatic complex catalyzes the chemical reactions that are required for mRNA capping. Synthesis proceeds as a multi-step biochemical reaction. The capping moiety can be modified to modulate functionality of mRNA such as its stability or efficiency of translation.

As used herein, "in vitro transcribed RNA" refers to RNA, preferably mRNA, that has been synthesized in vitro. Generally, the in vitro transcribed RNA is generated from an in vitro transcription vector. The in vitro transcription vector comprises a template that is used to generate the in vitro transcribed RNA.

As used herein, a "poly(A)" is a series of adenosines attached by polyadenylation to the mRNA. In the preferred embodiment of a construct for transient expression, the polyA is between 50 and 5000 (SEQ ID NO: 1043), preferably greater than 64, more preferably greater than 100, most preferably greater than 300 or 400 (SEQ ID NO: 2024). poly(A) sequences can be modified chemically or enzymatically to modulate mRNA functionality such as localization, stability or efficiency of translation.

As used herein, "polyadenylation" refers to the covalent linkage of a polyadenylyl moiety, or its modified variant, to a messenger RNA molecule. In eukaryotic organisms, most messenger RNA (mRNA) molecules are polyadenylated at the 3' end. The 3' poly(A) tail is a long sequence of adenine nucleotides (often several hundred) added to the pre-mRNA through the action of an enzyme, polyadenylate polymerase. In higher eukaryotes, the poly(A) tail is added onto transcripts that contain a specific sequence, the polyadenylation signal. The poly(A) tail and the protein bound to it aid in protecting mRNA from degradation by exonucleases. Polyadenylation is also important for transcription termination, export of the mRNA from the nucleus, and translation. Polyadenylation occurs in the nucleus immediately after transcription of DNA into RNA, but additionally can also occur later in the cytoplasm. After transcription has been terminated, the mRNA chain is cleaved through the action of an endonuclease complex associated with RNA polymerase. The cleavage site is usually characterized by the presence of the base sequence AAUAAA near the cleavage site. After the mRNA has been cleaved, adenosine residues are added to the free 3' end at the cleavage site.

As used herein, "transient" refers to expression of a non-integrated transgene for a period of hours, days or weeks, wherein the period of time of expression is less than the period of time for expression of the gene if integrated into the genome or contained within a stable plasmid replicon in the host cell.

As used herein, the terms “treat”, “treatment” and “treating” refer to the reduction or amelioration of the progression, severity and/or duration of a proliferative disorder, or the amelioration of one or more symptoms (preferably, one or more discernible symptoms) of a proliferative disorder resulting from the administration of one or more therapies (e.g., one or more therapeutic agents such as a CAR of the invention). In specific embodiments, the terms “treat”, “treatment” and “treating” refer to the amelioration of at least one measurable physical parameter of a proliferative disorder, such as growth of a tumor, not necessarily discernible by the patient. In other embodiments the terms “treat”, “treatment” and “treating” -refer to the inhibition of the progression of a proliferative disorder, either physically by, e.g., stabilization of a discernible symptom, physiologically by, e.g., stabilization of a physical parameter, or both. In other embodiments the terms “treat”, “treatment” and “treating” refer to the reduction or stabilization of tumor size or cancerous cell count.

The term “signal transduction pathway” refers to the biochemical relationship between a variety of signal transduction molecules that play a role in the transmission of a signal from one portion of a cell to another portion of a cell. The phrase “cell surface receptor” includes molecules and complexes of molecules capable of receiving a signal and transmitting signal across the membrane of a cell.

The term “subject” is intended to include living organisms in which an immune response can be elicited (e.g., mammals, human).

The term, a “substantially purified” cell refers to a cell that is essentially free of other cell types. A substantially purified cell also refers to a cell which has been separated from other cell types with which it is normally associated in its naturally occurring state. In some instances, a population of substantially purified cells refers to a homogenous population of cells. In other instances, this term refers simply to cell that have been separated from the cells with which they are naturally associated in their natural state. In some aspects, the cells are cultured in vitro. In other aspects, the cells are not cultured in vitro.

The term “therapeutic” as used herein means a treatment. A therapeutic effect is obtained by reduction, suppression, remission, or eradication of a disease state.

The term “prophylaxis” as used herein means the prevention of or protective treatment for a disease or disease state.

In the context of the present invention, "tumor antigen" or "hyperproliferative disorder antigen" or "antigen associated with a hyperproliferative disorder" refers to antigens that are common to specific hyperproliferative disorders. In certain aspects, the hyperproliferative disorder antigens of the present invention are derived from, cancers including but not limited to primary or metastatic melanoma, thymoma, lymphoma, sarcoma, lung cancer, liver cancer, non-Hodgkin lymphoma, Hodgkin lymphoma,

leukemias, uterine cancer, cervical cancer, bladder cancer, kidney cancer and adenocarcinomas such as breast cancer, prostate cancer (e.g., castrate-resistant or therapy-resistant prostate cancer, or metastatic prostate cancer), ovarian cancer, pancreatic cancer, and the like, or a plasma cell proliferative disorder, e.g., asymptomatic myeloma (smoldering multiple myeloma or indolent myeloma), monoclonal gammapathy of undetermined significance (MGUS), Waldenstrom's macroglobulinemia, plasmacytomas (e.g., plasma cell dyscrasia, solitary myeloma, solitary plasmacytoma, extramedullary plasmacytoma, and multiple plasmacytoma), systemic amyloid light chain amyloidosis, and POEMS syndrome (also known as Crow-Fukase syndrome, Takatsuki disease, and PEP syndrome).

The term "transfected" or "transformed" or "transduced" refers to a process by which exogenous nucleic acid is transferred or introduced into the host cell. A "transfected" or "transformed" or "transduced" cell is one which has been transfected, transformed or transduced with exogenous nucleic acid. The cell includes the primary subject cell and its progeny.

The term "specifically binds," refers to an antibody, or a ligand, which recognizes and binds with a cognate binding partner (e.g., a stimulatory and/or costimulatory molecule present on a T cell) protein present in a sample, but which antibody or ligand does not substantially recognize or bind other molecules in the sample.

"Regulatable chimeric antigen receptor (RCAR)," as used herein, refers to a set of polypeptides, typically two in the simplest embodiments, which when in an immune effector cell, provides the cell with specificity for a target cell, typically a cancer cell, and with intracellular signal generation. In some embodiments, an RCAR comprises at least an extracellular antigen binding domain, a transmembrane domain and a cytoplasmic signaling domain (also referred to herein as "an intracellular signaling domain") comprising a functional signaling domain derived from a stimulatory molecule and/or costimulatory molecule as defined herein in the context of a CAR molecule. In some embodiments, the set of polypeptides in the RCAR are not contiguous with each other, e.g., are in different polypeptide chains. In some embodiments, the RCAR includes a dimerization switch that, upon the presence of a dimerization molecule, can couple the polypeptides to one another, e.g., can couple an antigen binding domain to an intracellular signaling domain. In some embodiments, the RCAR is expressed in a cell (e.g., an immune effector cell) as described herein, e.g., an RCAR-expressing cell (also referred to herein as "RCARX cell"). In an embodiment the RCARX cell is a T cell, and is referred to as a RCART cell. In an embodiment the RCARX cell is an NK cell, and is referred to as a RCARN cell. The RCAR can provide the RCAR-expressing cell with specificity for a target cell, typically a cancer cell, and with regulatable intracellular signal generation or proliferation, which can optimize an immune effector property of the RCAR-expressing cell. In embodiments, an RCAR cell relies at least in part, on

an antigen binding domain to provide specificity to a target cell that comprises the antigen bound by the antigen binding domain.

"Membrane anchor" or "membrane tethering domain", as that term is used herein, refers to a polypeptide or moiety, e.g., a myristoyl group, sufficient to anchor an extracellular or intracellular domain to the plasma membrane.

"Switch domain," as that term is used herein, e.g., when referring to an RCAR, refers to an entity, typically a polypeptide-based entity, that, in the presence of a dimerization molecule, associates with another switch domain. The association results in a functional coupling of a first entity linked to, e.g., fused to, a first switch domain, and a second entity linked to, e.g., fused to, a second switch domain. A first and second switch domain are collectively referred to as a dimerization switch. In embodiments, the first and second switch domains are the same as one another, e.g., they are polypeptides having the same primary amino acid sequence, and are referred to collectively as a homodimerization switch. In embodiments, the first and second switch domains are different from one another, e.g., they are polypeptides having different primary amino acid sequences, and are referred to collectively as a heterodimerization switch. In embodiments, the switch is intracellular. In embodiments, the switch is extracellular. In embodiments, the switch domain is a polypeptide-based entity, e.g., FKBP or FRB-based, and the dimerization molecule is small molecule, e.g., a rapalogue. In embodiments, the switch domain is a polypeptide-based entity, e.g., an scFv that binds a myc peptide, and the dimerization molecule is a polypeptide, a fragment thereof, or a multimer of a polypeptide, e.g., a myc ligand or multimers of a myc ligand that bind to one or more myc scFvs. In embodiments, the switch domain is a polypeptide-based entity, e.g., myc receptor, and the dimerization molecule is an antibody or fragments thereof, e.g., myc antibody.

"Dimerization molecule," as that term is used herein, e.g., when referring to an RCAR, refers to a molecule that promotes the association of a first switch domain with a second switch domain. In embodiments, the dimerization molecule does not naturally occur in the subject, or does not occur in concentrations that would result in significant dimerization. In embodiments, the dimerization molecule is a small molecule, e.g., rapamycin or a rapalogue, e.g, RAD001.

The term "bioequivalent" refers to an amount of an agent other than the reference compound (e.g., RAD001), required to produce an effect equivalent to the effect produced by the reference dose or reference amount of the reference compound (e.g., RAD001). In an embodiment the effect is the level of mTOR inhibition, e.g., as measured by P70 S6 kinase inhibition, e.g., as evaluated in an in vivo or in vitro assay, e.g., as measured by an assay described herein, e.g., the Boulay assay, or measurement of phosphorylated S6 levels by western blot. In an embodiment, the effect is alteration of the ratio of PD-1

positive/PD-1 negative T cells, as measured by cell sorting. In an embodiment a bioequivalent amount or dose of an mTOR inhibitor is the amount or dose that achieves the same level of P70 S6 kinase inhibition as does the reference dose or reference amount of a reference compound. In an embodiment, a bioequivalent amount or dose of an mTOR inhibitor is the amount or dose that achieves the same level of alteration in the ratio of PD-1 positive/PD-1 negative T cells as does the reference dose or reference amount of a reference compound.

The term "low, immune enhancing, dose" when used in conjuction with an mTOR inhibitor, e.g., an allosteric mTOR inhibitor, e.g., RAD001 or rapamycin, or a catalytic mTOR inhibitor, refers to a dose of mTOR inhibitor that partially, but not fully, inhibits mTOR activity, e.g., as measured by the inhibition of P70 S6 kinase activity. Methods for evaluating mTOR activity, e.g., by inhibition of P70 S6 kinase, are discussed herein. The dose is insufficient to result in complete immune suppression but is sufficient to enhance the immune response. In an embodiment, the low, immune enhancing, dose of mTOR inhibitor results in a decrease in the number of PD-1 positive immune effector cells, e.g., T cells or NK cells, and/or an increase in the number of PD-1 negative immune effector cells, e.g., T cells or NK cells, or an increase in the ratio of PD-1 negative immune effector cells (e.g., T cells or NK cells) /PD-1 positive immune effector cells (e.g., T cells or NK cells).

In an embodiment, the low, immune enhancing, dose of mTOR inhibitor results in an increase in the number of naive T cells. In an embodiment, the low, immune enhancing, dose of mTOR inhibitor results in one or more of the following:

an increase in the expression of one or more of the following markers: CD62Lhigh, CD127high, CD27+, and BCL2, e.g., on memory T cells, e.g., memory T cell precursors;

a decrease in the expression of KLRG1, e.g., on memory T cells, e.g., memory T cell precursors; and

an increase in the number of memory T cell precursors, e.g., cells with any one or combination of the following characteristics: increased CD62Lhigh, increased CD127high, increased CD27+, decreased KLRG1, and increased BCL2;

wherein any of the changes described above occurs, e.g., at least transiently, e.g., as compared to a non-treated subject.

"Refractory" as used herein refers to a disease, e.g., cancer, that does not respond to a treatment. In embodiments, a refractory cancer can be resistant to a treatment before or at the beginning of the treatment. In other embodiments, the refractory cancer can become resistant during a treatment. A refractory cancer is also called a resistant cancer.

"Relapsed" or a "relapse" as used herein refers to the reappearance of a disease (e.g., cancer) or the signs and symptoms of a disease such as cancer after a period of improvement or responsiveness, e.g., after prior treatment of a therapy, e.g., cancer therapy. For example, the period of responsiveness may involve the level of cancer cells falling below a certain threshold, e.g., below 20%, 15%, 10%, 5%, 4%, 3%, 2%, or 1%. The reappearance may involve the level of cancer cells rising above a certain threshold, e.g., above 20%, 15%, 10%, 5%, 4%, 3%, 2%, or 1%.

In one aspect, a "responder" of a therapy can be a subject having complete response, very good partial response, or partial response after receiving the therapy. In one aspect, a "non-responder" of a therapy can be a subject having minor response, stable disease, or progressive disease after receiving the therapy. In some embodiments, the subject has multiple myeloma and the response of the subject to a multiple myeloma therapy is determined based on IMWG 2016 criteria, e.g., as disclosed in Kumar, et al., Lancet Oncol. 17, e328-346 (2016), hereby incorporated herein by reference in its entirety, e.g., as described in Table 7.

Ranges: throughout this disclosure, various aspects of the invention can be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 2.7, 3, 4, 5, 5.3, and 6. As another example, a range such as 95-99% identity, includes something with 95%, 96%, 97%, 98% or 99% identity, and includes subranges such as 96-99%, 96-98%, 96-97%, 97-99%, 97-98% and 98-99% identity. This applies regardless of the breadth of the range.

A "gene editing system" as the term is used herein, refers to a system, e.g., one or more molecules, that direct and effect an alteration, e.g., a deletion, of one or more nucleic acids at or near a site of genomic DNA targeted by said system. Gene editing systems are known in the art, and are described more fully below.

Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*,

University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

The term "alkyl," as used herein, refers to a monovalent saturated, straight- or branched-chain hydrocarbon such as a straight or branched group of 1-12, 1-10, or 1-6 carbon atoms, referred to herein as C_1-C_{12} alkyl, C_1-C_{10} alkyl, and C_1-C_6 alkyl, respectively. Examples of alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, sec-pentyl, iso-pentyl, tert-butyl, n-pentyl, neopentyl, n-hexyl, sec-hexyl, and the like.

The terms "alkenyl" and "alkynyl" as used herein refer to unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond, respectively. Exemplary alkenyl groups include, but are not limited to, $-CH=CH_2$ and $-CH_2CH=CH_2$.

The term "aryl" as used herein refers to a monocyclic, bicyclic or polycyclic hydrocarbon ring system, wherein at least one ring is aromatic. Representative aryl groups include fully aromatic ring systems, such as phenyl (e.g., (C_6) aryl), naphthyl (e.g., (C_{10}) aryl), and anthracenyl (e.g., (C_{14}) aryl), and ring systems where an aromatic carbon ring is fused to one or more non-aromatic carbon rings, such as indanyl, phthalimidyl, naphthimidyl, or tetrahydronaphthyl, and the like.

The term "carbocyclyl" as used herein refers to monocyclic, or fused, spiro-fused, and/or bridged bicyclic or polycyclic hydrocarbon ring system containing 3-18 carbon atoms, wherein each ring is either completely saturated or contains one or more units of unsaturation, but where no ring is aromatic. Representative carbocyclyl groups include cycloalkyl groups (*e.g.*, cyclopentyl, cyclobutyl, cyclopentyl, cyclohexyl and the like), and cycloalkenyl groups (*e.g.*, cyclopentenyl, cyclohexenyl, cyclopentadienyl, and the like).

The term "carbonyl" as used herein refers to –C=O.

The term "cyano" as used herein refers to –CN.

The terms "halo" or "halogen" as used herein refer to fluorine (fluoro, –F), chlorine (chloro, –Cl), bromine (bromo, –Br), or iodine (iodo, –I).

The term "heteroalkyl" as used herein refers to a monovalent saturated straight or branched alkyl chain wherein at least one carbon atom in the chain is replaced with a heteroatom, such as O, S, or N, provided that upon substitution, the chain comprises at least one carbon atom. In some embodiments, a heteroalkyl group may comprise, e.g., 1-12, 1-10, or 1-6 carbon atoms, referred to herein as C_1-C_{12} heteroalkyl, C_1-C_{10} heteroalkyl, and C_1-C_6 heteroalkyl. In certain instances, a heteroalkyl group comprises 1, 2, 3, or 4 independently selected heteroatoms in place of 1, 2, 3, or 4

individual carbon atoms in the alkyl chain. Representative heteroalkyl groups include –$CH_2NHC(O)CH_3$, -$CH_2CH_2OCH_3$, -$CH_2CH_2NHCH_3$, -$CH_2CH_2N(CH_3)CH_3$, and the like.

The term "heteroaryl" as used herein refers to a monocyclic, bicyclic or polycyclic ring system wherein at least one ring is both aromatic and comprises a heteroatom; and wherein no other rings are heterocyclyl (as defined below). Representative heteroaryl groups include ring systems where (i) each ring comprises a heteroatom and is aromatic, *e.g.*, imidazolyl, oxazolyl, thiazolyl, triazolyl, pyrrolyl, furanyl, thiophenyl pyrazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, indolizinyl, purinyl, naphthyridinyl, and pteridinyl; (ii) each ring is aromatic or carbocyclyl, at least one aromatic ring comprises a heteroatom and at least one other ring is a hydrocarbon ring or *e.g.*, indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, pyrido[2,3-*b*]-1,4-oxazin-3(4H)-one, thiazolo-[4,5-*c*]-pyridinyl, 4,5,6,7-tetrahydrothieno[2,3-*c*]pyridinyl, 5,6-dihydro-4H-thieno[2,3-*c*]pyrrolyl, 4,5,6,7,8-tetrahydroquinolinyl and 5,6,7,8-tetrahydroisoquinolinyl; and (iii) each ring is aromatic or carbocyclyl, and at least one aromatic ring shares a bridgehead heteroatom with another aromatic ring, *e.g.*, 4H-quinolizinyl. In certain embodiments, the heteroaryl is a monocyclic or bicyclic ring, wherein each of said rings contains 5 or 6 ring atoms where 1, 2, 3, or 4 of said ring atoms are a heteroatom independently selected from N, O, and S.

The term "heterocyclyl" as used herein refers to a monocyclic, or fused, spiro-fused, and/or bridged bicyclic and polycyclic ring systems where at least one ring is saturated or partially unsaturated (but not aromatic) and comprises a heteroatom. A heterocyclyl can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure and any of the ring atoms can be optionally substituted. Representative heterocyclyls include ring systems in which (i) every ring is non-aromatic and at least one ring comprises a heteroatom, *e.g.*, tetrahydrofuranyl, tetrahydrothienyl, pyrrolidinyl, pyrrolidonyl, piperidinyl, pyrrolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, and quinuclidinyl; (ii) at least one ring is non-aromatic and comprises a heteroatom and at least one other ring is an aromatic carbon ring, *e.g.*, 1,2,3,4-tetrahydroquinolinyl; and (iii) at least one ring is non-aromatic and comprises a heteroatom and at least one other ring is aromatic and comprises a heteroatom, *e.g.*, 3,4-dihydro-1H-pyrano[4,3-c]pyridinyl, and 1,2,3,4-tetrahydro-2,6-naphthyridinyl. In certain embodiments, the heterocyclyl is a monocyclic or bicyclic ring, wherein each of said rings contains 3-7 ring atoms where 1, 2, 3, or 4 of said ring atoms are a heteroatom independently selected from N, O, and S.

As described herein, compounds of the invention may contain "optionally substituted" moieties. In general, the term "substituted", whether preceded by the term "optionally" or not, means that one or

more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an "optionally substituted" group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at each position. Combinations of substituents envisioned under this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term "stable", as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

The term "oxo" as used herein refers to =O.

The term "thiocarbonyl" as used herein refers to C=S.

As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge et al., describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, 66, 1–19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid or by using other methods known in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2–hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3–phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}$ alkyl$)_4^-$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate, and aryl sulfonate.

The term "solvate" refers to forms of the compound that are associated with a solvent, usually by a solvolysis reaction. This physical association may include hydrogen bonding. Conventional solvents include water, methanol, ethanol, acetic acid, DMSO, THF, diethyl ether, and the like. The compounds of Formula (I), Formula (I-a), and/or Formula (II) may be prepared, *e.g.*, in crystalline form, and may be solvated. Suitable solvates include pharmaceutically acceptable solvates and further include both stoichiometric solvates and non-stoichiometric solvates. In certain instances, the solvate will be capable of isolation, for example, when one or more solvent molecules are incorporated in the crystal lattice of a crystalline solid. "Solvate" encompasses both solution-phase and isolable solvates. Representative solvates include hydrates, ethanolates, and methanolates.

The term "hydrate" refers to a compound which is associated with water. Typically, the number of the water molecules contained in a hydrate of a compound is in a definite ratio to the number of the compound molecules in the hydrate. Therefore, a hydrate of a compound may be represented, for example, by the general formula R·x H_2O, wherein R is the compound and wherein x is a number greater than 0. A given compound may form more than one type of hydrates, including, *e.g.*, monohydrates (x is 1), lower hydrates (x is a number greater than 0 and smaller than 1, *e.g.*, hemihydrates (R·0.5 H_2O)), and polyhydrates (x is a number greater than 1, *e.g.*, dihydrates (R·2 H_2O) and hexahydrates (R·6 H_2O)).

It is to be understood that compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers". Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers".

Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers". When a compound has an asymmetric center, for example, it is bonded to four different groups and a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (*i.e.*, as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture".

The term "tautomers" refer to compounds that are interchangeable forms of a particular compound structure, and that vary in the displacement of hydrogen atoms and electrons. Thus, two structures may be in equilibrium through the movement of π electrons and an atom (usually H). For example, enols and ketones are tautomers because they are rapidly interconverted by treatment with either acid or base. Another example of tautomerism is the aci- and nitro- forms of phenylnitromethane that are likewise formed by treatment with acid or base.

Tautomeric forms may be relevant to the attainment of the optimal chemical reactivity and biological activity of a compound of interest.

Unless otherwise stated, structures depicted herein are also meant to include all isomeric (*e.g.*, enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, Z and E double bond isomers, and Z and E conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures including the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents in accordance with the present invention.

Where a particular enantiomer is preferred, it may, in some embodiments be provided substantially free of the corresponding enantiomer, and may also be referred to as "optically enriched." "Optically-enriched," as used herein, means that the compound is made up of a significantly greater proportion of one enantiomer. In certain embodiments the compound is made up of at least about 90% by weight of a preferred enantiomer. In other embodiments the compound is made up of at least about 95%, 98%, or 99% by weight of a preferred enantiomer. Preferred enantiomers may be isolated from racemic mixtures by any method known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts or prepared by asymmetric syntheses. See, for example, Jacques et al., *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen, et al., *Tetrahedron* 33:2725 (1977); Eliel, E.L. *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); Wilen, S.H. *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972).

Various aspects of the compositions and methods herein are described in further detail below. Additional definitions are set out throughout the specification.

Detailed Description

The present invention provides, at least in part, a method of treating a subject having a disease associated with BCMA expression, comprising administering to the subject an effective amount of a cell (e.g., a population of cells) that expresses a CAR molecule that binds BCMA (a "BCMA CAR-expressing cell"). In some embodiments, the disease associated with expression of BCMA is a

hematologic cancer, e.g., ALL, CLL, DLBCL, or multiple myeloma. In some embodiments, the BCMA CAR-expressing cell therapy is administered based on the acquisition of a level of a biomarker from a patient sample. In some embodiments, the BCMA CAR-expressing cell therapy is administered to the subject in combination with a second therapy. In some embodiments, the BCMA CAR-expressing cell therapy and the second therapy are administered simultaneously or sequentially.

Chimeric antigen receptor (CAR)

In one aspect, disclosed herein are methods using a cell (e.g., a population of cells) that expresses a CAR molecule. In one aspect, an exemplary CAR construct comprises an optional leader sequence (e.g., a leader sequence described herein), an antigen binding domain (e.g., an antigen binding domain described herein), a hinge (e.g., a hinge region described herein), a transmembrane domain (e.g., a transmembrane domain described herein), and an intracellular stimulatory domain (e.g., an intracellular stimulatory domain described herein). In one aspect, an exemplary CAR construct comprises an optional leader sequence (e.g., a leader sequence described herein), an extracellular antigen binding domain (e.g., an antigen binding domain described herein), a hinge (e.g., a hinge region described herein), a transmembrane domain (e.g., a transmembrane domain described herein), an intracellular costimulatory signaling domain (e.g., a costimulatory signaling domain described herein) and/or an intracellular primary signaling domain (e.g., a primary signaling domain described herein).

Sequences of non-limiting examples of various components that can be part of a CAR molecule described herein, are listed in **Table 1**, where "aa" stands for amino acids, and "na" stands for nucleic acids that encode the corresponding peptide.

Table 1. Sequences of various components of CAR (aa – amino acid sequence, na – nucleic acid sequence).

SEQ ID NO:	description	Sequence
1007	EF-1 promoter	CGTGAGGCTCCGGTGCCCGTCAGTGGGCAGAGCGCACATCGC CCACAGTCCCCGAGAAGTTGGGGGGAGGGGTCGGCAATTGAA CCGGTGCCTAGAGAAGGTGGCGCGGGGTAAACTGGGAAAGT GATGTCGTGTACTGGCTCCGCCTTTTTCCCGAGGGTGGGGGAG AACCGTATATAAGTGCAGTAGTCGCCGTGAACGTTCTTTTTCG CAACGGGTTTGCCGCCAGAACACAGGTAAGTGCCGTGTGTGG TTCCCGCGGGCCTGGCCTCTTTACGGGTTATGGCCCTTGCGTG CCTTGAATTACTTCCACCTGGCTGCAGTACGTGATTCTTGATC CCGAGCTTCGGGTTGGAAGTGGGTGGGAGAGTTCGAGGCCTT GCGCTTAAGGAGCCCCTTCGCCTCGTGCTTGAGTTGAGGCCTG GCCTGGGCGCTGGGGCCGCCGCGTGCGAATCTGGTGGCACCT TCGCGCCTGTCTCGCTGCTTTCGATAAGTCTCTAGCCATTTAA AATTTTTGATGACCTGCTGCGACGCTTTTTTTCTGGCAAGATA GTCTTGTAAATGCGGGCCAAGATCTGCACACTGGTATTTCGGT

		TTTTGGGGCCGCGGGCGGCGACGGGGCCCGTGCGTCCCAGCG CACATGTTCGGCGAGGCGGGGCCTGCGAGCGCGGCCACCGAG AATCGGACGGGGGTAGTCTCAAGCTGGCCGGCCTGCTCTGGT GCCTGGCCTCGCGCCGCCGTGTATCGCCCCGCCCTGGGCGGC AAGGCTGGCCCGGTCGGCACCAGTTGCGTGAGCGGAAAGATG GCCGCTTCCCGGCCCTGCTGCAGGGAGCTCAAAATGGAGGAC GCGGCGCTCGGGAGAGCGGGCGGGTGAGTCACCCACACAAA GGAAAAGGGCCTTTCCGTCCTCAGCCGTCGCTTCATGTGACTC CACGGAGTACCGGGCGCCGTCCAGGCACCTCGATTAGTTCTC GAGCTTTTGGAGTACGTCGTCTTTAGGTTGGGGGGAGGGGTTT TATGCGATGGAGTTTCCCCACACTGAGTGGGTGGAGACTGAA GTTAGGCCAGCTTGGCACTTGATGTAATTCTCCTTGGAATTTG CCCTTTTTGAGTTTGGATCTTGGTTCATTCTCAAGCCTCAGAC AGTGGTTCAAAGTTTTTTTCTTCCATTTCAGGTGTCGTGA
1008	Leader (aa)	MALPVTALLLPLALLLHAARP
1009	Leader (na)	ATGGCCCTGCCTGTGACAGCCCTGCTGCTGCCTCTGGCTCTGC TGCTGCATGCCGCTAGACCC
1010	Leader (na)	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTC TGCTCCACGCCGCTCGGCCC
1011	CD8 hinge (aa)	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACD
1012	CD8 hinge (na)	ACCACGACGCCAGCGCCGCGACCACCAACACCGGCGCCCACC ATCGCGTCGCAGCCCCTGTCCCTGCGCCCAGAGGCGTGCCGG CCAGCGGCGGGGGGCGCAGTGCACACGAGGGGGCTGGACTT CGCCTGTGAT
1013	Ig4 hinge (aa)	ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTL PPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ KSLSLSLGKM
1014	Ig4 hinge (na)	GAGAGCAAGTACGGCCCTCCCTGCCCCCCTTGCCCTGCCCCCG AGTTCCTGGGCGGACCCAGCGTGTTCCTGTTCCCCCCCAAGCC CAAGGACACCCTGATGATCAGCCGGACCCCCGAGGTGACCTG TGTGGTGGTGGACGTGTCCCAGGAGGACCCCGAGGTCCAGTT CAACTGGTACGTGGACGGCGTGGAGGTGCACAACGCCAAGAC CAAGCCCCGGGAGGAGCAGTTCAATAGCACCTACCGGGTGGT GTCCGTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAA GGAATACAAGTGTAAGGTGTCCAACAAGGGCCTGCCCAGCAG CATCGAGAAAACCATCAGCAAGGCCAAGGGCCAGCCTCGGG AGCCCCAGGTGTACACCCTGCCCCCTAGCCAAGAGGAGATGA CCAAGAACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCT ACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAG CCCGAGAACAACTACAAGACCACCCCCCCTGTGCTGGACAGC GACGGCAGCTTCTTCCTGTACAGCCGGCTGACCGTGGACAAG AGCCGGTGGCAGGAGGGCAACGTCTTTAGCTGCTCCGTGATG CACGAGGCCCTGCACAACCACTACACCCAGAAGAGCCTGAGC CTGTCCCTGGGCAAGATG
1015	IgD hinge (aa)	RWPESPKAQASSVPTAQPQAEGSLAKATTAPATTRNTGRGGEEK KKEKEKEEQEERETKTPECPSHTQPLGVYLLTPAVQDLWLRDKA TFTCFVVGSDLKDAHLTWEVAGKVPTGGVEEGLLERHSNGSQS

		QHSRLTLPRSLWNAGTSVTCTLNHPSLPPQRLMALREPAAQAPV KLSLNLLASSDPPEAASWLLCEVSGFSPPNILLMWLEDQREVNTS GFAPARPPPQPGSTTFWAWSVLRVPAPPSPQPATYTCVVSHEDS RTLLNASRSLEVSYVTDH
1016	IgD hinge (na)	AGGTGGCCCGAAAGTCCCAAGGCCCAGGCATCTAGTGTTCCT ACTGCACAGCCCCAGGCAGAAGGCAGCCTAGCCAAAGCTACT ACTGCACCTGCCACTACGCGCAATACTGGCCGTGGCGGGGAG GAGAAGAAAAAGGAGAAAGAGAAAGAAGAACAGGAAGAGA GGGAGACCAAGACCCCTGAATGTCCATCCCATACCCAGCCGC TGGGCGTCTATCTCTTGACTCCCGCAGTACAGGACTTGTGGCT TAGAGATAAGGCCACCTTTACATGTTTCGTCGTGGGCTCTGAC CTGAAGGATGCCCATTTGACTTGGGAGGTTGCCGGAAAGGTA CCCACAGGGGGGGTTGAGGAAGGGTTGCTGGAGCGCCATTCC AATGGCTCTCAGAGCCAGCACTCAAGACTCACCCTTCCGAGA TCCCTGTGGAACGCCGGGACCTCTGTCACATGTACTCTAAATC ATCCTAGCCTGCCCCCACAGCGTCTGATGGCCCTTAGAGAGC CAGCCGCCCAGGCACCAGTTAAGCTTAGCCTGAATCTGCTCG CCAGTAGTGATCCCCCAGAGGCCGCCAGCTGGCTCTTATGCG AAGTGTCCGGCTTTAGCCCGCCCAACATCTTGCTCATGTGGCT GGAGGACCAGCGAGAAGTGAACACCAGCGGCTTCGCTCCAGC CCGGCCCCCACCCCAGCCGGGTTCTACCACATTCTGGGCCTGG AGTGTCTTAAGGGTCCCAGCACCACCTAGCCCCCAGCCAGCC ACATACACCTGTGTTGTGTCCCATGAAGATAGCAGGACCCTG CTAAATGCTTCTAGGAGTCTGGAGGTTTCCTACGTGACTGACC ATT
1017	GS hinge/linker (aa)	GGGGSGGGGS
1018	GS hinge/linker (na)	GGTGGCGGAGGTTCTGGAGGTGGAGGTTCC
1019	CD8 transmembrane (TM) (aa)	IYIWAPLAGTCGVLLLSLVITLYC
1020	CD8 transmembrane (TM) (na)	ATCTACATCTGGGCGCCCTTGGCCGGGACTTGTGGGGTCCTTC TCCTGTCACTGGTTATCACCCTTTACTGC
1021	CD8 TM (na)	ATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGC TGCTTTCACTCGTGATCACTCTTTACTGT
1022	4-1BB intracellular domain (aa)	KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL
1023	4-1BB intracellular domain (na)	AAACGGGGCAGAAAGAAACTCCTGTATATATTCAAACAACCA TTTATGAGACCAGTACAAACTACTCAAGAGGAAGATGGCTGT AGCTGCCGATTTCCAGAAGAAGAAGAAGGAGGATGTGAACT G
1024	4-1BB intracellular domain (na)	AAGCGCGGTCGGAAGAAGCTGCTGTACATCTTTAAGCAACCC TTCATGAGGCCTGTGCAGACTACTCAAGAGGAGGACGGCTGT TCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTG
1025	CD27 (aa)	QRRKYRSNKGESPVEPAEPCRYSCPREEEGSTIPIQEDYRKPEPAC SP

1026	CD27 (na)	AGGAGTAAGAGGAGCAGGCTCCTGCACAGTGACTACATGAAC ATGACTCCCCGCCGCCCCGGGCCCACCCGCAAGCATTACCAG CCCTATGCCCCACCACGCGACTTCGCAGCCTATCGCTCC
1027	CD3-zeta (aa)	RVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDP EMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKG HDGLYQGLSTATKDTYDALHMQALPPR
1028	CD3-zeta (na)	AGAGTGAAGTTCAGCAGGAGCGCAGACGCCCCCGCGTACAA GCAGGGCCAGAACCAGCTCTATAACGAGCTCAATCTAGGACG AAGAGAGGAGTACGATGTTTTGGACAAGAGACGTGGCCGGG ACCCTGAGATGGGGGGAAAGCCGAGAAGGAAGAACCCTCAG GAAGGCCTGTACAATGAACTGCAGAAAGATAAGATGGCGGA GGCCTACAGTGAGATTGGGATGAAAGGCGAGCGCCGGAGGG GCAAGGGGCACGATGGCCTTTACCAGGGTCTCAGTACAGCCA CCAAGGACACCTACGACGCCCTTCACATGCAGGCCCTGCCCC CTCGC
1029	CD3-zeta (na)	CGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAG CAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGG AGAGAGGAGTACGACGTGCTGGACAAGCGGAGAGGACGGGA CCCAGAAATGGGCGGGAAGCCGCGCAGAAAGAATCCCCAAG AGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGAA GCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGG CAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCAC CAAGGACACCTATGACGCTCTTCACATGCAGGCCCTGCCGCC TCGG
1030	CD3-zeta (aa)	RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDP EMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKG HDGLYQGLSTATKDTYDALHMQALPPR
1031	CD3-zeta (na)	AGAGTGAAGTTCAGCAGGAGCGCAGACGCCCCCGCGTACCAG CAGGGCCAGAACCAGCTCTATAACGAGCTCAATCTAGGACGA AGAGAGGAGTACGATGTTTTGGACAAGAGACGTGGCCGGGA CCCTGAGATGGGGGGAAAGCCGAGAAGGAAGAACCCTCAGG AAGGCCTGTACAATGAACTGCAGAAAGATAAGATGGCGGAG GCCTACAGTGAGATTGGGATGAAAGGCGAGCGCCGGAGGGG CAAGGGGCACGATGGCCTTTACCAGGGTCTCAGTACAGCCAC CAAGGACACCTACGACGCCCTTCACATGCAGGCCCTGCCCCC TCGC
1032	linker	GGGGS
1033	linker	GGTGGCGGAGGTTCTGGAGGTGGAGGTTCC
1034	PD-1 extracellular domain (aa)	Pgwfldspdrpwnpptfspallvvtegdnatftcsfsntsesfvlnwyrmspsnqtdklaafpedrs qpgqdcrfrvtqlpngrdfhmsvvrarrndsgtylcgaislapkaqikeslraelrvterraevptahp spsprpagqfqtlv
1035	PD-1 extracellular domain (na)	Cccggatggtttctggactctccggatcgcccgtggaatcccccaaccttctcaccggcactcttggtt gtgactgagggcgataatgcgaccttcacgtgctcgttctccaacacctccgaatcattcgtgctgaact ggtaccgcatgagcccgtcaaaccagaccgacaagctcgccgcgtttccggaagatcggtcgcaac cgggacaggattgtcggttccgcgtgactcaactgccgaatggcagagacttccacatgagcgtggtc cgcgctaggcgaaacgactccgggacctacctgtgcggagccatctcgctggcgcctaaggcccaa atcaaagagagcttgagggccgaactgagagtgaccgagcgcagagctgaggtgccaactgcacat ccatccccatcgcctcggcctgcggggcagtttcagaccctggtc

1036	PD-1 CAR (aa) with signal	Malpvtalllplalllhaarppgwfldspdrpwnpptfspallvvtegdnatftcsfsntsesfvlnwy rmspsnqtdklaafpedrsqpgqdcrfrvtqlpngrdfhmsvvrarrndsgtylcgaislapkaqik eslraelrvterraevptahpspsprpagqfqtlvtttpaprpptpaptiasqplslrpeacrpaaggav htrgldfacdiyiwaplagtcgvlllslvitlyckrgrkkllyifkqpfmrpvqttqeedgcscrfpeee eggcelrvkfsrsadapaykqgqnqlynelnlgrreeydvldkrrgrdpemggkprrknpqegly nelqkdkmaeayseigmkgerrrgkghdglyqglstatkdtydalhmqalppr
1037	PD-1 CAR (na)	Atggccctccctgtcactgccctgcttctccccctcgcactcctgctccacgccgctagaccacccgg atggtttctggactctccggatcgcccgtggaatcccccaaccttctcaccggcactcttggttgtgactg agggcgataatgcgaccttcacgtgctcgttctccaacacctccgaatcattcgtgctgaactggtaccg catgagcccgtcaaaccagaccgacaagctcgccgcgtttccggaagatcggtcgcaaccgggaca ggattgtcggttccgcgtgactcaactgccgaatggcagagacttccacatgagcgtggtccgcgcta ggcgaaacgactccgggacctacctgtgcggagccatctcgctggcgcctaaggcccaaatcaaag agagcttgagggccgaactgagagtgaccgagcgcagagctgaggtgccaactgcacatccatccc catcgcctcggcctgcggggcagtttcagaccctggtcacgaccactccggcgccgcgcccaccga ctccggccccaactatcgcgagccagcccctgtcgctgaggccggaagcatgccgccctgccgccg gaggtgctgtgcatacccggggattggacttcgcatgcgacatctacatttgggctcctctcgccggaa cttgtggcgtgctccttctgtccctggtcatcaccctgtactgcaagcggggtcggaaaaagcttctgta cattttcaagcagcccttcatgaggcccgtgcaaaccacccaggaggaggacggttgctcctgccggt tccccgaagaggaagaaggaggttgcgagctgcgcgtgaagttctcccggagcgccgacgccccc gcctataagcagggccagaaccagctgtacaacgaactgaacctgggacggcgggaagagtacgat gtgctggacaagcggcgcggccgggaccccgaaatgggcgggaagcctagaagaaagaaccctc aggaaggcctgtataacgagctgcagaaggacaagatggccgaggcctactccgaaattgggatga agggagagcggcggaggggaaaggggcacgacggcctgtaccaaggactgtccaccgccaccaa ggacacatacgatgccctgcacatgcaggcccttcccccctcgc
1038	linker	(Gly-Gly-Gly-Ser)n, where n = 1-10
1039	linker	(Gly4 Ser)4
1040	linker	(Gly4 Ser)3
1041	linker	(Gly3Ser)
1042	linker	ASGGGGSGGRASGGGGS
1043	polyA	$[a]_{50\text{-}5000}$
1044	PD1 CAR (aa)	Pgwfldspdrpwnpptfspallvvtegdnatftcsfsntsesfvlnwyrmspsnqtdklaafpedrs qpgqdcrfrvtqlpngrdfhmsvvrarrndsgtylcgaislapkaqikeslraelrvterraevptahp spsprpagqfqtlvtttpaprpptpaptiasqplslrpeacrpaaggavhtrgldfacdiyiwaplagt cgvlllslvitlyckrgrkkllyifkqpfmrpvqttqeedgcscrfpeeeeggcelrvkfsrsadapay kqgqnqlynelnlgrreeydvldkrrgrdpemggkprrknpqeglynelqkdkmaeayseigm kgerrrgkghdglyqglstatkdtydalhmqalppr
1045	ICOS intracellular domain (aa)	TKKKYSSSVHDPNGEYMFMRAVNTAKKSRLTDVTL
1046	ICOS intracellular domain (na)	ACAAAAAAGAAGTATTCATCCAGTGTGCACGACCCTAACGGT GAATACATGTTCATGAGAGCAGTGAACACAGCCAAAAAATCC AGACTCACAGATGTGACCCTA
1047	ICOS TM domain (aa)	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACD FWLPIGCAAFVVVCILGCILICWL
1048	ICOS TM domain (na)	ACCACGACGCCAGCGCCGCGACCACCAACACCGGCGCCCACC ATCGCGTCGCAGCCCCTGTCCCTGCGCCCAGAGGCGTGCCGG CCAGCGGCGGGGGGCGCAGTGCACACGAGGGGGCTGGACTT CGCCTGTGATTTCTGGTTACCCATAGGATGTGCAGCCTTTGTT GTAGTCTGCATTTTGGGATGCATACTTATTTGTTGGCTT

1049	CD28 intracellular domain (aa)	RSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS
1050	CD28 intracellular domain (na)	AGGAGTAAGAGGAGCAGGCTCCTGCACAGTGACTACATGAAC ATGACTCCCCGCCGCCCCGGGCCCACCCGCAAGCATTACCAG CCCTATGCCCCACCACGCGACTTCGCAGCCTATCGCTCC

CAR Antigen Binding Domain

In one aspect, the portion of the CAR comprising the antigen binding domain comprises an antigen binding domain that targets a tumor antigen, e.g., a tumor antigen described herein. In some embodiments, the antigen binding domain binds to: CD19; CD123; CD22; CD30; CD171; CS-1; C-type lectin-like molecule-1, CD33; epidermal growth factor receptor variant III (EGFRvIII); ganglioside G2 (GD2); ganglioside GD3; TNF receptor family member; B-cell maturation antigen (BCMA); Tn antigen ((Tn Ag) or (GalNAcα-Ser/Thr)); prostate-specific membrane antigen (PSMA); Receptor tyrosine kinase-like orphan receptor 1 (ROR1); Fms-Like Tyrosine Kinase 3 (FLT3); Tumor-associated glycoprotein 72 (TAG72); CD38; CD44v6; Carcinoembryonic antigen (CEA); Epithelial cell adhesion molecule (EPCAM); B7H3 (CD276); KIT (CD117); Interleukin-13 receptor subunit alpha-2; Mesothelin; Interleukin 11 receptor alpha (IL-11Ra); prostate stem cell antigen (PSCA); Protease Serine 21; vascular endothelial growth factor receptor 2 (VEGFR2); Lewis(Y) antigen; CD24; Platelet-derived growth factor receptor beta (PDGFR-beta); Stage-specific embryonic antigen-4 (SSEA-4); CD20; Folate receptor alpha; Receptor tyrosine-protein kinase ERBB2 (Her2/neu); Mucin 1, cell surface associated (MUC1); epidermal growth factor receptor (EGFR); neural cell adhesion molecule (NCAM); Prostase; prostatic acid phosphatase (PAP); elongation factor 2 mutated (ELF2M); Ephrin B2; fibroblast activation protein alpha (FAP); insulin-like growth factor 1 receptor (IGF-I receptor), carbonic anhydrase IX (CAIX); Proteasome (Prosome, Macropain) Subunit, Beta Type, 9 (LMP2); glycoprotein 100 (gp100); oncogene fusion protein consisting of breakpoint cluster region (BCR) and Abelson murine leukemia viral oncogene homolog 1 (Abl) (bcr-abl); tyrosinase; ephrin type-A receptor 2 (EphA2); Fucosyl GM1; sialyl Lewis adhesion molecule (sLe); ganglioside GM3; transglutaminase 5 (TGS5); high molecular weight-melanoma-associated antigen (HMWMAA); o-acetyl-GD2 ganglioside (OAcGD2); Folate receptor beta; tumor endothelial marker 1 (TEM1/CD248); tumor endothelial marker 7-related (TEM7R); claudin 6 (CLDN6); thyroid stimulating hormone receptor (TSHR); G protein-coupled receptor class C group 5, member D (GPRC5D); chromosome X open reading frame 61 (CXORF61); CD97; CD179a; anaplastic lymphoma kinase (ALK); Polysialic acid; placenta-specific 1 (PLAC1); hexasaccharide portion of globoH glycoceramide (GloboH); mammary gland differentiation antigen (NY-BR-1); uroplakin 2 (UPK2); Hepatitis A virus cellular receptor 1 (HAVCR1); adrenoceptor beta 3 (ADRB3); pannexin 3 (PANX3); G protein-coupled receptor 20 (GPR20); lymphocyte antigen 6

complex, locus K 9 (LY6K); Olfactory receptor 51E2 (OR51E2); TCR Gamma Alternate Reading Frame Protein (TARP); Wilms tumor protein (WT1); Cancer/testis antigen 1 (NY-ESO-1); Cancer/testis antigen 2 (LAGE-1a); Melanoma-associated antigen 1 (MAGE-A1); ETS translocation-variant gene 6, located on chromosome 12p (ETV6-AML); sperm protein 17 (SPA17); X Antigen Family, Member 1A (XAGE1); angiopoietin-binding cell surface receptor 2 (Tie 2); melanoma cancer testis antigen-1 (MAD-CT-1); melanoma cancer testis antigen-2 (MAD-CT-2); Fos-related antigen 1; tumor protein p53 (p53); p53 mutant; prostein; surviving; telomerase; prostate carcinoma tumor antigen-1, melanoma antigen recognized by T cells 1; Rat sarcoma (Ras) mutant; human Telomerase reverse transcriptase (hTERT); sarcoma translocation breakpoints; melanoma inhibitor of apoptosis (ML-IAP); ERG (transmembrane protease, serine 2 (TMPRSS2) ETS fusion gene); N-Acetyl glucosaminyl-transferase V (NA17); paired box protein Pax-3 (PAX3); Androgen receptor; Cyclin B1; v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog (MYCN); Ras Homolog Family Member C (RhoC); Tyrosinase-related protein 2 (TRP-2); Cytochrome P450 1B1 (CYP1B1); CCCTC-Binding Factor (Zinc Finger Protein)-Like, Squamous Cell Carcinoma Antigen Recognized By T Cells 3 (SART3); Paired box protein Pax-5 (PAX5); proacrosin binding protein sp32 (OY-TES1); lymphocyte-specific protein tyrosine kinase (LCK); A kinase anchor protein 4 (AKAP-4); synovial sarcoma, X breakpoint 2 (SSX2); Receptor for Advanced Glycation Endproducts (RAGE-1); renal ubiquitous 1 (RU1); renal ubiquitous 2 (RU2); legumain; human papilloma virus E6 (HPV E6); human papilloma virus E7 (HPV E7); intestinal carboxyl esterase; heat shock protein 70-2 mutated (mut hsp70-2); CD79a; CD79b; CD72; Leukocyte-associated immunoglobulin-like receptor 1 (LAIR1); Fc fragment of IgA receptor (FCAR or CD89); Leukocyte immunoglobulin-like receptor subfamily A member 2 (LILRA2); CD300 molecule-like family member f (CD300LF); C-type lectin domain family 12 member A (CLEC12A); bone marrow stromal cell antigen 2 (BST2); EGF-like module-containing mucin-like hormone receptor-like 2 (EMR2); lymphocyte antigen 75 (LY75); Glypican-3 (GPC3); Fc receptor-like 5 (FCRL5); or immunoglobulin lambda-like polypeptide 1 (IGLL1).

The antigen binding domain can be any domain that binds to an antigen, including but not limited to a monoclonal antibody, a polyclonal antibody, a recombinant antibody, a human antibody, a humanized antibody, and a functional fragment thereof, including but not limited to a single-domain antibody such as a heavy chain variable domain (VH), a light chain variable domain (VL) and a variable domain (VHH) of camelid derived nanobody, and to an alternative scaffold known in the art to function as antigen binding domain, such as a recombinant fibronectin domain, a T cell receptor (TCR), or a fragment there of, e.g., single chain TCR, and the like. In some instances, it is beneficial for the antigen binding domain to be derived from the same species in which the CAR will ultimately be used in. For

example, for use in humans, it may be beneficial for the antigen binding domain of the CAR to comprise human or humanized residues for the antigen binding domain of an antibody or antibody fragment.

CAR Transmembrane domain

With respect to the transmembrane domain, in various embodiments, a CAR can be designed to comprise a transmembrane domain that is attached to the extracellular domain of the CAR. A transmembrane domain can include one or more additional amino acids adjacent to the transmembrane region, e.g., one or more amino acid associated with the extracellular region of the protein from which the transmembrane was derived (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 up to 15 amino acids of the extracellular region) and/or one or more additional amino acids associated with the intracellular region of the protein from which the transmembrane protein is derived (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 up to 15 amino acids of the intracellular region). In one aspect, the transmembrane domain is one that is associated with one of the other domains of the CAR. In some instances, the transmembrane domain can be selected or modified by amino acid substitution to avoid binding of such domains to the transmembrane domains of the same or different surface membrane proteins, e.g., to minimize interactions with other members of the receptor complex. In one aspect, the transmembrane domain is capable of homodimerization with another CAR on the cell surface of a CAR-expressing cell. In a different aspect, the amino acid sequence of the transmembrane domain may be modified or substituted so as to minimize interactions with the binding domains of the native binding partner present in the same CART.

The transmembrane domain may be derived either from a natural or from a recombinant source. Where the source is natural, the domain may be derived from any membrane-bound or transmembrane protein. In one aspect the transmembrane domain is capable of signaling to the intracellular domain(s) whenever the CAR has bound to a target. A transmembrane domain of particular use in this invention may include at least the transmembrane region(s) of e.g., the alpha, beta or zeta chain of the T-cell receptor, CD28, CD27, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137, CD154. In some embodiments, a transmembrane domain may include at least the transmembrane region(s) of, e.g., KIR2DS2, OX40, CD2, CD27, LFA-1 (CD11a, CD18), ICOS (CD278), 4-1BB (CD137), GITR, CD40, BAFFR, HVEM (LIGHTR), SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD160, CD19, IL2R beta, IL2R gamma, IL7R α, ITGA1, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, TNFR2, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, PAG/Cbp, NKG2D, NKG2C.

In some instances, the transmembrane domain can be attached to the extracellular region of the CAR, e.g., the antigen binding domain of the CAR, via a hinge, e.g., a hinge from a human protein. For example, in one embodiment, the hinge can be a human Ig (immunoglobulin) hinge, e.g., an IgG4 hinge, or a CD8a hinge. In one embodiment, the hinge or spacer comprises (e.g., consists of) the amino acid sequence of SEQ ID NO: 1011. In one aspect, the transmembrane domain comprises (e.g., consists of) a transmembrane domain of SEQ ID NO: 1019.

In one aspect, the hinge or spacer comprises an IgG4 hinge. For example, in one embodiment, the hinge or spacer comprises a hinge of the amino acid sequence of SEQ ID NO: 1013. In some embodiments, the hinge or spacer comprises a hinge encoded by a nucleotide sequence of SEQ ID NO: 1014.

In one aspect, the hinge or spacer comprises an IgD hinge. For example, in one embodiment, the hinge or spacer comprises a hinge of the amino acid sequence of SEQ ID NO: 1015. In some embodiments, the hinge or spacer comprises a hinge encoded by a nucleotide sequence of SEQ ID NO: 1016.

In one aspect, the transmembrane domain may be recombinant, in which case it will comprise predominantly hydrophobic residues such as leucine and valine. In one aspect a triplet of phenylalanine, tryptophan and valine can be found at each end of a recombinant transmembrane domain.

Optionally, a short oligo- or polypeptide linker, between 2 and 10 amino acids in length may form the linkage between the transmembrane domain and the cytoplasmic region of the CAR. A glycine-serine doublet provides a particularly suitable linker. For example, in one aspect, the linker comprises the amino acid sequence of SEQ ID NO: 1017. In some embodiments, the linker is encoded by a nucleotide sequence of SEQ ID NO: 1018.

In one aspect, the hinge or spacer comprises a KIR2DS2 hinge.

Cytoplasmic domain

The cytoplasmic domain or region of the CAR includes an intracellular signaling domain. An intracellular signaling domain is generally responsible for activation of at least one of the normal effector functions of the immune cell in which the CAR has been introduced.

Examples of intracellular signaling domains for use in a CAR described herein include the cytoplasmic sequences of the T cell receptor (TCR) and co-receptors that act in concert to initiate signal transduction following antigen receptor engagement, as well as any derivative or variant of these sequences and any recombinant sequence that has the same functional capability.

It is known that signals generated through the TCR alone are insufficient for full activation of the T cell and that a secondary and/or costimulatory signal is also required. Thus, T cell activation can

be said to be mediated by two distinct classes of cytoplasmic signaling sequences: those that initiate antigen-dependent primary activation through the TCR (primary intracellular signaling domains) and those that act in an antigen-independent manner to provide a secondary or costimulatory signal (secondary cytoplasmic domain, e.g., a costimulatory domain).

A primary signaling domain regulates primary activation of the TCR complex either in a stimulatory way, or in an inhibitory way. Primary intracellular signaling domains that act in a stimulatory manner may contain signaling motifs which are known as immunoreceptor tyrosine-based activation motifs or ITAMs.

Examples of ITAM containing primary intracellular signaling domains that are of particular use in the invention include those of TCR zeta, FcR gamma, FcR beta, CD3 gamma, CD3 delta , CD3 epsilon, CD5, CD22, CD79a, CD79b, CD278 (also known as "ICOS"), FcεRI, DAP10, DAP12, and CD66d. In one embodiment, a CAR of the invention comprises an intracellular signaling domain, e.g., a primary signaling domain of CD3-zeta, e.g., a CD3-zeta sequence described herein.

In one embodiment, a primary signaling domain comprises a modified ITAM domain, e.g., a mutated ITAM domain which has altered (e.g., increased or decreased) activity as compared to the native ITAM domain. In one embodiment, a primary signaling domain comprises a modified ITAM-containing primary intracellular signaling domain, e.g., an optimized and/or truncated ITAM-containing primary intracellular signaling domain. In an embodiment, a primary signaling domain comprises one, two, three, four or more ITAM motifs.

Costimulatory Signaling Domain

The intracellular signalling domain of the CAR can comprise the CD3-zeta signaling domain by itself or it can be combined with any other desired intracellular signaling domain(s) useful in the context of a CAR of the invention. For example, the intracellular signaling domain of the CAR can comprise a CD3 zeta chain portion and a costimulatory signaling domain. The costimulatory signaling domain refers to a portion of the CAR comprising the intracellular domain of a costimulatory molecule. In one embodiment, the intracellular domain is designed to comprise the signaling domain of CD3-zeta and the signaling domain of CD28. In one aspect, the intracellular domain is designed to comprise the signaling domain of CD3-zeta and the signaling domain of ICOS.

A costimulatory molecule can be a cell surface molecule other than an antigen receptor or its ligands that is required for an efficient response of lymphocytes to an antigen. Examples of such molecules include CD27, CD28, 4-1BB (CD137), OX40, CD30, CD40, PD-1, ICOS, lymphocyte function-associated antigen-1 (LFA-1), CD2, CD7, LIGHT, NKG2C, B7-H3, and a ligand that specifically binds with CD83, and the like. For example, CD27 costimulation has been demonstrated to enhance expansion, effector function, and survival of human CART cells in vitro and augments human

T cell persistence and antitumor activity in vivo (Song et al. Blood. 2012; 119(3):696-706). Further examples of such costimulatory molecules include CDS, ICAM-1, GITR, BAFFR, HVEM (LIGHTR), SLAMF7, NKp80 (KLRF1), NKp30, NKp44, NKp46, CD160, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, NKG2D, NKG2C and PAG/Cbp.

The intracellular signaling sequences within the cytoplasmic portion of the CAR may be linked to each other in a random or specified order. Optionally, a short oligo- or polypeptide linker, for example, between 2 and 10 amino acids (e.g., 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids) in length may form the linkage between intracellular signaling sequence. In one embodiment, a glycine-serine doublet can be used as a suitable linker. In one embodiment, a single amino acid, e.g., an alanine, a glycine, can be used as a suitable linker.

In one aspect, the intracellular signaling domain is designed to comprise two or more, e.g., 2, 3, 4, 5, or more, costimulatory signaling domains. In an embodiment, the two or more, e.g., 2, 3, 4, 5, or more, costimulatory signaling domains, are separated by a linker molecule, e.g., a linker molecule described herein. In one embodiment, the intracellular signaling domain comprises two costimulatory signaling domains. In some embodiments, the linker molecule is a glycine residue. In some embodiments, the linker is an alanine residue.

In one aspect, the intracellular signaling domain is designed to comprise the signaling domain of CD3-zeta and the signaling domain of CD28. In one aspect, the intracellular signaling domain is designed to comprise the signaling domain of CD3-zeta and the signaling domain of 4-1BB. In one aspect, the signaling domain of 4-1BB is a signaling domain of SEQ ID NO: 1022. In one aspect, the signaling domain of CD3-zeta is a signaling domain of SEQ ID NO: 1027.

In one aspect, the intracellular signaling domain is designed to comprise the signaling domain of CD3-zeta and the signaling domain of CD27. In one aspect, the signaling domain of CD27 comprises an amino acid sequence of SEQ ID NO: 1025. In one aspect, the signalling domain of CD27 is encoded by a nucleic acid sequence of SEQ ID NO: 1026.

In one aspect, the CAR-expressing cell described herein can further comprise a second CAR, e.g., a second CAR that includes a different antigen binding domain, e.g., to the same target or a different target (e.g., a target other than a cancer associated antigen described herein or a different cancer associated antigen described herein, *e.g.*, CD19, CD33, CLL-1, CD34, FLT3, or folate receptor beta). In one embodiment, the second CAR includes an antigen binding domain to a target expressed

the same cancer cell type as the cancer associated antigen. In one embodiment, the CAR-expressing cell comprises a first CAR that targets a first antigen and includes an intracellular signaling domain having a costimulatory signaling domain but not a primary signaling domain, and a second CAR that targets a second, different, antigen and includes an intracellular signaling domain having a primary signaling domain but not a costimulatory signaling domain. While not wishing to be bound by theory, placement of a costimulatory signaling domain, *e.g.*, 4-1BB, CD28, ICOS, CD27 or OX-40, onto the first CAR, and the primary signaling domain, *e.g.*, CD3 zeta, on the second CAR can limit the CAR activity to cells where both targets are expressed. In one embodiment, the CAR expressing cell comprises a first cancer associated antigen CAR that includes an antigen binding domain that binds a target antigen described herein, a transmembrane domain and a costimulatory domain and a second CAR that targets a different target antigen (e.g., an antigen expressed on that same cancer cell type as the first target antigen) and includes an antigen binding domain, a transmembrane domain and a primary signaling domain. In another embodiment, the CAR expressing cell comprises a first CAR that includes an antigen binding domain that binds a target antigen described herein, a transmembrane domain and a primary signaling domain and a second CAR that targets an antigen other than the first target antigen (e.g., an antigen expressed on the same cancer cell type as the first target antigen) and includes an antigen binding domain to the antigen, a transmembrane domain and a costimulatory signaling domain.

In another aspect, the disclosure features a population of CAR-expressing cells, e.g., CART cells. In some embodiments, the population of CAR-expressing cells comprises a mixture of cells expressing different CARs. For example, in one embodiment, the population of CART cells can include a first cell expressing a CAR having an antigen binding domain to a cancer associated antigen described herein, and a second cell expressing a CAR having a different antigen binding domain, e.g., an antigen binding domain to a different a cancer associated antigen described herein, e.g., an antigen binding domain to a cancer associated antigen described herein that differs from the cancer associate antigen bound by the antigen binding domain of the CAR expressed by the first cell. As another example, the population of CAR-expressing cells can include a first cell expressing a CAR that includes an antigen binding domain to a cancer associated antigen described herein, and a second cell expressing a CAR that includes an antigen binding domain to a target other than a cancer associate antigen as described herein. In one embodiment, the population of CAR-expressing cells includes, e.g., a first cell expressing a CAR that includes a primary intracellular signaling domain, and a second cell expressing a CAR that includes a secondary signaling domain.

In another aspect, the disclosure features a population of cells wherein at least one cell in the population expresses a CAR having an antigen binding domain to a cancer associated antigen described herein, and a second cell expressing another agent, e.g., an agent which enhances the activity of a CAR-expressing cell. For example, in one embodiment, the agent can be an agent which inhibits an inhibitory

molecule. Inhibitory molecules, e.g., PD-1, can, in some embodiments, decrease the ability of a CAR-expressing cell to mount an immune effector response. Examples of inhibitory molecules include PD-1, PD-L1, CTLA4, TIM3, CEACAM (CEACAM-1, CEACAM-3, and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, and TGF (e.g., TGFbeta). In one embodiment, the agent which inhibits an inhibitory molecule comprises a first polypeptide, e.g., an inhibitory molecule, associated with a second polypeptide that provides a positive signal to the cell, e.g., an intracellular signaling domain described herein. In one embodiment, the agent comprises a first polypeptide, e.g., of an inhibitory molecule such as PD-1, PD-L1, CTLA4, TIM3, CEACAM (CEACAM-1, CEACAM-3, and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 and TGF beta, or a fragment of any of these, and a second polypeptide which is an intracellular signaling domain described herein (e.g., comprising a costimulatory domain (e.g., 41BB, CD27, OX40 or CD28, e.g., as described herein) and/or a primary signaling domain (e.g., a CD3 zeta signaling domain described herein). In one embodiment, the agent comprises a first polypeptide of PD-1 or a fragment thereof, and a second polypeptide of an intracellular signaling domain described herein (e.g., a CD28 signaling domain described herein and/or a CD3 zeta signaling domain described herein).

BCMA CAR

In one aspect, the CAR disclosed herein binds to BCMA. Exemplary BCMA CARs can include sequences disclosed in Table 1 or 16 of WO2016/014565, incorporated herein by reference. The BCMA CAR construct can include an optional leader sequence; an optional hinge domain, e.g., a CD8 hinge domain; a transmembrane domain, e.g., a CD8 transmembrane domain; an intracellular domain, e.g., a 4-1BB intracellular domain; and a functional signaling domain, e.g., a CD3 zeta domain. In certain embodiments, the domains are contiguous and in the same reading frame to form a single fusion protein. In other embodiments, the domain are in separate polypeptides, e.g., as in an RCAR molecule as described herein.

The sequences of exemplary BCMA CAR molecules or fragments thereof are disclosed in Tables 2-5. In certain embodiments, the full length BCMA CAR molecule includes one or more CDRs, VH, VL, scFv, or full-length sequences of, BCMA-1, BCMA-2, BCMA-3, BCMA-4, BCMA-5, BCMA-6, BCMA-7, BCMA-8, BCMA-9, BCMA-10, BCMA-11, BCMA-12, BCMA-13, BCMA-14, BCMA-15, 149362, 149363, 149364, 149365, 149366, 149367, 149368, 149369, BCMA_EBB-C1978-A4, BCMA_EBB-C1978-G1, BCMA_EBB-C1979-C1, BCMA_EBB-C1978-C7, BCMA_EBB-C1978-D10, BCMA_EBB-C1979-C12, BCMA_EBB-C1980-G4, BCMA_EBB-C1980-D2, BCMA_EBB-C1978-A10, BCMA_EBB-C1978-D4, BCMA_EBB-C1980-A2, BCMA_EBB-C1981-C3,

BCMA_EBB-C1978-G4, A7D12.2, C11D5.3, C12A3.2, or C13F12.1, as disclosed in Tables 2-5, or a sequence substantially (e.g., 95-99%) identical thereto.

Additional exemplary BCMA-targeting sequences that can be used in the anti-BCMA CAR constructs are disclosed in WO 2017/021450, WO 2017/011804, WO 2017/025038, WO 2016/090327, WO 2016/130598, WO 2016/210293, WO 2016/090320, WO 2016/014789, WO 2016/094304, WO 2016/154055, WO 2015/166073, WO 2015/188119, WO 2015/158671, US 9,243,058, US 8,920,776, US 9,273,141, US 7,083,785, US 9,034,324, US 2007/0049735, US 2015/0284467, US 2015/0051266, US 2015/0344844, US 2016/0131655, US 2016/0297884, US 2016/0297885, US 2017/0051308, US 2017/0051252, US 2017/0051252, WO 2016/020332, WO 2016/087531, WO 2016/079177, WO 2015/172800, WO 2017/008169, US 9,340,621, US 2013/0273055, US 2016/0176973, US 2015/0368351, US 2017/0051068, US 2016/0368988, and US 2015/0232557, herein incorporated by reference in their entirety. In some embodiments, additional exemplary BCMA CAR constructs are generated using the VH and VL sequences from PCT Publication WO2012/0163805 (the contents of which are hereby incorporated by reference in its entirety).

Table 2. Amino Acid and Nucleic Acid Sequences of exemplary anti-BCMA scFv domains and BCMA CAR molecules. The amino acid sequences variable heavy chain and variable light chain sequences for each scFv is also provided.

Name/ Description	SEQ ID NO:	Sequence
139109		
139109- aa ScFv domain	49	EVQLVESGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVS GIVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAH GGESDVWGQGTTVTVSSASGGGGSGGRASGGGGSDIQLTQSPSSLSASV GDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSG SGSGTDFTLTISSLQPEDFATYYCQQSYSTPYTFGQGTKVEIK
139109- nt ScFv domain	64	GAAGTGCAATTGGTGGAATCAGGGGGAGGACTTGTGCAGCCTGGAGGAT CGCTGAGACTGTCATGTGCCGTGTCCGGCTTTGCCCTGTCCAACCACGG GATGTCCTGGGTCCGCCGCGCGCCTGGAAAGGGCCTCGAATGGGTGTCG GGTATTGTGTACAGCGGTAGCACCTACTATGCCGCATCCGTGAAGGGGA GATTCACCATCAGCCGGGACAACTCCAGGAACACTCTGTACCTCCAAAT GAATTCGCTGAGGCCAGAGGACACTGCCATCTACTACTGCTCCGCGCAT GGCGGAGAGTCCGACGTCTGGGGACAGGGGACCACCGTGACCGTGTCTA GCGCGTCCGGCGGAGGCGGCAGCGGGGGTCGGGCATCAGGGGGCGGCGG ATCGGACATCCAGCTCACCCAGTCCCCGAGCTCGCTGTCCGCCTCCGTG GGAGATCGGGTCACCATCACGTGCCGCGCCAGCCAGTCGATTTCCTCCT ACCTGAACTGGTACCAACAGAAGCCCGGAAAAGCCCCGAAGCTTCTCAT CTACGCCGCCTCGAGCCTGCAGTCAGGAGTGCCCTCACGGTTCTCCGGC TCCGGTTCCGGTACTGATTTCACCCTGACCATTTCCTCCCTGCAACCGG AGGACTTCGCTACTTACTACTGCCAGCAGTCGTACTCCACCCCCTACAC TTTCGGACAAGGCACCAAGGTCGAAATCAAG

139109- aa VH	79	EVQLVESGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVS GIVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAH GGESDVWGQGTTVTVSS
139109- aa VL	94	DIQLTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIY AASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPYTF GQGTKVEIK
139109- aa Full CAR	109	MALPVTALLLPLALLLHAARPEVQLVESGGGLVQPGGSLRLSCAVSGFA LSNHGMSWVRRAPGKGLEWVSGIVYSGSTYYAASVKGRFTISRDNSRNT LYLQMNSLRPEDTAIYYCSAHGGESDVWGQGTTVTVSSASGGGGSGGRA SGGGGSDIQLTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKA PKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSY STPYTFGQGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGA VHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQP FMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLY NELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEA YSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
139109- nt Full CAR	124	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCC ACGCCGCTCGGCCCGAAGTGCAATTGGTGGAATCAGGGGGAGGACTTGT GCAGCCTGGAGGATCGCTGAGACTGTCATGTGCCGTGTCCGGCTTTGCC CTGTCCAACCACGGGATGTCCTGGGTCCGCCGCGCGCCTGGAAAGGGCC TCGAATGGGTGTCGGGTATTGTGTACAGCGGTAGCACCTACTATGCCGC ATCCGTGAAGGGGAGATTCACCATCAGCCGGGACAACTCCAGGAACACT CTGTACCTCCAAATGAATTCGCTGAGGCCAGAGGACACTGCCATCTACT ACTGCTCCGCGCATGGCGGAGAGTCCGACGTCTGGGGACAGGGGACCAC CGTGACCGTGTCTAGCGCGTCCGGCGGAGGCGGCAGCGGGGGTCGGGCA TCAGGGGGCGGCGGATCGGACATCCAGCTCACCCAGTCCCCGAGCTCGC TGTCCGCCTCCGTGGGAGATCGGGTCACCATCACGTGCCGCGCCAGCCA GTCGATTTCCTCCTACCTGAACTGGTACCAACAGAAGCCCGGAAAAGCC CCGAAGCTTCTCATCTACGCCGCCTCGAGCCTGCAGTCAGGAGTGCCCT CACGGTTCTCCGGCTCCGGTTCCGGTACTGATTTCACCCTGACCATTTC CTCCCTGCAACCGGAGGACTTCGCTACTTACTACTGCCAGCAGTCGTAC TCCACCCCCTACACTTTCGGACAAGGCACCAAGGTCGAAATCAAGACCA CTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCA GCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCC GTGCATACCCGGGGTCTTGACTTCGCCTGCGATATCTACATTTGGGCCC CTCTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCACTCGTGATCACTCT TTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTACATCTTTAAGCAACCC TTCATGAGGCCTGTGCAGACTACTCAAGAGGAGGACGGCTGTTCATGCC GGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTGCGCGTGAAATTCAG CCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGGCAGAACCAGCTCTAC AACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACGTGCTGGACAAGC GGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGAAAGAATCC CCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGAAGCC TATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAGGCCACG ACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTATGACGC TCTTCACATGCAGGCCCTGCCGCCTCGG
Full CAR without leader sequence	392	EVQLVESGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVS GIVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAH GGESDVWGQGTTVTVSSASGGGGSGGRASGGGGSDIQLTQSPSSLSASV GDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSG SGSGTDFTLTISSLQPEDFATYYCQQSYSTPYTFGQGTKVEIKTTTPAP RPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGT

		CGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEE EEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRD PEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQ GLSTATKDTYDALHMQALPPR
Full CAR without linker, without leader sequence	393	EVQLVESGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVS GIVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAH GGESDVWGQGTTVTVSSDIQLTQSPSSLSASVGDRVTITCRASQSISSY LNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPE DFATYYCQQSYSTPYTFGQGTKVEIKTTTPAPRPPTPAPTIASQPLSLR PEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRG RKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADA PAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLY NELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQA LPPR
139103		
139103- aa ScFv domain	39	QVQLVESGGGLVQPGRSLRLSCAASGFTFSNYAMSWVRQAPGKGLGWVS GISRSGENTYYADSVKGRFTISRDNSKNTLYLQMNSLRDEDTAVYYCAR SPAHYYGGMDVWGQGTTVTVSSASGGGGSGGRASGGGGSDIVLTQSPGT LSLSPGERATLSCRASQSISSSFLAWYQQKPGQAPRLLIYGASRRATGI PDRFSGSGSGTDFTLTISRLEPEDSAVYYCQQYHSSPSWTFGQGTKLEI K
139103- nt ScFv domain	54	CAAGTGCAACTCGTGGAATCTGGTGGAGGACTCGTGCAACCCGGAAGAT CGCTTAGACTGTCGTGTGCCGCCAGCGGGTTCACTTTCTCGAACTACGC GATGTCCTGGGTCCGCCAGGCACCCGGAAAGGGACTCGGTTGGGTGTCC GGCATTTCCCGGTCCGGCGAAAATACCTACTACGCCGACTCCGTGAAGG GCCGCTTCACCATCTCAAGGGACAACAGCAAAAACACCCTGTACTTGCA AATGAACTCCCTGCGGGATGAAGATACAGCCGTGTACTATTGCGCCCGG TCGCCTGCCCATTACTACGGCGGAATGGACGTCTGGGGACAGGGAACCA CTGTGACTGTCAGCAGCGCGTCGGGTGGCGGCGGCTCAGGGGGTCGGGC CTCCGGGGGGGGAGGGTCCGACATCGTGCTGACCCAGTCCCCGGGAACC CTGAGCCTGAGCCCGGGAGAGCGCGCGACCCTGTCATGCCGGGCATCCC AGAGCATTAGCTCCTCCTTTCTCGCCTGGTATCAGCAGAAGCCCGGACA GGCCCCGAGGCTGCTGATCTACGGCGCTAGCAGAAGGGCTACCGGAATC CCAGACCGGTTCTCCGGCTCCGGTTCCGGGACCGATTTCACCCTTACTA TCTCGCGCCTGGAACCTGAGGACTCCGCCGTCTACTACTGCCAGCAGTA CCACTCATCCCCGTCGTGGACGTTCGGACAGGGCACCAAGCTGGAGATT AAG
139103- aa VH	69	QVQLVESGGGLVQPGRSLRLSCAASGFTFSNYAMSWVRQAPGKGLGWVS GISRSGENTYYADSVKGRFTISRDNSKNTLYLQMNSLRDEDTAVYYCAR SPAHYYGGMDVWGQGTTVTVSS
139103- aa VL	84	DIVLTQSPGTLSLSPGERATLSCRASQSISSSFLAWYQQKPGQAPRLLI YGASRRATGIPDRFSGSGSGTDFTLTISRLEPEDSAVYYCQQYHSSPSW TFGQGTKLEIK
139103- aa Full CAR	99	MALPVTALLLPLALLLHAARPQVQLVESGGGLVQPGRSLRLSCAASGFT FSNYAMSWVRQAPGKGLGWVSGISRSGENTYYADSVKGRFTISRDNSKN TLYLQMNSLRDEDTAVYYCARSPAHYYGGMDVWGQGTTVTVSSASGGGG SGGRASGGGGSDIVLTQSPGTLSLSPGERATLSCRASQSISSSFLAWYQ QKPGQAPRLLIYGASRRATGIPDRFSGSGSGTDFTLTISRLEPEDSAVY YCQQYHSSPSWTFGQGTKLEIKTTTPAPRPPTPAPTIASQPLSLRPEAC RPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKL LYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYK

		QGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQ KDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
139103- nt Full CAR	114	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCC ACGCCGCTCGGCCCCAAGTGCAACTCGTGGAATCTGGTGGAGGACTCGT GCAACCCGGAAGATCGCTTAGACTGTCGTGTGCCGCCAGCGGGTTCACT TTCTCGAACTACGCGATGTCCTGGGTCCGCCAGGCACCCGGAAAGGGAC TCGGTTGGGTGTCCGGCATTTCCCGGTCCGGCGAAAATACCTACTACGC CGACTCCGTGAAGGGCCGCTTCACCATCTCAAGGGACAACAGCAAAAAC ACCCTGTACTTGCAAATGAACTCCCTGCGGGATGAAGATACAGCCGTGT ACTATTGCGCCCGGTCGCCTGCCCATTACTACGGCGGAATGGACGTCTG GGGACAGGGAACCACTGTGACTGTCAGCAGCGCGTCGGGTGGCGGCGGC TCAGGGGGTCGGGCCTCCGGGGGGGGAGGGTCCGACATCGTGCTGACCC AGTCCCCGGGAACCCTGAGCCTGAGCCCGGGAGAGCGCGCGACCCTGTC ATGCCGGGCATCCCAGAGCATTAGCTCCTCCTTTCTCGCCTGGTATCAG CAGAAGCCCGGACAGGCCCCGAGGCTGCTGATCTACGGCGCTAGCAGAA GGGCTACCGGAATCCCAGACCGGTTCTCCGGCTCCGGTTCCGGGACCGA TTTCACCCTTACTATCTCGCGCCTGGAACCTGAGGACTCCGCCGTCTAC TACTGCCAGCAGTACCACTCATCCCCGTCGTGGACGTTCGGACAGGGCA CCAAGCTGGAGATTAAGACCACTACCCCAGCACCGAGGCCACCCACCCC GGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGT AGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTGACTTCGCCT GCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGCT GCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTG CTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAG AGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTG CGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAG CAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGG AGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGG GAAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAA AAGGATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAAC GCAGAAGAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGC CACCAAGGACACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
139105		
139105- aa ScFv domain	40	QVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVS GISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCSV HSFLAYWGQGTLVTVSSASGGGGSGGRASGGGGSDIVMTQTPLSLPVTP GEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVP DRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPYTFGQGTKVEIK
139105- nt ScFv domain	55	CAAGTGCAACTCGTCGAATCCGGTGGAGGTCTGGTCCAACCTGGTAGAA GCCTGAGACTGTCGTGTGCGGCCAGCGGATTCACCTTTGATGACTATGC TATGCACTGGGTGCGGCAGGCCCCAGGAAAGGGCCTGGAATGGGTGTCG GGAATTAGCTGGAACTCCGGGTCCATTGGCTACGCCGACTCCGTGAAGG GCCGCTTCACCATCTCCCGCGACAACGCAAAGAACTCCCTGTACTTGCA AATGAACTCGCTCAGGGCTGAGGATACCGCGCTGTACTACTGCTCCGTG CATTCCTTCCTGGCCTACTGGGGACAGGGAACTCTGGTCACCGTGTCGA GCGCCTCCGGCGGCGGGGGCTCGGGTGGACGGGCCTCGGGCGGAGGGGG GTCCGACATCGTGATGACCCAGACCCCGCTGAGCTTGCCCGTGACTCCC GGAGAGCCTGCATCCATCTCCTGCCGGTCATCCCAGTCCCTTCTCCACT CCAACGGATACAACTACCTCGACTGGTACCTCCAGAAGCCGGGACAGAG CCCTCAGCTTCTGATCTACCTGGGGTCAAATAGAGCCTCAGGAGTGCCG GATCGGTTCAGCGGATCTGGTTCGGGAACTGATTTCACTCTGAAGATTT

		CCCGCGTGGAAGCCGAGGACGTGGGCGTCTACTACTGTATGCAGGCGCT GCAGACCCCCTATACCTTCGGCCAAGGGACGAAAGTGGAGATCAAG
139105- aa VH	70	QVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVS GISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCSV HSFLAYWGQGTLVTVSS
139105- aa VL	85	DIVMTQTPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSP QLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQ TPYTFGQGTKVEIK
139105- aa Full CAR	100	MALPVTALLLPLALLLHAARPQVQLVESGGGLVQPGRSLRLSCAASGFT FDDYAMHWVRQAPGKGLEWVSGISWNSGSIGYADSVKGRFTISRDNAKN SLYLQMNSLRAEDTALYYCSVHSFLAYWGQGTLVTVSSASGGGGSGGRA SGGGGSDIVMTQTPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQ KPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYY CMQALQTPYTFGQGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRP AAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLY IFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQG QNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKD KMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
139105- nt Full CAR	115	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCC ACGCCGCTCGGCCCCAAGTGCAACTCGTCGAATCCGGTGGAGGTCTGGT CCAACCTGGTAGAAGCCTGAGACTGTCGTGTGCGGCCAGCGGATTCACC TTTGATGACTATGCTATGCACTGGGTGCGGCAGGCCCCAGGAAAGGGCC TGGAATGGGTGTCGGGAATTAGCTGGAACTCCGGGTCCATTGGCTACGC CGACTCCGTGAAGGGCCGCTTCACCATCTCCCGCGACAACGCAAAGAAC TCCCTGTACTTGCAAATGAACTCGCTCAGGGCTGAGGATACCGCGCTGT ACTACTGCTCCGTGCATTCCTTCCTGGCCTACTGGGGACAGGGAACTCT GGTCACCGTGTCGAGCGCCTCCGGCGGCGGGGGCTCGGGTGGACGGGCC TCGGGCGGAGGGGGGTCCGACATCGTGATGACCCAGACCCCGCTGAGCT TGCCCGTGACTCCCGGAGAGCCTGCATCCATCTCCTGCCGGTCATCCCA GTCCCTTCTCCACTCCAACGGATACAACTACCTCGACTGGTACCTCCAG AAGCCGGGACAGAGCCCTCAGCTTCTGATCTACCTGGGGTCAAATAGAG CCTCAGGAGTGCCGGATCGGTTCAGCGGATCTGGTTCGGGAACTGATTT CACTCTGAAGATTTCCCGCGTGGAAGCCGAGGACGTGGGCGTCTACTAC TGTATGCAGGCGCTGCAGACCCCCTATACCTTCGGCCAAGGGACGAAAG TGGAGATCAAGACCACTACCCCAGCACCGAGGCCACCCACCCCGGCTCC TACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCC GCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTGACTTCGCCTGCGATA TCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGCTGCTTTC ACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTAC ATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAGAGGAGG ACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACT GCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGG CAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACG ACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCC GCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGAT AAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAA GAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAA GGACACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
139111		
139111- aa ScFv domain	41	EVQLLESGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVS GIVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAH GGESDVWGQGTTVTVSSASGGGGSGGRASGGGGSDIVMTQTPLSLSVTP

		GQPASISCKSSQSLLRNDGKTPLYWYLQKAGQPPQLLIYEVSNRFSGVP DRFSGSGSGTDFTLKISRVEAEDVGAYYCMQNIQFPSFGGGTKLEIK
139111- nt ScFv domain	56	GAAGTGCAATTGTTGGAATCTGGAGGAGGACTTGTGCAGCCTGGAGGAT CACTGAGACTTTCGTGTGCGGTGTCAGGCTTCGCCCTGAGCAACCACGG CATGAGCTGGGTGCGGAGAGCCCCGGGGAAGGGTCTGGAATGGGTGTCC GGGATCGTCTACTCCGGTTCAACTTACTACGCCGCAAGCGTGAAGGGTC GCTTCACCATTTCCCGCGATAACTCCCGGAACACCCTGTACCTCCAAAT GAACTCCCTGCGGCCCGAGGACACCGCCATCTACTACTGTTCCGCGCAT GGAGGAGAGTCCGATGTCTGGGGACAGGGCACTACCGTGACCGTGTCGA GCGCCTCGGGGGGGAGGAGGCTCCGGCGGTCGCGCCTCCGGGGGGGGTGG CAGCGACATTGTGATGACGCAGACTCCACTCTCGCTGTCCGTGACCCCG GGACAGCCCGCGTCCATCTCGTGCAAGAGCTCCCAGAGCCTGCTGAGGA ACGACGGAAAGACTCCTCTGTATTGGTACCTCCAGAAGGCTGGACAGCC CCCGCAACTGCTCATCTACGAAGTGTCAAATCGCTTCTCCGGGGTGCCG GATCGGTTTTCCGGCTCGGGATCGGGCACCGACTTCACCCTGAAAATCT CCAGGGTCGAGGCCGAGGACGTGGGAGCCTACTACTGCATGCAAAACAT CCAGTTCCCTTCCTTCGGCGGCGGCACAAAGCTGGAGATTAAG
139111- aa VH	71	EVQLLESGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVS GIVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAH GGESDVWGQGTTVTVSS
139111- aa VL	86	DIVMTQTPLSLSVTPGQPASISCKSSQSLLRNDGKTPLYWYLQKAGQPP QLLIYEVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGAYYCMQNIQ FPSFGGGTKLEIK
139111- aa Full CAR	101	MALPVTALLLPLALLLHAARPEVQLLESGGGLVQPGGSLRLSCAVSGFA LSNHGMSWVRRAPGKGLEWVSGIVYSGSTYYAASVKGRFTISRDNSRNT LYLQMNSLRPEDTAIYYCSAHGGESDVWGQGTTVTVSSASGGGGSGGRA SGGGGSDIVMTQTPLSLSVTPGQPASISCKSSQSLLRNDGKTPLYWYLQ KAGQPPQLLIYEVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGAYY CMQNIQFPSFGGGTKLEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPA AGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYI FKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQ NQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDK MAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
139111- nt Full CAR	116	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCC ACGCCGCTCGGCCCGAAGTGCAATTGTTGGAATCTGGAGGAGGACTTGT GCAGCCTGGAGGATCACTGAGACTTTCGTGTGCGGTGTCAGGCTTCGCC CTGAGCAACCACGGCATGAGCTGGGTGCGGAGAGCCCCGGGGAAGGGTC TGGAATGGGTGTCCGGGATCGTCTACTCCGGTTCAACTTACTACGCCGC AAGCGTGAAGGGTCGCTTCACCATTTCCCGCGATAACTCCCGGAACACC CTGTACCTCCAAATGAACTCCCTGCGGCCCGAGGACACCGCCATCTACT ACTGTTCCGCGCATGGAGGAGAGTCCGATGTCTGGGGACAGGGCACTAC CGTGACCGTGTCGAGCGCCTCGGGGGGGAGGAGGCTCCGGCGGTCGCGCC TCCGGGGGGGGTGGCAGCGACATTGTGATGACGCAGACTCCACTCTCGC TGTCCGTGACCCCGGGACAGCCCGCGTCCATCTCGTGCAAGAGCTCCCA GAGCCTGCTGAGGAACGACGGAAAGACTCCTCTGTATTGGTACCTCCAG AAGGCTGGACAGCCCCCGCAACTGCTCATCTACGAAGTGTCAAATCGCT TCTCCGGGGTGCCGGATCGGTTTTCCGGCTCGGGATCGGGCACCGACTT CACCCTGAAAATCTCCAGGGTCGAGGCCGAGGACGTGGGAGCCTACTAC TGCATGCAAAACATCCAGTTCCCTTCCTTCGGCGGCGGCACAAAGCTGG AGATTAAGACCACTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTAC CATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCA GCTGGTGGGGCCGTGCATACCCGGGGTCTTGACTTCGCCTGCGATATCT

		ACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCACT CGTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTACATC TTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAGAGGAGGACG GCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTGCG CGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGGCAG AACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACG TGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCG CAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAG ATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAG GCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGA CACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
139100		
139100- aa ScFv domain	42	QVQLVQSGAEVRKTGASVKVSCKASGYIFDNFGINWVRQAPGQGLEWMG WINPKNNNTNYAQKFQGRVTITADESTNTAYMEVSSLRSEDTAVYYCAR GPYYYQSYMDVWGQGTMVTVSSASGGGGSGGRASGGGGSDIVMTQTPLS LPVTPGEPASISCRSSQSLLHSNGYNYLNWYLQKPGQSPQLLIYLGSKR ASGVPDRFSGSGSGTDFTLHITRVGAEDVGVYYCMQALQTPYTFGQGTK LEIK
139100- nt ScFv domain	57	CAAGTCCAACTCGTCCAGTCCGGCGCAGAAGTCAGAAAAACCGGTGCTA GCGTGAAAGTGTCCTGCAAGGCCTCCGGCTACATTTTCGATAACTTCGG AATCAACTGGGTCAGACAGGCCCCGGGCCAGGGGCTGGAATGGATGGGA TGGATCAACCCCAAGAACAACAACACCAACTACGCACAGAAGTTCCAGG GCCGCGTGACTATCACCGCCGATGAATCGACCAATACCGCCTACATGGA GGTGTCCTCCCTGCGGTCGGAGGACACTGCCGTGTATTACTGCGCGAGG GGCCCATACTACTACCAAAGCTACATGGACGTCTGGGGACAGGGAACCA TGGTGACCGTGTCATCCGCCTCCGGTGGTGGAGGCTCCGGGGGGCGGGC TTCAGGAGGCGGAGGAAGCGATATTGTGATGACCCAGACTCCGCTTAGC CTGCCCGTGACTCCTGGAGAACCGGCCTCCATTTCCTGCCGGTCCTCGC AATCACTCCTGCATTCCAACGGTTACAACTACCTGAATTGGTACCTCCA GAAGCCTGGCCAGTCGCCCCAGTTGCTGATCTATCTGGGCTCGAAGCGC GCCTCCGGGGTGCCTGACCGGTTTAGCGGATCTGGGAGCGGCACGGACT TCACTCTCCACATCACCCGCGTGGGAGCGGAGGACGTGGGAGTGTACTA CTGTATGCAGGCGCTGCAGACTCCGTACACATTCGGACAGGGCACCAAG CTGGAGATCAAG
139100- aa VH	72	QVQLVQSGAEVRKTGASVKVSCKASGYIFDNFGINWVRQAPGQGLEWMG WINPKNNNTNYAQKFQGRVTITADESTNTAYMEVSSLRSEDTAVYYCAR GPYYYQSYMDVWGQGTMVTVSS
139100- aa VL	87	DIVMTQTPLSLPVTPGEPASISCRSSQSLLHSNGYNYLNWYLQKPGQSP QLLIYLGSKRASGVPDRFSGSGSGTDFTLHITRVGAEDVGVYYCMQALQ TPYTFGQGTKLEIK
139100- aa Full CAR	102	MALPVTALLLPLALLLHAARPQVQLVQSGAEVRKTGASVKVSCKASGYI FDNFGINWVRQAPGQGLEWMGWINPKNNNTNYAQKFQGRVTITADESTN TAYMEVSSLRSEDTAVYYCARGPYYYQSYMDVWGQGTMVTVSSASGGGG SGGRASGGGGSDIVMTQTPLSLPVTPGEPASISCRSSQSLLHSNGYNYL NWYLQKPGQSPQLLIYLGSKRASGVPDRFSGSGSGTDFTLHITRVGAED VGVYYCMQALQTPYTFGQGTKLEIKTTTPAPRPPTPAPTIASQPLSLRP EACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGR KKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAP AYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYN ELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQAL PPR

139100- nt Full CAR	117	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCC ACGCCGCTCGGCCCCAAGTCCAACTCGTCCAGTCCGGCGCAGAAGTCAG AAAAACCGGTGCTAGCGTGAAAGTGTCCTGCAAGGCCTCCGGCTACATT TTCGATAACTTCGGAATCAACTGGGTCAGACAGGCCCCGGGCCAGGGGC TGGAATGGATGGGATGGATCAACCCCAAGAACAACAACACCAACTACGC ACAGAAGTTCCAGGGCCGCGTGACTATCACCGCCGATGAATCGACCAAT ACCGCCTACATGGAGGTGTCCTCCCTGCGGTCGGAGGACACTGCCGTGT ATTACTGCGCGAGGGGCCCATACTACTACCAAAGCTACATGGACGTCTG GGGACAGGGAACCATGGTGACCGTGTCATCCGCCTCCGGTGGTGGAGGC TCCGGGGGGCGGGCTTCAGGAGGCGGAGGAAGCGATATTGTGATGACCC AGACTCCGCTTAGCCTGCCCGTGACTCCTGGAGAACCGGCCTCCATTTC CTGCCGGTCCTCGCAATCACTCCTGCATTCCAACGGTTACAACTACCTG AATTGGTACCTCCAGAAGCCTGGCCAGTCGCCCCAGTTGCTGATCTATC TGGGCTCGAAGCGCGCCTCCGGGGTGCCTGACCGGTTTAGCGGATCTGG GAGCGGCACGGACTTCACTCTCCACATCACCCGCGTGGGAGCGGAGGAC GTGGGAGTGTACTACTGTATGCAGGCGCTGCAGACTCCGTACACATTCG GACAGGGCACCAAGCTGGAGATCAAGACCACTACCCCAGCACCGAGGCC ACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCG GAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTG ACTTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGG GGTCCTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGG AAGAAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGA CTACTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGA AGGCGGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCA GCCTACAAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTC GGAGAGAGGAGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGA AATGGGCGGGAAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAAC GAGCTCCAAAAGGATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGA AAGGGGAACGCAGAAGAGGCAAAGGCCACGACGGACTGTACCAGGGACT CAGCACCGCCACCAAGGACACCTATGACGCTCTTCACATGCAGGCCCTG CCGCCTCGG
139101		
139101- aa ScFv domain	43	QVQLQESGGGLVQPGGSLRLSCAASGFTFSSDAMTWVRQAPGKGLEWVS VISGSGGTTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK LDSSGYYYARGPRYWGQGTLVTVSSASGGGGSGGRASGGGGSDIQLTQS PSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYGASTLAS GVPARFSGSGSGTHFTLTINSLQSEDSATYYCQQSYKRASFGQGTKVEI K
139101- nt ScFv domain	58	CAAGTGCAACTTCAAGAATCAGGCGGAGGACTCGTGCAGCCCGGAGGAT CATTGCGGCTCTCGTGCGCCGCCTCGGGCTTCACCTTCTCGAGCGACGC CATGACCTGGGTCCGCCAGGCCCCGGGGAAGGGGCTGGAATGGGTGTCT GTGATTTCCGGCTCCGGGGGAACTACGTACTACGCCGATTCCGTGAAAG GTCGCTTCACTATCTCCCGGGACAACAGCAAGAACACCCTTTATCTGCA AATGAATTCCCTCCGCGCCGAGGACACCGCCGTGTACTACTGCGCCAAG CTGGACTCCTCGGGCTACTACTATGCCCGGGGTCCGAGATACTGGGGAC AGGGAACCCTCGTGACCGTGTCCTCCGCGTCCGGCGGAGGAGGGTCGGG AGGGCGGGCCTCCGGCGGCGGCGGTTCGGACATCCAGCTGACCCAGTCC CCATCCTCACTGAGCGCAAGCGTGGGCGACAGAGTCACCATTACATGCA GGGCGTCCCAGAGCATCAGCTCCTACCTGAACTGGTACCAACAGAAGCC TGGAAAGGCTCCTAAGCTGTTGATCTACGGGGCTTCGACCCTGGCATCC GGGGTGCCCGCGAGGTTTAGCGGAAGCGGTAGCGGCACTCACTTCACTC TGACCATTAACAGCCTCCAGTCCGAGGATTCAGCCACTTACTACTGTCA

		GCAGTCCTACAAGCGGGCCAGCTTCGGACAGGGCACTAAGGTCGAGATC AAG
139101- aa VH	73	QVQLQESGGGLVQPGGSLRLSCAASGFTFSSDAMTWVRQAPGKGLEWVS VISGSGGTTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK LDSSGYYYARGPRYWGQGTLVTVSS
139101- aa VL	88	DIQLTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIY GASTLASGVPARFSGSGSGTHFTLTINSLQSEDSATYYCQQSYKRASFG QGTKVEIK
139101- aa Full CAR	103	MALPVTALLLPLALLLHAARPQVQLQESGGGLVQPGGSLRLSCAASGFT FSSDAMTWVRQAPGKGLEWVSVISGSGGTTYYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAKLDSSGYYYARGPRYWGQGTLVTVSSASG GGGSGGRASGGGGSDIQLTQSPSSLSASVGDRVTITCRASQSISSYLNW YQQKPGKAPKLLIYGASTLASGVPARFSGSGSGTHFTLTINSLQSEDSA TYYCQQSYKRASFGQGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEAC RPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKL LYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYK QGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQ KDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
139101- nt Full CAR	118	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCC ACGCCGCTCGGCCCCAAGTGCAACTTCAAGAATCAGGCGGAGGACTCGT GCAGCCCGGAGGATCATTGCGGCTCTCGTGCGCCGCCTCGGGCTTCACC TTCTCGAGCGACGCCATGACCTGGGTCCGCCAGGCCCCGGGGAAGGGGC TGGAATGGGTGTCTGTGATTTCCGGCTCCGGGGGAACTACGTACTACGC CGATTCCGTGAAAGGTCGCTTCACTATCTCCCGGGACAACAGCAAGAAC ACCCTTTATCTGCAAATGAATTCCCTCCGCGCCGAGGACACCGCCGTGT ACTACTGCGCCAAGCTGGACTCCTCGGGCTACTACTATGCCCGGGGTCC GAGATACTGGGGACAGGGAACCCTCGTGACCGTGTCCTCCGCGTCCGGC GGAGGAGGGTCGGGAGGGCGGGCCTCCGGCGGCGGCGGTTCGGACATCC AGCTGACCCAGTCCCCATCCTCACTGAGCGCAAGCGTGGGCGACAGAGT CACCATTACATGCAGGGCGTCCCAGAGCATCAGCTCCTACCTGAACTGG TACCAACAGAAGCCTGGAAAGGCTCCTAAGCTGTTGATCTACGGGGCTT CGACCCTGGCATCCGGGGTGCCCGCGAGGTTTAGCGGAAGCGGTAGCGG CACTCACTTCACTCTGACCATTAACAGCCTCCAGTCCGAGGATTCAGCC ACTTACTACTGTCAGCAGTCCTACAAGCGGGCCAGCTTCGGACAGGGCA CTAAGGTCGAGATCAAGACCACTACCCCAGCACCGAGGCCACCCACCCC GGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGT AGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTGACTTCGCCT GCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGCT GCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTG CTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAG AGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTG CGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAG CAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGG AGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGG GAAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAA AAGGATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAAC GCAGAAGAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGC CACCAAGGACACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
139102		
139102- aa ScFv domain	44	QVQLVQSGAEVKKPGASVKVSCKASGYTFSNYGITWVRQAPGQGLEWMG WISAYNGNTNYAQKFQGRVTMTRNTSISTAYMELSSLRSEDTAVYYCAR GPYYYYMDVWGKGTMVTVSSASGGGGSGGRASGGGGSEIVMTQSPLSLP

		VTPGEPASISCRSSQSLLYSNGYNYVDWYLQKPGQSPQLLIYLGSNRAS GVPDRFSGSGSGTDFKLQISRVEAEDVGIYYCMQGRQFPYSFGQGTKVE IK
139102- nt ScFv domain	59	CAAGTCCAACTGGTCCAGAGCGGTGCAGAAGTGAAGAAGCCCGGAGCGA GCGTGAAAGTGTCCTGCAAGGCTTCCGGGTACACCTTCTCCAACTACGG CATCACTTGGGTGCGCCAGGCCCCGGGACAGGGCCTGGAATGGATGGGG TGGATTTCCGCGTACAACGGCAATACGAACTACGCTCAGAAGTTCCAGG GTAGAGTGACCATGACTAGGAACACCTCCATTTCCACCGCCTACATGGA ACTGTCCTCCCTGCGGAGCGAGGACACCGCCGTGTACTATTGCGCCCGG GGACCATACTACTACTACATGGATGTCTGGGGGAAGGGGACTATGGTCA CCGTGTCATCCGCCTCGGGAGGCGGCGGATCAGGAGGACGCGCCTCTGG TGGTGGAGGATCGGAGATCGTGATGACCCAGAGCCCTCTCTCCTTGCCC GTGACTCCTGGGGAGCCCGCATCCATTTCATGCCGGAGCTCCCAGTCAC TTCTCTACTCCAACGGCTATAACTACGTGGATTGGTACCTCCAAAAGCC GGGCCAGAGCCCGCAGCTGCTGATCTACCTGGGCTCGAACAGGGCCAGC GGAGTGCCTGACCGGTTCTCCGGGTCGGGAAGCGGGACCGACTTCAAGC TGCAAATCTCGAGAGTGGAGGCCGAGGACGTGGGAATCTACTACTGTAT GCAGGGCCGCCAGTTTCCGTACTCGTTCGGACAGGGCACCAAAGTGGAA ATCAAG
139102- aa VH	74	QVQLVQSGAEVKKPGASVKVSCKASGYTFSNYGITWVRQAPGQGLEWMG WISAYNGNTNYAQKFQGRVTMTRNTSISTAYMELSSLRSEDTAVYYCAR GPYYYYMDVWGKGTMVTVSS
139102- aa VL	89	EIVMTQSPLSLPVTPGEPASISCRSSQSLLYSNGYNYVDWYLQKPGQSP QLLIYLGSNRASGVPDRFSGSGSGTDFKLQISRVEAEDVGIYYCMQGRQ FPYSFGQGTKVEIK
139102- aa Full CAR	104	MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYT FSNYGITWVRQAPGQGLEWMGWISAYNGNTNYAQKFQGRVTMTRNTSIS TAYMELSSLRSEDTAVYYCARGPYYYYMDVWGKGTMVTVSSASGGGGSG GRASGGGGSEIVMTQSPLSLPVTPGEPASISCRSSQSLLYSNGYNYVDW YLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFKLQISRVEAEDVG IYYCMQGRQFPYSFGQGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEA CRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKK LLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAY KQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNEL QKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPP R
139102- nt Full CAR	119	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCC ACGCCGCTCGGCCCCAAGTCCAACTGGTCCAGAGCGGTGCAGAAGTGAA GAAGCCCGGAGCGAGCGTGAAAGTGTCCTGCAAGGCTTCCGGGTACACC TTCTCCAACTACGGCATCACTTGGGTGCGCCAGGCCCCGGGACAGGGCC TGGAATGGATGGGGTGGATTTCCGCGTACAACGGCAATACGAACTACGC TCAGAAGTTCCAGGGTAGAGTGACCATGACTAGGAACACCTCCATTTCC ACCGCCTACATGGAACTGTCCTCCCTGCGGAGCGAGGACACCGCCGTGT ACTATTGCGCCCGGGGACCATACTACTACTACATGGATGTCTGGGGGAA GGGGACTATGGTCACCGTGTCATCCGCCTCGGGAGGCGGCGGATCAGGA GGACGCGCCTCTGGTGGTGGAGGATCGGAGATCGTGATGACCCAGAGCC CTCTCTCCTTGCCCGTGACTCCTGGGGAGCCCGCATCCATTTCATGCCG GAGCTCCCAGTCACTTCTCTACTCCAACGGCTATAACTACGTGGATTGG TACCTCCAAAAGCCGGGCCAGAGCCCGCAGCTGCTGATCTACCTGGGCT CGAACAGGGCCAGCGGAGTGCCTGACCGGTTCTCCGGGTCGGGAAGCGG GACCGACTTCAAGCTGCAAATCTCGAGAGTGGAGGCCGAGGACGTGGGA ATCTACTACTGTATGCAGGGCCGCCAGTTTCCGTACTCGTTCGGACAGG

		GCACCAAAGTGGAAATCAAGACCACTACCCCAGCACCGAGGCCACCCAC CCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCA TGTAGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTGACTTCG CCTGCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTCCT GCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAG CTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTC AAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGG CTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTAC AAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAG AGGAGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGG CGGGAAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTC CAAAAGGATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGG AACGCAGAAGAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCAC CGCCACCAAGGACACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCT CGG
139104		
139104- aa ScFv domain	45	EVQLLETGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVS GIVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAH GGESDVWGQGTTVTVSSASGGGGSGGRASGGGGSEIVLTQSPATLSVSP GESATLSCRASQSVSSNLAWYQQKPGQAPRLLIYGASTRASGIPDRFSG SGSGTDFTLTISSLQAEDVAVYYCQQYGSSLTFGGGTKVEIK
139104- nt ScFv domain	60	GAAGTGCAATTGCTCGAAACTGGAGGAGGTCTGGTGCAACCTGGAGGAT CACTTCGCCTGTCCTGCGCCGTGTCGGGCTTTGCCCTGTCCAACCATGG AATGAGCTGGGTCCGCCGCGCGCCGGGGAAGGGCCTCGAATGGGTGTCC GGCATCGTCTACTCCGGCTCCACCTACTACGCCGCGTCCGTGAAGGGCC GGTTCACGATTTCACGGGACAACTCGCGGAACACCCTGTACCTCCAAAT GAATTCCCTTCGGCCGGAGGATACTGCCATCTACTACTGCTCCGCCCAC GGTGGCGAATCCGACGTCTGGGGCCAGGGAACCACCGTGACCGTGTCCA GCGCGTCCGGGGGAGGAGGAAGCGGGGGTAGAGCATCGGGTGGAGGCGG ATCAGAGATCGTGCTGACCCAGTCCCCCGCCACCTTGAGCGTGTCACCA GGAGAGTCCGCCACCCTGTCATGCCGCGCCAGCCAGTCCGTGTCCTCCA ACCTGGCTTGGTACCAGCAGAAGCCGGGGCAGGCCCCTAGACTCCTGAT CTATGGGGCGTCGACCCGGGCATCTGGAATTCCCGATAGGTTCAGCGGA TCGGGCTCGGGCACTGACTTCACTCTGACCATCTCCTCGCTGCAAGCCG AGGACGTGGCTGTGTACTACTGTCAGCAGTACGGAAGCTCCCTGACTTT CGGTGGCGGGACCAAAGTCGAGATTAAG
139104- aa VH	75	EVQLLETGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVS GIVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAH GGESDVWGQGTTVTVSS
139104- aa VL	90	EIVLTQSPATLSVSPGESATLSCRASQSVSSNLAWYQQKPGQAPRLLIY GASTRASGIPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYGSSLTFG GGTKVEIK
139104- aa Full CAR	105	MALPVTALLLPLALLLHAARPEVQLLETGGGLVQPGGSLRLSCAVSGFA LSNHGMSWVRRAPGKGLEWVSGIVYSGSTYYAASVKGRFTISRDNSRNT LYLQMNSLRPEDTAIYYCSAHGGESDVWGQGTTVTVSSASGGGGSGGRA SGGGGSEIVLTQSPATLSVSPGESATLSCRASQSVSSNLAWYQQKPGQA PRLLIYGASTRASGIPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYG SSLTFGGGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAV HTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPF MRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYN ELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAY SEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

139104- nt Full CAR	120	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCC ACGCCGCTCGGCCCGAAGTGCAATTGCTCGAAACTGGAGGAGGTCTGGT GCAACCTGGAGGATCACTTCGCCTGTCCTGCGCCGTGTCGGGCTTTGCC CTGTCCAACCATGGAATGAGCTGGGTCCGCCGCGCGCCGGGGAAGGGCC TCGAATGGGTGTCCGGCATCGTCTACTCCGGCTCCACCTACTACGCCGC GTCCGTGAAGGGCCGGTTCACGATTTCACGGGACAACTCGCGGAACACC CTGTACCTCCAAATGAATTCCCTTCGGCCGGAGGATACTGCCATCTACT ACTGCTCCGCCCACGGTGGCGAATCCGACGTCTGGGGCCAGGGAACCAC CGTGACCGTGTCCAGCGCGTCCGGGGGAGGAGGAAGCGGGGGTAGAGCA TCGGGTGGAGGCGGATCAGAGATCGTGCTGACCCAGTCCCCCGCCACCT TGAGCGTGTCACCAGGAGAGTCCGCCACCCTGTCATGCCGCGCCAGCCA GTCCGTGTCCTCCAACCTGGCTTGGTACCAGCAGAAGCCGGGGCAGGCC CCTAGACTCCTGATCTATGGGGCGTCGACCCGGGCATCTGGAATTCCCG ATAGGTTCAGCGGATCGGGCTCGGGCACTGACTTCACTCTGACCATCTC CTCGCTGCAAGCCGAGGACGTGGCTGTGTACTACTGTCAGCAGTACGGA AGCTCCCTGACTTTCGGTGGCGGGACCAAAGTCGAGATTAAGACCACTA CCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCC TCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCCGTG CATACCCGGGGTCTTGACTTCGCCTGCGATATCTACATTTGGGCCCCTC TGGCTGGTACTTGCGGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTA CTGTAAGCGCGGTCGGAAGAAGCTGCTGTACATCTTTAAGCAACCCTTC ATGAGGCCTGTGCAGACTACTCAAGAGGAGGACGGCTGTTCATGCCGGT TCCCAGAGGAGGAGGAAGGCGGCTGCGAACTGCGCGTGAAATTCAGCCG CAGCGCAGATGCTCCAGCCTACAAGCAGGGGCAGAACCAGCTCTACAAC GAACTCAATCTTGGTCGGAGAGAGGAGTACGACGTGCTGGACAAGCGGA GAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGAAAGAATCCCCA AGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGAAGCCTAT AGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAGGCCACGACG GACTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTATGACGCTCT TCACATGCAGGCCCTGCCGCCTCGG
139106		
139106- aa ScFv domain	46	EVQLVETGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVS GIVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAH GGESDVWGQGTTVTVSSASGGGGSGGRASGGGGSEIVMTQSPATLSVSP GERATLSCRASQSVSSKLAWYQQKPGQAPRLLMYGASIRATGIPDRFSG SGSGTEFTLTISSLEPEDFAVYYCQQYGSSSWTFGQGTKVEIK
139106- nt ScFv domain	61	GAAGTGCAATTGGTGGAAACTGGAGGAGGACTTGTGCAACCTGGAGGAT CATTGAGACTGAGCTGCGCAGTGTCGGGATTCGCCCTGAGCAACCATGG AATGTCCTGGGTCAGAAGGGCCCCTGGAAAAGGCCTCGAATGGGTGTCA GGGATCGTGTACTCCGGTTCCACTTACTACGCCGCCTCCGTGAAGGGGC GCTTCACTATCTCACGGGATAACTCCCGCAATACCCTGTACCTCCAAAT GAACAGCCTGCGGCCGGAGGATACCGCCATCTACTACTGTTCCGCCCAC GGTGGAGAGTCTGACGTCTGGGGCCAGGGAACTACCGTGACCGTGTCCT CCGCGTCCGGCGGTGGAGGGAGCGGCGGCCGCGCCAGCGGCGGCGGAGG CTCCGAGATCGTGATGACCCAGAGCCCCGCTACTCTGTCGGTGTCGCCC GGAGAAAGGGCGACCCTGTCCTGCCGGGCGTCGCAGTCCGTGAGCAGCA AGCTGGCTTGGTACCAGCAGAAGCCGGGCCAGGCACCACGCCTGCTTAT GTACGGTGCCTCCATTCGGGCCACCGGAATCCCGGACCGGTTCTCGGGG TCGGGGTCCGGTACCGAGTTCACACTGACCATTTCCTCGCTCGAGCCCG AGGACTTTGCCGTCTATTACTGCCAGCAGTACGGCTCCTCCTCATGGAC GTTCGGCCAGGGGACCAAGGTCGAAATCAAG

139106- aa VH	76	EVQLVETGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVS GIVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAH GGESDVWGQGTTVTVSS
139106- aa VL	91	EIVMTQSPATLSVSPGERATLSCRASQSVSSKLAWYQQKPGQAPRLLMY GASIRATGIPDRFSGSGSGTEFTLTISSLEPEDFAVYYCQQYGSSSWTF GQGTKVEIK
139106- aa Full CAR	106	MALPVTALLLPLALLLHAARPEVQLVETGGGLVQPGGSLRLSCAVSGFA LSNHGMSWVRRAPGKGLEWVSGIVYSGSTYYAASVKGRFTISRDNSRNT LYLQMNSLRPEDTAIYYCSAHGGESDVWGQGTTVTVSSASGGGGSGGRA SGGGGSEIVMTQSPATLSVSPGERATLSCRASQSVSSKLAWYQQKPGQA PRLLMYGASIRATGIPDRFSGSGSGTEFTLTISSLEPEDFAVYYCQQYG SSSWTFGQGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGA VHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQP FMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLY NELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEA YSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
139106- nt Full CAR	121	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCC ACGCCGCTCGGCCCGAAGTGCAATTGGTGGAAACTGGAGGAGGACTTGT GCAACCTGGAGGATCATTGAGACTGAGCTGCGCAGTGTCGGGATTCGCC CTGAGCAACCATGGAATGTCCTGGGTCAGAAGGGCCCCTGGAAAAGGCC TCGAATGGGTGTCAGGGATCGTGTACTCCGGTTCCACTTACTACGCCGC CTCCGTGAAGGGGCGCTTCACTATCTCACGGGATAACTCCCGCAATACC CTGTACCTCCAAATGAACAGCCTGCGGCCGGAGGATACCGCCATCTACT ACTGTTCCGCCCACGGTGGAGAGTCTGACGTCTGGGGCCAGGGAACTAC CGTGACCGTGTCCTCCGCGTCCGGCGGTGGAGGGAGCGGCGGCCGCGCC AGCGGCGGCGGAGGCTCCGAGATCGTGATGACCCAGAGCCCCGCTACTC TGTCGGTGTCGCCCGGAGAAAGGGCGACCCTGTCCTGCCGGGCGTCGCA GTCCGTGAGCAGCAAGCTGGCTTGGTACCAGCAGAAGCCGGGCCAGGCA CCACGCCTGCTTATGTACGGTGCCTCCATTCGGGCCACCGGAATCCCGG ACCGGTTCTCGGGGTCGGGGTCCGGTACCGAGTTCACACTGACCATTTC CTCGCTCGAGCCCGAGGACTTTGCCGTCTATTACTGCCAGCAGTACGGC TCCTCCTCATGGACGTTCGGCCAGGGGACCAAGGTCGAAATCAAGACCA CTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCA GCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCC GTGCATACCCGGGGTCTTGACTTCGCCTGCGATATCTACATTTGGGCCC CTCTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCACTCGTGATCACTCT TTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTACATCTTTAAGCAACCC TTCATGAGGCCTGTGCAGACTACTCAAGAGGAGGACGGCTGTTCATGCC GGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTGCGCGTGAAATTCAG CCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGGCAGAACCAGCTCTAC AACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACGTGCTGGACAAGC GGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGAAAGAATCC CCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGAAGCC TATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAGGCCACG ACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTATGACGC TCTTCACATGCAGGCCCTGCCGCCTCGG
139107		
139107- aa ScFv domain	47	EVQLVETGGGVVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVS GIVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAH GGESDVWGQGTTVTVSSASGGGGSGGRASGGGGSEIVLTQSPGTLSLSP GERATLSCRASQSVGSTNLAWYQQKPGQAPRLLIYDASNRATGIPDRFS GGGSGTDFTLTISRLEPEDFAVYYCQQYGSSPPWTFGQGTKVEIK

139107- nt ScFv domain	62	GAAGTGCAATTGGTGGAGACTGGAGGAGGAGTGGTGCAACCTGGAGGAA GCCTGAGACTGTCATGCGCGGTGTCGGGCTTCGCCCTCTCCAACCACGG AATGTCCTGGGTCCGCCGGGCCCCTGGGAAAGGACTTGAATGGGTGTCC GGCATCGTGTACTCGGGTTCCACCTACTACGCGGCCTCAGTGAAGGGCC GGTTTACTATTAGCCGCGACAACTCCAGAAACACACTGTACCTCCAAAT GAACTCGCTGCGGCCGGAAGATACCGCTATCTACTACTGCTCCGCCCAT GGGGGAGAGTCGGACGTCTGGGGACAGGGCACCACTGTCACTGTGTCCA GCGCTTCCGGCGGTGGTGGAAGCGGGGGACGGGCCTCAGGAGGCGGTGG CAGCGAGATTGTGCTGACCCAGTCCCCCGGGACCCTGAGCCTGTCCCCG GGAGAAAGGGCCACCCTCTCCTGTCGGGCATCCCAGTCCGTGGGGTCTA CTAACCTTGCATGGTACCAGCAGAAGCCCGGCCAGGCCCCTCGCCTGCT GATCTACGACGCGTCCAATAGAGCCACCGGCATCCCGGATCGCTTCAGC GGAGGCGGATCGGGCACCGACTTCACCCTCACCATTTCAAGGCTGGAAC CGGAGGACTTCGCCGTGTACTACTGCCAGCAGTATGGTTCGTCCCCACC CTGGACGTTCGGCCAGGGGACTAAGGTCGAGATCAAG
139107- aa VH	77	EVQLVETGGGVVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVS GIVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAH GGESDVWGQGTTVTVSS
139107- aa VL	92	EIVLTQSPGTLSLSPGERATLSCRASQSVGSTNLAWYQQKPGQAPRLLI YDASNRATGIPDRFSGGGSGTDFTLTISRLEPEDFAVYYCQQYGSSPPW TFGQGTKVEIK
139107- aa Full CAR	107	MALPVTALLLPLALLLHAARPEVQLVETGGGVVQPGGSLRLSCAVSGFA LSNHGMSWVRRAPGKGLEWVSGIVYSGSTYYAASVKGRFTISRDNSRNT LYLQMNSLRPEDTAIYYCSAHGGESDVWGQGTTVTVSSASGGGGSGGRA SGGGGSEIVLTQSPGTLSLSPGERATLSCRASQSVGSTNLAWYQQKPGQ APRLLIYDASNRATGIPDRFSGGGSGTDFTLTISRLEPEDFAVYYCQQY GSSPPWTFGQGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAG GAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFK QPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQ LYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMA EAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
139107- nt Full CAR	122	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCC ACGCCGCTCGGCCCGAAGTGCAATTGGTGGAGACTGGAGGAGGAGTGGT GCAACCTGGAGGAAGCCTGAGACTGTCATGCGCGGTGTCGGGCTTCGCC CTCTCCAACCACGGAATGTCCTGGGTCCGCCGGGCCCCTGGGAAAGGAC TTGAATGGGTGTCCGGCATCGTGTACTCGGGTTCCACCTACTACGCGGC CTCAGTGAAGGGCCGGTTTACTATTAGCCGCGACAACTCCAGAAACACA CTGTACCTCCAAATGAACTCGCTGCGGCCGGAAGATACCGCTATCTACT ACTGCTCCGCCCATGGGGGAGAGTCGGACGTCTGGGGACAGGGCACCAC TGTCACTGTGTCCAGCGCTTCCGGCGGTGGTGGAAGCGGGGGACGGGCC TCAGGAGGCGGTGGCAGCGAGATTGTGCTGACCCAGTCCCCCGGGACCC TGAGCCTGTCCCCGGGAGAAAGGGCCACCCTCTCCTGTCGGGCATCCCA GTCCGTGGGGTCTACTAACCTTGCATGGTACCAGCAGAAGCCCGGCCAG GCCCCTCGCCTGCTGATCTACGACGCGTCCAATAGAGCCACCGGCATCC CGGATCGCTTCAGCGGAGGCGGATCGGGCACCGACTTCACCCTCACCAT TTCAAGGCTGGAACCGGAGGACTTCGCCGTGTACTACTGCCAGCAGTAT GGTTCGTCCCCACCCTGGACGTTCGGCCAGGGGACTAAGGTCGAGATCA AGACCACTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGC CTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGT GGGGCCGTGCATACCCGGGGTCTTGACTTCGCCTGCGATATCTACATTT GGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCACTCGTGAT CACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTACATCTTTAAG

		CAACCCTTCATGAGGCCTGTGCAGACTACTCAAGAGGAGGACGGCTGTT CATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTGCGCGTGAA ATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGGCAGAACCAG CTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACGTGCTGG ACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGAAA GAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCA GAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAG GCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTA TGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
139108		
139108- aa ScFv domain	48	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLEWVS YISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR ESGDGMDVWGQGTTVTVSSASGGGGSGGRASGGGGSDIQMTQSPSSLSA SVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSYTLAFGQGTKVDIK
139108- nt ScFv domain	63	CAAGTGCAACTCGTGGAATCTGGTGGAGGACTCGTGAAACCTGGAGGAT CATTGAGACTGTCATGCGCGGCCTCGGGATTCACGTTCTCCGATTACTA CATGAGCTGGATTCGCCAGGCTCCGGGGAAGGGACTGGAATGGGTGTCC TACATTTCCTCATCCGGCTCCACCATCTACTACGCGGACTCCGTGAAGG GGAGATTCACCATTAGCCGCGATAACGCCAAGAACAGCCTGTACCTTCA GATGAACTCCCTGCGGGCTGAAGATACTGCCGTCTACTACTGCGCAAGG GAGAGCGGAGATGGGATGGACGTCTGGGGACAGGGTACCACTGTGACCG TGTCGTCGGCCTCCGGCGGAGGGGGTTCGGGTGGAAGGGCCAGCGGCGG CGGAGGCAGCGACATCCAGATGACCCAGTCCCCCTCATCGCTGTCCGCC TCCGTGGGCGACCGCGTCACCATCACATGCCGGGCCTCACAGTCGATCT CCTCCTACCTCAATTGGTATCAGCAGAAGCCCGGAAAGGCCCCTAAGCT TCTGATCTACGCAGCGTCCTCCCTGCAATCCGGGGTCCCATCTCGGTTC TCCGGCTCGGGCAGCGGTACCGACTTCACTCTGACCATCTCGAGCCTGC AGCCGGAGGACTTCGCCACTTACTACTGTCAGCAAAGCTACACCCTCGC GTTTGGCCAGGGCACCAAAGTGGACATCAAG
139108- aa VH	78	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLEWVS YISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR ESGDGMDVWGQGTTVTVSS
139108- aa VL	93	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIY AASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYTLAFGQ GTKVDIK
139108- aa Full CAR	108	MALPVTALLLPLALLLHAARPQVQLVESGGGLVKPGGSLRLSCAASGFT FSDYYMSWIRQAPGKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKN SLYLQMNSLRAEDTAVYYCARESGDGMDVWGQGTTVTVSSASGGGGSGG RASGGGGSDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQ SYTLAFGQGTKVDIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGA VHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQP FMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLY NELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEA YSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
139108- nt Full CAR	123	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCC ACGCCGCTCGGCCCCAAGTGCAACTCGTGGAATCTGGTGGAGGACTCGT GAAACCTGGAGGATCATTGAGACTGTCATGCGCGGCCTCGGGATTCACG TTCTCCGATTACTACATGAGCTGGATTCGCCAGGCTCCGGGGAAGGGAC TGGAATGGGTGTCCTACATTTCCTCATCCGGCTCCACCATCTACTACGC GGACTCCGTGAAGGGGAGATTCACCATTAGCCGCGATAACGCCAAGAAC

		AGCCTGTACCTTCAGATGAACTCCCTGCGGGCTGAAGATACTGCCGTCT ACTACTGCGCAAGGGAGAGCGGAGATGGGATGGACGTCTGGGGACAGGG TACCACTGTGACCGTGTCGTCGGCCTCCGGCGGAGGGGGTTCGGGTGGA AGGGCCAGCGGCGGCGGAGGCAGCGACATCCAGATGACCCAGTCCCCCT CATCGCTGTCCGCCTCCGTGGGCGACCGCGTCACCATCACATGCCGGGC CTCACAGTCGATCTCCTCCTACCTCAATTGGTATCAGCAGAAGCCCGGA AAGGCCCCTAAGCTTCTGATCTACGCAGCGTCCTCCCTGCAATCCGGGG TCCCATCTCGGTTCTCCGGCTCGGGCAGCGGTACCGACTTCACTCTGAC CATCTCGAGCCTGCAGCCGGAGGACTTCGCCACTTACTACTGTCAGCAA AGCTACACCCTCGCGTTTGGCCAGGGCACCAAAGTGGACATCAAGACCA CTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCA GCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCC GTGCATACCCGGGGTCTTGACTTCGCCTGCGATATCTACATTTGGGCCC CTCTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCACTCGTGATCACTCT TTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTACATCTTTAAGCAACCC TTCATGAGGCCTGTGCAGACTACTCAAGAGGAGGACGGCTGTTCATGCC GGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTGCGCGTGAAATTCAG CCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGGCAGAACCAGCTCTAC AACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACGTGCTGGACAAGC GGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGAAAGAATCC CCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGAAGCC TATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAGGCCACG ACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTATGACGC TCTTCACATGCAGGCCCTGCCGCCTCGG
139110		
139110- aa ScFv domain	50	QVQLVQSGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLEWVS YISSSGNTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR STMVREDYWGQGTLVTVSSASGGGGSGGRASGGGGSDIVLTQSPLSLPV TLGQPASISCKSSESLVHNSGKTYLNWFHQRPGQSPRRLIYEVSNRDSG VPDRFTGSGSGTDFTLKISRVEAEDVGVYYCMQGTHWPGTFGQGTKLEI K
139110- nt ScFv domain	65	CAAGTGCAACTGGTGCAAAGCGGAGGAGGATTGGTCAAACCCGGAGGAA GCCTGAGACTGTCATGCGCGGCCTCTGGATTCACCTTCTCCGATTACTA CATGTCATGGATCAGACAGGCCCCGGGGAAGGGCCTCGAATGGGTGTCC TACATCTCGTCCTCCGGGAACACCATCTACTACGCCGACAGCGTGAAGG GCCGCTTTACCATTTCCCGCGACAACGCAAAGAACTCGCTGTACCTTCA GATGAATTCCCTGCGGGCTGAAGATACCGCGGTGTACTATTGCGCCCGG TCCACTATGGTCCGGGAGGACTACTGGGGACAGGGCACACTCGTGACCG TGTCCAGCGCGAGCGGGGGTGGAGGCAGCGGTGGACGCGCCTCCGGCGG CGGCGGTTCAGACATCGTGCTGACTCAGTCGCCCCTGTCGCTGCCGGTC ACCCTGGGCCAACCGGCCTCAATTAGCTGCAAGTCCTCGGAGAGCCTGG TGCACAACTCAGGAAAGACTTACCTGAACTGGTTCCATCAGCGGCCTGG ACAGTCCCCACGGAGGCTCATCTATGAAGTGTCCAACAGGGATTCGGGG GTGCCCGACCGCTTCACTGGCTCCGGGTCCGGCACCGACTTCACCTTGA AAATCTCCAGAGTGGAAGCCGAGGACGTGGGCGTGTACTACTGTATGCA GGGTACCCACTGGCCTGGAACCTTTGGACAAGGAACTAAGCTCGAGATT AAG
139110- aa VH	80	QVQLVQSGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLEWVS YISSSGNTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR STMVREDYWGQGTLVTVSS

139110- aa VL	95	DIVLTQSPLSLPVTLGQPASISCKSSESLVHNSGKTYLNWFHQRPGQSP RRLIYEVSNRDSGVPDRFTGSGSGTDFTLKISRVEAEDVGVYYCMQGTH WPGTFGQGTKLEIK
139110- aa Full CAR	110	MALPVTALLLPLALLLHAARPQVQLVQSGGGLVKPGGSLRLSCAASGFT FSDYYMSWIRQAPGKGLEWVSYISSSGNTIYYADSVKGRFTISRDNAKN SLYLQMNSLRAEDTAVYYCARSTMVREDYWGQGTLVTVSSASGGGGSGG RASGGGGSDIVLTQSPLSLPVTLGQPASISCKSSESLVHNSGKTYLNWF HQRPGQSPRRLIYEVSNRDSGVPDRFTGSGSGTDFTLKISRVEAEDVGV YYCMQGTHWPGTFGQGTKLEIKTTTPAPRPPTPAPTIASQPLSLRPEAC RPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKL LYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYK QGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQ KDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
139110- nt Full CAR	125	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCC ACGCCGCTCGGCCCCAAGTGCAACTGGTGCAAAGCGGAGGAGGATTGGT CAAACCCGGAGGAAGCCTGAGACTGTCATGCGCGGCCTCTGGATTCACC TTCTCCGATTACTACATGTCATGGATCAGACAGGCCCCGGGGAAGGGCC TCGAATGGGTGTCCTACATCTCGTCCTCCGGGAACACCATCTACTACGC CGACAGCGTGAAGGGCCGCTTTACCATTTCCCGCGACAACGCAAAGAAC TCGCTGTACCTTCAGATGAATTCCCTGCGGGCTGAAGATACCGCGGTGT ACTATTGCGCCCGGTCCACTATGGTCCGGGAGGACTACTGGGGACAGGG CACACTCGTGACCGTGTCCAGCGCGAGCGGGGGTGGAGGCAGCGGTGGA CGCGCCTCCGGCGGCGGCGGTTCAGACATCGTGCTGACTCAGTCGCCCC TGTCGCTGCCGGTCACCCTGGGCCAACCGGCCTCAATTAGCTGCAAGTC CTCGGAGAGCCTGGTGCACAACTCAGGAAAGACTTACCTGAACTGGTTC CATCAGCGGCCTGGACAGTCCCCACGGAGGCTCATCTATGAAGTGTCCA ACAGGGATTCGGGGGTGCCCGACCGCTTCACTGGCTCCGGGTCCGGCAC CGACTTCACCTTGAAAATCTCCAGAGTGGAAGCCGAGGACGTGGGCGTG TACTACTGTATGCAGGGTACCCACTGGCCTGGAACCTTTGGACAAGGAA CTAAGCTCGAGATTAAGACCACTACCCCAGCACCGAGGCCACCCACCCC GGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGT AGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTGACTTCGCCT GCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGCT GCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTG CTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAG AGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTG CGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAG CAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGG AGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGG GAAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAA AAGGATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAAC GCAGAAGAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGC CACCAAGGACACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
139112		
139112- aa ScFv domain	51	QVQLVESGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVS GIVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAH GGESDVWGQGTTVTVSSASGGGGSGGRASGGGGSDIRLTQSPSPLSASV GDRVTITCQASEDINKFLNWYHQTPGKAPKLLIYDASTLQTGVPSRFSG SGSGTDFTLTINSLQPEDIGTYYCQQYESLPLTFGGGTKVEIK
139112- nt ScFv domain	66	CAAGTGCAACTCGTGGAATCTGGTGGAGGACTCGTGCAACCCGGTGGAA GCCTTAGGCTGTCGTGCGCCGTCAGCGGGTTTGCTCTGAGCAACCATGG AATGTCCTGGGTCCGCCGGGCACCGGGAAAAGGGCTGGAATGGGTGTCC

		GGCATCGTGTACAGCGGGTCAACCTATTACGCCGCGTCCGTGAAGGGCA GATTCACTATCTCAAGAGACAACAGCCGGAACACCCTGTACTTGCAAAT GAATTCCCTGCGCCCCGAGGACACCGCCATCTACTACTGCTCCGCCCAC GGAGGAGAGTCGGACGTGTGGGGCCAGGGAACGACTGTGACTGTGTCCA GCGCATCAGGAGGGGGTGGTTCGGGCGGCCGGGCCTCGGGGGGAGGAGG TTCCGACATTCGGCTGACCCAGTCCCCGTCCCCACTGTCGGCCTCCGTC GGCGACCGCGTGACCATCACTTGTCAGGCGTCCGAGGACATTAACAAGT TCCTGAACTGGTACCACCAGACCCCTGGAAAGGCCCCCAAGCTGCTGAT CTACGATGCCTCGACCCTTCAAACTGGAGTGCCTAGCCGGTTCTCCGGG TCCGGCTCCGGCACTGATTTCACTCTGACCATCAACTCATTGCAGCCGG AAGATATCGGGACCTACTATTGCCAGCAGTACGAATCCCTCCCGCTCAC ATTCGGCGGGGGAACCAAGGTCGAGATTAAG
139112- aa VH	81	QVQLVESGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVS GIVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAH GGESDVWGQGTTVTVSS
139112- aa VL	96	DIRLTQSPSPLSASVGDRVTITCQASEDINKFLNWYHQTPGKAPKLLIY DASTLQTGVPSRFSGSGSGTDFTLTINSLQPEDIGTYYCQQYESLPLTF GGGTKVEIK
139112- aa Full CAR	111	MALPVTALLLPLALLLHAARPQVQLVESGGGLVQPGGSLRLSCAVSGFA LSNHGMSWVRRAPGKGLEWVSGIVYSGSTYYAASVKGRFTISRDNSRNT LYLQMNSLRPEDTAIYYCSAHGGESDVWGQGTTVTVSSASGGGGSGGRA SGGGGSDIRLTQSPSPLSASVGDRVTITCQASEDINKFLNWYHQTPGKA PKLLIYDASTLQTGVPSRFSGSGSGTDFTLTINSLQPEDIGTYYCQQYE SLPLTFGGGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGA VHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQP FMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLY NELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEA YSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
139112- nt Full CAR	126	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCC ACGCCGCTCGGCCCCAAGTGCAACTCGTGGAATCTGGTGGAGGACTCGT GCAACCCGGTGGAAGCCTTAGGCTGTCGTGCGCCGTCAGCGGGTTTGCT CTGAGCAACCATGGAATGTCCTGGGTCCGCCGGGCACCGGGAAAAGGGC TGGAATGGGTGTCCGGCATCGTGTACAGCGGGTCAACCTATTACGCCGC GTCCGTGAAGGGCAGATTCACTATCTCAAGAGACAACAGCCGGAACACC CTGTACTTGCAAATGAATTCCCTGCGCCCCGAGGACACCGCCATCTACT ACTGCTCCGCCCACGGAGGAGAGTCGGACGTGTGGGGCCAGGGAACGAC TGTGACTGTGTCCAGCGCATCAGGAGGGGGTGGTTCGGGCGGCCGGGCC TCGGGGGGAGGAGGTTCCGACATTCGGCTGACCCAGTCCCCGTCCCCAC TGTCGGCCTCCGTCGGCGACCGCGTGACCATCACTTGTCAGGCGTCCGA GGACATTAACAAGTTCCTGAACTGGTACCACCAGACCCCTGGAAAGGCC CCCAAGCTGCTGATCTACGATGCCTCGACCCTTCAAACTGGAGTGCCTA GCCGGTTCTCCGGGTCCGGCTCCGGCACTGATTTCACTCTGACCATCAA CTCATTGCAGCCGGAAGATATCGGGACCTACTATTGCCAGCAGTACGAA TCCCTCCCGCTCACATTCGGCGGGGGAACCAAGGTCGAGATTAAGACCA CTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCA GCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCC GTGCATACCCGGGGTCTTGACTTCGCCTGCGATATCTACATTTGGGCCC CTCTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCACTCGTGATCACTCT TTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTACATCTTTAAGCAACCC TTCATGAGGCCTGTGCAGACTACTCAAGAGGAGGACGGCTGTTCATGCC GGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTGCGCGTGAAATTCAG CCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGGCAGAACCAGCTCTAC

		AACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACGTGCTGGACAAGC GGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGAAAGAATCC CCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGAAGCC TATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAGGCCACG ACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTATGACGC TCTTCACATGCAGGCCCTGCCGCCTCGG
139113		
139113- aa ScFv domain	52	EVQLVETGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVS GIVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAH GGESDVWGQGTTVTVSSASGGGGSGGRASGGGGSETTLTQSPATLSVSP GERATLSCRASQSVGSNLAWYQQKPGQGPRLLIYGASTRATGIPARFSG SGSGTEFTLTISSLQPEDFAVYYCQQYNDWLPVTFGQGTKVEIK
139113- nt ScFv domain	67	GAAGTGCAATTGGTGGAAACTGGAGGAGGACTTGTGCAACCTGGAGGAT CATTGCGGCTCTCATGCGCTGTCTCCGGCTTCGCCCTGTCAAATCACGG GATGTCGTGGGTCAGACGGGCCCCGGGAAAGGGTCTGGAATGGGTGTCG GGGATTGTGTACAGCGGCTCCACCTACTACGCCGCTTCGGTCAAGGGCC GCTTCACTATTTCACGGGACAACAGCCGCAACACCCTCTATCTGCAAAT GAACTCTCTCCGCCCGGAGGATACCGCCATCTACTACTGCTCCGCACAC GGCGGCGAATCCGACGTGTGGGGACAGGGAACCACTGTCACCGTGTCGT CCGCATCCGGTGGCGGAGGATCGGGTGGCCGGGCCTCCGGGGGCGGCGG CAGCGAGACTACCCTGACCCAGTCCCCTGCCACTCTGTCCGTGAGCCCG GGAGAGAGAGCCACCCTTAGCTGCCGGGCCAGCCAGAGCGTGGGCTCCA ACCTGGCCTGGTACCAGCAGAAGCCAGGACAGGGTCCCAGGCTGCTGAT CTACGGAGCCTCCACTCGCGCGACCGGCATCCCCGCGAGGTTCTCCGGG TCGGGTTCCGGGACCGAGTTCACCCTGACCATCTCCTCCCTCCAACCGG AGGACTTCGCGGTGTACTACTGTCAGCAGTACAACGATTGGCTGCCCGT GACATTTGGACAGGGGACGAAGGTGGAAATCAAA
139113- aa VH	82	EVQLVETGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVS GIVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAH GGESDVWGQGTTVTVSS
139113- aa VL	97	ETTLTQSPATLSVSPGERATLSCRASQSVGSNLAWYQQKPGQGPRLLIY GASTRATGIPARFSGSGSGTEFTLTISSLQPEDFAVYYCQQYNDWLPVT FGQGTKVEIK
139113- aa Full CAR	112	MALPVTALLLPLALLLHAARPEVQLVETGGGLVQPGGSLRLSCAVSGFA LSNHGMSWVRRAPGKGLEWVSGIVYSGSTYYAASVKGRFTISRDNSRNT LYLQMNSLRPEDTAIYYCSAHGGESDVWGQGTTVTVSSASGGGGSGGRA SGGGGSETTLTQSPATLSVSPGERATLSCRASQSVGSNLAWYQQKPGQG PRLLIYGASTRATGIPARFSGSGSGTEFTLTISSLQPEDFAVYYCQQYN DWLPVTFGQGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGG AVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQ PFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQL YNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAE AYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
139113- nt Full CAR	127	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCC ACGCCGCTCGGCCCGAAGTGCAATTGGTGGAAACTGGAGGAGGACTTGT GCAACCTGGAGGATCATTGCGGCTCTCATGCGCTGTCTCCGGCTTCGCC CTGTCAAATCACGGGATGTCGTGGGTCAGACGGGCCCCGGGAAAGGGTC TGGAATGGGTGTCGGGGATTGTGTACAGCGGCTCCACCTACTACGCCGC TTCGGTCAAGGGCCGCTTCACTATTTCACGGGACAACAGCCGCAACACC CTCTATCTGCAAATGAACTCTCTCCGCCCGGAGGATACCGCCATCTACT ACTGCTCCGCACACGGCGGCGAATCCGACGTGTGGGGACAGGGAACCAC TGTCACCGTGTCGTCCGCATCCGGTGGCGGAGGATCGGGTGGCCGGGCC

		TCCGGGGGCGGCGGCAGCGAGACTACCCTGACCCAGTCCCCTGCCACTC TGTCCGTGAGCCCGGGAGAGAGAGCCACCCTTAGCTGCCGGGCCAGCCA GAGCGTGGGCTCCAACCTGGCCTGGTACCAGCAGAAGCCAGGACAGGGT CCCAGGCTGCTGATCTACGGAGCCTCCACTCGCGCGACCGGCATCCCCG CGAGGTTCTCCGGGTCGGGTTCCGGGACCGAGTTCACCCTGACCATCTC CTCCCTCCAACCGGAGGACTTCGCGGTGTACTACTGTCAGCAGTACAAC GATTGGCTGCCCGTGACATTTGGACAGGGGACGAAGGTGGAAATCAAAA CCACTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTC CCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGG GCCGTGCATACCCGGGGTCTTGACTTCGCCTGCGATATCTACATTTGGG CCCCTCTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCACTCGTGATCAC TCTTTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTACATCTTTAAGCAA CCCTTCATGAGGCCTGTGCAGACTACTCAAGAGGAGGACGGCTGTTCAT GCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTGCGCGTGAAATT CAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGGCAGAACCAGCTC TACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACGTGCTGGACA AGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGAAAGAA TCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGAA GCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAGGCC ACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTATGA CGCTCTTCACATGCAGGCCCTGCCGCCTCGG
139114		
139114- aa ScFv domain	53	EVQLVESGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVS GIVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAH GGESDVWGQGTTVTVSSASGGGGSGGRASGGGGSEIVLTQSPGTLSLSP GERATLSCRASQSIGSSSLAWYQQKPGQAPRLLMYGASSRASGIPDRFS GSGSGTDFTLTISRLEPEDFAVYYCQQYAGSPPFTFGQGTKVEIK
139114- nt ScFv domain	68	GAAGTGCAATTGGTGGAATCTGGTGGAGGACTTGTGCAACCTGGAGGAT CACTGAGACTGTCATGCGCGGTGTCCGGTTTTGCCCTGAGCAATCATGG GATGTCGTGGGTCCGGCGCGCCCCCGGAAAGGGTCTGGAATGGGTGTCG GGTATCGTCTACTCCGGGAGCACTTACTACGCCGCGAGCGTGAAGGGCC GCTTCACCATTTCCCGCGATAACTCCCGCAACACCCTGTACTTGCAAAT GAACTCGCTCCGGCCTGAGGACACTGCCATCTACTACTGCTCCGCACAC GGAGGAGAATCCGACGTGTGGGGCCAGGGAACTACCGTGACCGTCAGCA GCGCCTCCGGCGGCGGGGGCTCAGGCGGACGGGCTAGCGGCGGCGGTGG CTCCGAGATCGTGCTGACCCAGTCGCCTGGCACTCTCTCGCTGAGCCCC GGGGAAAGGGCAACCCTGTCCTGTCGGGCCAGCCAGTCCATTGGATCAT CCTCCCTCGCCTGGTATCAGCAGAAACCGGGACAGGCTCCGCGGCTGCT TATGTATGGGGCCAGCTCAAGAGCCTCCGGCATTCCCGACCGGTTCTCC GGGTCCGGTTCCGGCACCGATTTCACCCTGACTATCTCGAGGCTGGAGC CAGAGGACTTCGCCGTGTACTACTGCCAGCAGTACGCGGGGTCCCCGCC GTTCACGTTCGGACAGGGAACCAAGGTCGAGATCAAG
139114- aa VH	83	EVQLVESGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVS GIVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAH GGESDVWGQGTTVTVSS
139114- aa VL	98	EIVLTQSPGTLSLSPGERATLSCRASQSIGSSSLAWYQQKPGQAPRLLM YGASSRASGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYAGSPPF TFGQGTKVEIK
139114- aa Full CAR	113	MALPVTALLLPLALLLHAARPEVQLVESGGGLVQPGGSLRLSCAVSGFA LSNHGMSWVRRAPGKGLEWVSGIVYSGSTYYAASVKGRFTISRDNSRNT LYLQMNSLRPEDTAIYYCSAHGGESDVWGQGTTVTVSSASGGGGSGGRA SGGGGSEIVLTQSPGTLSLSPGERATLSCRASQSIGSSSLAWYQQKPGQ

		APRLLMYGASSRASGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQY AGSPPFTFGQGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAG GAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFK QPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQ LYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMA EAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
139114- nt Full CAR	128	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCC ACGCCGCTCGGCCCGAAGTGCAATTGGTGGAATCTGGTGGAGGACTTGT GCAACCTGGAGGATCACTGAGACTGTCATGCGCGGTGTCCGGTTTTGCC CTGAGCAATCATGGGATGTCGTGGGTCCGGCGCGCCCCCGGAAAGGGTC TGGAATGGGTGTCGGGTATCGTCTACTCCGGGAGCACTTACTACGCCGC GAGCGTGAAGGGCCGCTTCACCATTTCCCGCGATAACTCCCGCAACACC CTGTACTTGCAAATGAACTCGCTCCGGCCTGAGGACACTGCCATCTACT ACTGCTCCGCACACGGAGGAGAATCCGACGTGTGGGGCCAGGGAACTAC CGTGACCGTCAGCAGCGCCTCCGGCGGCGGGGGCTCAGGCGGACGGGCT AGCGGCGGCGGTGGCTCCGAGATCGTGCTGACCCAGTCGCCTGGCACTC TCTCGCTGAGCCCCGGGGAAAGGGCAACCCTGTCCTGTCGGGCCAGCCA GTCCATTGGATCATCCTCCCTCGCCTGGTATCAGCAGAAACCGGGACAG GCTCCGCGGCTGCTTATGTATGGGGCCAGCTCAAGAGCCTCCGGCATTC CCGACCGGTTCTCCGGGTCCGGTTCCGGCACCGATTTCACCCTGACTAT CTCGAGGCTGGAGCCAGAGGACTTCGCCGTGTACTACTGCCAGCAGTAC GCGGGGTCCCCGCCGTTCACGTTCGGACAGGGAACCAAGGTCGAGATCA AGACCACTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGC CTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGT GGGGCCGTGCATACCCGGGGTCTTGACTTCGCCTGCGATATCTACATTT GGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCACTCGTGAT CACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTACATCTTTAAG CAACCCTTCATGAGGCCTGTGCAGACTACTCAAGAGGAGGACGGCTGTT CATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTGCGCGTGAA ATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGGCAGAACCAG CTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACGTGCTGG ACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGAAA GAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCA GAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAG GCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTA TGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
149362		
149362-aa ScFv domain	129	QVQLQESGPGLVKPSETLSLTCTVSGGSISSSYYYWGWIRQPPGKGLEW IGSIYYSGSAYYNPSLKSRVTISVDTSKNQFSLRLSSVTAADTAVYYCA RHWQEWPDAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSETTLTQSPAFM SATPGDKVIISCKASQDIDDAMNWYQQKPGEAPLFIIQSATSPVPGIPP RFSGSGFGTDFSLTINNIESEDAAYYFCLQHDNFPLTFGQGTKLEIK
149362-nt ScFv domain	150	CAAGTGCAGCTTCAGGAAAGCGGACCGGGCCTGGTCAAGCCATCCGAAA CTCTCTCCCTGACTTGCACTGTGTCTGGCGGTTCCATCTCATCGTCGTA CTACTACTGGGGCTGGATTAGGCAGCCGCCCGGAAAGGGACTGGAGTGG ATCGGAAGCATCTACTATTCCGGCTCGGCGTACTACAACCCTAGCCTCA AGTCGAGAGTGACCATCTCCGTGGATACCTCCAAGAACCAGTTTTCCCT GCGCCTGAGCTCCGTGACCGCCGCTGACACCGCCGTGTACTACTGTGCT CGGCATTGGCAGGAATGGCCCGATGCCTTCGACATTTGGGGCCAGGGCA CTATGGTCACTGTGTCATCCGGGGGTGGAGGCAGCGGGGGAGGAGGGTC CGGGGGGGGAGGTTCAGAGACAACCTTGACCCAGTCACCCGCATTCATG TCCGCCACTCCGGGAGACAAGGTCATCATCTCGTGCAAAGCGTCCCAGG

		ATATCGACGATGCCATGAATTGGTACCAGCAGAAGCCTGGCGAAGCGCC GCTGTTCATTATCCAATCCGCAACCTCGCCCGTGCCTGGAATCCCACCG CGGTTCAGCGGCAGCGGTTTCGGAACCGACTTTTCCCTGACCATTAACA ACATTGAGTCCGAGGACGCCGCCTACTACTTCTGCCTGCAACACGACAA CTTCCCTCTCACGTTCGGCCAGGGAACCAAGCTGGAAATCAAG
149362-aa VH	171	QVQLQESGPGLVKPSETLSLTCTVSGGSISSSYYYWGWIRQPPGKGLEW IGSIYYSGSAYYNPSLKSRVTISVDTSKNQFSLRLSSVTAADTAVYYCA RHWQEWPDAFDIWGQGTMVTVSS
149362-aa VL	192	ETTLTQSPAFMSATPGDKVIISCKASQDIDDAMNWYQQKPGEAPLFIIQ SATSPVPGIPPRFSGSGFGTDFSLTINNIESEDAAYYFCLQHDNFPLTF GQGTKLEIK
149362-aa Full CAR	213	MALPVTALLLPLALLLHAARPQVQLQESGPGLVKPSETLSLTCTVSGGS ISSSYYYWGWIRQPPGKGLEWIGSIYYSGSAYYNPSLKSRVTISVDTSK NQFSLRLSSVTAADTAVYYCARHWQEWPDAFDIWGQGTMVTVSSGGGGS GGGGSGGGGSETTLTQSPAFMSATPGDKVIISCKASQDIDDAMNWYQQK PGEAPLFIIQSATSPVPGIPPRFSGSGFGTDFSLTINNIESEDAAYYFC LQHDNFPLTFGQGTKLEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPA AGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYI FKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQ NQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDK MAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
149362-nt Full CAR	234	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCC ACGCCGCTCGGCCCCAAGTGCAGCTTCAGGAAAGCGGACCGGGCCTGGT CAAGCCATCCGAAACTCTCTCCCTGACTTGCACTGTGTCTGGCGGTTCC ATCTCATCGTCGTACTACTACTGGGGCTGGATTAGGCAGCCGCCCGGAA AGGGACTGGAGTGGATCGGAAGCATCTACTATTCCGGCTCGGCGTACTA CAACCCTAGCCTCAAGTCGAGAGTGACCATCTCCGTGGATACCTCCAAG AACCAGTTTTCCCTGCGCCTGAGCTCCGTGACCGCCGCTGACACCGCCG TGTACTACTGTGCTCGGCATTGGCAGGAATGGCCCGATGCCTTCGACAT TTGGGGCCAGGGCACTATGGTCACTGTGTCATCCGGGGGTGGAGGCAGC GGGGGAGGAGGGTCCGGGGGGGGAGGTTCAGAGACAACCTTGACCCAGT CACCCGCATTCATGTCCGCCACTCCGGGAGACAAGGTCATCATCTCGTG CAAAGCGTCCCAGGATATCGACGATGCCATGAATTGGTACCAGCAGAAG CCTGGCGAAGCGCCGCTGTTCATTATCCAATCCGCAACCTCGCCCGTGC CTGGAATCCCACCGCGGTTCAGCGGCAGCGGTTTCGGAACCGACTTTTC CCTGACCATTAACAACATTGAGTCCGAGGACGCCGCCTACTACTTCTGC CTGCAACACGACAACTTCCCTCTCACGTTCGGCCAGGGAACCAAGCTGG AAATCAAGACCACTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTAC CATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCA GCTGGTGGGGCCGTGCATACCCGGGGTCTTGACTTCGCCTGCGATATCT ACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCACT CGTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTACATC TTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAGAGGAGGACG GCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTGCG CGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGGCAG AACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACG TGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCG CAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAG ATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAG GCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGA CACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
149363		

149363-aa ScFv domain	130	VNLRESGPALVKPTQTLTLTCTFSGFSLRTSGMCVSWIRQPPGKALEWL ARIDWDEDKFYSTSLKTRLTISKDTSDNQVVLRMTNMDPADTATYYCAR SGAGGTSATAFDIWGPGTMVTVSSGGGGSGGGGSGGGGSDIQMTQSPSS LSASVGDRVTITCRASQDIYNNLAWFQLKPGSAPRSLMYAANKSQSGVP SRFSGSASGTDFTLTISSLQPEDFATYYCQHYYRFPYSFGQGTKLEIK
149363-nt ScFv domain	151	CAAGTCAATCTGCGCGAATCCGGCCCCGCCTTGGTCAAGCCTACCCAGA CCCTCACTCTGACCTGTACTTTCTCCGGCTTCTCCCTGCGGACTTCCGG GATGTGCGTGTCCTGGATCAGACAGCCTCCGGGAAAGGCCCTGGAGTGG CTCGCTCGCATTGACTGGGATGAGGACAAGTTCTACTCCACCTCACTCA AGACCAGGCTGACCATCAGCAAAGATACCTCTGACAACCAAGTGGTGCT CCGCATGACCAACATGGACCCAGCCGACACTGCCACTTACTACTGCGCG AGGAGCGGAGCGGGCGGAACCTCCGCCACCGCCTTCGATATTTGGGGCC CGGGTACCATGGTCACCGTGTCAAGCGGAGGAGGGGGTCCGGGGGCGG CGGTTCCGGGGGAGGCGGATCGGACATTCAGATGACTCAGTCACCATCG TCCCTGAGCGCTAGCGTGGGCGACAGAGTGACAATCACTTGCCGGGCAT CCCAGGACATCTATAACAACCTTGCGTGGTTCCAGCTGAAGCCTGGTTC CGCACCGCGGTCACTTATGTACGCCGCCAACAAGAGCCAGTCGGGAGTG CCGTCCCGGTTTTCCGGTTCGGCCTCGGGAACTGACTTCACCCTGACGA TCTCCAGCCTGCAACCCGAGGATTTCGCCACCTACTACTGCCAGCACTA CTACCGCTTTCCCTACTCGTTCGGACAGGGAACCAAGCTGGAAATCAAG
149363-aa VH	172	QVNLRESGPALVKPTQTLTLTCTFSGFSLRTSGMCVSWIRQPPGKALEW LARIDWDEDKFYSTSLKTRLTISKDTSDNQVVLRMTNMDPADTATYYCA RSGAGGTSATAFDIWGPGTMVTVSS
149363-aa VL	193	DIQMTQSPSSLSASVGDRVTITCRASQDIYNNLAWFQLKPGSAPRSLMY AANKSQSGVPSRFSGSASGTDFTLTISSLQPEDFATYYCQHYYRFPYSF GQGTKLEIK
149363-aa Full CAR	214	MALPVTALLLPLALLLHAARPQVNLRESGPALVKPTQTLTLTCTFSGFS LRTSGMCVSWIRQPPGKALEWLARIDWDEDKFYSTSLKTRLTISKDTSD NQVVLRMTNMDPADTATYYCARSGAGGTSATAFDIWGPGTMVTVSSGGG GSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDIYNNLAWFQ LKPGSAPRSLMYAANKSQSGVPSRFSGSASGTDFTLTISSLQPEDFATY YCQHYYRFPYSFGQGTKLEIKTTTPAPRPPTPAPTIASQPLSLRPEACR PAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLL YIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQ GQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQK DKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
149363-nt Full CAR	235	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCC ACGCCGCTCGGCCCCAAGTCAATCTGCGCGAATCCGGCCCCGCCTTGGT CAAGCCTACCCAGACCCTCACTCTGACCTGTACTTTCTCCGGCTTCTCC CTGCGGACTTCCGGGATGTGCGTGTCCTGGATCAGACAGCCTCCGGGAA AGGCCCTGGAGTGGCTCGCTCGCATTGACTGGGATGAGGACAAGTTCTA CTCCACCTCACTCAAGACCAGGCTGACCATCAGCAAAGATACCTCTGAC AACCAAGTGGTGCTCCGCATGACCAACATGGACCCAGCCGACACTGCCA CTTACTACTGCGCGAGGAGCGGAGCGGGCGGAACCTCCGCCACCGCCTT CGATATTTGGGGCCCGGGTACCATGGTCACCGTGTCAAGCGGAGGAGGG GGGTCCGGGGGCGGCGGTTCCGGGGGAGGCGGATCGGACATTCAGATGA CTCAGTCACCATCGTCCCTGAGCGCTAGCGTGGGCGACAGAGTGACAAT CACTTGCCGGGCATCCCAGGACATCTATAACAACCTTGCGTGGTTCCAG CTGAAGCCTGGTTCCGCACCGCGGTCACTTATGTACGCCGCCAACAAGA GCCAGTCGGGAGTGCCGTCCCGGTTTTCCGGTTCGGCCTCGGGAACTGA CTTCACCCTGACGATCTCCAGCCTGCAACCCGAGGATTTCGCCACCTAC TACTGCCAGCACTACTACCGCTTTCCCTACTCGTTCGGACAGGGAACCA

		AGCTGGAAATCAAGACCACTACCCCAGCACCGAGGCCACCCACCCCGGC TCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGA CCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTGACTTCGCCTGCG ATATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGCTGCT TTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTGCTG TACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAGAGG AGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGA ACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAG GGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGT ACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAA GCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAG GATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCA GAAGAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCAC CAAGGACACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
149364		
149364-aa ScFv domain	131	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVS SISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAK TIAAVYAFDIWGQGTTVTVSSGGGGSGGGGSGGGGSEIVLTQSPLSLPV TPEEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRASG VPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPYTFGQGTKLEI K
149364-nt ScFv domain	152	GAAGTGCAGCTTGTCGAATCCGGGGGGGGACTGGTCAAGCCGGGCGGAT CACTGAGACTGTCCTGCGCCGCGAGCGGCTTCACGTTCTCCTCCTACTC CATGAACTGGGTCCGCCAAGCCCCCGGGAAGGGACTGGAATGGGTGTCC TCTATCTCCTCGTCGTCGTCCTACATCTACTACGCCGACTCCGTGAAGG GAAGATTCACCATTTCCCGCGACAACGCAAAGAACTCACTGTACTTGCA AATGAACTCACTCCGGGCCGAAGATACTGCTGTGTACTATTGCGCCAAG ACTATTGCCGCCGTCTACGCTTTCGACATCTGGGGCCAGGGAACCACCG TGACTGTGTCGTCCGGTGGTGGTGGCTCGGGCGGAGGAGGAAGCGGCGG CGGGGGGTCCGAGATTGTGCTGACCCAGTCGCCACTGAGCCTCCCTGTG ACCCCCGAGGAACCCGCCAGCATCAGCTGCCGGTCCAGCCAGTCCCTGC TCCACTCCAACGGATACAATTACCTCGATTGGTACCTTCAGAAGCCTGG ACAAAGCCCGCAGCTGCTCATCTACTTGGGATCAAACCGCGCGTCAGGA GTGCCTGACCGGTTCTCCGGCTCGGGCAGCGGTACCGATTTCACCCTGA AAATCTCCAGGGTGGAGGCAGAGGACGTGGGAGTGTATTACTGTATGCA GGCGCTGCAGACTCCGTACACATTTGGGCAGGGCACCAAGCTGGAGATC AAG
149364-aa VH	173	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVS SISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAK TIAAVYAFDIWGQGTTVTVSS
149364-aa VL	194	EIVLTQSPLSLPVTPEEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSP QLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQ TPYTFGQGTKLEIK
149364-aa Full CAR	215	MALPVTALLLPLALLLHAARPEVQLVESGGGLVKPGGSLRLSCAASGFT FSSYSMNWVRQAPGKGLEWVSSISSSSSYIYYADSVKGRFTISRDNAKN SLYLQMNSLRAEDTAVYYCAKTIAAVYAFDIWGQGTTVTVSSGGGGSGG GGSGGGGSEIVLTQSPLSLPVTPEEPASISCRSSQSLLHSNGYNYLDWY LQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGV YYCMQALQTPYTFGQGTKLEIKTTTPAPRPPTPAPTIASQPLSLRPEAC RPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKL LYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYK

		QGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQ KDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
149364-nt Full CAR	236	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCC ACGCCGCTCGGCCCGAAGTGCAGCTTGTCGAATCCGGGGGGGGACTGGT CAAGCCGGGCGGATCACTGAGACTGTCCTGCGCCGCGAGCGGCTTCACG TTCTCCTCCTACTCCATGAACTGGGTCCGCCAAGCCCCCGGGAAGGGAC TGGAATGGGTGTCCTCTATCTCCTCGTCGTCGTCCTACATCTACTACGC CGACTCCGTGAAGGGAAGATTCACCATTTCCCGCGACAACGCAAAGAAC TCACTGTACTTGCAAATGAACTCACTCCGGGCCGAAGATACTGCTGTGT ACTATTGCGCCAAGACTATTGCCGCCGTCTACGCTTTCGACATCTGGGG CCAGGGAACCACCGTGACTGTGTCGTCCGGTGGTGGTGGCTCGGGCGGA GGAGGAAGCGGCGGCGGGGGGTCCGAGATTGTGCTGACCCAGTCGCCAC TGAGCCTCCCTGTGACCCCCGAGGAACCCGCCAGCATCAGCTGCCGGTC CAGCCAGTCCCTGCTCCACTCCAACGGATACAATTACCTCGATTGGTAC CTTCAGAAGCCTGGACAAAGCCCGCAGCTGCTCATCTACTTGGGATCAA ACCGCGCGTCAGGAGTGCCTGACCGGTTCTCCGGCTCGGGCAGCGGTAC CGATTTCACCCTGAAAATCTCCAGGGTGGAGGCAGAGGACGTGGGAGTG TATTACTGTATGCAGGCGCTGCAGACTCCGTACACATTTGGGCAGGGCA CCAAGCTGGAGATCAAGACCACTACCCCAGCACCGAGGCCACCCACCCC GGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGT AGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTGACTTCGCCT GCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGCT GCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTG CTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAG AGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTG CGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAG CAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGG AGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGG GAAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAA AAGGATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAAC GCAGAAGAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGC CACCAAGGACACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
149365		
149365-aa ScFv domain	132	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLEWVS YISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR DLRGAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSSYVLTQSPSVSAAPG YTATISCGGNNIGTKSVHWYQQKPGQAPLLVIRDDSVRPSKIPGRFSGS NSGNMATLTISGVQAGDEADFYCQVWDSDSEHVVFGGGTKLTVL
149365-nt ScFv domain	153	GAAGTCCAGCTCGTGGAGTCCGGCGGAGGCCTTGTGAAGCCTGGAGGTT CGCTGAGACTGTCCTGCGCCGCCTCCGGCTTCACCTTCTCCGACTACTA CATGTCCTGGATCAGACAGGCCCCGGGAAAGGGCCTGGAATGGGTGTCC TACATCTCGTCATCGGGCAGCACTATCTACTACGCGGACTCAGTGAAGG GGCGGTTCACCATTTCCCGGGATAACGCGAAGAACTCGCTGTATCTGCA AATGAACTCACTGAGGGCCGAGGACACCGCCGTGTACTACTGCGCCCGC GATCTCCGCGGGGCATTTGACATCTGGGGACAGGGAACCATGGTCACAG TGTCCAGCGGAGGGGGAGGATCGGGTGGCGGAGGTTCCGGGGGTGGAGG CTCCTCCTACGTGCTGACTCAGAGCCCAAGCGTCAGCGCTGCGCCCGGT TACACGGCAACCATCTCCTGTGGCGGAAACAACATTGGGACCAAGTCTG TGCACTGGTATCAGCAGAAGCCGGGCCAAGCTCCCCTGTTGGTGATCCG CGATGACTCCGTGCGGCCTAGCAAAATTCCGGGACGGTTCTCCGGCTCC AACAGCGGCAATATGGCCACTCTCACCATCTCGGGAGTGCAGGCCGGAG

		ATGAAGCCGACTTCTACTGCCAAGTCTGGGACTCAGACTCCGAGCATGT GGTGTTCGGGGGCGGAACCAAGCTGACTGTGCTC
149365-aa VH	174	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLEWVS YISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR DLRGAFDIWGQGTMVTVSS
149365-aa VL	195	SYVLTQSPSVSAAPGYTATISCGGNNIGTKSVHWYQQKPGQAPLLVIRD DSVRPSKIPGRFSGSNSGNMATLTISGVQAGDEADFYCQVWDSDSEHVV FGGGTKLTVL
149365-aa Full CAR	216	MALPVTALLLPLALLLHAARPEVQLVESGGGLVKPGGSLRLSCAASGFT FSDYYMSWIRQAPGKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKN SLYLQMNSLRAEDTAVYYCARDLRGAFDIWGQGTMVTVSSGGGGSGGGG SGGGGSSYVLTQSPSVSAAPGYTATISCGGNNIGTKSVHWYQQKPGQAP LLVIRDDSVRPSKIPGRFSGSNSGNMATLTISGVQAGDEADFYCQVWDS DSEHVVFGGGTKLTVLTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGG AVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQ PFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQL YNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAE AYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
149365-nt Full CAR	237	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCC ACGCCGCTCGGCCCGAAGTCCAGCTCGTGGAGTCCGGCGGAGGCCTTGT GAAGCCTGGAGGTTCGCTGAGACTGTCCTGCGCCGCCTCCGGCTTCACC TTCTCCGACTACTACATGTCCTGGATCAGACAGGCCCCGGGAAAGGGCC TGGAATGGGTGTCCTACATCTCGTCATCGGGCAGCACTATCTACTACGC GGACTCAGTGAAGGGGCGGTTCACCATTTCCCGGGATAACGCGAAGAAC TCGCTGTATCTGCAAATGAACTCACTGAGGGCCGAGGACACCGCCGTGT ACTACTGCGCCCGCGATCTCCGCGGGGCATTTGACATCTGGGGACAGGG AACCATGGTCACAGTGTCCAGCGGAGGGGGAGGATCGGGTGGCGGAGGT TCCGGGGGTGGAGGCTCCTCCTACGTGCTGACTCAGAGCCCAAGCGTCA GCGCTGCGCCCGGTTACACGGCAACCATCTCCTGTGGCGGAAACAACAT TGGGACCAAGTCTGTGCACTGGTATCAGCAGAAGCCGGGCCAAGCTCCC CTGTTGGTGATCCGCGATGACTCCGTGCGGCCTAGCAAAATTCCGGGAC GGTTCTCCGGCTCCAACAGCGGCAATATGGCCACTCTCACCATCTCGGG AGTGCAGGCCGGAGATGAAGCCGACTTCTACTGCCAAGTCTGGGACTCA GACTCCGAGCATGTGGTGTTCGGGGGCGGAACCAAGCTGACTGTGCTCA CCACTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTC CCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGG GCCGTGCATACCCGGGGTCTTGACTTCGCCTGCGATATCTACATTTGGG CCCCTCTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCACTCGTGATCAC TCTTTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTACATCTTTAAGCAA CCCTTCATGAGGCCTGTGCAGACTACTCAAGAGGAGGACGGCTGTTCAT GCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTGCGCGTGAAATT CAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGGCAGAACCAGCTC TACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACGTGCTGGACA AGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGAAAGAA TCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGAA GCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAGGCC ACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTATGA CGCTCTTCACATGCAGGCCCTGCCGCCTCGG
149366		
149366-aa ScFv domain	133	QVQLVQSGAEVKKPGASVKVSCKPSGYTVTSHYIHWVRRAPGQGLEWMG MINPSGGVTAYSQTLQGRVTMTSDTSSSTVYMELSSLRSEDTAMYYCAR EGSGSGWYFDFWGRGTLVTVSSGGGGSGGGGSGGGGSSYVLTQPPSVSV

		SPGQTASITCSGDGLSKKYVSWYQQKAGQSPVVLISRDKERPSGIPDRF SGSNSADTATLTISGTQAMDEADYYCQAWDDTTVVFGGGTKLTVL
149366-nt ScFv domain	154	CAAGTGCAGCTGGTGCAGAGCGGGGCCGAAGTCAAGAAGCCGGGAGCCT CCGTGAAAGTGTCCTGCAAGCCTTCGGGATACACCGTGACCTCCCACTA CATTCATTGGGTCCGCCGCGCCCCCGGCCAAGGACTCGAGTGGATGGGC ATGATCAACCCTAGCGGCGGAGTGACCGCGTACAGCCAGACGCTGCAGG GACGCGTGACTATGACCTCGGATACCTCCTCCTCCACCGTCTATATGGA ACTGTCCAGCCTGCGGTCCGAGGATACCGCCATGTACTACTGCGCCCGG GAAGGATCAGGCTCCGGGTGGTATTTCGACTTCTGGGGAAGAGGCACCC TCGTGACTGTGTCATCTGGGGGAGGGGGTTCCGGTGGTGGCGGATCGGG AGGAGGCGGTTCATCCTACGTGCTGACCCAGCCACCCTCCGTGTCCGTG AGCCCCGGCCAGACTGCATCGATTACATGTAGCGGCGACGGCCTCTCCA AGAAATACGTGTCGTGGTACCAGCAGAAGGCCGGACAGAGCCCGGTGGT GCTGATCTCAAGAGATAAGGAGCGGCCTAGCGGAATCCCGGACAGGTTC TCGGGTTCCAACTCCGCGGACACTGCTACTCTGACCATCTCGGGGACCC AGGCTATGGACGAAGCCGATTACTACTGCCAAGCCTGGGACGACACTAC TGTCGTGTTTGGAGGGGGCACCAAGTTGACCGTCCTT
149366-aa VH	175	QVQLVQSGAEVKKPGASVKVSCKPSGYTVTSHYIHWVRRAPGQGLEWMG MINPSGGVTAYSQTLQGRVTMTSDTSSSTVYMELSSLRSEDTAMYYCAR EGSGSGWYFDFWGRGTLVTVSS
149366-aa VL	196	SYVLTQPPSVSVSPGQTASITCSGDGLSKKYVSWYQQKAGQSPVVLISR DKERPSGIPDRFSGSNSADTATLTISGTQAMDEADYYCQAWDDTTVVFG GGTKLTVL
149366-aa Full CAR	217	MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKPSGYT VTSHYIHWVRRAPGQGLEWMGMINPSGGVTAYSQTLQGRVTMTSDTSSS TVYMELSSLRSEDTAMYYCAREGSGSGWYFDFWGRGTLVTVSSGGGGSG GGGSGGGGSSYVLTQPPSVSVSPGQTASITCSGDGLSKKYVSWYQQKAG QSPVVLISRDKERPSGIPDRFSGSNSADTATLTISGTQAMDEADYYCQA WDDTTVVFGGGTKLTVLTTTPAPRPPTPAPTIASQPLSLRPEACRPAAG GAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFK QPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQ LYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMA EAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
149366-nt Full CAR	238	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCC ACGCCGCTCGGCCCCAAGTGCAGCTGGTGCAGAGCGGGGCCGAAGTCAA GAAGCCGGGAGCCTCCGTGAAAGTGTCCTGCAAGCCTTCGGGATACACC GTGACCTCCCACTACATTCATTGGGTCCGCCGCGCCCCCGGCCAAGGAC TCGAGTGGATGGGCATGATCAACCCTAGCGGCGGAGTGACCGCGTACAG CCAGACGCTGCAGGGACGCGTGACTATGACCTCGGATACCTCCTCCTCC ACCGTCTATATGGAACTGTCCAGCCTGCGGTCCGAGGATACCGCCATGT ACTACTGCGCCCGGGAAGGATCAGGCTCCGGGTGGTATTTCGACTTCTG GGGAAGAGGCACCCTCGTGACTGTGTCATCTGGGGGAGGGGGTTCCGGT GGTGGCGGATCGGGAGGAGGCGGTTCATCCTACGTGCTGACCCAGCCAC CCTCCGTGTCCGTGAGCCCCGGCCAGACTGCATCGATTACATGTAGCGG CGACGGCCTCTCCAAGAAATACGTGTCGTGGTACCAGCAGAAGGCCGGA CAGAGCCCGGTGGTGCTGATCTCAAGAGATAAGGAGCGGCCTAGCGGAA TCCCGGACAGGTTCTCGGGTTCCAACTCCGCGGACACTGCTACTCTGAC CATCTCGGGGACCCAGGCTATGGACGAAGCCGATTACTACTGCCAAGCC TGGGACGACACTACTGTCGTGTTTGGAGGGGGCACCAAGTTGACCGTCC TTACCACTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGC CTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGT GGGGCCGTGCATACCCGGGGTCTTGACTTCGCCTGCGATATCTACATTT

		GGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCACTCGTGAT CACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTACATCTTTAAG CAACCCTTCATGAGGCCTGTGCAGACTACTCAAGAGGAGGACGGCTGTT CATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTGCGCGTGAA ATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGGCAGAACCAG CTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACGTGCTGG ACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGAAA GAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCA GAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAG GCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTA TGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
149367		
149367-aa ScFv domain	134	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQHPGKGLEW IGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCA RAGIAARLRGAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSDIVMTQSPS SVSASVGDRVIITCRASQGIRNWLAWYQQKPGKAPNLLIYAASNLQSGV PSRFSGSGSGADFTLTISSLQPEDVATYYCQKYNSAPFTFGPGTKVDIK
149367-nt ScFv domain	155	CAAGTGCAGCTTCAGGAGAGCGGCCCGGGACTCGTGAAGCCGTCCCAGA CCCTGTCCCTGACTTGCACCGTGTCGGGAGGAAGCATCTCGAGCGGAGG CTACTATTGGTCGTGGATTCGGCAGCACCCTGGAAAGGGCCTGGAATGG ATCGGCTACATCTACTACTCCGGCTCGACCTACTACAACCCATCGCTGA AGTCCAGAGTGACAATCTCAGTGGACACGTCCAAGAATCAGTTCAGCCT GAAGCTCTCTTCCGTGACTGCGGCCGACACCGCCGTGTACTACTGCGCA CGCGCTGGAATTGCCGCCCGGCTGAGGGGTGCCTTCGACATTTGGGGAC AGGGCACCATGGTCACCGTGTCCTCCGGCGGCGGAGGTTCCGGGGGTGG AGGCTCAGGAGGAGGGGGGTCCGACATCGTCATGACTCAGTCGCCCTCA AGCGTCAGCGCGTCCGTCGGGGACAGAGTGATCATCACCTGTCGGGCGT CCCAGGGAATTCGCAACTGGCTGGCCTGGTATCAGCAGAAGCCCGGAAA GGCCCCCAACCTGTTGATCTACGCCGCCTCAAACCTCCAATCCGGGGTG CCGAGCCGCTTCAGCGGCTCCGGTTCGGGTGCCGATTTCACTCTGACCA TCTCCTCCCTGCAACCTGAAGATGTGGCTACCTACTACTGCCAAAAGTA CAACTCCGCACCTTTTACTTTCGGACCGGGGACCAAAGTGGACATTAAG
149367-aa VH	176	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQHPGKGLEW IGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCA RAGIAARLRGAFDIWGQGTMVTVSS
149367-aa VL	197	DIVMTQSPSSVSASVGDRVIITCRASQGIRNWLAWYQQKPGKAPNLLIY AASNLQSGVPSRFSGSGSGADFTLTISSLQPEDVATYYCQKYNSAPFTF GPGTKVDIK
149367-aa Full CAR	218	MALPVTALLLPLALLLHAARPQVQLQESGPGLVKPSQTLSLTCTVSGGS ISSGGYYWSWIRQHPGKGLEWIGYIYYSGSTYYNPSLKSRVTISVDTSK NQFSLKLSSVTAADTAVYYCARAGIAARLRGAFDIWGQGTMVTVSSGGG GSGGGGSGGGGSDIVMTQSPSSVSASVGDRVIITCRASQGIRNWLAWYQ QKPGKAPNLLIYAASNLQSGVPSRFSGSGSGADFTLTISSLQPEDVATY YCQKYNSAPFTFGPGTKVDIKTTTPAPRPPTPAPTIASQPLSLRPEACR PAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLL YIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQ GQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQK DKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
149367-nt Full CAR	239	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCC ACGCCGCTCGGCCCCAAGTGCAGCTTCAGGAGAGCGGCCCGGGACTCGT GAAGCCGTCCCAGACCCTGTCCCTGACTTGCACCGTGTCGGGAGGAAGC ATCTCGAGCGGAGGCTACTATTGGTCGTGGATTCGGCAGCACCCTGGAA

		AGGGCCTGGAATGGATCGGCTACATCTACTACTCCGGCTCGACCTACTA CAACCCATCGCTGAAGTCCAGAGTGACAATCTCAGTGGACACGTCCAAG AATCAGTTCAGCCTGAAGCTCTCTTCCGTGACTGCGGCCGACACCGCCG TGTACTACTGCGCACGCGCTGGAATTGCCGCCCGGCTGAGGGGTGCCTT CGACATTTGGGGACAGGGCACCATGGTCACCGTGTCCTCCGGCGGCGGA GGTTCCGGGGGTGGAGGCTCAGGAGGAGGGGGGTCCGACATCGTCATGA CTCAGTCGCCCTCAAGCGTCAGCGCGTCCGTCGGGGACAGAGTGATCAT CACCTGTCGGGCGTCCCAGGGAATTCGCAACTGGCTGGCCTGGTATCAG CAGAAGCCCGGAAAGGCCCCCAACCTGTTGATCTACGCCGCCTCAAACC TCCAATCCGGGGTGCCGAGCCGCTTCAGCGGCTCCGGTTCGGGTGCCGA TTTCACTCTGACCATCTCCTCCCTGCAACCTGAAGATGTGGCTACCTAC TACTGCCAAAAGTACAACTCCGCACCTTTTACTTTCGGACCGGGGACCA AAGTGGACATTAAGACCACTACCCCAGCACCGAGGCCACCCACCCCGGC TCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGA CCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTGACTTCGCCTGCG ATATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGCTGCT TTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTGCTG TACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAGAGG AGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGA ACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAG GGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGT ACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAA GCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAG GATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCA GAAGAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCAC CAAGGACACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
149368		
149368-aa ScFv domain	135	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCAR RGGYQLLRWDVGLLRSAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSSYV LTQPPSVSVAPGQTARITCGGNNIGSKSVHWYQQKPGQAPVLVLYGKNN RPSGVPDRFSGSRSGTTASLTITGAQAEDEADYYCSSRDSSGDHLRVFG TGTKVTVL
149368-nt ScFv domain	156	CAAGTGCAGCTGGTCCAGTCGGGCGCCGAGGTCAAGAAGCCCGGGAGCT CTGTGAAAGTGTCCTGCAAGGCCTCCGGGGGCACCTTTAGCTCCTACGC CATCTCCTGGGTCCGCCAAGCACCGGGTCAAGGCCTGGAGTGGATGGGG GGAATTATCCCTATCTTCGGCACTGCCAACTACGCCCAGAAGTTCCAGG GACGCGTGACCATTACCGCGGACGAATCCACCTCCACCGCTTATATGGA GCTGTCCAGCTTGCGCTCGGAAGATACCGCCGTGTACTACTGCGCCCGG AGGGGTGGATACCAGCTGCTGAGATGGGACGTGGGCCTCCTGCGGTCGG CGTTCGACATCTGGGGCCAGGGCACTATGGTCACTGTGTCCAGCGGAGG AGGCGGATCGGGAGGCGGCGGATCAGGGGGAGGCGGTTCCAGCTACGTG CTTACTCAACCCCCTTCGGTGTCCGTGGCCCCGGGACAGACCGCCAGAA TCACTTGCGGAGGAAACAACATTGGGTCCAAGAGCGTGCATTGGTACCA GCAGAAGCCAGGACAGGCCCCTGTGCTGGTGCTCTACGGGAAGAACAAT CGGCCCAGCGGAGTGCCGGACAGGTTCTCGGGTTCACGCTCCGGTACAA CCGCTTCACTGACTATCACCGGGGCCCAGGCAGAGGATGAAGCGGACTA CTACTGTTCCTCCCGGGATTCATCCGGCGACCACCTCCGGGTGTTCGGA ACCGGAACGAAGGTCACCGTGCTG
149368-aa VH	177	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG GIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCAR RGGYQLLRWDVGLLRSAFDIWGQGTMVTVSS

149368-aa VL	198	SYVLTQPPSVSVAPGQTARITCGGNNIGSKSVHWYQQKPGQAPVLVLYG KNNRPSGVPDRFSGSRSGTTASLTITGAQAEDEADYYCSSRDSSGDHLR VFGTGTKVTVL
149368-aa Full CAR	219	MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGSSVKVSCKASGGT FSSYAISWVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTS TAYMELSSLRSEDTAVYYCARRGGYQLLRWDVGLLRSAFDIWGQGTMVT VSSGGGGSGGGGSGGGGSSYVLTQPPSVSVAPGQTARITCGGNNIGSKS VHWYQQKPGQAPVLVLYGKNNRPSGVPDRFSGSRSGTTASLTITGAQAE DEADYYCSSRDSSGDHLRVFGTGTKVTVLTTTPAPRPPTPAPTIASQPL SLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRS ADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQE GLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALH MQALPPR
149368-nt Full CAR	240	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCC ACGCCGCTCGGCCCCAAGTGCAGCTGGTCCAGTCGGGCGCCGAGGTCAA GAAGCCCGGGAGCTCTGTGAAAGTGTCCTGCAAGGCCTCCGGGGGCACC TTTAGCTCCTACGCCATCTCCTGGGTCCGCCAAGCACCGGGTCAAGGCC TGGAGTGGATGGGGGGAATTATCCCTATCTTCGGCACTGCCAACTACGC CCAGAAGTTCCAGGGACGCGTGACCATTACCGCGGACGAATCCACCTCC ACCGCTTATATGGAGCTGTCCAGCTTGCGCTCGGAAGATACCGCCGTGT ACTACTGCGCCCGGAGGGGTGGATACCAGCTGCTGAGATGGGACGTGGG CCTCCTGCGGTCGGCGTTCGACATCTGGGGCCAGGGCACTATGGTCACT GTGTCCAGCGGAGGAGGCGGATCGGGAGGCGGCGGATCAGGGGGAGGCG GTTCCAGCTACGTGCTTACTCAACCCCCTTCGGTGTCCGTGGCCCCGGG ACAGACCGCCAGAATCACTTGCGGAGGAAACAACATTGGGTCCAAGAGC GTGCATTGGTACCAGCAGAAGCCAGGACAGGCCCCTGTGCTGGTGCTCT ACGGGAAGAACAATCGGCCCAGCGGAGTGCCGGACAGGTTCTCGGGTTC ACGCTCCGGTACAACCGCTTCACTGACTATCACCGGGGCCCAGGCAGAG GATGAAGCGGACTACTACTGTTCCTCCCGGGATTCATCCGGCGACCACC TCCGGGTGTTCGGAACCGGAACGAAGGTCACCGTGCTGACCACTACCCC AGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTG TCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGCATA CCCGGGGTCTTGACTTCGCCTGCGATATCTACATTTGGGCCCCTCTGGC TGGTACTTGCGGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTACTGT AAGCGCGGTCGGAAGAAGCTGCTGTACATCTTTAAGCAACCCTTCATGA GGCCTGTGCAGACTACTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCC AGAGGAGGAGGAAGGCGGCTGCGAACTGCGCGTGAAATTCAGCCGCAGC GCAGATGCTCCAGCCTACAAGCAGGGGCAGAACCAGCTCTACAACGAAC TCAATCTTGGTCGGAGAGAGGAGTACGACGTGCTGGACAAGCGGAGAGG ACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGAAAGAATCCCCAAGAG GGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGAAGCCTATAGCG AGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAGGCCACGACGGACT GTACCAGGGACTCAGCACCGCCACCAAGGACACCTATGACGCTCTTCAC ATGCAGGCCCTGCCGCCTCGG
149369		
149369-aa ScFv domain	136	EVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIRQSPSRGLEW LGRTYYRSKWYSFYAISLKSRIIINPDTSKNQFSLQLKSVTPEDTAVYY CARSSPEGLFLYWFDPWGQGTLVTVSSGGDGSGGGGSGGGGSSSELTQD PAVSVALGQTIRITCQGDSLGNYYATWYQQKPGQAPVLVIYGTNNRPSG IPDRFSASSSGNTASLTITGAQAEDEADYYCNSRDSSGHHLLFGTGTKV TVL

149369-nt ScFv domain	157	GAAGTGCAGCTCCAACAGTCAGGACCGGGGCTCGTGAAGCCATCCCAGA CCCTGTCCCTGACTTGTGCCATCTCGGGAGATAGCGTGTCATCGAACTC CGCCGCCTGGAACTGGATTCGGCAGAGCCCGTCCCGCGGACTGGAGTGG CTTGGAAGGACCTACTACCGGTCCAAGTGGTACTCTTTCTACGCGATCT CGCTGAAGTCCCGCATTATCATTAACCCTGATACCTCCAAGAATCAGTT CTCCCTCCAACTGAAATCCGTCACCCCCGAGGACACAGCAGTGTATTAC TGCGCACGGAGCAGCCCCGAAGGACTGTTCCTGTATTGGTTTGACCCCT GGGGCCAGGGGACTCTTGTGACCGTGTCGAGCGGCGGAGATGGGTCCGG TGGCGGTGGTTCGGGGGGCGGCGGATCATCATCCGAACTGACCCAGGAC CCGGCTGTGTCCGTGGCGCTGGGACAAACCATCCGCATTACGTGCCAGG GAGACTCCCTGGGCAACTACTACGCCACTTGGTACCAGCAGAAGCCGGG CCAAGCCCCTGTGTTGGTCATCTACGGGACCAACAACAGACCTTCCGGC ATCCCCGACCGGTTCAGCGCTTCGTCCTCCGGCAACACTGCCAGCCTGA CCATCACTGGAGCGCAGGCCGAAGATGAGGCCGACTACTACTGCAACAG CAGAGACTCCTCGGGTCATCACCTCTTGTTCGGAACTGGAACCAAGGTC ACCGTGCTG
149369-aa VH	178	EVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIRQSPSRGLEW LGRTYYRSKWYSFYAISLKSRIIINPDTSKNQFSLQLKSVTPEDTAVYY CARSSPEGLFLYWFDPWGQGTLVTVSS
149369-aa VL	199	SSELTQDPAVSVALGQTIRITCQGDSLGNYYATWYQQKPGQAPVLVIYG TNNRPSGIPDRFSASSSGNTASLTITGAQAEDEADYYCNSRDSSGHHLL FGTGTKVTVL
149369-aa Full CAR	220	MALPVTALLLPLALLLHAARPEVQLQQSGPGLVKPSQTLSLTCAISGDS VSSNSAAWNWIRQSPSRGLEWLGRTYYRSKWYSFYAISLKSRIIINPDT SKNQFSLQLKSVTPEDTAVYYCARSSPEGLFLYWFDPWGQGTLVTVSSG GDGSGGGGSGGGGSSSELTQDPAVSVALGQTIRITCQGDSLGNYYATWY QQKPGQAPVLVIYGTNNRPSGIPDRFSASSSGNTASLTITGAQAEDEAD YYCNSRDSSGHHLLFGTGTKVTVLTTTPAPRPPTPAPTIASQPLSLRPE ACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRK KLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPA YKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNE LQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALP PR
149369-nt Full CAR	241	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCC ACGCCGCTCGGCCCGAAGTGCAGCTCCAACAGTCAGGACCGGGGCTCGT GAAGCCATCCCAGACCCTGTCCCTGACTTGTGCCATCTCGGGAGATAGC GTGTCATCGAACTCCGCCGCCTGGAACTGGATTCGGCAGAGCCCGTCCC GCGGACTGGAGTGGCTTGGAAGGACCTACTACCGGTCCAAGTGGTACTC TTTCTACGCGATCTCGCTGAAGTCCCGCATTATCATTAACCCTGATACC TCCAAGAATCAGTTCTCCCTCCAACTGAAATCCGTCACCCCCGAGGACA CAGCAGTGTATTACTGCGCACGGAGCAGCCCCGAAGGACTGTTCCTGTA TTGGTTTGACCCCTGGGGCCAGGGGACTCTTGTGACCGTGTCGAGCGGC GGAGATGGGTCCGGTGGCGGTGGTTCGGGGGGCGGCGGATCATCATCCG AACTGACCCAGGACCCGGCTGTGTCCGTGGCGCTGGGACAAACCATCCG CATTACGTGCCAGGGAGACTCCCTGGGCAACTACTACGCCACTTGGTAC CAGCAGAAGCCGGGCCAAGCCCCTGTGTTGGTCATCTACGGGACCAACA ACAGACCTTCCGGCATCCCCGACCGGTTCAGCGCTTCGTCCTCCGGCAA CACTGCCAGCCTGACCATCACTGGAGCGCAGGCCGAAGATGAGGCCGAC TACTACTGCAACAGCAGAGACTCCTCGGGTCATCACCTCTTGTTCGGAA CTGGAACCAAGGTCACCGTGCTGACCACTACCCCAGCACCGAGGCCACC CACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAG GCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTGACT

		TCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGT CCTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAG AAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTA CTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGG CGGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCC TACAAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGA GAGAGGAGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAAT GGGCGGGAAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAG CTCCAAAAGGATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAG GGGAACGCAGAAGAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAG CACCGCCACCAAGGACACCTATGACGCTCTTCACATGCAGGCCCTGCCG CCTCGG
BCMA_EBB-C1978-A4		
BCMA_EBB-C1978-A4 - aa ScFv domain	137	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS AISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK VEGSGSLDYWGQGTLVTVSSGGGGSGGGGSGGGGSEIVMTQSPGTLSLS PGERATLSCRASQSVSSAYLAWYQQKPGQPPRLLISGASTRATGIPDRF GGSGSGTDFTLTISRLEPEDFAVYYCQHYGSSFNGSSLFTFGQGTRLEI K
BCMA_EBB-C1978-A4 - nt ScFv domain	158	GAAGTGCAGCTCGTGGAGTCAGGAGGCGGCCTGGTCCAGCCGGGAGGGT CCCTTAGACTGTCATGCGCCGCAAGCGGATTCACTTTCTCCTCCTATGC CATGAGCTGGGTCCGCCAAGCCCCCGGAAAGGGACTGGAATGGGTGTCC GCCATCTCGGGGTCTGGAGGCTCAACTTACTACGCTGACTCCGTGAAGG GACGGTTCACCATTAGCCGCGACAACTCCAAGAACACCCTCTACCTCCA AATGAACTCCCTGCGGGCCGAGGATACCGCCGTCTACTACTGCGCCAAA GTGGAAGGTTCAGGATCGCTGGACTACTGGGGACAGGGTACTCTCGTGA CCGTGTCATCGGGCGGAGGAGGTTCCGGCGGTGGCGGCTCCGGCGGCGG AGGGTCGGAGATCGTGATGACCCAGAGCCCTGGTACTCTGAGCCTTTCG CCGGGAGAAAGGGCCACCCTGTCCTGCCGCGCTTCCCAATCCGTGTCCT CCGCGTACTTGGCGTGGTACCAGCAGAAGCCGGGACAGCCCCCTCGGCT GCTGATCAGCGGGGCCAGCACCCGGGCAACCGGAATCCCAGACAGATTC GGGGGTTCCGGCAGCGGCACAGATTTCACCCTGACTATTTCGAGGTTGG AGCCCGAGGACTTTGCGGTGTATTACTGTCAGCACTACGGGTCGTCCTT TAATGGCTCCAGCCTGTTCACGTTCGGACAGGGGACCCGCCTGGAAATC AAG
BCMA_EBB-C1978-A4 - aa VH	179	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS AISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK VEGSGSLDYWGQGTLVTVSS
BCMA_EBB-C1978-A4 - aa VL	200	EIVMTQSPGTLSLSPGERATLSCRASQSVSSAYLAWYQQKPGQPPRLLI SGASTRATGIPDRFGGSGSGTDFTLTISRLEPEDFAVYYCQHYGSSFNG SSLFTFGQGTRLEIK
BCMA_EBB-C1978-A4 - aa Full CART	221	MALPVTALLLPLALLLHAARPEVQLVESGGGLVQPGGSLRLSCAASGFT FSSYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAKVEGSGSLDYWGQGTLVTVSSGGGGSGGG GSGGGGSEIVMTQSPGTLSLSPGERATLSCRASQSVSSAYLAWYQQKPG QPPRLLISGASTRATGIPDRFGGSGSGTDFTLTISRLEPEDFAVYYCQH YGSSFNGSSLFTFGQGTRLEIKTTTPAPRPPTPAPTIASQPLSLRPEAC RPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKL LYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYK

		QGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQ KDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
BCMA_EBB-C1978-A4 - nt Full CART	242	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCC ACGCCGCTCGGCCCGAAGTGCAGCTCGTGGAGTCAGGAGGCGGCCTGGT CCAGCCGGGAGGGTCCCTTAGACTGTCATGCGCCGCAAGCGGATTCACT TTCTCCTCCTATGCCATGAGCTGGGTCCGCCAAGCCCCCGGAAAGGGAC TGGAATGGGTGTCCGCCATCTCGGGGTCTGGAGGCTCAACTTACTACGC TGACTCCGTGAAGGGACGGTTCACCATTAGCCGCGACAACTCCAAGAAC ACCCTCTACCTCCAAATGAACTCCCTGCGGGCCGAGGATACCGCCGTCT ACTACTGCGCCAAAGTGGAAGGTTCAGGATCGCTGGACTACTGGGGACA GGGTACTCTCGTGACCGTGTCATCGGGCGGAGGAGGTTCCGGCGGTGGC GGCTCCGGCGGCGGAGGGTCGGAGATCGTGATGACCCAGAGCCCTGGTA CTCTGAGCCTTTCGCCGGGAGAAAGGGCCACCCTGTCCTGCCGCGCTTC CCAATCCGTGTCCTCCGCGTACTTGGCGTGGTACCAGCAGAAGCCGGGA CAGCCCCCTCGGCTGCTGATCAGCGGGGCCAGCACCCGGGCAACCGGAA TCCCAGACAGATTCGGGGGTTCCGGCAGCGGCACAGATTTCACCCTGAC TATTTCGAGGTTGGAGCCCGAGGACTTTGCGGTGTATTACTGTCAGCAC TACGGGTCGTCCTTTAATGGCTCCAGCCTGTTCACGTTCGGACAGGGGA CCCGCCTGGAAATCAAGACCACTACCCCAGCACCGAGGCCACCCACCCC GGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGT AGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTGACTTCGCCT GCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGCT GCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTG CTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAG AGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTG CGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAG CAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGG AGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGG GAAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAA AAGGATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAAC GCAGAAGAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGC CACCAAGGACACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
BCMA_EBB-C1978-G1		
BCMA_EBB-C1978-G1 - aa ScFv domain	138	EVQLVETGGGLVQPGGSLRLSCAASGITFSRYPMSWVRQAPGKGL EWVSGISDSGVSTYYADSAKGRFTISRDNSKNTLFLQMSSLRDEDT AVYYCVTRAGSEASDIWGQGTMVTVSSGGGGSGGGGSGGGGSEI VLTQSPATLSLSPGERATLSCRASQSVSNSLAWYQQKPGQAPRLLI YDASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAIYYCQQFGTSSG LTFGGGTKLEIK
BCMA_EBB-C1978-G1 - nt ScFv domain	159	GAAGTGCAACTGGTGGAAACCGGTGGCGGCCTGGTGCAGCCTGGAGGAT CATTGAGGCTGTCATGCGCGGCCAGCGGTATTACCTTCTCCCGGTACCC CATGTCCTGGGTCAGACAGGCCCCGGGGAAAGGGCTTGAATGGGTGTCC GGGATCTCGGACTCCGGTGTCAGCACTTACTACGCCGACTCCGCCAAGG GACGCTTCACCATTTCCCGGGACAACTCGAAGAACACCCTGTTCCTCCA AATGAGCTCCCTCCGGGACGAGGATACTGCAGTGTACTACTGCGTGACC CGCGCCGGGTCCGAGGCGTCTGACATTTGGGGACAGGGCACTATGGTCA CCGTGTCGTCCGGCGGAGGGGGCTCGGGAGGCGGTGGCAGCGGAGGAGG AGGGTCCGAGATCGTGCTGACCCAATCCCCGGCCACCCTCTCGCTGAGC CCTGGAGAAAGGGCAACCTTGTCCTGTCGCGCGAGCCAGTCCGTGAGCA ACTCCCTGGCCTGGTACCAGCAGAAGCCCGGACAGGCTCCGAGACTTCT GATCTACGACGCTTCGAGCCGGGCCACTGGAATCCCCGACCGCTTTTCG GGGTCCGGCTCAGGAACCGATTTCACCCTGACAATCTCACGGCTGGAGC

		CAGAGGATTTCGCCATCTATTACTGCCAGCAGTTCGGTACTTCCTCCGG CCTGACTTTCGGAGGCGGCACGAAGCTCGAAATCAAG
BCMA_EBB-C1978-G1 - aa VH	180	EVQLVETGGGLVQPGGSLRLSCAASGITFSRYPMSWVRQAPGKGLEWVS GISDSGVSTYYADSAKGRFTISRDNSKNTLFLQMSSLRDEDTAVYYCVT RAGSEASDIWGQGTMVTVSS
BCMA_EBB-C1978-G1 - aa VL	201	EIVLTQSPATLSLSPGERATLSCRASQSVSNSLAWYQQKPGQAPRLLIY DASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAIYYCQQFGTSSGLT FGGGTKLEIK
BCMA_EBB-C1978-G1 - aa Full CART	222	MALPVTALLLPLALLLHAARPEVQLVETGGGLVQPGGSLRLSCAA SGITFSRYPMSWVRQAPGKGLEWVSGISDSGVSTYYADSAKGRFTI SRDNSKNTLFLQMSSLRDEDTAVYYCVTRAGSEASDIWGQGTMV TVSSGGGGSGGGGSGGGGSEIVLTQSPATLSLSPGERATLSCRASQ SVSNSLAWYQQKPGQAPRLLIYDASSRATGIPDRFSGSGSGTDFTL TISRLEPEDFAIYYCQQFGTSSGLTFGGGTKLEIKTTTPAPRPPTPAP TIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVL LLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEE GGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRR GRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRG KGHDGLYQGLSTATKDTYDALHMQALPPR
BCMA_EBB-C1978-G1 - nt Full CART	243	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCC ACGCCGCTCGGCCCGAAGTGCAACTGGTGGAAACCGGTGGCGGCCTGGT GCAGCCTGGAGGATCATTGAGGCTGTCATGCGCGGCCAGCGGTATTACC TTCTCCCGGTACCCCATGTCCTGGGTCAGACAGGCCCCGGGGAAAGGGC TTGAATGGGTGTCCGGGATCTCGGACTCCGGTGTCAGCACTTACTACGC CGACTCCGCCAAGGGACGCTTCACCATTTCCCGGGACAACTCGAAGAAC ACCCTGTTCCTCCAAATGAGCTCCCTCCGGGACGAGGATACTGCAGTGT ACTACTGCGTGACCCGCGCCGGGTCCGAGGCGTCTGACATTTGGGGACA GGGCACTATGGTCACCGTGTCGTCCGGCGGAGGGGGCTCGGGAGGCGGT GGCAGCGGAGGAGGAGGGTCCGAGATCGTGCTGACCCAATCCCCGGCCA CCCTCTCGCTGAGCCCTGGAGAAAGGGCAACCTTGTCCTGTCGCGCGAG CCAGTCCGTGAGCAACTCCCTGGCCTGGTACCAGCAGAAGCCCGGACAG GCTCCGAGACTTCTGATCTACGACGCTTCGAGCCGGGCCACTGGAATCC CCGACCGCTTTTCGGGGTCCGGCTCAGGAACCGATTTCACCCTGACAAT CTCACGGCTGGAGCCAGAGGATTTCGCCATCTATTACTGCCAGCAGTTC GGTACTTCCTCCGGCCTGACTTTCGGAGGCGGCACGAAGCTCGAAATCA AGACCACTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGC CTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGT GGGGCCGTGCATACCCGGGGTCTTGACTTCGCCTGCGATATCTACATTT GGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCACTCGTGAT CACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTACATCTTTAAG CAACCCTTCATGAGGCCTGTGCAGACTACTCAAGAGGAGGACGGCTGTT CATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTGCGCGTGAA ATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGGCAGAACCAG CTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACGTGCTGG ACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGAAA GAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCA GAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAG GCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTA TGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG

BCMA_EBB-C1979-C1		
BCMA_EBB-C1979-C1 - aa ScFv domain	139	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS AISGSGGSTYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCAR ATYKRELRYYYGMDVWGQGTMVTVSSGGGGSGGGGSGGGGSEIVMTQSP GTVSLSPGERATLSCRASQSVSSSFLAWYQQKPGQAPRLLIYGASSRAT GIPDRFSGSGSGTDFTLTISRLEPEDSAVYYCQQYHSSPSWTFGQGTRL EIK
BCMA_EBB-C1979-C1 - nt ScFv domain	160	CAAGTGCAGCTCGTGGAATCGGGTGGCGGACTGGTGCAGCCGGGGGGCT CACTTAGACTGTCCTGCGCGGCCAGCGGATTCACTTTCTCCTCCTACGC CATGTCCTGGGTCAGACAGGCCCCTGGAAAGGGCCTGGAATGGGTGTCC GCAATCAGCGGCAGCGGCGGCTCGACCTATTACGCGGATTCAGTGAAGG GCAGATTCACCATTTCCCGGGACAACGCCAAGAACTCCTTGTACCTTCA AATGAACTCCCTCCGCGCGGAAGATACCGCAATCTACTACTGCGCTCGG GCCACTTACAAGAGGGAACTGCGCTACTACTACGGGATGGACGTCTGGG GCCAGGGAACCATGGTCACCGTGTCCAGCGGAGGAGGAGGATCGGGAGG AGGCGGTAGCGGGGGTGGAGGGTCGGAGATCGTGATGACCCAGTCCCCC GGCACTGTGTCGCTGTCCCCCGGCGAACGGGCCACCCTGTCATGTCGGG CCAGCCAGTCAGTGTCGTCAAGCTTCCTCGCCTGGTACCAGCAGAAACC GGGACAAGCTCCCCGCCTGCTGATCTACGGAGCCAGCAGCCGGGCCACC GGTATTCCTGACCGGTTCTCCGGTTCGGGGTCCGGGACCGACTTTACTC TGACTATCTCTCGCCTCGAGCCAGAGGACTCCGCCGTGTATTACTGCCA GCAGTACCACTCCTCCCCGTCCTGGACGTTCGGACAGGGCACAAGGCTG GAGATTAAG
BCMA_EBB-C1979-C1 - aa VH	181	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS AISGSGGSTYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCAR ATYKRELRYYYGMDVWGQGTMVTVSS
BCMA_EBB-C1979-C1 - aa VL	202	EIVMTQSPGTVSLSPGERATLSCRASQSVSSSFLAWYQQKPGQAPRLLI YGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDSAVYYCQQYHSSPSW TFGQGTRLEIK
BCMA_EBB-C1979-C1 - aa Full CART	223	MALPVTALLLPLALLLHAARPQVQLVESGGGLVQPGGSLRLSCAASGFT FSSYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNAKN SLYLQMNSLRAEDTAIYYCARATYKRELRYYYGMDVWGQGTMVTVSSGG GGSGGGGSGGGGSEIVMTQSPGTVSLSPGERATLSCRASQSVSSSFLAW YQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDSA VYYCQQYHSSPSWTFGQGTRLEIKTTTPAPRPPTPAPTIASQPLSLRPE ACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRK KLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPA YKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNE LQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALP PR
BCMA_EBB-C1979-C1 - nt Full CART	244	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCC ACGCCGCTCGGCCCCAAGTGCAGCTCGTGGAATCGGGTGGCGGACTGGT GCAGCCGGGGGGCTCACTTAGACTGTCCTGCGCGGCCAGCGGATTCACT TTCTCCTCCTACGCCATGTCCTGGGTCAGACAGGCCCCTGGAAAGGGCC TGGAATGGGTGTCCGCAATCAGCGGCAGCGGCGGCTCGACCTATTACGC GGATTCAGTGAAGGGCAGATTCACCATTTCCCGGGACAACGCCAAGAAC TCCTTGTACCTTCAAATGAACTCCCTCCGCGCGGAAGATACCGCAATCT ACTACTGCGCTCGGGCCACTTACAAGAGGGAACTGCGCTACTACTACGG GATGGACGTCTGGGGCCAGGGAACCATGGTCACCGTGTCCAGCGGAGGA

		GGAGGATCGGGAGGAGGCGGTAGCGGGGGTGGAGGGTCGGAGATCGTGA TGACCCAGTCCCCCGGCACTGTGTCGCTGTCCCCCGGCGAACGGGCCAC CCTGTCATGTCGGGCCAGCCAGTCAGTGTCGTCAAGCTTCCTCGCCTGG TACCAGCAGAAACCGGGACAAGCTCCCCGCCTGCTGATCTACGGAGCCA GCAGCCGGGCCACCGGTATTCCTGACCGGTTCTCCGGTTCGGGGTCCGG GACCGACTTTACTCTGACTATCTCTCGCCTCGAGCCAGAGGACTCCGCC GTGTATTACTGCCAGCAGTACCACTCCTCCCCGTCCTGGACGTTCGGAC AGGGCACAAGGCTGGAGATTAAGACCACTACCCCAGCACCGAGGCCACC CACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAG GCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTGACT TCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGT CCTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAG AAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTA CTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGG CGGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCC TACAAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGA GAGAGGAGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAAT GGGCGGGAAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAG CTCCAAAAGGATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAG GGGAACGCAGAAGAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAG CACCGCCACCAAGGACACCTATGACGCTCTTCACATGCAGGCCCTGCCG CCTCGG
BCMA_EBB-C1978-C7		
BCMA_EBB-C1978-C7 - aa ScFv domain	140	EVQLVETGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS AISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNTLKAEDTAVYYCAR ATYKRELRYYYGMDVWGQGTTVTVSSGGGGSGGGGSGGGGSEIVLTQSP STLSLSPGESATLSCRASQSVSTTFLAWYQQKPGQAPRLLIYGSSNRAT GIPDRFSGSGSGTDFTLTIRRLEPEDFAVYYCQQYHSSPSWTFGQGTKV EIK
BCMA_EBB-C1978-C7 - nt ScFv domain	161	GAGGTGCAGCTTGTGGAAACCGGTGGCGGACTGGTGCAGCCCGGAGGAA GCCTCAGGCTGTCCTGCGCCGCGTCCGGCTTCACCTTCTCCTCGTACGC CATGTCCTGGGTCCGCCAGGCCCCCGGAAAGGGCCTGGAATGGGTGTCC GCCATCTCTGGAAGCGGAGGTTCCACGTACTACGCGGACAGCGTCAAGG GAAGGTTCACAATCTCCCGCGATAATTCGAAGAACACTCTGTACCTTCA AATGAACACCCTGAAGGCCGAGGACACTGCTGTGTACTACTGCGCACGG GCCACCTACAAGAGAGAGCTCCGGTACTACTACGGAATGGACGTCTGGG GCCAGGGAACTACTGTGACCGTGTCCTCGGGAGGGGGTGGCTCCGGGGG GGGCGGCTCCGGCGGAGGCGGTTCCGAGATTGTGCTGACCCAGTCACCT TCAACTCTGTCGCTGTCCCCGGGAGAGAGCGCTACTCTGAGCTGCCGGG CCAGCCAGTCCGTGTCCACCACCTTCCTCGCCTGGTATCAGCAGAAGCC GGGGCAGGCACCACGGCTCTTGATCTACGGGTCAAGCAACAGAGCGACC GGAATTCCTGACCGCTTCTCGGGGAGCGGTTCAGGCACCGACTTCACCC TGACTATCCGGCGCCTGGAACCCGAAGATTTCGCCGTGTATTACTGTCA ACAGTACCACTCCTCGCCGTCCTGGACCTTTGGCCAAGGAACCAAAGTG GAAATCAAG
BCMA_EBB-C1978-C7 - aa VH	182	EVQLVETGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS AISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNTLKAEDTAVYYCAR ATYKRELRYYYGMDVWGQGTTVTVSS

BCMA_EBB-C1978-C7 - aa VL	203	EIVLTQSPSTLSLSPGESATLSCRASQSVSTTFLAWYQQKPGQAPRLLI YGSSNRATGIPDRFSGSGSGTDFTLTIRRLEPEDFAVYYCQQYHSSPSW TFGQGTKVEIK
BCMA_EBB-C1978-C7 - aa Full CART	224	MALPVTALLLPLALLLHAARPEVQLVETGGGLVQPGGSLRLSCAASGFT FSSYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKN TLYLQMNTLKAEDTAVYYCARATYKRELRYYYGMDVWGQGTTVTVSSGG GGSGGGGSGGGGSEIVLTQSPSTLSLSPGESATLSCRASQSVSTTFLAW YQQKPGQAPRLLIYGSSNRATGIPDRFSGSGSGTDFTLTIRRLEPEDFA VYYCQQYHSSPSWTFGQGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPE ACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRK KLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPA YKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNE LQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALP PR
BCMA_EBB-C1978-C7 - nt Full CART	245	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCC ACGCCGCTCGGCCCGAGGTGCAGCTTGTGGAAACCGGTGGCGGACTGGT GCAGCCCGGAGGAAGCCTCAGGCTGTCCTGCGCCGCGTCCGGCTTCACC TTCTCCTCGTACGCCATGTCCTGGGTCCGCCAGGCCCCCGGAAAGGGCC TGGAATGGGTGTCCGCCATCTCTGGAAGCGGAGGTTCCACGTACTACGC GGACAGCGTCAAGGGAAGGTTCACAATCTCCCGCGATAATTCGAAGAAC ACTCTGTACCTTCAAATGAACACCCTGAAGGCCGAGGACACTGCTGTGT ACTACTGCGCACGGGCCACCTACAAGAGAGAGCTCCGGTACTACTACGG AATGGACGTCTGGGGCCAGGGAACTACTGTGACCGTGTCCTCGGGAGGG GGTGGCTCCGGGGGGGGCGGCTCCGGCGGAGGCGGTTCCGAGATTGTGC TGACCCAGTCACCTTCAACTCTGTCGCTGTCCCCGGGAGAGAGCGCTAC TCTGAGCTGCCGGGCCAGCCAGTCCGTGTCCACCACCTTCCTCGCCTGG TATCAGCAGAAGCCGGGGCAGGCACCACGGCTCTTGATCTACGGGTCAA GCAACAGAGCGACCGGAATTCCTGACCGCTTCTCGGGGAGCGGTTCAGG CACCGACTTCACCCTGACTATCCGGCGCCTGGAACCCGAAGATTTCGCC GTGTATTACTGTCAACAGTACCACTCCTCGCCGTCCTGGACCTTTGGCC AAGGAACCAAAGTGGAAATCAAGACCACTACCCCAGCACCGAGGCCACC CACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAG GCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTGACT TCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGT CCTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAG AAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTA CTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGG CGGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCC TACAAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGA GAGAGGAGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAAT GGGCGGGAAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAG CTCCAAAAGGATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAG GGGAACGCAGAAGAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAG CACCGCCACCAAGGACACCTATGACGCTCTTCACATGCAGGCCCTGCCG CCTCGG
BCMA_EBB-C1978-D10		
BCMA_EBB-C1978-D10 - aa ScFv domain	141	EVQLVETGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVS GISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRDEDTAVYYCAR VGKAVPDVWGQGTTVTVSSGGGGSGGGGSGGGGSDIVMTQTPSSLSASV GDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSG SGSGTDFTLTISSLQPEDFATYYCQQSYSTPYSFGQGTRLEIK

BCMA_EBB-C1978-D10-nt ScFv domain	162	GAAGTGCAGCTCGTGGAAACTGGAGGTGGACTCGTGCAGCCTGGACGGT CGCTGCGGCTGAGCTGCGCTGCATCCGGCTTCACCTTCGACGATTATGC CATGCACTGGGTCAGACAGGCGCCAGGGAAGGGACTTGAGTGGGTGTCC GGTATCAGCTGGAATAGCGGCTCAATCGGATACGCGGACTCCGTGAAGG GAAGGTTCACCATTTCCCGCGACAACGCCAAGAACTCCCTGTACTTGCA AATGAACAGCCTCCGGGATGAGGACACTGCCGTGTACTACTGCGCCCGC GTCGGAAAAGCTGTGCCCGACGTCTGGGGCCAGGGAACCACTGTGACCG TGTCCAGCGGCGGGGGTGGATCGGGCGGTGGAGGGTCCGGTGGAGGGGG CTCAGATATTGTGATGACCCAGACCCCCTCGTCCCTGTCCGCCTCGGTC GGCGACCGCGTGACTATCACATGTAGAGCCTCGCAGAGCATCTCCAGCT ACCTGAACTGGTATCAGCAGAAGCCGGGGAAGGCCCCGAAGCTCCTGAT CTACGCGGCATCATCACTGCAATCGGGAGTGCCGAGCCGGTTTTCCGGG TCCGGCTCCGGCACCGACTTCACGCTGACCATTTCTTCCCTGCAACCCG AGGACTTCGCCACTTACTACTGCCAGCAGTCCTACTCCACCCCTTACTC CTTCGGCCAAGGAACCAGGCTGGAAATCAAG
BCMA_EBB-C1978-D10 - aa VH	183	EVQLVETGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVS GISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRDEDTAVYYCAR VGKAVPDVWGQGTTVTVSS
BCMA_EBB-C1978-D10-aa VL	204	DIVMTQTPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIY AASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPYSF GQGTRLEIK
BCMA_EBB-C1978-D10 - aa Full CART	225	MALPVTALLLPLALLLHAARPEVQLVETGGGLVQPGRSLRLSCAASGFT FDDYAMHWVRQAPGKGLEWVSGISWNSGSIGYADSVKGRFTISRDNAKN SLYLQMNSLRDEDTAVYYCARVGKAVPDVWGQGTTVTVSSGGGGSGGGG SGGGGSDIVMTQTPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKA PKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSY STPYSFGQGTRLEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGA VHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQP FMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLY NELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEA YSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
BCMA_EBB-C1978-D10 - nt Full CART	246	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCC ACGCCGCTCGGCCCGAAGTGCAGCTCGTGGAAACTGGAGGTGGACTCGT GCAGCCTGGACGGTCGCTGCGGCTGAGCTGCGCTGCATCCGGCTTCACC TTCGACGATTATGCCATGCACTGGGTCAGACAGGCGCCAGGGAAGGGAC TTGAGTGGGTGTCCGGTATCAGCTGGAATAGCGGCTCAATCGGATACGC GGACTCCGTGAAGGGAAGGTTCACCATTTCCCGCGACAACGCCAAGAAC TCCCTGTACTTGCAAATGAACAGCCTCCGGGATGAGGACACTGCCGTGT ACTACTGCGCCCGCGTCGGAAAAGCTGTGCCCGACGTCTGGGGCCAGGG AACCACTGTGACCGTGTCCAGCGGCGGGGGTGGATCGGGCGGTGGAGGG TCCGGTGGAGGGGGCTCAGATATTGTGATGACCCAGACCCCCTCGTCCC TGTCCGCCTCGGTCGGCGACCGCGTGACTATCACATGTAGAGCCTCGCA GAGCATCTCCAGCTACCTGAACTGGTATCAGCAGAAGCCGGGGAAGGCC CCGAAGCTCCTGATCTACGCGGCATCATCACTGCAATCGGGAGTGCCGA GCCGGTTTTCCGGGTCCGGCTCCGGCACCGACTTCACGCTGACCATTTC TTCCCTGCAACCCGAGGACTTCGCCACTTACTACTGCCAGCAGTCCTAC TCCACCCCTTACTCCTTCGGCCAAGGAACCAGGCTGGAAATCAAGACCA CTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCA GCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCC GTGCATACCCGGGGTCTTGACTTCGCCTGCGATATCTACATTTGGGCCC

		CTCTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCACTCGTGATCACTCT TTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTACATCTTTAAGCAACCC TTCATGAGGCCTGTGCAGACTACTCAAGAGGAGGACGGCTGTTCATGCC GGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTGCGCGTGAAATTCAG CCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGGCAGAACCAGCTCTAC AACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACGTGCTGGACAAGC GGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGAAAGAATCC CCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGAAGCC TATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAGGCCACG ACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTATGACGC TCTTCACATGCAGGCCCTGCCGCCTCGG
BCMA_EBB-C1979-C12		
BCMA_EBB-C1979-C12-aa ScFv domain	142	EVQLVESGGGLVQPGRSLRLSCTASGFTFDDYAMHWVRQRPGKGLEWVA SINWKGNSLAYGDSVKGRFAISRDNAKNTVFLQMNSLRTEDTAVYYCAS HQGVAYYNYAMDVWGRGTLVTVSSGGGGSGGGGSGGGGSEIVLTQSPGT LSLSPGERATLSCRATQSIGSSFLAWYQQRPGQAPRLLIYGASQRATGI PDRFSGRGSGTDFTLTISRVEPEDSAVYYCQHYESSPSWTFGQGTKVEI K
BCMA_EBB-C1979-C12 - nt ScFv domain	163	GAAGTGCAGCTCGTGGAGAGCGGGGGAGGATTGGTGCAGCCCGGAAGGT CCCTGCGGCTCTCCTGCACTGCGTCTGGCTTCACCTTCGACGACTACGC GATGCACTGGGTCAGACAGCGCCCGGGAAAGGGCCTGGAATGGGTCGCC TCAATCAACTGGAAGGGAAACTCCCTGGCCTATGGCGACAGCGTGAAGG GCCGCTTCGCCATTTCGCGCGACAACGCCAAGAACACCGTGTTTCTGCA AATGAATTCCCTGCGGACCGAGGATACCGCTGTGTACTACTGCGCCAGC CACCAGGGCGTGGCATACTATAACTACGCCATGGACGTGTGGGGAAGAG GGACGCTCGTCACCGTGTCCTCCGGGGGCGGTGGATCGGGTGGAGGAGG AAGCGGTGGCGGGGGCAGCGAAATCGTGCTGACTCAGAGCCCGGGAACT CTTTCACTGTCCCCGGGAGAACGGGCCACTCTCTCGTGCCGGGCCACCC AGTCCATCGGCTCCTCCTTCCTTGCCTGGTACCAGCAGAGGCCAGGACA GGCGCCCCGCCTGCTGATCTACGGTGCTTCCCAACGCGCCACTGGCATT CCTGACCGGTTCAGCGGCAGAGGGTCGGGAACCGATTTCACACTGACCA TTTCCCGGGTGGAGCCCGAAGATTCGGCAGTCTACTACTGTCAGCATTA CGAGTCCTCCCCTTCATGGACCTTCGGTCAAGGGACCAAAGTGGAGATC AAG
BCMA_EBB-C1979-C12 - aa VH	184	EVQLVESGGGLVQPGRSLRLSCTASGFTFDDYAMHWVRQRPGKGLEWVA SINWKGNSLAYGDSVKGRFAISRDNAKNTVFLQMNSLRTEDTAVYYCAS HQGVAYYNYAMDVWGRGTLVTVSS
BCMA_EBB-C1979-C12 - aa VL	205	EIVLTQSPGTLSLSPGERATLSCRATQSIGSSFLAWYQQRPGQAPRLLI YGASQRATGIPDRFSGRGSGTDFTLTISRVEPEDSAVYYCQHYESSPSW TFGQGTKVEIK
BCMA_EBB-C1979-C12 - aa Full CART	226	MALPVTALLLPLALLLHAARPEVQLVESGGGLVQPGRSLRLSCTASGFT FDDYAMHWVRQRPGKGLEWVASINWKGNSLAYGDSVKGRFAISRDNAKN TVFLQMNSLRTEDTAVYYCASHQGVAYYNYAMDVWGRGTLVTVSSGGGG SGGGGSGGGGSEIVLTQSPGTLSLSPGERATLSCRATQSIGSSFLAWYQ QRPGQAPRLLIYGASQRATGIPDRFSGRGSGTDFTLTISRVEPEDSAVY YCQHYESSPSWTFGQGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEAC RPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKL LYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYK QGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQ KDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

BCMA_EBB-C1979-C12 - nt Full CART	247	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCC ACGCCGCTCGGCCCGAAGTGCAGCTCGTGGAGAGCGGGGGAGGATTGGT GCAGCCCGGAAGGTCCCTGCGGCTCTCCTGCACTGCGTCTGGCTTCACC TTCGACGACTACGCGATGCACTGGGTCAGACAGCGCCCGGGAAAGGGCC TGGAATGGGTCGCCTCAATCAACTGGAAGGGAAACTCCCTGGCCTATGG CGACAGCGTGAAGGGCCGCTTCGCCATTTCGCGCGACAACGCCAAGAAC ACCGTGTTTCTGCAAATGAATTCCCTGCGGACCGAGGATACCGCTGTGT ACTACTGCGCCAGCCACCAGGGCGTGGCATACTATAACTACGCCATGGA CGTGTGGGGAAGAGGGACGCTCGTCACCGTGTCCTCCGGGGGCGGTGGA TCGGGTGGAGGAGGAAGCGGTGGCGGGGGCAGCGAAATCGTGCTGACTC AGAGCCCGGGAACTCTTTCACTGTCCCCGGGAGAACGGGCCACTCTCTC GTGCCGGGCCACCCAGTCCATCGGCTCCTCCTTCCTTGCCTGGTACCAG CAGAGGCCAGGACAGGCGCCCCGCCTGCTGATCTACGGTGCTTCCCAAC GCGCCACTGGCATTCCTGACCGGTTCAGCGGCAGAGGGTCGGGAACCGA TTTCACACTGACCATTTCCCGGGTGGAGCCCGAAGATTCGGCAGTCTAC TACTGTCAGCATTACGAGTCCTCCCCTTCATGGACCTTCGGTCAAGGGA CCAAAGTGGAGATCAAGACCACTACCCCAGCACCGAGGCCACCCACCCC GGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGT AGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTGACTTCGCCT GCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGCT GCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTG CTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAG AGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTG CGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAG CAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGG AGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGG GAAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAA AAGGATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAAC GCAGAAGAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGC CACCAAGGACACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
BCMA_EBB-C1980-G4		
BCMA_EBB-C1980-G4- aa ScFv domain	143	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGL EWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAED TAVYYCAKVVRDGMDVWGQGTTVTVSSGGGGSGGGGSGGGGSE IVLTQSPATLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRL LIYGASSRATGIPDRFSGNGSGTDFTLTISRLEPEDFAVYYCQQYGS PPRFTFGPGTKVDIK
BCMA_EBB-C1980-G4- nt ScFv domain	164	GAGGTGCAGTTGGTCGAAAGCGGGGGCGGGCTTGTGCAGCCTGGCGGAT CACTGCGGCTGTCCTGCGCGGCATCAGGCTTCACGTTTTCTTCCTACGC CATGTCCTGGGTGCGCCAGGCCCCTGGAAAGGGACTGGAATGGGTGTCC GCGATTTCGGGGTCCGGCGGGAGCACCTACTACGCCGATTCCGTGAAGG GCCGCTTCACTATCTCGCGGGACAACTCCAAGAACACCCTCTACCTCCA AATGAATAGCCTGCGGGCCGAGGATACCGCCGTCTACTATTGCGCTAAG GTCGTGCGCGACGGAATGGACGTGTGGGGACAGGGTACCACCGTGACAG TGTCCTCGGGGGGAGGCGGTAGCGGCGGAGGAGGAAGCGGTGGTGGAGG TTCCGAGATTGTGCTGACTCAATCACCCGCGACCCTGAGCCTGTCCCCC GGCGAAAGGGCCACTCTGTCCTGTCGGGCCAGCCAATCAGTCTCCTCCT CGTACCTGGCCTGGTACCAGCAGAAGCCAGGACAGGCTCCGAGACTCCT TATCTATGGCGCATCCTCCCGCGCCACCGGAATCCCGGATAGGTTCTCG GGAAACGGATCGGGGACCGACTTCACTCTCACCATCTCCCGGCTGGAAC CGGAGGACTTCGCCGTGTACTACTGCCAGCAGTACGGCAGCCCGCCTAG ATTCACTTTCGGCCCCGGCACCAAAGTGGACATCAAG

BCMA_EBB-C1980-G4- aa VH	185	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS AISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK VVRDGMDVWGQGTTVTVSS
BCMA_EBB-C1980-G4- aa VL	206	EIVLTQSPATLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLI YGASSRATGIPDRFSGNGSGTDFTLTISRLEPEDFAVYYCQQYGSPPRF TFGPGTKVDIK
BCMA_EBB-C1980-G4- aa Full CART	227	MALPVTALLLPLALLLHAARPEVQLVESGGGLVQPGGSLRLSCAA SGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNSLRAEDTAVYYCAKVVRDGMDVWGQGTT VTVSSGGGGSGGGGSGGGGSEIVLTQSPATLSLSPGERATLSCRAS QSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGNGSGTDF TLTISRLEPEDFAVYYCQQYGSPPRFTFGPGTKVDIKTTTPAPRPPT PAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTC GVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFP EEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVL DKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKG ERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
BCMA_EBB-C1980-G4- nt Full CART	248	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCC ACGCCGCTCGGCCCGAGGTGCAGTTGGTCGAAAGCGGGGGCGGGCTTGT GCAGCCTGGCGGATCACTGCGGCTGTCCTGCGCGGCATCAGGCTTCACG TTTTCTTCCTACGCCATGTCCTGGGTGCGCCAGGCCCCTGGAAAGGGAC TGGAATGGGTGTCCGCGATTTCGGGGTCCGGCGGGAGCACCTACTACGC CGATTCCGTGAAGGGCCGCTTCACTATCTCGCGGGACAACTCCAAGAAC ACCCTCTACCTCCAAATGAATAGCCTGCGGGCCGAGGATACCGCCGTCT ACTATTGCGCTAAGGTCGTGCGCGACGGAATGGACGTGTGGGGACAGGG TACCACCGTGACAGTGTCCTCGGGGGGAGGCGGTAGCGGCGGAGGAGGA AGCGGTGGTGGAGGTTCCGAGATTGTGCTGACTCAATCACCCGCGACCC TGAGCCTGTCCCCCGGCGAAAGGGCCACTCTGTCCTGTCGGGCCAGCCA ATCAGTCTCCTCCTCGTACCTGGCCTGGTACCAGCAGAAGCCAGGACAG GCTCCGAGACTCCTTATCTATGGCGCATCCTCCCGCGCCACCGGAATCC CGGATAGGTTCTCGGGAAACGGATCGGGGACCGACTTCACTCTCACCAT CTCCCGGCTGGAACCGGAGGACTTCGCCGTGTACTACTGCCAGCAGTAC GGCAGCCCGCCTAGATTCACTTTCGGCCCCGGCACCAAAGTGGACATCA AGACCACTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGC CTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGT GGGGCCGTGCATACCCGGGGTCTTGACTTCGCCTGCGATATCTACATTT GGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCACTCGTGAT CACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTACATCTTTAAG CAACCCTTCATGAGGCCTGTGCAGACTACTCAAGAGGAGGACGGCTGTT CATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTGCGCGTGAA ATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGGCAGAACCAG CTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACGTGCTGG ACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGAAA GAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCA GAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAG GCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTA TGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
BCMA_EBB-C1980-D2		
BCMA_EBB-C1980-D2- aa ScFv domain	144	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS AISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK IPQTGTFDYWGQGTLVTVSSGGGGSGGGGSGGGGSEIVLTQSPGTLSLS

		PGERATLSCRASQSVSSSYLAWYQQRPGQAPRLLIYGASSRATGIPDRF SGSGSGTDFTLTISRLEPEDFAVYYCQHYGSSPSWTFGQGTRLEIK
BCMA_EBB-C1980-D2- nt ScFv domain	165	GAAGTGCAGCTGCTGGAGTCCGGCGGTGGATTGGTGCAACCGGGGGGAT CGCTCAGACTGTCCTGTGCGGCGTCAGGCTTCACCTTCTCGAGCTACGC CATGTCATGGGTCAGACAGGCCCCTGGAAAGGGTCTGGAATGGGTGTCC GCCATTTCCGGGAGCGGGGGATCTACATACTACGCCGATAGCGTGAAGG GCCGCTTCACCATTTCCCGGGACAACTCCAAGAACACTCTCTATCTGCA AATGAACTCCCTCCGCGCTGAGGACACTGCCGTGTACTACTGCGCCAAA ATCCCTCAGACCGGCACCTTCGACTACTGGGGACAGGGGACTCTGGTCA CCGTCAGCAGCGGTGGCGGAGGTTCGGGGGGAGGAGGAAGCGGCGGCGG AGGGTCCGAGATTGTGCTGACCCAGTCACCCGGCACTTTGTCCCTGTCG CCTGGAGAAAGGGCCACCCTTTCCTGCCGGGCATCCCAATCCGTGTCCT CCTCGTACCTGGCCTGGTACCAGCAGAGGCCCGGACAGGCCCCACGGCT TCTGATCTACGGAGCAAGCAGCCGCGCGACCGGTATCCCGGACCGGTTT TCGGGCTCGGGCTCAGGAACTGACTTCACCCTCACCATCTCCCGCCTGG AACCCGAAGATTTCGCTGTGTATTACTGCCAGCACTACGGCAGCTCCCC GTCCTGGACGTTCGGCCAGGGAACTCGGCTGGAGATCAAG
BCMA_EBB-C1980-D2- aa VH	186	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS AISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK IPQTGTFDYWGQGTLVTVSS
BCMA_EBB-C1980-D2- aa VL	207	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQRPGQAPRLLI YGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQHYGSSPSW TFGQGTRLEIK
BCMA_EBB-C1980-D2- aa Full CART	228	MALPVTALLLPLALLLHAARPEVQLLESGGGLVQPGGSLRLSCAASGFT FSSYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAKIPQTGTFDYWGQGTLVTVSSGGGGSGGG GSGGGGSEIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQRPG QAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQH YGSSPSWTFGQGTRLEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAA GGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIF KQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQN QLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
BCMA_EBB-C1980-D2- nt Full CART	249	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCC ACGCCGCTCGGCCCGAAGTGCAGCTGCTGGAGTCCGGCGGTGGATTGGT GCAACCGGGGGGATCGCTCAGACTGTCCTGTGCGGCGTCAGGCTTCACC TTCTCGAGCTACGCCATGTCATGGGTCAGACAGGCCCCTGGAAAGGGTC TGGAATGGGTGTCCGCCATTTCCGGGAGCGGGGGATCTACATACTACGC CGATAGCGTGAAGGGCCGCTTCACCATTTCCCGGGACAACTCCAAGAAC ACTCTCTATCTGCAAATGAACTCCCTCCGCGCTGAGGACACTGCCGTGT ACTACTGCGCCAAAATCCCTCAGACCGGCACCTTCGACTACTGGGGACA GGGGACTCTGGTCACCGTCAGCAGCGGTGGCGGAGGTTCGGGGGGAGGA GGAAGCGGCGGCGGAGGGTCCGAGATTGTGCTGACCCAGTCACCCGGCA CTTTGTCCCTGTCGCCTGGAGAAAGGGCCACCCTTTCCTGCCGGGCATC CCAATCCGTGTCCTCCTCGTACCTGGCCTGGTACCAGCAGAGGCCCGGA CAGGCCCCACGGCTTCTGATCTACGGAGCAAGCAGCCGCGCGACCGGTA TCCCGGACCGGTTTTCGGGCTCGGGCTCAGGAACTGACTTCACCCTCAC CATCTCCCGCCTGGAACCCGAAGATTTCGCTGTGTATTACTGCCAGCAC TACGGCAGCTCCCCGTCCTGGACGTTCGGCCAGGGAACTCGGCTGGAGA TCAAGACCACTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCAT CGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCAGCT GGTGGGGCCGTGCATACCCGGGGTCTTGACTTCGCCTGCGATATCTACA

		TTTGGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCACTCGT GATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTACATCTTT AAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAGAGGAGGACGGCT GTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTGCGCGT GAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGGCAGAAC CAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACGTGC TGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAG AAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATG GCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCA AAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGACAC CTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
BCMA_EBB-C1978-A10		
BCMA_EBB-C1978-A10-aa ScFv domain	145	EVQLVETGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKG LEWVSAISGSGGSTYYADSVKGRFTMSRENDKNSVFLQMNSLRVE DTGVYYCARANYKRELRYYYGMDVWGQGTMVTVSSGGGGSGG GGSGGGGSEIVMTQSPGTLSLSPGESATLSCRASQRVASNYLAWY QHKPGQAPSLLISGASSRATGVPDRFSGSGSGTDFTLAISRLEPEDS AVYYCQHYDSSPSWTFGQGTKVEIK
BCMA_EBB-C1978-A10-nt ScFv domain	166	GAAGTGCAACTGGTGGAAACCGGTGGAGGACTCGTGCAGCCTGGCGGCA GCCTCCGGCTGAGCTGCGCCGCTTCGGGATTCACCTTTTCCTCCTACGC GATGTCTTGGGTCAGACAGGCCCCCGGAAAGGGGCTGGAATGGGTGTCA GCCATCTCCGGCTCCGGCGGATCAACGTACTACGCCGACTCCGTGAAAG GCCGGTTCACCATGTCGCGCGAGAATGACAAGAACTCCGTGTTCCTGCA AATGAACTCCCTGAGGGTGGAGGACACCGGAGTGTACTATTGTGCGCGC GCCAACTACAAGAGAGAGCTGCGGTACTACTACGGAATGGACGTCTGGG GACAGGGAACTATGGTGACCGTGTCATCCGGTGGAGGGGGAAGCGGCGG TGGAGGCAGCGGGGGCGGGGGTTCAGAAATTGTCATGACCCAGTCCCCG GGAACTCTTTCCCTCTCCCCCGGGGAATCCGCGACTTTGTCCTGCCGGG CCAGCCAGCGCGTGGCCTCGAACTACCTCGCATGGTACCAGCATAAGCC AGGCCAAGCCCCTTCCCTGCTGATTTCCGGGGCTAGCAGCCGCGCCACT GGCGTGCCGGATAGGTTCTCGGGAAGCGGCTCGGGTACCGATTTCACCC TGGCAATCTCGCGGCTGGAACCGGAGGATTCGGCCGTGTACTACTGCCA GCACTATGACTCATCCCCCTCCTGGACATTCGGACAGGGCACCAAGGTC GAGATCAAG
BCMA_EBB-C1978-A10-aa VH	187	EVQLVETGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS AISGSGGSTYYADSVKGRFTMSRENDKNSVFLQMNSLRVEDTGVYYCAR ANYKRELRYYYGMDVWGQGTMVTVSS
BCMA_EBB-C1978-A10-aa VL	208	EIVMTQSPGTLSLSPGESATLSCRASQRVASNYLAWYQHKPGQAPSLLI SGASSRATGVPDRFSGSGSGTDFTLAISRLEPEDSAVYYCQHYDSSPSW TFGQGTKVEIK
BCMA_EBB-C1978-A10-aa Full CART	229	MALPVTALLLPLALLLHAARPEVQLVETGGGLVQPGGSLRLSCAA SGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFT MSRENDKNSVFLQMNSLRVEDTGVYYCARANYKRELRYYYGMD VWGQGTMVTVSSGGGGSGGGGSGGGGSEIVMTQSPGTLSLSPGES ATLSCRASQRVASNYLAWYQHKPGQAPSLLISGASSRATGVPDRF SGSGSGTDFTLAISRLEPEDSAVYYCQHYDSSPSWTFGQGTKVEIK TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIY IWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQE EDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLG

		RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEA YSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
BCMA_EBB-C1978-A10-nt Full CART	250	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCC ACGCCGCTCGGCCCGAAGTGCAACTGGTGGAAACCGGTGGAGGACTCGT GCAGCCTGGCGGCAGCCTCCGGCTGAGCTGCGCCGCTTCGGGATTCACC TTTTCCTCCTACGCGATGTCTTGGGTCAGACAGGCCCCCGGAAAGGGGC TGGAATGGGTGTCAGCCATCTCCGGCTCCGGCGGATCAACGTACTACGC CGACTCCGTGAAAGGCCGGTTCACCATGTCGCGCGAGAATGACAAGAAC TCCGTGTTCCTGCAAATGAACTCCCTGAGGGTGGAGGACACCGGAGTGT ACTATTGTGCGCGCGCCAACTACAAGAGAGAGCTGCGGTACTACTACGG AATGGACGTCTGGGGACAGGGAACTATGGTGACCGTGTCATCCGGTGGA GGGGGAAGCGGCGGTGGAGGCAGCGGGGGCGGGGGTTCAGAAATTGTCA TGACCCAGTCCCCGGGAACTCTTTCCCTCTCCCCCGGGGAATCCGCGAC TTTGTCCTGCCGGGCCAGCCAGCGCGTGGCCTCGAACTACCTCGCATGG TACCAGCATAAGCCAGGCCAAGCCCCTTCCCTGCTGATTTCCGGGGCTA GCAGCCGCGCCACTGGCGTGCCGGATAGGTTCTCGGGAAGCGGCTCGGG TACCGATTTCACCCTGGCAATCTCGCGGCTGGAACCGGAGGATTCGGCC GTGTACTACTGCCAGCACTATGACTCATCCCCCTCCTGGACATTCGGAC AGGGCACCAAGGTCGAGATCAAGACCACTACCCCAGCACCGAGGCCACC CACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAG GCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTGACT TCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGT CCTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAG AAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTA CTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGG CGGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCC TACAAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGA GAGAGGAGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAAT GGGCGGGAAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAG CTCCAAAAGGATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAG GGGAACGCAGAAGAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAG CACCGCCACCAAGGACACCTATGACGCTCTTCACATGCAGGCCCTGCCG CCTCGG
BCMA_EBB-C1978-D4		
BCMA_EBB-C1978-D4- aa ScFv domain	146	EVQLLETGGGLVQPGGSLRLSCAASGFSFSSYAMSWVRQAPGKGLEWVS AISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK ALVGATGAFDIWGQGTLVTVSSGGGGSGGGGSGGGGSEIVLTQSPGTLS LSPGERATLSCRASQSLSSNFLAWYQQKPGQAPGLLIYGASNWATGTPD RFSGSGSGTDFTLTITRLEPEDFAVYYCQYYGTSPMYTFGQGTKVEIK
BCMA_EBB-C1978-D4- nt ScFv domain	167	GAAGTGCAGCTGCTCGAAACCGGTGGAGGGCTGGTGCAGCCAGGGGGCT CCCTGAGGCTTTCATGCGCCGCTAGCGGATTCTCCTTCTCCTCTTACGC CATGTCGTGGGTCCGCCAAGCCCCTGGAAAAGGCCTGGAATGGGTGTCC GCGATTTCCGGGAGCGGAGGTTCGACCTATTACGCCGACTCCGTGAAGG GCCGCTTTACCATCTCCCGGGATAACTCCAAGAACACTCTGTACCTCCA AATGAACTCGCTGAGAGCCGAGGACACCGCCGTGTATTACTGCGCGAAG GCGCTGGTCGGCGCGACTGGGGCATTCGACATCTGGGGACAGGGAACTC TTGTGACCGTGTCGAGCGGAGGCGGCGGCTCCGGCGGAGGAGGGAGCGG GGGCGGTGGTTCCGAAATCGTGTTGACTCAGTCCCCGGGAACCCTGAGC TTGTCACCCGGGGAGCGGGCCACTCTCTCCTGTCGCGCCTCCCAATCGC TCTCATCCAATTTCCTGGCCTGGTACCAGCAGAAGCCCGGACAGGCCCC GGGCCTGCTCATCTACGGCGCTTCAAACTGGGCAACGGGAACCCCTGAT CGGTTCAGCGGAAGCGGATCGGGTACTGACTTTACCCTGACCATCACCA

		GACTGGAACCGGAGGACTTCGCCGTGTACTACTGCCAGTACTACGGCAC CTCCCCCATGTACACATTCGGACAGGGTACCAAGGTCGAGATTAAG
BCMA_EBB-C1978-D4- aa VH	188	EVQLLETGGGLVQPGGSLRLSCAASGFSFSSYAMSWVRQAPGKGLEWVS AISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK ALVGATGAFDIWGQGTLVTVSS
BCMA_EBB-C1978-D4- aa VL	209	EIVLTQSPGTLSLSPGERATLSCRASQSLSSNFLAWYQQKPGQAPGLLI YGASNWATGTPDRFSGSGSGTDFTLTITRLEPEDFAVYYCQYYGTSPMY TFGQGTKVEIK
BCMA_EBB-C1978-D4- aa Full CART	230	MALPVTALLLPLALLLHAARPEVQLLETGGGLVQPGGSLRLSCAASGFS FSSYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAKALVGATGAFDIWGQGTLVTVSSGGGGSG GGGSGGGGSEIVLTQSPGTLSLSPGERATLSCRASQSLSSNFLAWYQQK PGQAPGLLIYGASNWATGTPDRFSGSGSGTDFTLTITRLEPEDFAVYYC QYYGTSPMYTFGQGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRP AAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLY IFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQG QNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKD KMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
BCMA_EBB-C1978-D4- nt Full CART	251	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCC ACGCCGCTCGGCCCGAAGTGCAGCTGCTCGAAACCGGTGGAGGGCTGGT GCAGCCAGGGGGCTCCCTGAGGCTTTCATGCGCCGCTAGCGGATTCTCC TTCTCCTCTTACGCCATGTCGTGGGTCCGCCAAGCCCCTGGAAAAGGCC TGGAATGGGTGTCCGCGATTTCCGGGAGCGGAGGTTCGACCTATTACGC CGACTCCGTGAAGGGCCGCTTTACCATCTCCCGGGATAACTCCAAGAAC ACTCTGTACCTCCAAATGAACTCGCTGAGAGCCGAGGACACCGCCGTGT ATTACTGCGCGAAGGCGCTGGTCGGCGCGACTGGGGCATTCGACATCTG GGGACAGGGAACTCTTGTGACCGTGTCGAGCGGAGGCGGCGGCTCCGGC GGAGGAGGGAGCGGGGGCGGTGGTTCCGAAATCGTGTTGACTCAGTCCC CGGGAACCCTGAGCTTGTCACCCGGGGAGCGGGCCACTCTCTCCTGTCG CGCCTCCCAATCGCTCTCATCCAATTTCCTGGCCTGGTACCAGCAGAAG CCCGGACAGGCCCCGGGCCTGCTCATCTACGGCGCTTCAAACTGGGCAA CGGGAACCCCTGATCGGTTCAGCGGAAGCGGATCGGGTACTGACTTTAC CCTGACCATCACCAGACTGGAACCGGAGGACTTCGCCGTGTACTACTGC CAGTACTACGGCACCTCCCCCATGTACACATTCGGACAGGGTACCAAGG TCGAGATTAAGACCACTACCCCAGCACCGAGGCCACCCACCCCGGCTCC TACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCC GCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTGACTTCGCCTGCGATA TCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGCTGCTTTC ACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTAC ATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAGAGGAGG ACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACT GCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGG CAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACG ACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCC GCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGAT AAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAA GAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAA GGACACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
BCMA_EBB-C1980-A2		

BCMA_EBB-C1980-A2- aa ScFv domain	147	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS AISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCVL WFGEGFDPWGQGTLVTVSSGGGGSGGGGSGGGGSDIVLTQSPLSLPVTP GEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVP DRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPLTFGGGTKVDIK
BCMA_EBB-C1980-A2- nt ScFv domain	168	GAAGTGCAGCTGCTTGAGAGCGGTGGAGGTCTGGTGCAGCCCGGGGGAT CACTGCGCCTGTCCTGTGCCGCGTCCGGTTTCACTTTCTCCTCGTACGC CATGTCGTGGGTCAGACAGGCACCGGGAAAGGGACTGGAATGGGTGTCA GCCATTTCGGGTTCGGGGGGCAGCACCTACTACGCTGACTCCGTGAAGG GCCGGTTCACCATTTCCCGCGACAACTCCAAGAACACCTTGTACCTCCA AATGAACTCCCTGCGGGCCGAAGATACCGCCGTGTATTACTGCGTGCTG TGGTTCGGAGAGGGATTCGACCCGTGGGGACAAGGAACACTCGTGACTG TGTCATCCGGCGGAGGCGGCAGCGGTGGCGGCGGTTCCGGCGGCGGCGG ATCTGACATCGTGTTGACCCAGTCCCCTCTGAGCCTGCCGGTCACTCCT GGCGAACCAGCCAGCATCTCCTGCCGGTCGAGCCAGTCCCTCCTGCACT CCAATGGGTACAACTACCTCGATTGGTATCTGCAAAAGCCGGGCCAGAG CCCCCAGCTGCTGATCTACCTTGGGTCAAACCGCGCTTCCGGGGTGCCT GATAGATTCTCCGGGTCCGGGAGCGGAACCGACTTTACCCTGAAAATCT CGAGGGTGGAGGCCGAGGACGTCGGAGTGTACTACTGCATGCAGGCGCT CCAGACTCCCCTGACCTTCGGAGGAGGAACGAAGGTCGACATCAAGA
BCMA_EBB-C1980-A2- aa VH	189	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS AISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCVL WFGEGFDPWGQGTLVTVSS
BCMA_EBB-C1980-A2- aa VL	210	DIVLTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSP QLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQ TPLTFGGGTKVDIK
BCMA_EBB-C1980-A2- aa Full CART	231	MALPVTALLLPLALLLHAARPEVQLLESGGGLVQPGGSLRLSCAASGFT FSSYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCVLWFGEGFDPWGQGTLVTVSSGGGGSGGGG SGGGGSDIVLTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQ KPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYY CMQALQTPLTFGGGTKVDIKTTTPAPRPPTPAPTIASQPLSLRPEACRP AAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLY IFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQG QNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKD KMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
BCMA_EBB-C1980-A2- nt Full CART	252	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCC ACGCCGCTCGGCCCGAAGTGCAGCTGCTTGAGAGCGGTGGAGGTCTGGT GCAGCCCGGGGGATCACTGCGCCTGTCCTGTGCCGCGTCCGGTTTCACT TTCTCCTCGTACGCCATGTCGTGGGTCAGACAGGCACCGGGAAAGGGAC TGGAATGGGTGTCAGCCATTTCGGGTTCGGGGGGCAGCACCTACTACGC TGACTCCGTGAAGGGCCGGTTCACCATTTCCCGCGACAACTCCAAGAAC ACCTTGTACCTCCAAATGAACTCCCTGCGGGCCGAAGATACCGCCGTGT ATTACTGCGTGCTGTGGTTCGGAGAGGGATTCGACCCGTGGGGACAAGG AACACTCGTGACTGTGTCATCCGGCGGAGGCGGCAGCGGTGGCGGCGGT TCCGGCGGCGGCGGATCTGACATCGTGTTGACCCAGTCCCCTCTGAGCC TGCCGGTCACTCCTGGCGAACCAGCCAGCATCTCCTGCCGGTCGAGCCA GTCCCTCCTGCACTCCAATGGGTACAACTACCTCGATTGGTATCTGCAA AAGCCGGGCCAGAGCCCCCAGCTGCTGATCTACCTTGGGTCAAACCGCG CTTCCGGGGTGCCTGATAGATTCTCCGGGTCCGGGAGCGGAACCGACTT TACCCTGAAAATCTCGAGGGTGGAGGCCGAGGACGTCGGAGTGTACTAC TGCATGCAGGCGCTCCAGACTCCCCTGACCTTCGGAGGAGGAACGAAGG

		TCGACATCAAGACCACTACCCCAGCACCGAGGCCACCCACCCCGGCTCC TACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCC GCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTGACTTCGCCTGCGATA TCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGCTGCTTTC ACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTAC ATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAGAGGAGG ACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACT GCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGG CAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACG ACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCC GCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGAT AAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAA GAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAA GGACACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
BCMA_EBB-C1981-C3		
BCMA_EBB-C1981-C3- aa ScFv domain	148	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS AISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK VGYDSSGYYRDYYGMDVWGQGTTVTVSSGGGGSGGGGSGGGGSEIVLTQ SPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGTSSR ATGISDRFSGSGSGTDFTLTISRLEPEDFAVYYCQHYGNSPPKFTFGPG TKLEIK
BCMA_EBB-C1981-C3- nt ScFv domain	169	CAAGTGCAGCTCGTGGAGTCAGGCGGAGGACTGGTGCAGCCCGGGGGCT CCCTGAGACTTTCCTGCGCGGCATCGGGTTTTACCTTCTCCTCCTATGC TATGTCCTGGGTGCGCCAGGCCCCGGGAAAGGGACTGGAATGGGTGTCC GCAATCAGCGGTAGCGGGGGCTCAACATACTACGCCGACTCCGTCAAGG GTCGCTTCACTATTTCCCGGGACAACTCCAAGAATACCCTGTACCTCCA AATGAACAGCCTCAGGGCCGAGGATACTGCCGTGTACTACTGCGCCAAA GTCGGATACGATAGCTCCGGTTACTACCGGGACTACTACGGAATGGACG TGTGGGGACAGGGCACCACCGTGACCGTGTCAAGCGGCGGAGGCGGTTC AGGAGGGGGAGGCTCCGGCGGTGGAGGGTCCGAAATCGTCCTGACTCAG TCGCCTGGCACTCTGTCGTTGTCCCCGGGGGAGCGCGCTACCCTGTCGT GTCGGGCGTCGCAGTCCGTGTCGAGCTCCTACCTCGCGTGGTACCAGCA GAAGCCCGGACAGGCCCCTAGACTTCTGATCTACGGCACTTCTTCACGC GCCACCGGGATCAGCGACAGGTTCAGCGGCTCCGGCTCCGGGACCGACT TCACCCTGACCATTAGCCGGCTGGAGCCTGAAGATTTCGCCGTGTATTA CTGCCAACACTACGGAAACTCGCCGCCAAAGTTCACGTTCGGACCCGGA ACCAAGCTGGAAATCAAG
BCMA_EBB-C1981-C3- aa VH	190	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS AISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK VGYDSSGYYRDYYGMDVWGQGTTVTVSS
BCMA_EBB-C1981-C3- aa VL	211	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLI YGTSSRATGISDRFSGSGSGTDFTLTISRLEPEDFAVYYCQHYGNSPPK FTFGPGTKLEIK

BCMA_EBB-C1981-C3- aa Full CART	232	MALPVTALLLPLALLLHAARPQVQLVESGGGLVQPGGSLRLSCAASGFT FSSYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAKVGYDSSGYYRDYYGMDVWGQGTTVTVSS GGGGSGGGGSGGGGSEIVLTQSPGTLSLSPGERATLSCRASQSVSSSYL AWYQQKPGQAPRLLIYGTSSRATGISDRFSGSGSGTDFTLTISRLEPED FAVYYCQHYGNSPPKFTFGPGTKLEIKTTTPAPRPPTPAPTIASQPLSL RPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKR GRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSAD APAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGL YNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQ ALPPR
BCMA_EBB-C1981-C3- nt Full CART	253	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCC ACGCCGCTCGGCCCCAAGTGCAGCTCGTGGAGTCAGGCGGAGGACTGGT GCAGCCCGGGGGCTCCCTGAGACTTTCCTGCGCGGCATCGGGTTTTACC TTCTCCTCCTATGCTATGTCCTGGGTGCGCCAGGCCCCGGGAAAGGGAC TGGAATGGGTGTCCGCAATCAGCGGTAGCGGGGGCTCAACATACTACGC CGACTCCGTCAAGGGTCGCTTCACTATTTCCCGGGACAACTCCAAGAAT ACCCTGTACCTCCAAATGAACAGCCTCAGGGCCGAGGATACTGCCGTGT ACTACTGCGCCAAAGTCGGATACGATAGCTCCGGTTACTACCGGGACTA CTACGGAATGGACGTGTGGGGACAGGGCACCACCGTGACCGTGTCAAGC GGCGGAGGCGGTTCAGGAGGGGGAGGCTCCGGCGGTGGAGGGTCCGAAA TCGTCCTGACTCAGTCGCCTGGCACTCTGTCGTTGTCCCCGGGGGAGCG CGCTACCCTGTCGTGTCGGGCGTCGCAGTCCGTGTCGAGCTCCTACCTC GCGTGGTACCAGCAGAAGCCCGGACAGGCCCCTAGACTTCTGATCTACG GCACTTCTTCACGCGCCACCGGGATCAGCGACAGGTTCAGCGGCTCCGG CTCCGGGACCGACTTCACCCTGACCATTAGCCGGCTGGAGCCTGAAGAT TTCGCCGTGTATTACTGCCAACACTACGGAAACTCGCCGCCAAAGTTCA CGTTCGGACCCGGAACCAAGCTGGAAATCAAGACCACTACCCCAGCACC GAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTG CGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACCCGGG GTCTTGACTTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGTAC TTGCGGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGC GGTCGGAAGAAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTG TGCAGACTACTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGA GGAGGAAGGCGGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGAT GCTCCAGCCTACAAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATC TTGGTCGGAGAGAGGAGTACGACGTGCTGGACAAGCGGAGAGGACGGGA CCCAGAAATGGGCGGGAAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTG TACAACGAGCTCCAAAAGGATAAGATGGCAGAAGCCTATAGCGAGATTG GTATGAAAGGGGAACGCAGAAGAGGCAAAGGCCACGACGGACTGTACCA GGGACTCAGCACCGCCACCAAGGACACCTATGACGCTCTTCACATGCAG GCCCTGCCGCCTCGG
BCMA_EBB-C1978-G4		
BCMA_EBB-C1978-G4- aa ScFv domain	149	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS AISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK MGWSSGYLGAFDIWGQGTTVTVSSGGGGSGGGGSGGGGSEIVLTQSPGT LSLSPGERATLSCRASQSVASSFLAWYQQKPGQAPRLLIYGASGRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQHYGGSPRLTFGGGTKVDI K
BCMA_EBB-C1978-G4- nt ScFv domain	170	GAAGTCCAACTGGTGGAGTCCGGGGGAGGGCTCGTGCAGCCCGGAGGCA GCCTTCGGCTGTCGTGCGCCGCCTCCGGGTTCACGTTCTCATCCTACGC GATGTCGTGGGTCAGACAGGCACCAGGAAAGGGACTGGAATGGGTGTCC

		GCCATTAGCGGCTCCGGCGGTAGCACCTACTATGCCGACTCAGTGAAGG GAAGGTTCACTATCTCCCGCGACAACAGCAAGAACACCCTGTACCTCCA AATGAACTCTCTGCGGGCCGAGGATACCGCGGTGTACTATTGCGCCAAG ATGGGTTGGTCCAGCGGATACTTGGGAGCCTTCGACATTTGGGGACAGG GCACTACTGTGACCGTGTCCTCCGGGGGTGGCGGATCGGGAGGCGGCGG CTCGGGTGGAGGGGGTTCCGAAATCGTGTTGACCCAGTCACCGGGAACC CTCTCGCTGTCCCCGGGAGAACGGGCTACACTGTCATGTAGAGCGTCCC AGTCCGTGGCTTCCTCGTTCCTGGCCTGGTACCAGCAGAAGCCGGGACA GGCACCCCGCCTGCTCATCTACGGAGCCAGCGGCCGGGCGACCGGCATC CCTGACCGCTTCTCCGGTTCCGGCTCGGGCACCGACTTTACTCTGACCA TTAGCAGGCTTGAGCCCGAGGATTTTGCCGTGTACTACTGCCAACACTA CGGGGGGAGCCCTCGCCTGACCTTCGGAGGCGGAACTAAGGTCGATATC AAAA
BCMA_EBB-C1978-G4- aa VH	191	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS AISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK MGWSSGYLGAFDIWGQGTTVTVSS
BCMA_EBB-C1978-G4- aa VL	212	EIVLTQSPGTLSLSPGERATLSCRASQSVASSFLAWYQQKPGQAPRLLI YGASGRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQHYGGSPRL TFGGGTKVDIK
BCMA_EBB-C1978-G4- aa Full CART	233	MALPVTALLLPLALLLHAARPEVQLVESGGGLVQPGGSLRLSCAASGFT FSSYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAKMGWSSGYLGAFDIWGQGTTVTVSSGGGG SGGGGSGGGGSEIVLTQSPGTLSLSPGERATLSCRASQSVASSFLAWYQ QKPGQAPRLLIYGASGRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVY YCQHYGGSPRLTFGGGTKVDIKTTTPAPRPPTPAPTIASQPLSLRPEAC RPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKL LYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYK QGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQ KDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
BCMA_EBB-C1978-G4- nt Full CART	254	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCC ACGCCGCTCGGCCCGAAGTCCAACTGGTGGAGTCCGGGGGAGGGCTCGT GCAGCCCGGAGGCAGCCTTCGGCTGTCGTGCGCCGCCTCCGGGTTCACG TTCTCATCCTACGCGATGTCGTGGGTCAGACAGGCACCAGGAAAGGGAC TGGAATGGGTGTCCGCCATTAGCGGCTCCGGCGGTAGCACCTACTATGC CGACTCAGTGAAGGGAAGGTTCACTATCTCCCGCGACAACAGCAAGAAC ACCCTGTACCTCCAAATGAACTCTCTGCGGGCCGAGGATACCGCGGTGT ACTATTGCGCCAAGATGGGTTGGTCCAGCGGATACTTGGGAGCCTTCGA CATTTGGGGACAGGGCACTACTGTGACCGTGTCCTCCGGGGGTGGCGGA TCGGGAGGCGGCGGCTCGGGTGGAGGGGGTTCCGAAATCGTGTTGACCC AGTCACCGGGAACCCTCTCGCTGTCCCCGGGAGAACGGGCTACACTGTC ATGTAGAGCGTCCCAGTCCGTGGCTTCCTCGTTCCTGGCCTGGTACCAG CAGAAGCCGGGACAGGCACCCCGCCTGCTCATCTACGGAGCCAGCGGCC GGGCGACCGGCATCCCTGACCGCTTCTCCGGTTCCGGCTCGGGCACCGA CTTTACTCTGACCATTAGCAGGCTTGAGCCCGAGGATTTTGCCGTGTAC TACTGCCAACACTACGGGGGGAGCCCTCGCCTGACCTTCGGAGGCGGAA CTAAGGTCGATATCAAAACCACTACCCCAGCACCGAGGCCACCCACCCC GGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGT AGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTGACTTCGCCT GCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGCT GCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTG CTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAG AGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTG

		CGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAG CAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGG AGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGG GAAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAA AAGGATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAAC GCAGAAGAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGC CACCAAGGACACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG

Table 3. Heavy Chain Variable Domain CDRs according to the Kabat numbering scheme (Kabat et al. (1991), "Sequences of Proteins of Immunological Interest," 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD)

Candidate	HCDR1	SEQ ID NO	HCDR2	SEQ ID NO	HCDR3	SEQ ID NO
139109	NHGMS	1051	GIVYSGSTYYAA SVKG	1091	HGGESDV	1131
139103	NYAMS	1052	GISRSGENTYYA DSVKG	1092	SPAHYYGGMDV	1132
139105	DYAMH	1053	GISWNSGSIGYA DSVKG	1093	HSFLAY	1133
139111	NHGMS	1054	GIVYSGSTYYAA SVKG	1094	HGGESDV	1134
139100	NFGIN	1055	WINPKNNNTNYA QKFQG	1095	GPYYYQSYMDV	1135
139101	SDAMT	1056	VISGSGGTTYYA DSVKG	1096	LDSSGYYYARG PRY	1136
139102	NYGIT	1057	WISAYNGNTNYA QKFQG	1097	GPYYYYMDV	1137
139104	NHGMS	1058	GIVYSGSTYYAA SVKG	1098	HGGESDV	1138
139106	NHGMS	1059	GIVYSGSTYYAA SVKG	1099	HGGESDV	1139
139107	NHGMS	1060	GIVYSGSTYYAA SVKG	1100	HGGESDV	1140
139108	DYYMS	1061	YISSSGSTIYYAD SVKG	1101	ESGDGMDV	1141
139110	DYYMS	1062	YISSSGNTIYYAD SVKG	1102	STMVREDY	1142
139112	NHGMS	1063	GIVYSGSTYYAA SVKG	1103	HGGESDV	1143
139113	NHGMS	1064	GIVYSGSTYYAA SVKG	1104	HGGESDV	1144
139114	NHGMS	1065	GIVYSGSTYYAA SVKG	1105	HGGESDV	1145
149362	SSYYYW G	1066	SIYYSGSAYYNPS LKS	1106	HWQEWPDAFDI	1146
149363	TSGMCVS	1067	RIDWDEDKFYST SLKT	1107	SGAGGTSATAF DI	1147
149364	SYSMN	1068	SISSSSSYIYYADS VKG	1108	TIAAVYAFDI	1148
149365	DYYMS	1069	YISSSGSTIYYAD SVKG	1109	DLRGAFDI	1149
149366	SHYIH	1070	MINPSGGVTAYS QTLQG	1110	EGSGSGWYFDF	1150

149367	SGGYYWS	1071	YIYYSGSTYYNPSLKS	1111	AGIAARLRGAFDI	1151
149368	SYAIS	1072	GIIPIFGTANYAQKFQG	1112	RGGYQLLRWDVGLLRSAFDI	1152
149369	SNSAAWN	1073	RTYYRSKWYSFYAISLKS	1113	SSPEGLFLYWFDP	1153
BCMA_EBB-C1978-A4	SYAMS	1074	AISGSGGSTYYADSVKG	1114	VEGSGSLDY	1154
BCMA_EBB-C1978-G1	RYPMS	1075	GISDSGVSTYYADSAKG	1115	RAGSEASDI	1155
BCMA_EBB-C1979-C1	SYAMS	1076	AISGSGGSTYYADSVKG	1116	ATYKRELRYYYGMDV	1156
BCMA_EBB-C1978-C7	SYAMS	1077	AISGSGGSTYYADSVKG	1117	ATYKRELRYYYGMDV	1157
BCMA_EBB-C1978-D10	DYAMH	1078	GISWNSGSIGYADSVKG	1118	VGKAVPDV	1158
BCMA_EBB-C1979-C12	DYAMH	1079	SINWKGNSLAYGDSVKG	1119	HQGVAYYNYAMDV	1159
BCMA_EBB-C1980-G4	SYAMS	1080	AISGSGGSTYYADSVKG	1120	VVRDGMDV	1160
BCMA_EBB-C1980-D2	SYAMS	1081	AISGSGGSTYYADSVKG	1121	IPQTGTFDY	1161
BCMA_EBB-C1978-A10	SYAMS	1082	AISGSGGSTYYADSVKG	1122	ANYKRELRYYYGMDV	1162
BCMA_EBB-C1978-D4	SYAMS	1083	AISGSGGSTYYADSVKG	1123	ALVGATGAFDI	1163
BCMA_EBB-C1980-A2	SYAMS	1084	AISGSGGSTYYADSVKG	1124	WFGEGFDP	1164
BCMA_EBB-C1981-C3	SYAMS	1085	AISGSGGSTYYADSVKG	1125	VGYDSSGYYRDYYGMDV	1165
BCMA_EBB-C1978-G4	SYAMS	1086	AISGSGGSTYYADSVKG	1126	MGWSSGYLGAFDI	1166
A7D12.2	NFGMN	1087	WINTYTGESYFADDFKG	1127	GEIYYGYDGGFAY	1167
C11D5.3	DYSIN	1088	WINTETREPAYAYDFRG	1128	DYSYAMDY	1168
C12A3.2	HYSMN	1089	RINTESGVPIYADDFKG	1129	DYLYSLDF	1169
C13F12.1	HYSMN	1090	RINTETGEPLYADDFKG	1130	DYLYSCDY	1170

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Table 4. Light Chain Variable Domain CDRs according to the Kabat numbering scheme (Kabat et al. (1991), "Sequences of Proteins of Immunological Interest," 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD)

Candidate	**LCDR1**	**SEQ ID NO**	**LCDR2**	**SEQ ID NO**	**LCDR3**	**SEQ ID NO**
139109	RASQSISSYLN	1171	AASSLQS	1211	QQSYSTPYT	1251
139103	RASQSISSSFLA	1172	GASRRAT	1212	QQYHSSPSWT	1252

139105	RSSQSLLHSNGYNYLD	1173	LGSNRAS	1213	MQALQTPYT	1253
139111	KSSQSLLRNDGKTPLY	1174	EVSNRFS	1214	MQNIQFPS	1254
139100	RSSQSLLHSNGYNYLN	1175	LGSKRAS	1215	MQALQTPYT	1255
139101	RASQSISSYLN	1176	GASTLAS	1216	QQSYKRAS	1256
139102	RSSQSLLYSNGYNYVD	1177	LGSNRAS	1217	MQGRQFPYS	1257
139104	RASQSVSSNLA	1178	GASTRAS	1218	QQYGSSLT	1258
139106	RASQSVSSKLA	1179	GASIRAT	1219	QQYGSSSWT	1259
139107	RASQSVGSTNLA	1180	DASNRAT	1220	QQYGSSPPWT	1260
139108	RASQSISSYLN	1181	AASSLQS	1221	QQSYTLA	1261
139110	KSSESLVHNSGKTYLN	1182	EVSNRDS	1222	MQGTHWPGT	1262
139112	QASEDINKFLN	1183	DASTLQT	1223	QQYESLPLT	1263
139113	RASQSVGSNLA	1184	GASTRAT	1224	QQYNDWLPVT	1264
139114	RASQSIGSSSLA	1185	GASSRAS	1225	QQYAGSPPFT	1265
149362	KASQDIDDAMN	1186	SATSPVP	1226	LQHDNFPLT	1266
149363	RASQDIYNNLA	1187	AANKSQS	1227	QHYYRFPYS	1267
149364	RSSQSLLHSNGYNYLD	1188	LGSNRAS	1228	MQALQTPYT	1268
149365	GGNNIGTKSVH	1189	DDSVRPS	1229	QVWDSDSEHVV	1269
149366	SGDGLSKKYVS	1190	RDKERPS	1230	QAWDDTTVV	1270
149367	RASQGIRNWLA	1191	AASNLQS	1231	QKYNSAPFT	1271
149368	GGNNIGSKSVH	1192	GKNNRPS	1232	SSRDSSGDHLRV	1272
149369	QGDSLGNYYAT	1193	GTNNRPS	1233	NSRDSSGHHLL	1273
BCMA_EBB-C1978-A4	RASQSVSSAYLA	1194	GASTRAT	1234	QHYGSSFNGSSLFT	1274
BCMA_EBB-C1978-G1	RASQSVSNSLA	1195	DASSRAT	1235	QQFGTSSGLT	1275
BCMA_EBB-C1979-C1	RASQSVSSSFLA	1196	GASSRAT	1236	QQYHSSPSWT	1276
BCMA_EBB-C1978-C7	RASQSVSTTFLA	1197	GSSNRAT	1237	QQYHSSPSWT	1277
BCMA_EBB-C1978-D10	RASQSISSYLN	1198	AASSLQS	1238	QQSYSTPYS	1278
BCMA_EBB-C1979-C12	RATQSIGSSFLA	1199	GASQRAT	1239	QHYESSPSWT	1279
BCMA_EBB-C1980-G4	RASQSVSSSYLA	1200	GASSRAT	1240	QQYGSPPRFT	1280
BCMA_EBB-C1980-D2	RASQSVSSSYLA	1201	GASSRAT	1241	QHYGSSPSWT	1281
BCMA_EBB-C1978-A10	RASQRVASNYLA	1202	GASSRAT	1242	QHYDSSPSWT	1282
BCMA_EBB-C1978-D4	RASQSLSSNFLA	1203	GASNWAT	1243	QYYGTSPMYT	1283
BCMA_EBB-C1980-A2	RSSQSLLHSNGYNYLD	1204	LGSNRAS	1244	MQALQTPLT	1284

BCMA_EBB-C1981-C3	RASQSVSSSYLA	1205	GTSSRAT	1245	QHYGNSPPKFT	1285
BCMA_EBB-C1978-G4	RASQSVASSFLA	1206	GASGRAT	1246	QHYGGSPRLT	1286
A7D12.2	RASQDVNTAVS	1207	SASYRYT	1247	QQHYSTPWT	1287
C11D5.3	RASESVSVIGAHLIH	1208	LASNLET	1248	LQSRIFPRT	1288
C12A3.2	RASESVTILGSHLIY	1209	LASNVQT	1249	LQSRTIPRT	1289
C13F12.1	RASESVTILGSHLIY	1210	LASNVQT	1250	LQSRTIPRT	1290

Table 5. Additional exemplary BCMA CAR sequences

Name	SEQ ID NO:
A7D12.2 VH	255
A7D12.2 VL	259
A7D12.2 scFv domain	263
A7D12.2 Full CART	267
C11D5.3 VH	256
C11D5.3 VL	260
C11D5.3 scFv domain	264
C11D5.3 Full CART	268
C12A3.2 VH	257
C12A3.2 VL	261
C12A3.2 scFv domain	265
C12A3.2 Full CART	269
C13F12.1 VH	258
C13F12.1 VL	262
C13F12.1 scFv domain	266
C13F12.1 Full CART	270

RNA Transfection

Disclosed herein are methods for producing an in vitro transcribed RNA CAR. The present invention also includes a CAR encoding RNA construct that can be directly transfected into a cell. A method for generating mRNA for use in transfection can involve in vitro transcription (IVT) of a template with specially designed primers, followed by polyA addition, to produce a construct containing 3' and 5' untranslated sequence ("UTR"), a 5' cap and/or Internal Ribosome Entry Site (IRES), the nucleic acid to be expressed, and a polyA tail, typically 50-2000 bases (SEQ ID NO: 2025) in length. RNA so produced can efficiently transfect different kinds of cells. In one aspect, the template includes sequences for the CAR.

In one aspect the anti-BCMA CAR is encoded by a messenger RNA (mRNA). In one aspect the mRNA encoding the anti-BCMA CAR is introduced into an immune effector cell, e.g., a T cell or a NK cell, for production of a CAR-expressing cell (e.g., CART cell or CAR-expressing NK cell).

In one embodiment, the in vitro transcribed RNA CAR can be introduced to a cell as a form of transient transfection. The RNA is produced by in vitro transcription using a polymerase chain reaction (PCR)-generated template. DNA of interest from any source can be directly converted by PCR into a template for in vitro mRNA synthesis using appropriate primers and RNA polymerase. The source of the DNA can be, for example, genomic DNA, plasmid DNA, phage DNA, cDNA, synthetic DNA sequence or any other appropriate source of DNA. The desired temple for in vitro transcription is a CAR of the present invention. For example, the template for the RNA CAR comprises an extracellular region comprising a single chain variable domain of an anti-tumor antibody; a hinge region, a transmembrane domain (e.g., a transmembrane domain of CD8a); and a cytoplasmic region that includes an intracellular signaling domain, e.g., comprising the signaling domain of CD3-zeta and the signaling domain of 4-1BB.

In one embodiment, the DNA to be used for PCR contains an open reading frame. The DNA can be from a naturally occurring DNA sequence from the genome of an organism. In one embodiment, the nucleic acid can include some or all of the 5' and/or 3' untranslated regions (UTRs). The nucleic acid can include exons and introns. In one embodiment, the DNA to be used for PCR is a human nucleic acid sequence. In another embodiment, the DNA to be used for PCR is a human nucleic acid sequence including the 5' and 3' UTRs. The DNA can alternatively be an artificial DNA sequence that is not normally expressed in a naturally occurring organism. An exemplary artificial DNA sequence is one that contains portions of genes that are ligated together to form an open reading frame that encodes a fusion protein. The portions of DNA that are ligated together can be from a single organism or from more than one organism.

PCR is used to generate a template for in vitro transcription of mRNA which is used for transfection. Methods for performing PCR are well known in the art. Primers for use in PCR are designed to have regions that are substantially complementary to regions of the DNA to be used as a template for the PCR. "Substantially complementary," as used herein, refers to sequences of nucleotides where a majority or all of the bases in the primer sequence are complementary, or one or more bases are non-complementary, or mismatched. Substantially complementary sequences are able to anneal or hybridize with the intended DNA target under annealing conditions used for PCR. The primers can be designed to be substantially complementary to any portion of the DNA template. For example, the primers can be designed to amplify the portion of a nucleic acid that is normally transcribed in cells (the open reading frame), including 5' and 3' UTRs. The primers can also be designed to amplify a portion of a nucleic acid that encodes a particular domain of interest. In one embodiment, the primers are designed to amplify the coding region of a human cDNA, including all or portions of the 5' and 3' UTRs. Primers useful for PCR can be generated by synthetic methods that are well known in the art. "Forward primers"

are primers that contain a region of nucleotides that are substantially complementary to nucleotides on the DNA template that are upstream of the DNA sequence that is to be amplified. "Upstream" is used herein to refer to a location 5, to the DNA sequence to be amplified relative to the coding strand. "Reverse primers" are primers that contain a region of nucleotides that are substantially complementary to a double-stranded DNA template that are downstream of the DNA sequence that is to be amplified. "Downstream" is used herein to refer to a location 3' to the DNA sequence to be amplified relative to the coding strand.

Any DNA polymerase useful for PCR can be used in the methods disclosed herein. The reagents and polymerase are commercially available from a number of sources.

Chemical structures with the ability to promote stability and/or translation efficiency may also be used. The RNA preferably has 5' and 3' UTRs. In one embodiment, the 5' UTR is between one and 3000 nucleotides in length. The length of 5' and 3' UTR sequences to be added to the coding region can be altered by different methods, including, but not limited to, designing primers for PCR that anneal to different regions of the UTRs. Using this approach, one of ordinary skill in the art can modify the 5' and 3' UTR lengths required to achieve optimal translation efficiency following transfection of the transcribed RNA.

The 5' and 3' UTRs can be the naturally occurring, endogenous 5' and 3' UTRs for the nucleic acid of interest. Alternatively, UTR sequences that are not endogenous to the nucleic acid of interest can be added by incorporating the UTR sequences into the forward and reverse primers or by any other modifications of the template. The use of UTR sequences that are not endogenous to the nucleic acid of interest can be useful for modifying the stability and/or translation efficiency of the RNA. For example, it is known that AU-rich elements in 3' UTR sequences can decrease the stability of mRNA. Therefore, 3' UTRs can be selected or designed to increase the stability of the transcribed RNA based on properties of UTRs that are well known in the art.

In one embodiment, the 5' UTR can contain the Kozak sequence of the endogenous nucleic acid. Alternatively, when a 5' UTR that is not endogenous to the nucleic acid of interest is being added by PCR as described above, a consensus Kozak sequence can be redesigned by adding the 5' UTR sequence. Kozak sequences can increase the efficiency of translation of some RNA transcripts, but does not appear to be required for all RNAs to enable efficient translation. The requirement for Kozak sequences for many mRNAs is known in the art. In other embodiments the 5' UTR can be 5'UTR of an RNA virus whose RNA genome is stable in cells. In other embodiments various nucleotide analogues can be used in the 3' or 5' UTR to impede exonuclease degradation of the mRNA.

To enable synthesis of RNA from a DNA template without the need for gene cloning, a promoter of transcription should be attached to the DNA template upstream of the sequence to be transcribed. When a sequence that functions as a promoter for an RNA polymerase is added to the 5' end of the forward primer, the RNA polymerase promoter becomes incorporated into the PCR product upstream of the open reading frame that is to be transcribed. In one preferred embodiment, the promoter is a T7 polymerase promoter, as described elsewhere herein. Other useful promoters include, but are not limited to, T3 and SP6 RNA polymerase promoters. Consensus nucleotide sequences for T7, T3 and SP6 promoters are known in the art.

In a preferred embodiment, the mRNA has both a cap on the 5' end and a 3' poly(A) tail which determine ribosome binding, initiation of translation and stability mRNA in the cell. On a circular DNA template, for instance, plasmid DNA, RNA polymerase produces a long concatameric product which is not suitable for expression in eukaryotic cells. The transcription of plasmid DNA linearized at the end of the 3' UTR results in normal sized mRNA which is not effective in eukaryotic transfection even if it is polyadenylated after transcription.

On a linear DNA template, phage T7 RNA polymerase can extend the 3' end of the transcript beyond the last base of the template (Schenborn and Mierendorf, Nuc Acids Res., 13:6223-36 (1985); Nacheva and Berzal-Herranz, Eur. J. Biochem., 270:1485-65 (2003).

The conventional method of integration of polyA/T stretches into a DNA template is molecular cloning. However polyA/T sequence integrated into plasmid DNA can cause plasmid instability, which is why plasmid DNA templates obtained from bacterial cells are often highly contaminated with deletions and other aberrations. This makes cloning procedures not only laborious and time consuming but often not reliable. That is why a method which allows construction of DNA templates with polyA/T 3' stretch without cloning highly desirable.

The polyA/T segment of the transcriptional DNA template can be produced during PCR by using a reverse primer containing a polyT tail, such as 100T tail (SEQ ID NO: 2026) (size can be 50-5000 T (SEQ ID NO: 2027)), or after PCR by any other method, including, but not limited to, DNA ligation or in vitro recombination. Poly(A) tails also provide stability to RNAs and reduce their degradation. Generally, the length of a poly(A) tail positively correlates with the stability of the transcribed RNA. In one embodiment, the poly(A) tail is between 100 and 5000 adenosines (SEQ ID NO: 2028).

Poly(A) tails of RNAs can be further extended following in vitro transcription with the use of a poly(A) polymerase, such as E. coli polyA polymerase (E-PAP). In one embodiment, increasing the length of a poly(A) tail from 100 nucleotides to between 300 and 400 nucleotides (SEQ ID NO: 2024)

results in about a two-fold increase in the translation efficiency of the RNA. Additionally, the attachment of different chemical groups to the 3' end can increase mRNA stability. Such attachment can contain modified/artificial nucleotides, aptamers and other compounds. For example, ATP analogs can be incorporated into the poly(A) tail using poly(A) polymerase. ATP analogs can further increase the stability of the RNA.

5' caps on also provide stability to RNA molecules. In a preferred embodiment, RNAs produced by the methods disclosed herein include a 5' cap. The 5' cap is provided using techniques known in the art and described herein (Cougot, et al., Trends in Biochem. Sci., 29:436-444 (2001); Stepinski, et al., RNA, 7:1468-95 (2001); Elango, et al., Biochim. Biophys. Res. Commun., 330:958-966 (2005)).

The RNAs produced by the methods disclosed herein can also contain an internal ribosome entry site (IRES) sequence. The IRES sequence may be any viral, chromosomal or artificially designed sequence which initiates cap-independent ribosome binding to mRNA and facilitates the initiation of translation. Any solutes suitable for cell electroporation, which can contain factors facilitating cellular permeability and viability such as sugars, peptides, lipids, proteins, antioxidants, and surfactants can be included.

RNA can be introduced into target cells using any of a number of different methods, for instance, commercially available methods which include, but are not limited to, electroporation (Amaxa Nucleofector-II (Amaxa Biosystems, Cologne, Germany)), (ECM 830 (BTX) (Harvard Instruments, Boston, Mass.) or the Gene Pulser II (BioRad, Denver, Colo.), Multiporator (Eppendort, Hamburg Germany), cationic liposome mediated transfection using lipofection, polymer encapsulation, peptide mediated transfection, or biolistic particle delivery systems such as “gene guns” (see, for example, Nishikawa, et al. Hum Gene Ther., 12(8):861-70 (2001).

Non-viral delivery methods

In some aspects, non-viral methods can be used to deliver a nucleic acid encoding a CAR described herein into a cell or tissue or a subject.

In some embodiments, the non-viral method includes the use of a transposon (also called a transposable element). In some embodiments, a transposon is a piece of DNA that can insert itself at a location in a genome, for example, a piece of DNA that is capable of self-replicating and inserting its copy into a genome, or a piece of DNA that can be spliced out of a longer nucleic acid and inserted into another place in a genome. For example, a transposon comprises a DNA sequence made up of inverted repeats flanking genes for transposition.

Exemplary methods of nucleic acid delivery using a transposon include a Sleeping Beauty

transposon system (SBTS) and a piggyBac (PB) transposon system. See, e.g., Aronovich et al. Hum. Mol. Genet. 20.R1(2011):R14-20; Singh et al. Cancer Res. 15(2008):2961–2971; Huang et al. Mol. Ther. 16(2008):580–589; Grabundzija et al. Mol. Ther. 18(2010):1200–1209; Kebriaei et al. Blood. 122.21(2013):166; Williams. Molecular Therapy 16.9(2008):1515–16; Bell et al. Nat. Protoc. 2.12(2007):3153-65; and Ding et al. Cell. 122.3(2005):473-83, all of which are incorporated herein by reference.

The SBTS includes two components: 1) a transposon containing a transgene and 2) a source of transposase enzyme. The transposase can transpose the transposon from a carrier plasmid (or other donor DNA) to a target DNA, such as a host cell chromosome/genome. For example, the transposase binds to the carrier plasmid/donor DNA, cuts the transposon (including transgene(s)) out of the plasmid, and inserts it into the genome of the host cell. See, e.g., Aronovich et al. *supra.*

Exemplary transposons include a pT2-based transposon. See, e.g., Grabundzija et al. Nucleic Acids Res. 41.3(2013):1829-47; and Singh et al. Cancer Res. 68.8(2008): 2961–2971, all of which are incorporated herein by reference. Exemplary transposases include a Tc1/mariner-type transposase, e.g., the SB10 transposase or the SB11 transposase (a hyperactive transposase which can be expressed, e.g., from a cytomegalovirus promoter). See, e.g., Aronovich et al.; Kebriaei et al.; and Grabundzija et al., all of which are incorporated herein by reference.

Use of the SBTS permits efficient integration and expression of a transgene, e.g., a nucleic acid encoding a CAR described herein. Provided herein are methods of generating a cell, e.g., T cell or NK cell, that stably expresses a CAR described herein, e.g., using a transposon system such as SBTS.

In accordance with methods described herein, in some embodiments, one or more nucleic acids, e.g., plasmids, containing the SBTS components are delivered to a cell (e.g., T or NK cell). For example, the nucleic acid(s) are delivered by standard methods of nucleic acid (e.g., plasmid DNA) delivery, e.g., methods described herein, e.g., electroporation, transfection, or lipofection. In some embodiments, the nucleic acid contains a transposon comprising a transgene, e.g., a nucleic acid encoding a CAR described herein. In some embodiments, the nucleic acid contains a transposon comprising a transgene (e.g., a nucleic acid encoding a CAR described herein) as well as a nucleic acid sequence encoding a transposase enzyme. In other embodiments, a system with two nucleic acids is provided, e.g., a dual-plasmid system, e.g., where a first plasmid contains a transposon comprising a transgene, and a second plasmid contains a nucleic acid sequence encoding a transposase enzyme. For example, the first and the second nucleic acids are co-delivered into a host cell.

In some embodiments, cells, e.g., T or NK cells, are generated that express a CAR described herein by using a combination of gene insertion using the SBTS and genetic editing using a nuclease (e.g.,

Zinc finger nucleases (ZFNs), Transcription Activator-Like Effector Nucleases (TALENs), the CRISPR/Cas system, or engineered meganuclease re-engineered homing endonucleases).

In some embodiments, use of a non-viral method of delivery permits reprogramming of cells, e.g., T or NK cells, and direct infusion of the cells into a subject. Advantages of non-viral vectors include but are not limited to the ease and relatively low cost of producing sufficient amounts required to meet a patient population, stability during storage, and lack of immunogenicity.

Nucleic Acid Constructs Encoding a CAR

The present invention also provides nucleic acid molecules encoding one or more CAR constructs described herein. In one aspect, the nucleic acid molecule is provided as a messenger RNA transcript. In one aspect, the nucleic acid molecule is provided as a DNA construct.

Accordingly, in one aspect, the invention pertains to an isolated nucleic acid molecule encoding a chimeric antigen receptor (CAR), wherein the CAR comprises an antigen binding domain, a transmembrane domain, and an intracellular signaling domain comprising a stimulatory domain, e.g., a costimulatory signaling domain and/or a primary signaling domain, e.g., zeta chain.

The nucleic acid sequences coding for the desired molecules can be obtained using recombinant methods known in the art, such as, for example by screening libraries from cells expressing the gene, by deriving the gene from a vector known to include the same, or by isolating directly from cells and tissues containing the same, using standard techniques. Alternatively, the gene of interest can be produced synthetically, rather than cloned.

The present invention also provides vectors in which a DNA of the present invention is inserted. Vectors derived from retroviruses such as the lentivirus are suitable tools to achieve long-term gene transfer since they allow long-term, stable integration of a transgene and its propagation in daughter cells. Lentiviral vectors have the added advantage over vectors derived from onco-retroviruses such as murine leukemia viruses in that they can transduce non-proliferating cells, such as hepatocytes. They also have the added advantage of low immunogenicity. A retroviral vector may also be, e.g., a gammaretroviral vector. A gammaretroviral vector may include, e.g., a promoter, a packaging signal (ψ), a primer binding site (PBS), one or more (e.g., two) long terminal repeats (LTR), and a transgene of interest, e.g., a gene encoding a CAR. A gammaretroviral vector may lack viral structural gens such as gag, pol, and env. Exemplary gammaretroviral vectors include Murine Leukemia Virus (MLV), Spleen-Focus Forming Virus (SFFV), and Myeloproliferative Sarcoma Virus (MPSV), and vectors derived therefrom. Other gammaretroviral vectors are described, e.g., in Tobias Maetzig et al., "Gammaretroviral Vectors: Biology, Technology and Application" Viruses. 2011 Jun; 3(6): 677–713.

In another embodiment, the vector comprising the nucleic acid encoding the desired CAR of the invention is an adenoviral vector (A5/35). In another embodiment, the expression of nucleic acids encoding CARs can be accomplished using of transposons such as sleeping beauty, CRISPR, CAS9, and zinc finger nucleases. See below June et al. 2009*Nature Reviews Immunology* 9.10: 704-716, is incorporated herein by reference.

In brief summary, the expression of natural or synthetic nucleic acids encoding CARs is typically achieved by operably linking a nucleic acid encoding the CAR polypeptide or portions thereof to a promoter, and incorporating the construct into an expression vector. The vectors can be suitable for replication and integration eukaryotes. Typical cloning vectors contain transcription and translation terminators, initiation sequences, and promoters useful for regulation of the expression of the desired nucleic acid sequence.

The expression constructs of the present invention may also be used for nucleic acid immunization and gene therapy, using standard gene delivery protocols. Methods for gene delivery are known in the art. See, e.g., U.S. Pat. Nos. 5,399,346, 5,580,859, 5,589,466, incorporated by reference herein in their entireties. In another embodiment, the invention provides a gene therapy vector.

The nucleic acid can be cloned into a number of types of vectors. For example, the nucleic acid can be cloned into a vector including, but not limited to a plasmid, a phagemid, a phage derivative, an animal virus, and a cosmid. Vectors of particular interest include expression vectors, replication vectors, probe generation vectors, and sequencing vectors.

Further, the expression vector may be provided to a cell in the form of a viral vector. Viral vector technology is well known in the art and is described, for example, in Sambrook et al., 2012, MOLECULAR CLONING: A LABORATORY MANUAL, volumes 1 -4, Cold Spring Harbor Press, NY), and in other virology and molecular biology manuals. Viruses, which are useful as vectors include, but are not limited to, retroviruses, adenoviruses, adeno- associated viruses, herpes viruses, and lentiviruses. In general, a suitable vector contains an origin of replication functional in at least one organism, a promoter sequence, convenient restriction endonuclease sites, and one or more selectable markers, (e.g., WO 01/96584; WO 01/29058; and U.S. Pat. No. 6,326,193).

A number of viral based systems have been developed for gene transfer into mammalian cells. For example, retroviruses provide a convenient platform for gene delivery systems. A selected gene can be inserted into a vector and packaged in retroviral particles using techniques known in the art. The recombinant virus can then be isolated and delivered to cells of the subject either in vivo or ex vivo. A number of retroviral systems are known in the art. In some embodiments, adenovirus vectors are used. A number of adenovirus vectors are known in the art. In one embodiment, lentivirus vectors are used.

Additional promoter elements, e.g., enhancers, regulate the frequency of transcriptional initiation. Typically, these are located in the region 30-110 bp upstream of the start site, although a number of promoters have been shown to contain functional elements downstream of the start site as well. The spacing between promoter elements frequently is flexible, so that promoter function is preserved when elements are inverted or moved relative to one another. In the thymidine kinase (tk) promoter, the spacing between promoter elements can be increased to 50 bp apart before activity begins to decline. Depending on the promoter, it appears that individual elements can function either cooperatively or independently to activate transcription.

An example of a promoter that is capable of expressing a CAR transgene in a mammalian T cell is the EF1a promoter. The native EF1a promoter drives expression of the alpha subunit of the elongation factor-1 complex, which is responsible for the enzymatic delivery of aminoacyl tRNAs to the ribosome. The EF1a promoter has been extensively used in mammalian expression plasmids and has been shown to be effective in driving CAR expression from transgenes cloned into a lentiviral vector. See, e.g., Milone et al., Mol. Ther. 17(8): 1453–1464 (2009).

Another example of a promoter is the immediate early cytomegalovirus (CMV) promoter sequence. This promoter sequence is a strong constitutive promoter sequence capable of driving high levels of expression of any polynucleotide sequence operatively linked thereto. However, other constitutive promoter sequences may also be used, including, but not limited to the simian virus 40 (SV40) early promoter, mouse mammary tumor virus (MMTV), human immunodeficiency virus (HIV) long terminal repeat (LTR) promoter, MoMuLV promoter, an avian leukemia virus promoter, an Epstein-Barr virus immediate early promoter, a Rous sarcoma virus promoter, as well as human gene promoters such as, but not limited to, the actin promoter, the myosin promoter, the elongation factor-1α promoter, the hemoglobin promoter, and the creatine kinase promoter. Further, the invention should not be limited to the use of constitutive promoters. Inducible promoters are also contemplated as part of the invention. The use of an inducible promoter provides a molecular switch capable of turning on expression of the polynucleotide sequence which it is operatively linked when such expression is desired, or turning off the expression when expression is not desired. Examples of inducible promoters include, but are not limited to a metallothionine promoter, a glucocorticoid promoter, a progesterone promoter, and a tetracycline promoter.

Another example of a promoter is the phosphoglycerate kinase (PGK) promoter. In embodiments, a truncated PGK promoter (e.g., a PGK promoter with one or more, e.g., 1, 2, 5, 10, 100, 200, 300, or 400, nucleotide deletions when compared to the wild-type PGK promoter sequence) may be desired. The nucleotide sequences of exemplary PGK promoters are provided below.

WT PGK Promoter

ACCCCTCTCTCCAGCCACTAAGCCAGTTGCTCCCTCGGCTGACGGCTGCACGCGAGGCCTCCGAACG
TCTTACGCCTTGTGGCGCGCCCGTCCTTGTCCCGGGTGTGATGGCGGGGTGTGGGGCGGAGGGCGTG
GCGGGGAAGGGCCGGCGACGAGAGCCGCGCGGGACGACTCGTCGGCGATAACCGGTGTCGGGTAGCG
CCAGCCGCGCGACGGTAACGAGGGACCGCGACAGGCAGACGCTCCCATGATCACTCTGCACGCCGAA
GGCAAATAGTGCAGGCCGTGCGGCGCTTGGCGTTCCTTGGAAGGGCTGAATCCCCGCCTCGTCCTTC
GCAGCGGCCCCCCGGGTGTTCCCATCGCCGCTTCTAGGCCCACTGCGACGCTTGCCTGCACTTCTTA
CACGCTCTGGGTCCCAGCCGCGGCGACGCAAAGGGCCTTGGTGCGGGTCTCGTCGGCGCAGGGACGC
GTTTGGGTCCCGACGGAACCTTTTCCGCGTTGGGGTTGGGGCACCATAAGCT
(SEQ ID NO: 1291)

Exemplary truncated PGK Promoters:

PGK100:
ACCCCTCTCTCCAGCCACTAAGCCAGTTGCTCCCTCGGCTGACGGCTGCACGCGAGGCCTCCGAACG
TCTTACGCCTTGTGGCGCGCCCGTCCTTGTCCCGGGTGTGATGGCGGGGTG
(SEQ ID NO: 1292)

PGK200:
ACCCCTCTCTCCAGCCACTAAGCCAGTTGCTCCCTCGGCTGACGGCTGCACGCGAGGCCTCCGAACG
TCTTACGCCTTGTGGCGCGCCCGTCCTTGTCCCGGGTGTGATGGCGGGGTGTGGGGCGGAGGGCGTG
GCGGGGAAGGGCCGGCGACGAGAGCCGCGCGGGACGACTCGTCGGCGATAACCGGTGTCGGGTAGCG
CCAGCCGCGCGACGGTAACG
(SEQ ID NO: 1293)

PGK300:
ACCCCTCTCTCCAGCCACTAAGCCAGTTGCTCCCTCGGCTGACGGCTGCACGCGAGGCCTCCGAACG
TCTTACGCCTTGTGGCGCGCCCGTCCTTGTCCCGGGTGTGATGGCGGGGTGTGGGGCGGAGGGCGTG
GCGGGGAAGGGCCGGCGACGAGAGCCGCGCGGGACGACTCGTCGGCGATAACCGGTGTCGGGTAGCG
CCAGCCGCGCGACGGTAACGAGGGACCGCGACAGGCAGACGCTCCCATGATCACTCTGCACGCCGAA
GGCAAATAGTGCAGGCCGTGCGGCGCTTGGCGTTCCTTGGAAGGGCTGAATCCCCG
(SEQ ID NO: 1294)

PGK400:
ACCCCTCTCTCCAGCCACTAAGCCAGTTGCTCCCTCGGCTGACGGCTGCACGCGAGGCCTCCGAACG
TCTTACGCCTTGTGGCGCGCCCGTCCTTGTCCCGGGTGTGATGGCGGGGTGTGGGGCGGAGGGCGTG
GCGGGGAAGGGCCGGCGACGAGAGCCGCGCGGGACGACTCGTCGGCGATAACCGGTGTCGGGTAGCG
CCAGCCGCGCGACGGTAACGAGGGACCGCGACAGGCAGACGCTCCCATGATCACTCTGCACGCCGAA
GGCAAATAGTGCAGGCCGTGCGGCGCTTGGCGTTCCTTGGAAGGGCTGAATCCCCGCCTCGTCCTTC
GCAGCGGCCCCCCGGGTGTTCCCATCGCCGCTTCTAGGCCCACTGCGACGCTTGCCTGCACTTCTTA
CACGCTCTGGGTCCCAGCCG
(SEQ ID NO: 1295)

A vector may also include, e.g., a signal sequence to facilitate secretion, a polyadenylation signal and transcription terminator (e.g., from Bovine Growth Hormone (BGH) gene), an element allowing episomal replication and replication in prokaryotes (e.g. SV40 origin and ColE1 or others known in the art) and/or elements to allow selection (e.g., ampicillin resistance gene and/or zeocin marker).

In order to assess the expression of a CAR polypeptide or portions thereof, the expression vector to be introduced into a cell can also contain either a selectable marker gene or a reporter gene or both to facilitate identification and selection of expressing cells from the population of cells sought to be transfected or infected through viral vectors. In other aspects, the selectable marker may be carried on a separate piece of DNA and used in a co- transfection procedure. Both selectable markers and reporter genes may be flanked with appropriate regulatory sequences to enable expression in the host cells. Useful selectable markers include, for example, antibiotic-resistance genes, such as neo and the like.

Reporter genes are used for identifying potentially transfected cells and for evaluating the functionality of regulatory sequences. In general, a reporter gene is a gene that is not present in or expressed by the recipient organism or tissue and that encodes a polypeptide whose expression is manifested by some easily detectable property, e.g., enzymatic activity. Expression of the reporter gene is assayed at a suitable time after the DNA has been introduced into the recipient cells. Suitable reporter genes may include genes encoding luciferase, beta-galactosidase, chloramphenicol acetyl transferase, secreted alkaline phosphatase, or the green fluorescent protein gene (e.g., Ui-Tei et al., 2000 FEBS Letters 479: 79-82). Suitable expression systems are well known and may be prepared using known techniques or obtained commercially. In general, the construct with the minimal 5' flanking region showing the highest level of expression of reporter gene is identified as the promoter. Such promoter regions may be linked to a reporter gene and used to evaluate agents for the ability to modulate promoter- driven transcription.

In one embodiment, the vector can further comprise a nucleic acid encoding a second CAR. In one embodiment, the second CAR includes an antigen binding domain to a target expressed on acute myeloid leukemia cells, such as, e.g., CD123, CD34, CLL-1, folate receptor beta, or FLT3; or a target expressed on a B cell, e.g., CD10, CD19, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, or CD79a. In one embodiment, the vector comprises a nucleic acid sequence encoding a first CAR that specifically binds a first antigen and includes an intracellular signaling domain having a costimulatory signaling domain but not a primary signaling domain, and a nucleic acid encoding a second CAR that specifically binds a second, different, antigen and includes an intracellular signaling domain having a primary signaling domain but not a costimulatory signaling domain. In one embodiment, the vector comprises a nucleic acid encoding a first BCMA CAR that includes a BCMA binding domain, a transmembrane domain and a costimulatory domain and a nucleic acid encoding a second CAR that targets an antigen other than BCMA (e.g., an antigen expressed on AML cells, e.g., CD123, CD34, CLL-1, folate receptor beta, or FLT3; or an antigen expressed on a B cell, e.g., CD10, CD19, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, or CD79a) and includes an antigen binding domain, a transmembrane domain and a primary signaling domain. In another

embodiment, the vector comprises a nucleic acid encoding a first BCMA CAR that includes a BCMA binding domain, a transmembrane domain and a primary signaling domain and a nucleic acid encoding a second CAR that specifically binds an antigen other than BCMA (e.g., an antigen expressed on AML cells, e.g., CD123, CD34, CLL-1, folate receptor beta, or FLT3; or an antigen expressed on a B cell, e.g., CD10, CD19, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, or CD79a) and includes an antigen binding domain to the antigen, a transmembrane domain and a costimulatory signaling domain.

In one embodiment, the vector comprises a nucleic acid encoding a BCMA CAR described herein and a nucleic acid encoding an inhibitory CAR. In one embodiment, the inhibitory CAR comprises an antigen binding domain that binds an antigen found on normal cells but not cancer cells, e.g., normal cells that also express BCMA. In one embodiment, the inhibitory CAR comprises the antigen binding domain, a transmembrane domain and an intracellular domain of an inhibitory molecule. For example, the intracellular domain of the inhibitory CAR can be an intracellular domain of PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, and TGFR beta.

In embodiments, the vector may comprise two or more nucleic acid sequences encoding a CAR, e.g., a BCMA CAR described herein and a second CAR, e.g., an inhibitory CAR or a CAR that specifically binds to an antigen other than BCMA (e.g., an antigen expressed on AML cells, e.g., CD123, CLL-1, CD34, FLT3, or folate receptor beta; or antigen expresson B cells, e.g., CD10, CD19, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, or CD79a). In such embodiments, the two or more nucleic acid sequences encoding the CAR are encoded by a single nucleic molecule in the same frame and as a single polypeptide chain. In this aspect, the two or more CARs, can, e.g., be separated by one or more peptide cleavage sites. (e.g., an auto-cleavage site or a substrate for an intracellular protease). Examples of peptide cleavage sites include the following, wherein the GSG residues are optional:

T2A: (GSG) E G R G S L L T C G D V E E N P G P (SEQ ID NO: 1296)

P2A: (GSG) A T N F S L L K Q A G D V E E N P G P (SEQ ID NO: 1297)

E2A: (GSG) Q C T N Y A L L K L A G D V E S N P G P (SEQ ID NO: 1298)

F2A: (GSG) V K Q T L N F D L L K L A G D V E S N P G P (SEQ ID NO: 1299)

Methods of introducing and expressing genes into a cell are known in the art. In the context of an expression vector, the vector can be readily introduced into a host cell, e.g., mammalian, bacterial,

yeast, or insect cell by any method in the art. For example, the expression vector can be transferred into a host cell by physical, chemical, or biological means.

Physical methods for introducing a polynucleotide into a host cell include calcium phosphate precipitation, lipofection, particle bombardment, microinjection, electroporation, and the like. Methods for producing cells comprising vectors and/or exogenous nucleic acids are well-known in the art. See, for example, Sambrook et al., 2012, MOLECULAR CLONING: A LABORATORY MANUAL, volumes 1 -4, Cold Spring Harbor Press, NY). A preferred method for the introduction of a polynucleotide into a host cell is calcium phosphate transfection

Biological methods for introducing a polynucleotide of interest into a host cell include the use of DNA and RNA vectors. Viral vectors, and especially retroviral vectors, have become the most widely used method for inserting genes into mammalian, e.g., human cells. Other viral vectors can be derived from lentivirus, poxviruses, herpes simplex virus I, adenoviruses and adeno-associated viruses, and the like. See, for example, U.S. Pat. Nos. 5,350,674 and 5,585,362.

Chemical means for introducing a polynucleotide into a host cell include colloidal dispersion systems, such as macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. An exemplary colloidal system for use as a delivery vehicle in vitro and in vivo is a liposome (e.g., an artificial membrane vesicle). Other methods of state-of-the-art targeted delivery of nucleic acids are available, such as delivery of polynucleotides with targeted nanoparticles or other suitable sub-micron sized delivery system.

In the case where a non-viral delivery system is utilized, an exemplary delivery vehicle is a liposome. The use of lipid formulations is contemplated for the introduction of the nucleic acids into a host cell (in vitro, ex vivo or in vivo). In another aspect, the nucleic acid may be associated with a lipid. The nucleic acid associated with a lipid may be encapsulated in the aqueous interior of a liposome, interspersed within the lipid bilayer of a liposome, attached to a liposome via a linking molecule that is associated with both the liposome and the oligonucleotide, entrapped in a liposome, complexed with a liposome, dispersed in a solution containing a lipid, mixed with a lipid, combined with a lipid, contained as a suspension in a lipid, contained or complexed with a micelle, or otherwise associated with a lipid. Lipid, lipid/DNA or lipid/expression vector associated compositions are not limited to any particular structure in solution. For example, they may be present in a bilayer structure, as micelles, or with a "collapsed" structure. They may also simply be interspersed in a solution, possibly forming aggregates that are not uniform in size or shape. Lipids are fatty substances which may be naturally occurring or synthetic lipids. For example, lipids include the fatty droplets that naturally occur in the cytoplasm as

well as the class of compounds which contain long-chain aliphatic hydrocarbons and their derivatives, such as fatty acids, alcohols, amines, amino alcohols, and aldehydes.

Lipids suitable for use can be obtained from commercial sources. For example, dimyristyl phosphatidylcholine ("DMPC") can be obtained from Sigma, St. Louis, MO; dicetyl phosphate ("DCP") can be obtained from K & K Laboratories (Plainview, NY); cholesterol ("Choi") can be obtained from Calbiochem-Behring; dimyristyl phosphatidylglycerol ("DMPG") and other lipids may be obtained from Avanti Polar Lipids, Inc. (Birmingham, AL.). Stock solutions of lipids in chloroform or chloroform/methanol can be stored at about -20°C. Chloroform is used as the only solvent since it is more readily evaporated than methanol. "Liposome" is a generic term encompassing a variety of single and multilamellar lipid vehicles formed by the generation of enclosed lipid bilayers or aggregates. Liposomes can be characterized as having vesicular structures with a phospholipid bilayer membrane and an inner aqueous medium. Multilamellar liposomes have multiple lipid layers separated by aqueous medium. They form spontaneously when phospholipids are suspended in an excess of aqueous solution. The lipid components undergo self-rearrangement before the formation of closed structures and entrap water and dissolved solutes between the lipid bilayers (Ghosh et al., 1991 Glycobiology 5: 505-10). However, compositions that have different structures in solution than the normal vesicular structure are also encompassed. For example, the lipids may assume a micellar structure or merely exist as nonuniform aggregates of lipid molecules. Also contemplated are lipofectamine-nucleic acid complexes.

Regardless of the method used to introduce exogenous nucleic acids into a host cell or otherwise expose a cell to the inhibitor of the present invention, in order to confirm the presence of the recombinant DNA sequence in the host cell, a variety of assays may be performed. Such assays include, for example, "molecular biological" assays well known to those of skill in the art, such as Southern and Northern blotting, RT-PCR and PCR; "biochemical" assays, such as detecting the presence or absence of a particular peptide, e.g., by immunological means (ELISAs and Western blots) or by assays described herein to identify agents falling within the scope of the invention.

The present invention further provides a vector comprising a CAR encoding nucleic acid molecule. In one aspect, a CAR vector can be directly transduced into a cell, *e.g.,* a T cell or NK cell. In one aspect, the vector is a cloning or expression vector, *e.g.,* a vector including, but not limited to, one or more plasmids (*e.g.*, expression plasmids, cloning vectors, minicircles, minivectors, double minute chromosomes), retroviral and lentiviral vector constructs. In one aspect, the vector is capable of expressing the CAR construct in mammalian T cells or NK cells. In one aspect, the mammalian T cell is a human T cell. In one aspect, the mammalian NK cell is a human NK cell.

Sources of cells

Prior to expansion and genetic modification, a source of cells, e.g., immune effector cells (e.g., T cells or NK cells), is obtained from a subject. The term "subject" is intended to include living organisms in which an immune response can be elicited (e.g., mammals). Examples of subjects include humans, dogs, cats, mice, rats, and transgenic species thereof. T cells can be obtained from a number of sources, including peripheral blood mononuclear cells, bone marrow, lymph node tissue, cord blood, thymus tissue, tissue from a site of infection, ascites, pleural effusion, spleen tissue, and tumors.

In certain aspects of the present invention, any number of immune effector cell (e.g., T cell or NK cell) lines available in the art, may be used. In certain aspects of the present invention, T cells can be obtained from a unit of blood collected from a subject using any number of techniques known to the skilled artisan, such as Ficoll™ separation. In one preferred aspect, cells from the circulating blood of an individual are obtained by apheresis. The apheresis product typically contains lymphocytes, including T cells, monocytes, granulocytes, B cells, other nucleated white blood cells, red blood cells, and platelets. In one aspect, the cells collected by apheresis may be washed to remove the plasma fraction and to place the cells in an appropriate buffer or media for subsequent processing steps. In one aspect of the invention, the cells are washed with phosphate buffered saline (PBS). In an alternative aspect, the wash solution lacks calcium and may lack magnesium or may lack many if not all divalent cations.

Initial activation steps in the absence of calcium can lead to magnified activation. As those of ordinary skill in the art would readily appreciate a washing step may be accomplished by methods known to those in the art, such as by using a semi-automated "flow-through" centrifuge (for example, the Cobe 2991 cell processor, the Baxter CytoMate, or the Haemonetics Cell Saver 5) according to the manufacturer's instructions. After washing, the cells may be resuspended in a variety of biocompatible buffers, such as, for example, Ca-free, Mg-free PBS, PlasmaLyte A, or other saline solution with or without buffer. Alternatively, the undesirable components of the apheresis sample may be removed and the cells directly resuspended in culture media.

It is recognized that the methods of the application can utilize culture media conditions comprising 5% or less, for example 2%, human AB serum, and employ known culture media conditions and compositions, for example those described in Smith *et al.*, "Ex vivo expansion of human T cells for adoptive immunotherapy using the novel Xeno-free CTS Immune Cell Serum Replacement" *Clinical & Translational Immunology* (2015) 4, e31; doi:10.1038/cti.2014.31.

In one aspect, T cells are isolated from peripheral blood lymphocytes by lysing the red blood cells and depleting the monocytes, for example, by centrifugation through a PERCOLLTM gradient or

by counterflow centrifugal elutriation. A specific subpopulation of T cells, such as CD3+, CD4+, CD8+, CD45RA+, and/or CD45RO+T cells, can be further isolated by positive or negative selection techniques. For example, in one aspect, T cells are isolated by incubation with anti-CD3/anti-CD28 (e.g., 3x28)-conjugated beads, such as DYNABEADS® M-450 CD3/CD28 T, for a time period sufficient for positive selection of the desired T cells. In one aspect, the time period is about 30 minutes. In a further aspect, the time period ranges from 30 minutes to 36 hours or longer and all integer values there between. In a further aspect, the time period is at least 1, 2, 3, 4, 5, or 6 hours. In yet another preferred aspect, the time period is 10 to 24 hours. In one aspect, the incubation time period is 24 hours. Longer incubation times may be used to isolate T cells in any situation where there are few T cells as compared to other cell types, such in isolating tumor infiltrating lymphocytes (TIL) from tumor tissue or from immunocompromised individuals. Further, use of longer incubation times can increase the efficiency of capture of CD8+ T cells. Thus, by simply shortening or lengthening the time T cells are allowed to bind to the CD3/CD28 beads and/or by increasing or decreasing the ratio of beads to T cells (as described further herein), subpopulations of T cells can be preferentially selected for or against at culture initiation or at other time points during the process. Additionally, by increasing or decreasing the ratio of anti-CD3 and/or anti-CD28 antibodies on the beads or other surface, subpopulations of T cells can be preferentially selected for or against at culture initiation or at other desired time points. The skilled artisan would recognize that multiple rounds of selection can also be used in the context of this invention. In certain aspects, it may be desirable to perform the selection procedure and use the "unselected" cells in the activation and expansion process. "Unselected" cells can also be subjected to further rounds of selection.

Enrichment of a T cell population by negative selection can be accomplished with a combination of antibodies directed to surface markers unique to the negatively selected cells. One method is cell sorting and/or selection via negative magnetic immunoadherence or flow cytometry that uses a cocktail of monoclonal antibodies directed to cell surface markers present on the cells negatively selected. For example, to enrich for CD4+ cells by negative selection, a monoclonal antibody cocktail typically includes antibodies to CD14, CD20, CD11b, CD16, HLA-DR, and CD8. In certain aspects, it may be desirable to enrich for or positively select for regulatory T cells which typically express CD4+, CD25+, CD62Lhi, GITR+, and FoxP3+. In certain aspects, it may be desirable to enrich for cells that are CD127low. Alternatively, in certain aspects, T regulatory cells are depleted by anti-C25 conjugated beads or other similar method of selection.

The methods described herein can include, e.g., selection of a specific subpopulation of immune effector cells, e.g., T cells, that are a T regulatory cell-depleted population, CD25+ depleted cells, using,

e.g., a negative selection technique, e.g., described herein. Preferably, the population of T regulatory depleted cells contains less than 30%, 25%, 20%, 15%, 10%, 5%, 4%, 3%, 2%, 1% of CD25+ cells.

In one embodiment, T regulatory cells, e.g., CD25+ T cells, are removed from the population using an anti-CD25 antibody, or fragment thereof, or a CD25-binding ligand, IL-2. In one embodiment, the anti-CD25 antibody, or fragment thereof, or CD25-binding ligand is conjugated to a substrate, e.g., a bead, or is otherwise coated on a substrate, e.g., a bead. In one embodiment, the anti-CD25 antibody, or fragment thereof, is conjugated to a substrate as described herein.

In one embodiment, the T regulatory cells, e.g., CD25+ T cells, are removed from the population using CD25 depletion reagent from Miltenyi™. In one embodiment, the ratio of cells to CD25 depletion reagent is 1e7 cells to 20 uL, or 1e7 cells to15 uL, or 1e7 cells to 10 uL, or 1e7 cells to 5 uL, or 1e7 cells to 2.5 uL, or 1e7 cells to 1.25 uL. In one embodiment, e.g., for T regulatory cells, e.g., CD25+ depletion, greater than 500 million cells/ml is used. In a further aspect, a concentration of cells of 600, 700, 800, or 900 million cells/ml is used.

In one embodiment, the population of immune effector cells to be depleted includes about 6 x 10^9 CD25+ T cells. In other aspects, the population of immune effector cells to be depleted include about 1 x 10^9 to 1x 10^{10} CD25+ T cell, and any integer value in between. In one embodiment, the resulting population T regulatory depleted cells has 2 x 10^9 T regulatory cells, e.g., CD25+ cells, or less (e.g., 1 x 10^9, 5 x 10^8, 1 x 10^8, 5 x 10^7, 1 x 10^7, or less CD25+ cells).

In one embodiment, the T regulatory cells, e.g., CD25+ cells, are removed from the population using the CliniMAC system with a depletion tubing set, such as, e.g., tubing 162-01. In one embodiment, the CliniMAC system is run on a depletion setting such as, e.g., DEPLETION2.1.

Without wishing to be bound by a particular theory, decreasing the level of negative regulators of immune cells (e.g., decreasing the number of unwanted immune cells, e.g., T_{REG} cells), in a subject prior to apheresis or during manufacturing of a CAR-expressing cell product can reduce the risk of subject relapse. For example, methods of depleting T_{REG} cells are known in the art. Methods of decreasing T_{REG} cells include, but are not limited to, cyclophosphamide, anti-GITR antibody (an anti-GITR antibody described herein), CD25-depletion, and combinations thereof.

In some embodiments, the manufacturing methods comprise reducing the number of (e.g., depleting) T_{REG} cells prior to manufacturing of the CAR-expressing cell. For example, manufacturing methods comprise contacting the sample, e.g., the apheresis sample, with an anti-GITR antibody and/or an anti-CD25 antibody (or fragment thereof, or a CD25-binding ligand), e.g., to deplete T_{REG} cells prior to manufacturing of the CAR-expressing cell (e.g., T cell, NK cell) product.

In an embodiment, a subject is pre-treated with one or more therapies that reduce T_{REG} cells prior to collection of cells for CAR-expressing cell product manufacturing, thereby reducing the risk of subject relapse to CAR-expressing cell treatment. In an embodiment, methods of decreasing T_{REG} cells include, but are not limited to, administration to the subject of one or more of cyclophosphamide, anti-GITR antibody, CD25-depletion, or a combination thereof. Administration of one or more of cyclophosphamide, anti-GITR antibody, CD25-depletion, or a combination thereof, can occur before, during or after an infusion of the CAR-expressing cell product.

In an embodiment, a subject is pre-treated with cyclophosphamide prior to collection of cells for CAR-expressing cell product manufacturing, thereby reducing the risk of subject relapse to CAR-expressing cell treatment. In an embodiment, a subject is pre-treated with an anti-GITR antibody prior to collection of cells for CAR-expressing cell product manufacturing, thereby reducing the risk of subject relapse to CAR-expressing cell treatment.

In one embodiment, the population of cells to be removed are neither the regulatory T cells or tumor cells, but cells that otherwise negatively affect the expansion and/or function of CART cells, e.g. cells expressing CD14, CD11b, CD33, CD15, or other markers expressed by potentially immune suppressive cells. In one embodiment, such cells are envisioned to be removed concurrently with regulatory T cells and/or tumor cells, or following said depletion, or in another order.

The methods described herein can include more than one selection step, e.g., more than one depletion step. Enrichment of a T cell population by negative selection can be accomplished, e.g., with a combination of antibodies directed to surface markers unique to the negatively selected cells. One method is cell sorting and/or selection via negative magnetic immunoadherence or flow cytometry that uses a cocktail of monoclonal antibodies directed to cell surface markers present on the cells negatively selected. For example, to enrich for CD4+ cells by negative selection, a monoclonal antibody cocktail can include antibodies to CD14, CD20, CD11b, CD16, HLA-DR, and CD8.

The methods described herein can further include removing cells from the population which express a tumor antigen, e.g., a tumor antigen that does not comprise CD25, e.g., CD19, CD30, CD38, CD123, CD20, CD14 or CD11b, to thereby provide a population of T regulatory depleted, e.g., CD25+ depleted, and tumor antigen depleted cells that are suitable for expression of a CAR, e.g., a CAR described herein. In one embodiment, tumor antigen expressing cells are removed simultaneously with the T regulatory, e.g., CD25+ cells. For example, an anti-CD25 antibody, or fragment thereof, and an anti-tumor antigen antibody, or fragment thereof, can be attached to the same substrate, e.g., bead, which can be used to remove the cells or an anti-CD25 antibody, or fragment thereof, or the anti-tumor antigen antibody, or fragment thereof, can be attached to separate beads, a mixture of which can be used

to remove the cells. In other embodiments, the removal of T regulatory cells, e.g., CD25+ cells, and the removal of the tumor antigen expressing cells is sequential, and can occur, e.g., in either order.

Also provided are methods that include removing cells from the population which express a check point inhibitor, e.g., a check point inhibitor described herein, e.g., one or more of PD1+ cells, LAG3+ cells, and TIM3+ cells, to thereby provide a population of T regulatory depleted, e.g., CD25+ depleted cells, and check point inhibitor depleted cells, e.g., PD1+, LAG3+ and/or TIM3+ depleted cells. Exemplary check point inhibitors include PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, and TGFR beta. In embodiments, the checkpoint inhibitor is PD1 or PD-L1. In one embodiment, check point inhibitor expressing cells are removed simultaneously with the T regulatory, e.g., CD25+ cells. For example, an anti-CD25 antibody, or fragment thereof, and an anti-check point inhibitor antibody, or fragment thereof, can be attached to the same bead which can be used to remove the cells, or an anti-CD25 antibody, or fragment thereof, and the anti-check point inhibitor antibody, or fragment there, can be attached to separate beads, a mixture of which can be used to remove the cells. In other embodiments, the removal of T regulatory cells, e.g., CD25+ cells, and the removal of the check point inhibitor expressing cells is sequential, and can occur, e.g., in either order.

In one embodiment, a T cell population can be selected that expresses one or more of IFN-γ, TNFα, IL-17A, IL-2, IL-3, IL-4, GM-CSF, IL-10, IL-13, granzyme B, and perforin, or other appropriate molecules, e.g., other cytokines. Methods for screening for cell expression can be determined, e.g., by the methods described in PCT Publication No.: WO 2013/126712.

For isolation of a desired population of cells by positive or negative selection, the concentration of cells and surface (e.g., particles such as beads) can be varied. In certain aspects, it may be desirable to significantly decrease the volume in which beads and cells are mixed together (e.g., increase the concentration of cells), to ensure maximum contact of cells and beads. For example, in one aspect, a concentration of 2 billion cells/ml is used. In one aspect, a concentration of 1 billion cells/ml is used. In a further aspect, greater than 100 million cells/ml is used. In a further aspect, a concentration of cells of 10, 15, 20, 25, 30, 35, 40, 45, or 50 million cells/ml is used. In yet one aspect, a concentration of cells from 75, 80, 85, 90, 95, or 100 million cells/ml is used. In further aspects, concentrations of 125 or 150 million cells/ml can be used. Using high concentrations can result in increased cell yield, cell activation, and cell expansion. Further, use of high cell concentrations allows more efficient capture of cells that may weakly express target antigens of interest, such as CD28-negative T cells, or from samples where there are many tumor cells present (e.g., leukemic blood, tumor tissue, etc.). Such populations of cells

may have therapeutic value and would be desirable to obtain. For example, using high concentration of cells allows more efficient selection of CD8+ T cells that normally have weaker CD28 expression.

In a related aspect, it may be desirable to use lower concentrations of cells. By significantly diluting the mixture of T cells and surface (e.g., particles such as beads), interactions between the particles and cells is minimized. This selects for cells that express high amounts of desired antigens to be bound to the particles. For example, CD4+ T cells express higher levels of CD28 and are more efficiently captured than CD8+ T cells in dilute concentrations. In one aspect, the concentration of cells used is 5 X 10e6/ml. In other aspects, the concentration used can be from about 1 X 10^5/ml to 1 X 10^6/ml, and any integer value in between.

In other aspects, the cells may be incubated on a rotator for varying lengths of time at varying speeds at either 2-10°C or at room temperature.

T cells for stimulation can also be frozen after a washing step. Wishing not to be bound by theory, the freeze and subsequent thaw step provides a more uniform product by removing granulocytes and to some extent monocytes in the cell population. After the washing step that removes plasma and platelets, the cells may be suspended in a freezing solution. While many freezing solutions and parameters are known in the art and will be useful in this context, one method involves using PBS containing 20% DMSO and 8% human serum albumin, or culture media containing 10% Dextran 40 and 5% Dextrose, 20% Human Serum Albumin and 7.5% DMSO, or 31.25% Plasmalyte-A, 31.25% Dextrose 5%, 0.45% NaCl, 10% Dextran 40 and 5% Dextrose, 20% Human Serum Albumin, and 7.5% DMSO or other suitable cell freezing media containing for example, Hespan and PlasmaLyte A, the cells then are frozen to -80°C at a rate of 1° per minute and stored in the vapor phase of a liquid nitrogen storage tank. Other methods of controlled freezing may be used as well as uncontrolled freezing immediately at -20° C or in liquid nitrogen.

In certain aspects, cryopreserved cells are thawed and washed as described herein and allowed to rest for one hour at room temperature prior to activation using the methods of the present invention.

Also contemplated in the context of the invention is the collection of blood samples or apheresis product from a subject at a time period prior to when the expanded cells as described herein might be needed. As such, the source of the cells to be expanded can be collected at any time point necessary, and desired cells, such as immune effector cells, e.g., T cells or NK cells, isolated and frozen for later use in cell therapy, e.g., T cell therapy, for any number of diseases or conditions that would benefit from cell therapy, e.g., T cell therapy, such as those described herein. In one aspect a blood sample or an apheresis is taken from a generally healthy subject. In certain aspects, a blood sample or an apheresis is taken from a generally healthy subject who is at risk of developing a disease, but who has not yet

developed a disease, and the cells of interest are isolated and frozen for later use. In certain aspects, the immune effector cells (e.g., T cells or NK cells) may be expanded, frozen, and used at a later time. In certain aspects, samples are collected from a patient shortly after diagnosis of a particular disease as described herein but prior to any treatments. In a further aspect, the cells are isolated from a blood sample or an apheresis from a subject prior to any number of relevant treatment modalities, including but not limited to treatment with agents such as natalizumab, efalizumab, antiviral agents, chemotherapy, radiation, immunosuppressive agents, such as cyclosporin, azathioprine, methotrexate, mycophenolate, and FK506, antibodies, or other immunoablative agents such as CAMPATH, anti-CD3 antibodies, cytoxan, fludarabine, cyclosporin, FK506, rapamycin, mycophenolic acid, steroids, FR901228, and irradiation.

In a further aspect of the present invention, T cells are obtained from a patient directly following treatment that leaves the subject with functional T cells. In this regard, it has been observed that following certain cancer treatments, in particular treatments with drugs that damage the immune system, shortly after treatment during the period when patients would normally be recovering from the treatment, the quality of T cells obtained may be optimal or improved for their ability to expand ex vivo. Likewise, following ex vivo manipulation using the methods described herein, these cells may be in a preferred state for enhanced engraftment and in vivo expansion. Thus, it is contemplated within the context of the present invention to collect blood cells, including T cells, dendritic cells, or other cells of the hematopoietic lineage, during this recovery phase. Further, in certain aspects, mobilization (for example, mobilization with GM-CSF) and conditioning regimens can be used to create a condition in a subject wherein repopulation, recirculation, regeneration, and/or expansion of particular cell types is favored, especially during a defined window of time following therapy. Illustrative cell types include T cells, B cells, dendritic cells, and other cells of the immune system.

In one embodiment, the immune effector cells expressing a CAR molecule, e.g., a CAR molecule described herein, are obtained from a subject that has received a low, immune enhancing dose of an mTOR inhibitor. In an embodiment, the population of immune effector cells, e.g., T cells, to be engineered to express a CAR, are harvested after a sufficient time, or after sufficient dosing of the low, immune enhancing, dose of an mTOR inhibitor, such that the level of PD1 negative immune effector cells, e.g., T cells, or the ratio of PD1 negative immune effector cells, e.g., T cells/ PD1 positive immune effector cells, e.g., T cells, in the subject or harvested from the subject has been, at least transiently, increased.

In other embodiments, population of immune effector cells, e.g., T cells, which have, or will be engineered to express a CAR, can be treated ex vivo by contact with an amount of an mTOR inhibitor

that increases the number of PD1 negative immune effector cells, e.g., T cells or increases the ratio of PD1 negative immune effector cells, e.g., T cells/ PD1 positive immune effector cells, e.g., T cells.

In one embodiment, a T cell population is diaglycerol kinase (DGK)-deficient. DGK-deficient cells include cells that do not express DGK RNA or protein, or have reduced or inhibited DGK activity. DGK-deficient cells can be generated by genetic approaches, e.g., administering RNA-interfering agents, e.g., siRNA, shRNA, miRNA, to reduce or prevent DGK expression. Alternatively, DGK-deficient cells can be generated by treatment with DGK inhibitors described herein.

In one embodiment, a T cell population is Ikaros-deficient. Ikaros-deficient cells include cells that do not express Ikaros RNA or protein, or have reduced or inhibited Ikaros activity, Ikaros-deficient cells can be generated by genetic approaches, e.g., administering RNA-interfering agents, e.g., siRNA, shRNA, miRNA, to reduce or prevent Ikaros expression. Alternatively, Ikaros-deficient cells can be generated by treatment with Ikaros inhibitors, e.g., lenalidomide.

In embodiments, a T cell population is DGK-deficient and Ikaros-deficient, e.g., does not express DGK and Ikaros, or has reduced or inhibited DGK and Ikaros activity. Such DGK and Ikaros-deficient cells can be generated by any of the methods described herein.

In an embodiment, the NK cells are obtained from the subject. In another embodiment, the NK cells are an NK cell line, e.g., NK-92 cell line (Conkwest).

Modifications of CAR cells, including allogeneic CAR cells

In embodiments described herein, the immune effector cell can be an allogeneic immune effector cell, e.g., T cell or NK cell. For example, the cell can be an allogeneic T cell, e.g., an allogeneic T cell lacking expression of a functional T cell receptor (TCR) and/or human leukocyte antigen (HLA), e.g., HLA class I and/or HLA class II, and/or beta-2 microglobulin (β_2m). Compositions of allogeneic CAR and methods thereof have been described in, e.g., pages 227-237 of WO 2016/014565, incorporated herein by reference in its entirety.

In some embodiments, a cell, e.g., a T cell or a NK cell, is modified to reduce the expression of a TCR, and/or HLA, and/or β_2m, and/or an inhibitory molecule described herein (e.g., PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, and TGFR beta), using, e.g., a method described herein, e.g., siRNA, shRNA, clustered regularly interspaced short palindromic repeats (CRISPR) transcription-activator like effector nuclease (TALEN), or zinc finger endonuclease (ZFN).

In some embodiments, a cell, e.g., a T cell or a NK cell is engineered to express a telomerase subunit, e.g., the catalytic subunit of telomerase, e.g., TERT, e.g., hTERT. In one embodiment, such modification improves persistence of the cell in a patient.

Activation and Expansion of T Cells

T cells may be activated and expanded generally using methods as described, for example, in U.S. Patents 6,352,694; 6,534,055; 6,905,680; 6,692,964; 5,858,358; 6,887,466; 6,905,681; 7,144,575; 7,067,318; 7,172,869; 7,232,566; 7,175,843; 5,883,223; 6,905,874; 6,797,514; 6,867,041; and U.S. Patent Application Publication No. 20060121005.

Generally, the T cells of the invention may be expanded by contact with a surface having attached thereto an agent that stimulates a CD3/TCR complex associated signal and a ligand that stimulates a costimulatory molecule on the surface of the T cells. In particular, T cell populations may be stimulated as described herein, such as by contact with an anti-CD3 antibody, or antigen-binding fragment thereof, or an anti-CD2 antibody immobilized on a surface, or by contact with a protein kinase C activator (e.g., bryostatin) in conjunction with a calcium ionophore. For co-stimulation of an accessory molecule on the surface of the T cells, a ligand that binds the accessory molecule is used. For example, a population of T cells can be contacted with an anti-CD3 antibody and an anti-CD28 antibody, under conditions appropriate for stimulating proliferation of the T cells. To stimulate proliferation of either CD4+ T cells or CD8+ T cells, an anti-CD3 antibody and an anti-CD28 antibody can be used. Examples of an anti-CD28 antibody include 9.3, B-T3, XR-CD28 (Diaclone, Besançon, France) can be used as can other methods commonly known in the art (Berg et al., Transplant Proc. 30(8):3975-3977, 1998; Haanen et al., J. Exp. Med. 190(9):13191328, 1999; Garland et al., J. Immunol Meth. 227(1-2):53-63, 1999).

In certain aspects, the primary stimulatory signal and the costimulatory signal for the T cell may be provided by different protocols. For example, the agents providing each signal may be in solution or coupled to a surface. When coupled to a surface, the agents may be coupled to the same surface (i.e., in "cis" formation) or to separate surfaces (i.e., in "trans" formation). Alternatively, one agent may be coupled to a surface and the other agent in solution. In one aspect, the agent providing the costimulatory signal is bound to a cell surface and the agent providing the primary activation signal is in solution or coupled to a surface. In certain aspects, both agents can be in solution. In one aspect, the agents may be in soluble form, and then cross-linked to a surface, such as a cell expressing Fc receptors or an antibody or other binding agent which will bind to the agents. In this regard, see for example, U.S. Patent

Application Publication Nos. 20040101519 and 20060034810 for artificial antigen presenting cells (aAPCs) that are contemplated for use in activating and expanding T cells in the present invention.

In one aspect, the two agents are immobilized on beads, either on the same bead, i.e., "cis," or to separate beads, i.e., "trans." By way of example, the agent providing the primary activation signal is an anti-CD3 antibody or an antigen-binding fragment thereof and the agent providing the costimulatory signal is an anti-CD28 antibody or antigen-binding fragment thereof; and both agents are co-immobilized to the same bead in equivalent molecular amounts. In one aspect, a 1:1 ratio of each antibody bound to the beads for CD4+ T cell expansion and T cell growth is used. In certain aspects of the present invention, a ratio of anti CD3:CD28 antibodies bound to the beads is used such that an increase in T cell expansion is observed as compared to the expansion observed using a ratio of 1:1. In one particular aspect an increase of from about 1 to about 3 fold is observed as compared to the expansion observed using a ratio of 1:1. In one aspect, the ratio of CD3:CD28 antibody bound to the beads ranges from 100:1 to 1:100 and all integer values there between. In one aspect of the present invention, more anti-CD28 antibody is bound to the particles than anti-CD3 antibody, i.e., the ratio of CD3:CD28 is less than one. In certain aspects of the invention, the ratio of anti CD28 antibody to anti CD3 antibody bound to the beads is greater than 2:1. In one particular aspect, a 1:100 CD3:CD28 ratio of antibody bound to beads is used. In one aspect, a 1:75 CD3:CD28 ratio of antibody bound to beads is used. In a further aspect, a 1:50 CD3:CD28 ratio of antibody bound to beads is used. In one aspect, a 1:30 CD3:CD28 ratio of antibody bound to beads is used. In one preferred aspect, a 1:10 CD3:CD28 ratio of antibody bound to beads is used. In one aspect, a 1:3 CD3:CD28 ratio of antibody bound to the beads is used. In yet one aspect, a 3:1 CD3:CD28 ratio of antibody bound to the beads is used.

Ratios of particles to cells from 1:500 to 500:1 and any integer values in between may be used to stimulate T cells or other target cells. As those of ordinary skill in the art can readily appreciate, the ratio of particles to cells may depend on particle size relative to the target cell. For example, small sized beads could only bind a few cells, while larger beads could bind many. In certain aspects the ratio of cells to particles ranges from 1:100 to 100:1 and any integer values in-between and in further aspects the ratio comprises 1:9 to 9:1 and any integer values in between, can also be used to stimulate T cells. The ratio of anti-CD3- and anti-CD28-coupled particles to T cells that result in T cell stimulation can vary as noted above, however certain preferred values include 1:100, 1:50, 1:40, 1:30, 1:20, 1:10, 1:9, 1:8, 1:7, 1:6, 1:5, 1:4, 1:3, 1:2, 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, 10:1, and 15:1 with one preferred ratio being at least 1:1 particles per T cell. In one aspect, a ratio of particles to cells of 1:1 or less is used. In one particular aspect, a preferred particle: cell ratio is 1:5. In further aspects, the ratio of particles to cells can be varied depending on the day of stimulation. For example, in one aspect, the ratio of particles to cells is from 1:1 to 10:1 on the first day and additional particles are added to the cells every day or

every other day thereafter for up to 10 days, at final ratios of from 1:1 to 1:10 (based on cell counts on the day of addition). In one particular aspect, the ratio of particles to cells is 1:1 on the first day of stimulation and adjusted to 1:5 on the third and fifth days of stimulation. In one aspect, particles are added on a daily or every other day basis to a final ratio of 1:1 on the first day, and 1:5 on the third and fifth days of stimulation. In one aspect, the ratio of particles to cells is 2:1 on the first day of stimulation and adjusted to 1:10 on the third and fifth days of stimulation. In one aspect, particles are added on a daily or every other day basis to a final ratio of 1:1 on the first day, and 1:10 on the third and fifth days of stimulation. One of skill in the art will appreciate that a variety of other ratios may be suitable for use in the present invention. In particular, ratios will vary depending on particle size and on cell size and type. In one aspect, the most typical ratios for use are in the neighborhood of 1:1, 2:1 and 3:1 on the first day.

In further aspects of the present invention, the cells, such as T cells, are combined with agent-coated beads, the beads and the cells are subsequently separated, and then the cells are cultured. In an alternative aspect, prior to culture, the agent-coated beads and cells are not separated but are cultured together. In a further aspect, the beads and cells are first concentrated by application of a force, such as a magnetic force, resulting in increased ligation of cell surface markers, thereby inducing cell stimulation.

By way of example, cell surface proteins may be ligated by allowing paramagnetic beads to which anti-CD3 and anti-CD28 are attached (3x28 beads) to contact the T cells. In one aspect the cells (for example, 10^4 to 10^9 T cells) and beads (for example, DYNABEADS® M-450 CD3/CD28 T paramagnetic beads at a ratio of 1:1) are combined in a buffer, for example PBS (without divalent cations such as, calcium and magnesium). Again, those of ordinary skill in the art can readily appreciate any cell concentration may be used. For example, the target cell may be very rare in the sample and comprise only 0.01% of the sample or the entire sample (i.e., 100%) may comprise the target cell of interest. Accordingly, any cell number is within the context of the present invention. In certain aspects, it may be desirable to significantly decrease the volume in which particles and cells are mixed together (i.e., increase the concentration of cells), to ensure maximum contact of cells and particles. For example, in one aspect, a concentration of about 10 billion cells/ml, 9 billion/ml, 8 billion/ml, 7 billion/ml, 6 billion/ml, 5 billion/ml, or 2 billion cells/ml is used. In one aspect, greater than 100 million cells/ml is used. In a further aspect, a concentration of cells of 10, 15, 20, 25, 30, 35, 40, 45, or 50 million cells/ml is used. In yet one aspect, a concentration of cells from 75, 80, 85, 90, 95, or 100 million cells/ml is used. In further aspects, concentrations of 125 or 150 million cells/ml can be used. Using high concentrations can result in increased cell yield, cell activation, and cell expansion. Further, use of high cell concentrations allows more efficient capture of cells that may weakly express target antigens of interest, such as CD28-negative T cells. Such populations of cells may have therapeutic value and

would be desirable to obtain in certain aspects. For example, using high concentration of cells allows more efficient selection of CD8+ T cells that normally have weaker CD28 expression.

In one embodiment, cells transduced with a nucleic acid encoding a CAR, e.g., a CAR described herein, are expanded, e.g., by a method described herein. In one embodiment, the cells are expanded in culture for a period of several hours (e.g., about 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 18, 21 hours) to about 14 days (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 days). In one embodiment, the cells are expanded for a period of 4 to 9 days. In one embodiment, the cells are expanded for a period of 8 days or less, e.g., 7, 6 or 5 days. In one embodiment, the cells, e.g., a BCMA CAR cell described herein, are expanded in culture for 5 days, and the resulting cells are more potent than the same cells expanded in culture for 9 days under the same culture conditions. Potency can be defined, e.g., by various T cell functions, e.g. proliferation, target cell killing, cytokine production, activation, migration, or combinations thereof. In one embodiment, the cells, e.g., a BCMA CAR cell described herein, expanded for 5 days show at least a one, two, three or four fold increase in cells doublings upon antigen stimulation as compared to the same cells expanded in culture for 9 days under the same culture conditions. In one embodiment, the cells, e.g., the cells expressing a BCMA CAR described herein, are expanded in culture for 5 days, and the resulting cells exhibit higher proinflammatory cytokine production, e.g., IFN-γ and/or GM-CSF levels, as compared to the same cells expanded in culture for 9 days under the same culture conditions. In one embodiment, the cells, e.g., a BCMA CAR cell described herein, expanded for 5 days show at least a one, two, three, four, five, ten fold or more increase in pg/ml of proinflammatory cytokine production, e.g., IFN-γ and/or GM-CSF levels, as compared to the same cells expanded in culture for 9 days under the same culture conditions.

In one aspect of the present invention, the mixture may be cultured for several hours (about 3 hours) to about 14 days or any hourly integer value in between. In one aspect, the mixture may be cultured for 21 days. In one aspect of the invention the beads and the T cells are cultured together for about eight days. In one aspect, the beads and T cells are cultured together for 2-3 days. Several cycles of stimulation may also be desired such that culture time of T cells can be 60 days or more. Conditions appropriate for T cell culture include an appropriate media (e.g., Minimal Essential Media or RPMI Media 1640 or, X-vivo 15, (Lonza)) that may contain factors necessary for proliferation and viability, including serum (e.g., fetal bovine or human serum), interleukin-2 (IL-2), insulin, IFN-γ, IL-4, IL-7, GM-CSF, IL-10, IL-12, IL-15, TGFβ, and TNF-α or any other additives for the growth of cells known to the skilled artisan. Other additives for the growth of cells include, but are not limited to, surfactant, plasmanate, and reducing agents such as N-acetyl-cysteine and 2-mercaptoethanol. Media can include RPMI 1640, AIM-V, DMEM, MEM, α-MEM, F-12, X-Vivo 15, and X-Vivo 20, Optimizer, with added amino acids, sodium pyruvate, and vitamins, either serum-free or supplemented with an appropriate

amount of serum (or plasma) or a defined set of hormones, and/or an amount of cytokine(s) sufficient for the growth and expansion of T cells. Antibiotics, e.g., penicillin and streptomycin, are included only in experimental cultures, not in cultures of cells that are to be infused into a subject. The target cells are maintained under conditions necessary to support growth, for example, an appropriate temperature (e.g., 37° C) and atmosphere (e.g., air plus 5% CO_2).

In one embodiment, the cells are expanded in an appropriate media (e.g., media described herein) that includes one or more interleukin that result in at least a 200-fold (e.g., 200-fold, 250-fold, 300-fold, 350-fold) increase in cells over a 14 day expansion period, e.g., as measured by a method described herein such as flow cytometry. In one embodiment, the cells are expanded in the presence of IL-15 and/or IL-7 (e.g., IL-15 and IL-7).

In embodiments, methods described herein, e.g., CAR-expressing cell manufacturing methods, comprise removing T regulatory cells, e.g., CD25+ T cells, from a cell population, e.g., using an anti-CD25 antibody, or fragment thereof, or a CD25-binding ligand, IL-2. Methods of removing T regulatory cells, e.g., CD25+ T cells, from a cell population are described herein. In embodiments, the methods, e.g., manufacturing methods, further comprise contacting a cell population (e.g., a cell population in which T regulatory cells, such as CD25+ T cells, have been depleted; or a cell population that has previously contacted an anti-CD25 antibody, fragment thereof, or CD25-binding ligand) with IL-15 and/or IL-7. For example, the cell population (e.g., that has previously contacted an anti-CD25 antibody, fragment thereof, or CD25-binding ligand) is expanded in the presence of IL-15 and/or IL-7.

In some embodiments a CAR-expressing cell described herein is contacted with a composition comprising a interleukin-15 (IL-15) polypeptide, a interleukin-15 receptor alpha (IL-15Ra) polypeptide, or a combination of both a IL-15 polypeptide and a IL-15Ra polypeptide e.g., hetIL-15, during the manufacturing of the CAR-expressing cell, e.g., ex vivo. In embodiments, a CAR-expressing cell described herein is contacted with a composition comprising a IL-15 polypeptide during the manufacturing of the CAR-expressing cell, e.g., ex vivo. In embodiments, a CAR-expressing cell described herein is contacted with a composition comprising a combination of both a IL-15 polypeptide and a IL-15 Ra polypeptide during the manufacturing of the CAR-expressing cell, e.g., ex vivo. In embodiments, a CAR-expressing cell described herein is contacted with a composition comprising hetIL-15 during the manufacturing of the CAR-expressing cell, e.g., ex vivo.

In one embodiment the CAR-expressing cell described herein is contacted with a composition comprising hetIL-15 during ex vivo expansion. In an embodiment, the CAR-expressing cell described herein is contacted with a composition comprising an IL-15 polypeptide during ex vivo expansion. In an embodiment, the CAR-expressing cell described herein is contacted with a composition comprising

both an IL-15 polypeptide and an IL-15Ra polypeptide during ex vivo expansion. In one embodiment the contacting results in the survival and proliferation of a lymphocyte subpopulation, e.g., CD8+ T cells.

T cells that have been exposed to varied stimulation times may exhibit different characteristics. For example, typical blood or apheresed peripheral blood mononuclear cell products have a helper T cell population (TH, CD4+) that is greater than the cytotoxic or suppressor T cell population. Ex vivo expansion of T cells by stimulating CD3 and CD28 receptors produces a population of T cells that prior to about days 8-9 consists predominately of TH cells, while after about days 8-9, the population of T cells comprises an increasingly greater population of TC cells. Accordingly, depending on the purpose of treatment, infusing a subject with a T cell population comprising predominately of TH cells may be advantageous. Similarly, if an antigen-specific subset of TC cells has been isolated it may be beneficial to expand this subset to a greater degree.

Further, in addition to CD4 and CD8 markers, other phenotypic markers vary significantly, but in large part, reproducibly during the course of the cell expansion process. Thus, such reproducibility enables the ability to tailor an activated T cell product for specific purposes.

Once a BCMA CAR is constructed, various assays can be used to evaluate the activity of the molecule, such as but not limited to, the ability to expand T cells following antigen stimulation, sustain T cell expansion in the absence of re-stimulation, and anti-cancer activities in appropriate in vitro and animal models. Assays to evaluate the effects of a BCMA CAR are described in further detail below

Western blot analysis of CAR expression in primary T cells can be used to detect the presence of monomers and dimers. See, *e.g.*, Milone *et al.*, Molecular Therapy 17(8): 1453-1464 (2009). Very briefly, T cells (1:1 mixture of $CD4^+$ and $CD8^+$ T cells) expressing the CARs are expanded *in vitro* for more than 10 days followed by lysis and SDS-PAGE under reducing conditions. CARs containing the full length TCR-ζ cytoplasmic domain and the endogenous TCR-ζ chain are detected by western blotting using an antibody to the TCR-ζ chain. The same T cell subsets are used for SDS-PAGE analysis under non-reducing conditions to permit evaluation of covalent dimer formation.

In vitro expansion of CAR^+ T cells following antigen stimulation can be measured by flow cytometry. For example, a mixture of $CD4^+$ and $CD8^+$ T cells are stimulated with αCD3/αCD28 aAPCs followed by transduction with lentiviral vectors expressing GFP under the control of the promoters to be analyzed. Exemplary promoters include the CMV IE gene, EF-1α, ubiquitin C, or phosphoglycerokinase (PGK) promoters. GFP fluorescence is evaluated on day 6 of culture in the $CD4^+$ and/or $CD8^+$ T cell subsets by flow cytometry. See, *e.g.*, Milone *et al.*, Molecular Therapy 17(8): 1453-1464 (2009). Alternatively, a mixture of $CD4^+$ and $CD8^+$ T cells are stimulated with αCD3/αCD28

coated magnetic beads on day 0, and transduced with CAR on day 1 using a bicistronic lentiviral vector expressing CAR along with eGFP using a 2A ribosomal skipping sequence. Cultures are re-stimulated with BCMA-expressing cells, such as multiple myeloma cell lines or K562-BCMA, following washing. Exogenous IL-2 is added to the cultures every other day at 100 IU/ml. GFP^+ T cells are enumerated by flow cytometry using bead-based counting. See, *e.g.*, Milone *et al.*, Molecular Therapy 17(8): 1453-1464 (2009).

Sustained CAR^+ T cell expansion in the absence of re-stimulation can also be measured. See, *e.g.*, Milone *et al.*, Molecular Therapy 17(8): 1453-1464 (2009). Briefly, mean T cell volume (fl) is measured on day 8 of culture using a Coulter Multisizer III particle counter, a Nexcelom Cellometer Vision or Millipore Scepter, following stimulation with αCD3/αCD28 coated magnetic beads on day 0, and transduction with the indicated CAR on day 1.

Animal models can also be used to measure a CART activity. For example, xenograft model using human BCMA-specific CAR^+ T cells to treat a primary human multiple myeloma in immunodeficient mice can be used. See, *e.g.*, Milone *et al.*, Molecular Therapy 17(8): 1453-1464 (2009). Very briefly, after establishment of MM, mice are randomized as to treatment groups. Different numbers of BCMA CART cells can be injected into immunodeficient mice bearing MM. Animals are assessed for disease progression and tumor burden at weekly intervals. Survival curves for the groups are compared using the log-rank test. In addition, absolute peripheral blood $CD4^+$ and $CD8^+$ T cell counts 4 weeks following T cell injection in the immunodeficient mice can also be analyzed. Mice are injected with multiple myeloma cells and 3 weeks later are injected with T cells engineered to express BCMA CAR, e.g., by a bicistronic lentiviral vector that encodes the CAR linked to eGFP. T cells are normalized to 45–50% input GFP^+ T cells by mixing with mock-transduced cells prior to injection, and confirmed by flow cytometry. Animals are assessed for leukemia at 1-week intervals. Survival curves for the CAR^+ T cell groups are compared using the log-rank test.

Assessment of cell proliferation and cytokine production has been previously described, *e.g.*, at Milone *et al.*, Molecular Therapy 17(8): 1453-1464 (2009). Briefly, assessment of CAR-mediated proliferation is performed in microtiter plates by mixing washed T cells with K562 cells expressing BCMA or other BCMA-expressing myeloma cells are irradiated with gamma-radiation prior to use. Anti-CD3 (clone OKT3) and anti- CD28 (clone 9.3) monoclonal antibodies are added to cultures with KT32-BBL cells to serve as a positive control for stimulating T-cell proliferation since these signals support long-term $CD8^+$ T cell expansion *ex vivo*. T cells are enumerated in cultures using CountBright™ fluorescent beads (Invitrogen, Carlsbad, CA) and flow cytometry as described by the manufacturer. CAR^+ T cells are identified by GFP expression using T cells that are engineered with eGFP-2A linked CAR-expressing lentiviral vectors. For CAR+ T cells not expressing GFP, the CAR+ T

cells are detected with biotinylated recombinant BCMA protein and a secondary avidin-PE conjugate. CD4+ and $CD8^+$ expression on T cells are also simultaneously detected with specific monoclonal antibodies (BD Biosciences). Cytokine measurements are performed on supernatants collected 24 hours following re-stimulation using the human TH1/TH2 cytokine cytometric bead array kit (BD Biosciences, San Diego, CA) according the manufacturer's instructions. Fluorescence is assessed using a FACScalibur flow cytometer, and data is analyzed according to the manufacturer's instructions.

Cytotoxicity can be assessed by a standard 51Cr-release assay. See, *e.g.*, Milone *et al.*, Molecular Therapy 17(8): 1453-1464 (2009). Briefly, target cells (e.g., K562 lines expressing BCMA and primary multiple myeloma cells) are loaded with 51Cr (as NaCrO4, New England Nuclear, Boston, MA) at 37°C for 2 hours with frequent agitation, washed twice in complete RPMI and plated into microtiter plates. Effector T cells are mixed with target cells in the wells in complete RPMI at varying ratios of effector cell:target cell (E:T). Additional wells containing media only (spontaneous release, SR) or a 1% solution of triton-X 100 detergent (total release, TR) are also prepared. After 4 hours of incubation at 37°C, supernatant from each well is harvested. Released 51Cr is then measured using a gamma particle counter (Packard Instrument Co., Waltham, MA). Each condition is performed in at least triplicate, and the percentage of lysis is calculated using the formula: % Lysis = (ER– SR) / (TR – SR), where ER represents the average 51Cr released for each experimental condition. Alternatively, cytotoxicity can also be assessed using a Bright-Glo™ Luciferase Assay.

Imaging technologies can be used to evaluate specific trafficking and proliferation of CARs in tumor-bearing animal models. Such assays have been described, for example, in Barrett *et al.*, Human Gene Therapy 22:1575-1586 (2011). Briefly, NOD/SCID/$\gamma c^{-/-}$ (NSG) mice or other immunodeficient are injected IV with multiple myeloma cells followed 7 days later with BCMA CART cells 4 hour after electroporation with the CAR constructs. The T cells are stably transfected with a lentiviral construct to express firefly luciferase, and mice are imaged for bioluminescence. Alternatively, therapeutic efficacy and specificity of a single injection of CAR^+ T cells in a multiple myeloma xenograft model can be measured as the following: NSG mice are injected with multiple myeloma cells transduced to stably express firefly luciferase, followed by a single tail-vein injection of T cells electroporated with BCMA CAR construct days later. Animals are imaged at various time points post injection. For example, photon-density heat maps of firefly luciferasepositive tumors in representative mice at day 5 (2 days before treatment) and day 8 (24 hr post CAR^+ PBLs) can be generated.

Alternatively, or in combination to the methods disclosed herein, methods and compositions for one or more of: detection and/or quantification of CAR-expressing cells (*e.g.*, *in vitro* or *in vivo* (e.g., clinical monitoring)); immune cell expansion and/or activation; and/or CAR-specific selection, that involve the use of a CAR ligand, are disclosed. In one exemplary embodiment, the CAR ligand is an

antibody that binds to the CAR molecule, e.g., binds to the extracellular antigen binding domain of CAR (e.g., an antibody that binds to the antigen binding domain, e.g., an anti-idiotypic antibody; or an antibody that binds to a constant region of the extracellular binding domain). In other embodiments, the CAR ligand is a CAR antigen molecule (e.g., a CAR antigen molecule as described herein).

In one aspect, a method for detecting and/or quantifying CAR-expressing cells is disclosed. For example, the CAR ligand can be used to detect and/or quantify CAR-expressing cells *in vitro* or *in vivo* (e.g., clinical monitoring of CAR-expressing cells in a patient, or dosing a patient). The method includes:

providing the CAR ligand (optionally, a labelled CAR ligand, e.g., a CAR ligand that includes a tag, a bead, a radioactive or fluorescent label);

acquiring the CAR-expressing cell (e.g., acquiring a sample containing CAR-expressing cells, such as a manufacturing sample or a clinical sample);

contacting the CAR-expressing cell with the CAR ligand under conditions where binding occurs, thereby detecting the level (e.g., amount) of the CAR-expressing cells present. Binding of the CAR-expressing cell with the CAR ligand can be detected using standard techniques such as FACS, ELISA and the like.

In another aspect, a method of expanding and/or activating cells (e.g., immune effector cells) is disclosed. The method includes:

providing a CAR-expressing cell (e.g., a first CAR-expressing cell or a transiently expressing CAR cell);

contacting said CAR-expressing cell with a CAR ligand, e.g., a CAR ligand as described herein), under conditions where immune cell expansion and/or proliferation occurs, thereby producing the activated and/or expanded cell population.

In certain embodiments, the CAR ligand is present on (e.g., is immobilized or attached to a substrate, e.g., a non-naturally occurring substrate). In some embodiments, the substrate is a non-cellular substrate. The non-cellular substrate can be a solid support chosen from, e.g., a plate (e.g., a microtiter plate), a membrane (e.g., a nitrocellulose membrane), a matrix, a chip or a bead. In embodiments, the CAR ligand is present in the substrate (e.g., on the substrate surface). The CAR ligand can be immobilized, attached, or associated covalently or non-covalently (e.g., cross-linked) to the substrate. In one embodiment, the CAR ligand is attached (e.g., covalently attached) to a bead. In the aforesaid embodiments, the immune cell population can be expanded *in vitro* or *ex vivo*. The

method can further include culturing the population of immune cells in the presence of the ligand of the CAR molecule, e.g., using any of the methods described herein.

In other embodiments, the method of expanding and/or activating the cells further comprises addition of a second stimulatory molecule, e.g., CD28. For example, the CAR ligand and the second stimulatory molecule can be immobilized to a substrate, e.g., one or more beads, thereby providing increased cell expansion and/or activation.

In yet another aspect, a method for selecting or enriching for a CAR expressing cell is provided. The method includes contacting the CAR expressing cell with a CAR ligand as described herein; and selecting the cell on the basis of binding of the CAR ligand.

In yet other embodiments, a method for depleting, reducing and/or killing a CAR expressing cell is provided. The method includes contacting the CAR expressing cell with a CAR ligand as described herein; and targeting the cell on the basis of binding of the CAR ligand, thereby reducing the number, and/or killing, the CAR-expressing cell. In one embodiment, the CAR ligand is coupled to a toxic agent (e.g., a toxin or a cell ablative drug). In another embodiment, the anti-idiotypic antibody can cause effector cell activity, e.g., ADCC or ADC activities.

Exemplary anti-CAR antibodies that can be used in the methods disclosed herein are described, e.g., in WO 2014/190273 and by Jena et al., "Chimeric Antigen Receptor (CAR)-Specific Monoclonal Antibody to Detect CD19-Specific T cells in Clinical Trials", PLOS March 2013 8:3 e57838, the contents of which are incorporated by reference. In one embodiment, the anti-idiotypic antibody molecule recognizes an anti-CD19 antibody molecule, e.g., an anti-CD19 scFv. For instance, the anti-idiotypic antibody molecule can compete for binding with the CD19-specific CAR mAb clone no. 136.20.1 described in Jena et al., PLOS March 2013 8:3 e57838; may have the same CDRs (e.g., one or more of, e.g., all of, VH CDR1, VH CDR2, CH CDR3, VL CDR1, VL CDR2, and VL CDR3, using the Kabat definition, the Chothia definition, or a combination of tthe Kabat and Chothia definitions) as the CD19-specific CAR mAb clone no. 136.20.1; may have one or more (e.g., 2) variable regions as the CD19-specific CAR mAb clone no. 136.20.1, or may comprise the CD19-specific CAR mAb clone no. 136.20.1. In some embodiments, the anti-idiotypic antibody was made according to a method described in Jena et al. In another embodiment, the anti-idiotypic antibody molecule is an anti-idiotypic antibody molecule described in WO 2014/190273. In some embodiments, the anti-idiotypic antibody molecule has the same CDRs (e.g., one or more of, e.g., all of, VH CDR1, VH CDR2, CH CDR3, VL CDR1, VL CDR2, and VL CDR3) as an antibody molecule of WO 2014/190273 such as 136.20.1; may have one or more (e.g., 2) variable regions of an antibody molecule of WO 2014/190273, or may comprise an antibody molecule of WO 2014/190273 such as

136.20.1. In other embodiments, the anti-CAR antibody binds to a constant region of the extracellular binding domain of the CAR molecule, e.g., as described in WO 2014/190273. In some embodiments, the anti-CAR antibody binds to a constant region of the extracellular binding domain of the CAR molecule, e.g., a heavy chain constant region (e.g., a CH2-CH3 hinge region) or light chain constant region. For instance, in some embodiments the anti-CAR antibody competes for binding with the 2D3 monoclonal antibody described in WO 2014/190273, has the same CDRs (e.g., one or more of, e.g., all of, VH CDR1, VH CDR2, CH CDR3, VL CDR1, VL CDR2, and VL CDR3) as 2D3, or has one or more (e.g., 2) variable regions of 2D3, or comprises 2D3 as described in WO 2014/190273.

In some aspects and embodiments, the compositions and methods herein are optimized for a specific subset of T cells, e.g., as described in US Serial No. 62/031,699 filed July 31, 2014, the contents of which are incorporated herein by reference in their entirety. In some embodiments, the optimized subsets of T cells display an enhanced persistence compared to a control T cell, e.g., a T cell of a different type (e.g., $CD8^+$ or $CD4^+$) expressing the same construct.

In some embodiments, a $CD4^+$ T cell comprises a CAR described herein, which CAR comprises an intracellular signaling domain suitable for (e.g., optimized for, e.g., leading to enhanced persistence in) a $CD4^+$ T cell, e.g., an ICOS domain. In some embodiments, a $CD8^+$ T cell comprises a CAR described herein, which CAR comprises an intracellular signaling domain suitable for (e.g., optimized for, e.g., leading to enhanced persistence of) a $CD8^+$ T cell, e.g., a 4-1BB domain, a CD28 domain, or another costimulatory domain other than an ICOS domain. In some embodiments, the CAR described herein comprises an antigen binding domain described herein, e.g., a CAR comprising an antigen binding domain that targets BCMA).

In an aspect, described herein is a method of treating a subject, e.g., a subject having cancer. The method includes administering to said subject, an effective amount of:

1) a $CD4^+$ T cell comprising a CAR (the CAR^{CD4+})

comprising:

an antigen binding domain, e.g., an antigen binding domain described herein, e.g., an antigen binding domain that targets BCMA;

a transmembrane domain; and

an intracellular signaling domain, e.g., a first costimulatory domain, e.g., an ICOS domain; and

2) a $CD8^+$ T cell comprising a CAR (the CAR^{CD8+}) comprising:

an antigen binding domain, e.g., an antigen binding domain described herein, e.g., an antigen binding domain that targets BCMA;

a transmembrane domain; and

an intracellular signaling domain, e.g., a second costimulatory domain, e.g., a 4-1BB domain, a CD28 domain, or another costimulatory domain other than an ICOS domain;

wherein the CAR^{CD4+} and the CAR^{CD8+} differ from one another.

Optionally, the method further includes administering:

3) a second CD8+ T cell comprising a CAR (the second CAR^{CD8+}) comprising:

an antigen binding domain, e.g., an antigen binding domain described herein, e.g., an antigen binding domain that specifically binds BCMA;

a transmembrane domain; and

an intracellular signaling domain, wherein the second CAR^{CD8+} comprises an intracellular signaling domain, e.g., a costimulatory signaling domain, not present on the CAR^{CD8+}, and, optionally, does not comprise an ICOS signaling domain.

Other assays, including those that are known in the art can also be used to evaluate the BCMA CAR constructs of the invention.

Therapeutic Application

BCMA Associated Diseases and/or Disorders

In one aspect, the invention provides methods for treating a disease associated with BCMA expression. In one aspect, the invention provides methods for treating a disease wherein part of the tumor is negative for BCMA and part of the tumor is positive for BCMA For example, the CAR of the invention is useful for treating subjects that have undergone treatment for a disease associated with elevated expression of BCMA, wherein the subject that has undergone treatment for elevated levels of BCMA exhibits a disease associated with elevated levels of BCMA. In embodiments, the CAR of the invention is useful for treating subjects that have undergone treatment for a disease associated with expression of BCMA, wherein the subject that has undergone treatment related to expression of BCMA exhibits a disease associated with expression of BCMA.

In one embodiment, the invention provides methods for treating a disease wherein BCMA is expressed on both normal cells and cancers cells, but is expressed at lower levels on normal cells. In one embodiment, the method further comprises selecting a CAR that binds of the invention with an affinity that allows the BCMA CAR to bind and kill the cancer cells expressing BCMA but less than 30%, 25%, 20%, 15%, 10%, 5% or less of the normal cells expressing BCMA are killed, e.g., as determined by an assay described herein. For example, a killing assay such as flow cytometry based on

Cr51 CTL can be used. In one embodiment, the BCMA CAR has an antigen binding domain that has a binding affinity KD of 10^{-4} M to 10^{-8} M, e.g., 10^{-5} M to 10^{-7} M, e.g., 10^{-6} M or 10^{-7} M, for the target antigen. In one embodiment, the BCMA antigen binding domain has a binding affinity that is at least five-fold, 10-fold, 20-fold, 30-fold, 50-fold, 100-fold or 1,000-fold less than a reference antibody, e.g., an antibody described herein.

In one aspect, the invention pertains to a vector comprising BCMA CAR operably linked to promoter for expression in mammalian immune effector cells, e.g., T cells or NK cells. In one aspect, the invention provides a recombinant immune effector cell, e.g., T cell or NK cell, expressing the BCMA CAR for use in treating BCMA-expressing tumors, wherein the recombinant immune effector cell (e.g., T cell or NK cell) expressing the BCMA CAR is termed a BCMA CAR-expressing cell (e.g., BCMA CART or BCMA CAR-expressing NK cell). In one aspect, the BCMA CAR-expressing cell (e.g., BCMA CART or BCMA CAR-expressing NK cell)of the invention is capable of contacting a tumor cell with at least one BCMA CAR of the invention expressed on its surface such that the BCMA CAR-expressing cell (e.g., BCMA CART or BCMA CAR-expressing NK cell)targets the tumor cell and growth of the tumor is inhibited.

In one aspect, the invention pertains to a method of inhibiting growth of a BCMA-expressing tumor cell, comprising contacting the tumor cell with a BCMA CAR-expressing cell (e.g., BCMA CART or BCMA CAR-expressing NK cell) of the present invention such that the BCMA CAR-expressing cell (e.g., BCMA CART or BCMA CAR-expressing NK cell) is activated in response to the antigen and targets the cancer cell, wherein the growth of the tumor is inhibited.

In one aspect, the invention pertains to a method of treating cancer in a subject. The method comprises administering to the subject a BCMA CAR-expressing cell (e.g., BCMA CART or BCMA CAR-expressing NK cell) of the present invention such that the cancer is treated in the subject. An example of a cancer that is treatable by the BCMA CAR-expressing cell (e.g., BCMA CART or BCMA CAR-expressing NK cell) of the invention is a cancer associated with expression of BCMA.

The invention includes a type of cellular therapy where immune effector cells (e.g., T cells or NK cells) are genetically modified to express a chimeric antigen receptor (CAR) and the BCMA CAR-expressing cell (e.g., BCMA CART or BCMA CAR-expressing NK cell) is infused to a recipient in need thereof. The infused cell is able to kill tumor cells in the recipient. Unlike antibody therapies, CAR-modified cells, e.g., T cells or NK cells, are able to replicate in vivo resulting in long-term persistence that can lead to sustained tumor control. In various aspects, the cells (e.g., T cells or NK cells) administered to the patient, or their progeny, persist in the patient for at least four months, five months, six months, seven months, eight months, nine months, ten months, eleven months, twelve

months, thirteen months, fourteen month, fifteen months, sixteen months, seventeen months, eighteen months, nineteen months, twenty months, twenty-one months, twenty-two months, twenty-three months, two years, three years, four years, or five years after administration of the cell (e.g., T cell or NK cell) to the patient.

The invention also includes a type of cellular therapy where immune effector cells (e.g., T cells or NK cells) are modified, e.g., by in vitro transcribed RNA, to transiently express a chimeric antigen receptor (CAR) and the immune effector cell (e.g., T cell or NK cell) is infused to a recipient in need thereof. The infused cell is able to kill tumor cells in the recipient. Thus, in various aspects, the immune effector cells (e.g., T cells or NK cells) administered to the patient, is present for less than one month, e.g., three weeks, two weeks, one week, after administration of the immune effector cell (e.g., T cell or NK cell) to the patient.

Without wishing to be bound by any particular theory, the anti-tumor immunity response elicited by the CAR-modified immune effector cells (e.g., T cells or NK cells) may be an active or a passive immune response, or alternatively may be due to a direct vs indirect immune response. In one aspect, the CAR transduced immune effector cells (e.g., T cells or NK cells) exhibit specific proinflammatory cytokine secretion and potent cytolytic activity in response to human cancer cells expressing the BCMA, resist soluble BCMA inhibition, mediate bystander killing and mediate regression of an established human tumor. For example, antigen-less tumor cells within a heterogeneous field of BCMA-expressing tumor may be susceptible to indirect destruction by BCMA-redirected immune effector cells (e.g., T cells or NK cells) that has previously reacted against adjacent antigen-positive cancer cells.

In one aspect, the fully-human CAR-modified immune effector cells (e.g., T cells or NK cells) of the invention may be a type of vaccine for ex vivo immunization and/or in vivo therapy in a mammal. In one aspect, the mammal is a human.

With respect to ex vivo immunization, at least one of the following occurs in vitro prior to administering the cell into a mammal: i) expansion of the cells, ii) introducing a nucleic acid encoding a CAR to the cells or iii) cryopreservation of the cells.

Ex vivo procedures are well known in the art and are discussed more fully below. Briefly, cells are isolated from a mammal (e.g., a human) and genetically modified (i.e., transduced or transfected in vitro) with a vector expressing a CAR disclosed herein. The CAR-modified cell can be administered to a mammalian recipient to provide a therapeutic benefit. The mammalian recipient may be a human and the CAR-modified cell can be autologous with respect to the recipient. Alternatively, the cells can be allogeneic, syngeneic or xenogeneic with respect to the recipient.

The procedure for ex vivo expansion of hematopoietic stem and progenitor cells is described in U.S. Pat. No. 5,199,942, incorporated herein by reference, can be applied to the cells of the present invention. Other suitable methods are known in the art, therefore the present invention is not limited to any particular method of ex vivo expansion of the cells. Briefly, ex vivo culture and expansion of T cells comprises: (1) collecting CD34+ hematopoietic stem and progenitor cells from a mammal from peripheral blood harvest or bone marrow explants; and (2) expanding such cells ex vivo. In addition to the cellular growth factors described in U.S. Pat. No. 5,199,942, other factors such as flt3-L, IL-1, IL-3 and c-kit ligand, can be used for culturing and expansion of the cells.

In addition to using a cell-based vaccine in terms of ex vivo immunization, the present invention also provides compositions and methods for in vivo immunization to elicit an immune response directed against an antigen in a patient.

Generally, the cells activated and expanded as described herein may be utilized in the treatment and prevention of diseases that arise in individuals who are immunocompromised. In particular, the CAR-modified immune effector cells (e.g., T cells or NK cells) of the invention are used in the treatment of diseases, disorders and conditions associated with expression of BCMA. In certain aspects, the cells of the invention are used in the treatment of patients at risk for developing diseases, disorders and conditions associated with expression of BCMA. Thus, the present invention provides methods for the treatment or prevention of diseases, disorders and conditions associated with expression of BCMA comprising administering to a subject in need thereof, a therapeutically effective amount of the CAR-modified immune effector cells (e.g., T cells or NK cells) of the invention.

In one aspect the CAR-expressing cells (e.g., CART cells or CAR-expressing NK cells) of the inventions may be used to treat a proliferative disease such as a cancer or malignancy or is a precancerous condition such as a myelodysplasia, a myelodysplastic syndrome or a preleukemia. In one aspect, the cancer is a hematolical cancer. Hematological cancer conditions are the types of cancer such as leukemia and malignant lymphoproliferative conditions that affect blood, bone marrow and the lymphatic system.In one aspect, the hematological cancer is a leukemia or a hematological. An example of a disease or disorder associated with BCMA is multiple myeloma (also known as MM) (See Claudio et al., *Blood*. 2002, 100(6):2175-86; and Novak et al., *Blood*. 2004, 103(2):689-94). Multiple myeloma, also known as plasma cell myeloma or Kahler's disease, is a cancer characterized by an accumulation of abnormal or malignant plasma B-cells in the bone marrow. Frequently, the cancer cells invade adjacent bone, destroying skeletal structures and resulting in bone pain and fractures. Most cases of myeloma also features the production of a paraprotein (also known as M proteins or myeloma proteins), which is an abnormal immunoglobulin produced in excess by the clonal proliferation of the malignant plasma cells. Blood serum paraprotein levels of more than 30g/L is diagnostic of multiple myeloma, according

to the diagnostic criteria of the International Myeloma Working Group (IMWG) (*See* Kyle et al. (2009), Leukemia. 23:3-9). Other symptoms or signs of multiple myeloma include reduced kidney function or renal failure, bone lesions, anemia, hypercalcemia, and neurological symptoms.

Criteria for distinguishing multiple myeloma from other plasma cell proliferative disorders have been established by the International Myeloma Working Group (*See* Kyle et al. (2009), Leukemia. 23:3-9). All three of the following criteria must be met:

- Clonal bone marrow plasma cells ≥10%
- Present of serum and/or urinary monoclonal protein (except in patients with true non-secretory multiple myeloma)
- Evidence of end-organ damage attributable to the underlying plasma cell proliferative disorder, specifically:
    - Hypercalcemia: serum calcium ≥11.5 mg/100 ml
    - Renal insufficienty: serum creatinine > 1.73 mmol/l
    - Anemia: normochromic, normocytic with a hemoglobin value of >2g/100 ml below the lower limit of normal, or a hemoglobin value <10g/100ml
    - Bone lesions: lytic lesions, severe osteopenia, or pathologic fractures.

Other plasma cell proliferative disorders that can be treated by the compositions and methods described herein include, but are not limited to, asymptomatic myeloma (smoldering multiple myeloma or indolent myeloma), monoclonal gammapathy of undetermined significance (MGUS), Waldenstrom's macroglobulinemia, plasmacytomas (e.g., plasma cell dyscrasia, solitary myeloma, solitary plasmacytoma, extramedullary plasmacytoma, and multiple plasmacytoma), systemic amyloid light chain amyloidosis, and POEMS syndrome (also known as Crow-Fukase syndrome, Takatsuki disease, and PEP syndrome).

Two staging systems are used in the staging of multiple myeloma: the International Staging System (ISS) (*See* Greipp et al. (2005), J. Clin. Oncol. 23 (15):3412-3420, herein incorporated by reference in its entirety) and the Durie-Salmon Staging system (DSS) (*See* Durie et al. (1975), Cancer 36 (3): 842-854, herein incorporated by reference in its entirety). The two staging systems are summarized in the table below:

Table 6. Staging systems for the staging of multiple myeloma

Stage	International Staging System		Durie-Salmon Staging System	
	Criteria	Median survival	Criteria	Median survival*
I	β_2M <3.5 mg/l and serum albumin ≥3.5 g/dL	62 months	All of the following: Hemoglobin level >10g/dL	IA: 62 months

			Serum calcium, normal or <12 mg/dL Bone x-ray, normal or 1 plasmacytoma only Low monoclonal protein production (IgG <5g/dL, IgA<3g/dL, Bence Jones protein <4g/dL per 24 hours	IB: 22 months
II	Neither stage I or stage III	44 months	Neither stage I or stage III	IIA: 58 months IIB: 354 months
III	β_2M ≥5.5 mg/l	29 months	One or more of the following: Hemoglobin level <8.5g/dL Serum calcium, normal or >12 mg/dL Advanced osteolytic lesions High monoclonal protein production (IgG >7g/dL, IgA>5g/dL, Bence Jones protein >12g/dL per 24 hours	IIIA: 45 months IIIB: 24 months

*The Durie-Salmon Staging system also includes a subclassification that designates the status of renal function. The designation of "A" or "B" is added after the stage number, wherein "A" indicates relatively normal renal function (serum creatinine value <2.0 mg/dL), and B indicates abnormal renal function (serum creatinine value >2.0 mg/dL).

A third staging system for multiple myeloma is referred to as Revised International Staging System (R-ISS) (*see* Palumbo A, Avet-Loiseau H, Oliva S, et al. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2015;33:2863-9, herein incorporated by reference in its entirety). R-ISS stage I includes ISS stage I (serum β2-microglobulin level < 3.5 mg/L and serum albumin level ≥ 3.5 g/dL), no high-risk CA [del(17p) and/or t(4;14) and/or t(14;16)], and normal LDH level (less than the upper limit of normal range). R-ISS stage III includes ISS stage III (serum β2-microglobulin level > 5.5 mg/L) and high-risk CA or high LDH level. R-ISS stage II includes all the other possible combinations.

The response of patients can be determined based on IMWG 2016 criteria, as disclosed in Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. The Lancet Oncology;17(8):e328-e346 (2016), herein incorporated by reference in its entirety. Table 7 provides IMWG 2016 criteria for response assessment.

Table 7. IMWG criteria for response assessment including criteria for minimal residual disease (MRD)

	Response criteria*
IMWG MRD criteria (requires a complete response as defined below)	

Sustained MRD-negative	MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (e.g., MRD-negative at 5 years)†
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF‡ on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells§ or higher
Imaging plus MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue¶
Standard IMWG response criteria‖	
Stringent complete response	Complete response as defined below plus normal FLC ratio** and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells)††
Complete response	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates
Very good partial response	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 h
Partial response	≥50% reduction of serum M-protein plus reduction in 24 h urinary M-protein by ≥90% or to <200 mg per 24 h; If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria; If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the size (SPD)§§ of soft tissue plasmacytomas is also required
Minimal response	≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50–89%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size (SPD)§§ of soft tissue plasmacytomas is also required
Stable disease	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease
Progressive disease ¶¶,‖‖	Any one or more of the following criteria: Increase of 25% from lowest confi rmed response value in one or more of the following criteria: Serum M-protein (absolute increase must be ≥0.5 g/dL);

	Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL; Urine M-protein (absolute increase must be ≥200 mg/24 h); In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL); In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%); Appearance of a new lesion(s), ≥50% increase from nadir in SPD§§ of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis; ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease
Clinical relapse	Clinical relapse requires one or more of the following criteria: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice; Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression); Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥1 cm) increase as measured serially by the SPD§§ of the measurable lesion; Hypercalcaemia (>11 mg/dL); Decrease in haemoglobin of ≥2 g/dL not related to therapy or other non-myeloma-related conditions; Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma; Hyperviscosity related to serum paraprotein
Relapse from complete response (to be used only if the end point is disease-free survival)	Any one or more of the following criteria: Reappearance of serum or urine M-protein by immunofixation or electrophoresis; Development of ≥5% plasma cells in the bone marrow; Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcaemia see above)
Relapse from MRD negative (to be used only if the end point is disease-free survival)	Any one or more of the following criteria: Loss of MRD negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma); Reappearance of serum or urine M-protein by immunofixation or electrophoresis; Development of ≥5% clonal plasma cells in the bone marrow; Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcaemia)
For MRD assessment, the first bone marrow aspirate should be sent to MRD (not for morphology) and this sample should be taken in one draw with a volume of minimally 2 mL (to obtain sufficient cells), but maximally 4–5 mL to avoid haemodilution. IMWG=International Myeloma Working Group. MRD=minimal residual disease. NGF=next-generation flow. NGS=next-generation sequencing. FLC=free light chain. M-protein=myeloma protein. SPD=sum of the products	

of the maximal perpendicular diameters of measured lesions. CRAB features=calcium elevation, renal failure, anaemia, lytic bone lesions. FCM=fl ow cytometry. SUV_{max}=maximum standardised uptake value. MFC=multiparameter flow cytometry. ^{18}F-FDG PET=^{18}F-fluorodeoxyglucose PET. ASCT=autologous stem cell transplantation.

*All response categories require two consecutive assessments made any time before starting any new therapy; for MRD there is no need for two consecutive assessments, but information on MRD after each treatment stage is recommended (eg, after induction, high-dose therapy/ASCT, consolidation, maintenance). MRD tests should be initiated only at the time of suspected complete response.

All categories of response and MRD require no known evidence of progressive or new bone lesions if radiographic studies were performed. However, radiographic studies are not required to satisfy these response requirements except for the requirement of FDG PET if imaging MRD-negative status is reported. †Sustained MRD negativity when reported should also annotate the method used (eg, sustained flow MRD-negative, sustained sequencing MRD-negative). ‡Bone marrow MFC should follow NGF guidelines (Paiva B, Gutierrez NC, Rosinol L, et al, Blood 2012; 119: 687–91). The reference NGF method is an eight-colour two-tube approach, which has been extensively validated. The two-tube approach improves reliability, consistency, and sensitivity because of the acquisition of a greater number of cells. The eight-colour technology is widely available globally and the NGF method has already been adopted in many flow laboratories worldwide. The complete eight-colour method is most efficient using a lyophilised mixture of antibodies which reduces errors, time, and costs. 5 million cells should be assessed. The FCM method employed should have a sensitivity of detection of at least 1 in 10^5 plasma cells. §DNA sequencing assay on bone marrow aspirate should use a validated assay such as LymphoSIGHT (Sequenta). ¶Criteria used by Zamagni and colleagues (Zamagni E, Nanni C, Mancuso K, et al. Clin Cancer Res 2015; 21: 4384–90), and expert panel (IMPetUs; Italian Myeloma criteria for PET Use) (Usmani SZ, Mitchell A, Waheed S, et al. Blood 2013; 121: 1819–23; Nanni C, Zamagni E, Versari A, et al. Eur J Nucl Med Mol Imaging 2015; 43: 414–21.). Baseline positive lesions were identified by presence of focal areas of increased uptake within bones, with or without any underlying lesion identified by CT and present on at least two consecutive slices. Alternatively, an SUV_{max}=2.5 within osteolytic CT areas >1 cm in size, or SUV_{max}=1.5 within osteolytic CT areas ≤1 cm in size were considered positive. Imaging should be performed once MRD negativity is determined by MFC or NGS. ||Derived from international uniform response criteria for multiple myeloma (Durie BG, Harousseau JL, Miguel JS, et al, Leukemia 2006; 20: 1467–73). Minor response definition and clarifications derived from Rajkumar and colleagues (Rajkumar SV, Harousseau JL, Durie B, et al, Blood 2011; 117: 4691–95). When the only method to measure disease is by serum FLC levels: complete response can be defined as a normal FLC ratio of 0.26 to 1.65 in addition to the complete response criteria listed previously. Very good partial response in such patients requires a ≥90% decrease in the difference between involved and uninvolved FLC levels. All response categories require two consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions or extramedullary plasmacytomas if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments do not need to be confirmed. Each category, except for stable disease, will be considered unconfirmed until the confirmatory test is performed. The date of the initial test is considered as the date of response for evaluation of time dependent outcomes such as duration of response. **All recommendations regarding clinical uses relating to serum FLC levels or FLC ratio are based on results obtained with the validated Freelite test (Binding Site, Birmingham, UK). ††Presence/absence of clonal cells on immunohistochemistry is based upon the κ/λ/L ratio. An abnormal κ/λ ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of >4:1 or <1:2. ‡‡Special attention should be given to the emergence of a different monoclonal protein following treatment, especially in the setting of patients having achieved a conventional complete response, often related to oligoclonal

reconstitution of the immune system. These bands typically disappear over time and in some studies have been associated with a better outcome. Also, appearance of monoclonal IgG κ in patients receiving monoclonal antibodies should be diff erentiated from the therapeutic antibody. §§Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumour size will be determined by the SPD. ¶¶Positive immunofi xation alone in a patient previously classifi ed as achieving a complete response will not be considered progression. For purposes of calculating time to progression and progression-free survival, patients who have achieved a complete response and are MRD-negative should be evaluated using criteria listed for progressive disease. Criteria for relapse from a complete response or relapse from MRD should be used only when calculating disease-free survival. ||||In the case where a value is felt to be a spurious result per physician discretion (eg, a possible laboratory error), that value will not be considered when determining the lowest value.

Standard treatment for multiple myeloma and associated diseases includes chemotherapy, stem cell transplant (autologous or allogeneic), radiation therapy, and other drug therapies. Frequently used anti-myeloma drugs include alkylating agents (e.g., bendamustine, cyclophosphamide and melphalan), proteasome inhibitors (e.g., bortezomib), corticosteroids (e.g., dexamethasone and prednisone), and immunomodulators (e.g., thalidomide and lenalidomide or Revlimid®), or any combination thereof. Biphosphonate drugs are also frequently administered in combination with the standard anti-MM treamtents to prevent bone loss. Patients older than 65-70 years of age are unlikely candidates for stem cell transplant. In some cases, double-autologous stem cell transplants are options for patients less than 60 years of age with suboptimal response to the first transplant. The compositions and methods of the present invention may be administered in combination with any of the currently prescribed treatments for multiple myeloma.

The first phase of treatment for multiple myeloma is induction therapy. The goal of induction therapy is to reduce the number of plasma cells in the bone marrow and the molecules (e.g., proteins) produced by the plasma cells. Induction therapy usually comprises a combination of 2 or 3 of the following types of drugs: targeted therapy, chemotherapy, or corticosteroids.

Induction therapy for patients who can have a stem cell transplant

Patients for a stem cell transplant are usually 70 years of age or younger and in generally good health. Patients can have induction therapy followed by high-dose chemotherapy and a stem cell transplant. Induction therapy is usually given for several cycles and may include one or more of the following drugs: CyBorD regimen – cyclophosphamide (Cytoxan, Procytox), bortezomib (Velcade) and dexamethasone (Decadron, Dexasone); VRD regimen – bortezomib, lenalidomide (Revlimid) and dexamethasone; thalidomide (Thalomid) and dexamethasone; lenalidomide and low-dose dexamethasone; bortezomib and dexamethasone; VTD regimen – bortezomib, thalidomide and dexamethasone; bortezomib, cyclophosphamide and prednisone; bortezomib, doxorubicin (Adriamycin)

and dexamethasone; dexamethasone; or liposomal doxorubicin (Caelyx, Doxil), vincristine (Oncovin) and dexamethasone

Induction therapy for patients who cannot have a stem cell transplant

Patients who cannot have a stem cell transplant may have induction therapy using one or more of the following drugs: CyBorD regimen – cyclophosphamide, bortezomib and dexamethasone; lenalidomide (Revlimid) and low-dose dexamethasone; MPT regimen – melphalan, prednisone and thalidomide; VMP regimen – bortezomib, melphalan and prednisone; MPL regimen – melphalan, prednisone and lenalidomide; melphalan and prednisone; bortezomib and dexamethasone; dexamethasone; liposomal doxorubicin, vincristine and dexamethasone; thalidomide and dexamethasone; VAD regimen – vincristine, doxorubicin and dexamethasone; or VRD regimen – bortezomib, lenalidomide and dexamethasone.

Another example of a disease or disorder associated with BCMA is Hodgkin's lymphoma and non-Hodgkin's lymphoma (*See* Chiu et al., *Blood*. 2007, 109(2):729-39; He et al., *J Immunol.* 2004, 172(5):3268-79).

Hodgkin's lymphoma (HL), also known as Hodgkin's disease, is a cancer of the lymphatic system that originates from white blood cells, or lymphocytes. The abnormal cells that comprise the lymphoma are called Reed-Sternberg cells. In Hodgkin's lymphoma, the cancer spreads from one lymph node group to another. Hodgkin's lymphoma can be subclassified into four pathologic subtypes based upon Reed-Sternberg cell morphology and the cell composition around the Reed-Sternberg cells (as determined through lymph node biopsy): nodular sclerosing HL, mixed-cellularity subtype, lymphocyte-rich or lymphocytic predominance, lymphocyte depleted. Some Hodgkin's lymphoma can also be nodular lymphocyte predominant Hodgkin's lymphoma, or can be unspecified. Symptoms and signs of Hodgkin's lymphoma include painless swelling in the lymph nodes in the neck, armpits, or groin, fever, night sweats, weight loss, fatigue, itching, or abdominal pain.

Non-Hodgkin's lymphoma (NHL) comprises a diverse group of blood cancers that include any kind of lymphoma other than Hodgkin's lymphoma. Subtypes of non-Hodgkin's lymphoma are classified primarily by cell morphology, chromosomal aberrations, and surface markers. NHL subtypes (or NHL-associated cancers) include B cell lymphomas such as, but not limited to, Burkitt's lymphoma, B-cell chronic lymphocytic leukemia (B-CLL), B-cell prolymphocytic leukemia (B-PLL), chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL) (e.g., intravascular large B-cell lymphoma and primary mediastinal B-cell lymphoma), follicular lymphoma (e.g., follicle center lymphoma, follicular small cleaved cell), hair cell leukemia, high grade B-cell lymphoma (Burkitt's

like), lymphoplasmacytic lymphoma (Waldenstrom's macroglublinemia), mantle cell lymphoma, marginal zone B-cell lymphomas (e.g., extranodal marginal zone B-cell lymphoma or mucosa-associated lymphoid tissue (MALT) lymphoma, nodal marginal zone B-cell lymphoma, and splenic marginal zone B-cell lymphoma), plasmacytoma/myeloma, precursor B-lymphoblastic leukemia/lymphoma (PB-LBL/L), primary central nervous system (CNS) lymphoma, primary intraocular lymphoma, small lymphocytic lymphoma (SLL); and T cell lymphomas, such as, but not limited to, anaplastic large cell lymphoma (ALCL), adult T-cell lymphoma/leukemia (e.g., smoldering, chronic, acute and lymphomatous), angiocentric lymphoma, angioimmunoblastic T-cell lymphoma, cutaneous T-cell lymphomas (e.g., mycosis fungoides, Sezary syndrome, etc.), extranodal natural killer/T-cell lymphoma (nasal-type), enteropathy type intestinal T-cell lymphoma, large granular lymphocyte leukemia, precursor T-lymphoblastic lymphoma/leukemia (T-LBL/L), T-cell chronic lymphocytic leukemia/prolymphocytic leukemia (T-CLL/PLL), and unspecified peripheral T-cell lymphoma. Symptoms and signs of Hodgkin's lymphoma include painless swelling in the lymph nodes in the neck, armpits, or groin, fever, night sweats, weight loss, fatigue, itching, abdominal pain, coughing, or chest pain.

The staging is the same for both Hodgkin's and non-Hodgkin's lymphoma, and refers to the extent of spread of the cancer cells within the body. In stage I, the lymphoma cells are in one lymph node group. In stage II, lymphoma cells are present in at least two lymph node groups, but both groups are on the same side of the diaphragm, or in one part of a tissue or organ and the lymph nodes near that organ on the same side of the diaphragm. In stage III, lymphoma cells are in lymph nodes on both sides of the diaphragm, or in one part of a tissue or organ near these lymph node groups or in the spleen. In stage IV, lymphoma cells are found in several parts of at least one organ or tissue, or lymphoma cells are in an organ and in lymph nodes on the other side of the diaphragm. In addition to the Roman numeral staging designation, the stages of can also be described by letters A, B, E, and S, wherein A refers to patients without symptoms, B refers to patients with symptoms, E refers to patients in which lymphoma is found in tissues outside the lymph system, and S refers to patients in which lymphoma is found in the spleen.

Hodgkin's lymphoma is commonly treated with radiation therapy, chemotherapy, or hematopoietic stem cell transplantation. The most common therapy for non-Hodgkin's lymphoma is R-CHOP, which consists of four different chemotherapies (cyclophosphamide, doxorubicin, vincristine, and prenisolone) and rituximab (Rituxan®). Other therapies commonly used to treat NHL include other chemotherapeutic agents, radiation therapy, stem cell transplantation (autologous or allogeneic bone marrow transplantation), or biological therapy, such as immunotherapy. Other examples of biological therapeutic agents include, but are not limited to, rituximab (Rituxan®), tositumomab (Bexxar®),

epratuzumab (LymphoCide®), and alemtuzumab (MabCampath®). The compositions and methods of the present invention may be administered in combination with any of the currently prescribed treatments for Hodgkin's lymphoma or non-Hodgkin's lymphoma.

BCMA expression has also been associated Waldenstrom's macroglobulinemia (WM), also known as lymphoplasmacytic lymphoma (LPL). (See Elsawa et al., *Blood*. 2006, 107(7):2882-8). Waldenstrom's macroglobulinemia was previously considered to be related to multiple myeloma, but has more recently been classified as a subtype of non-Hodgkin's lymphoma. WM is characterized by uncontrolled B-cell lymphocyte proliferation, resulting in anemia and production of excess amounts of paraprotein, or immunoglobulin M (IgM), which thickens the blood and results in hyperviscosity syndrome. Other symptoms or signs of WM include fever, night sweats, fatigue, anemia, weight loss, lymphadenopathy or splenomegaly, blurred vision, dizziness, nose bleeds, bleeding gums, unusual bruises, renal impairment or failure, amyloidosis, or peripheral neuropathy.

Standard treatment for WM consists of chemotherapy, specifically with rituximab (Rituxan®). Other chemotherapeutic drugs can be used in combination, such as chlorambucil (Leukeran®), cyclophosphamide (Neosar®), fludarabine (Fludara®), cladribine (Leustatin®), vincristine, and/or thalidomide. Corticosteriods, such as prednisone, can also be administered in combination with the chemotherapy. Plasmapheresis, or plasma exchange, is commonly used throughout treatment of the patient to alleviate some symptoms by removing the paraprotein from the blood. In some cases, stem cell transplantation is an option for some patients.

Another example of a disease or disorder associated with BCMA is brain cancer. Specifically, expression of BCMA has been associated with astrocytoma or glioblastoma (*See* Deshayes et al, *Oncogene*. 2004, 23(17):3005-12, Pelekanou et al., *PLoS One*. 2013, 8(12):e83250). Astrocytomas are tumors that arise from astrocytes, which are a type of glial cell in the brain. Glioblastoma (also known as glioblastoma multiforme or GBM) is the most malignant form of astrocytoma, and is considered the most advanced stage of brain cancer (stage IV). There are two variants of glioblastoma: giant cell glioblastoma and gliosarcoma. Other astrocytomas include juvenile pilocytic astrocytoma (JPA), fibrillary astrocytoma, pleomorphic xantroastrocytoma (PXA), desembryoplastic neuroepithelial tumor (DNET), and anaplastic astrocytoma (AA).

Symptoms or signs associated with glioblastoma or astrocytoma include increased pressure in the brain, headaches, seizures, memory loss, changes in behavior, loss in movement or sensation on one side of the body, language dysfunction, cognitive impairments, visual impairment, nausea, vomiting, and weakness in the arms or legs.

Surgical removal of the tumor (or resection) is the standard treatment for removal of as much of the glioma as possible without damaging or with minimal damage to the normal, surrounding brain. Radiation therapy and/or chemotherapy are often used after surgery to suppress and slow recurrent disease from any remaining cancer cells or satellite lesions. Radiation therapy includes whole brain radiotherapy (conventional external beam radiation), targeted three-dimensional conformal radiotherapy, and targeted radionuclides. Chemotherapeutic agents commonly used to treat glioblastoma include temozolomide, gefitinib or erlotinib, and cisplatin. Angiogenesis inhibitors, such as Bevacizumab (Avastin®), are also commonly used in combination with chemotherapy and/or radiotherapy.

Supportive treatment is also frequently used to relieve neurological symptoms and improve neurologic function, and is administered in combination any of the cancer therapies described herein. The primary supportive agents include anticonvulsants and corticosteroids. Thus, the compositions and methods of the present invention may be used in combination with any of the standard or supportive treatments to treat a glioblastoma or astrocytoma.

Non-cancer related diseases and disorders associated with BCMA expression can also be treated by the compositions and methods disclosed herein. Examples of non-cancer related diseases and disorders associated with BCMA expression include, but are not limited to: viral infections; e.g., HIV, fungal invections, e.g.,*C. neoformans*; irritable bowel disease; ulcerative colitis, and disorders related to mucosal immunity.

The CAR-modified immune effector cells (e.g., T cells or NK cells) of the present invention may be administered either alone, or as a pharmaceutical composition in combination with diluents and/or with other components such as IL-2 or other cytokines or cell populations.

The present invention provides for compositions and methods for treating cancer. In one aspect, the cancer is a hematologic cancer including but is not limited to hematolical cancer is a leukemia or a lymphoma. In one aspect, the CAR-expressing cells (e.g., CART cells or CAR-expressing NK cells)of the invention may be used to treat cancers and malignancies such as, but not limited to, e.g., acute leukemias including but not limited to, e.g., B-cell acute lymphoid leukemia ("BALL"), T-cell acute lymphoid leukemia ("TALL"), acute lymphoid leukemia (ALL); one or more chronic leukemias including but not limited to, e.g., chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL); additional hematologic cancers or hematologic conditions including, but not limited to, e.g., B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B cell lymphoma, Follicular lymphoma, Hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell

lymphoma, Marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia, and "preleukemia" which are a diverse collection of hematological conditions united by ineffective production (or dysplasia) of myeloid blood cells, and the like. Further a disease associated with BCMA expression includes, but not limited to, e.g., atypical and/or non-classical cancers, malignancies, precancerous conditions or proliferative diseases expressing BCMA.

In embodiments, a composition described herein can be used to treat a disease including but not limited to a plasma cell proliferative disorder, e.g., asymptomatic myeloma (smoldering multiple myeloma or indolent myeloma), monoclonal gammapathy of undetermined significance (MGUS), Waldenstrom's macroglobulinemia, plasmacytomas (e.g., plasma cell dyscrasia, solitary myeloma, solitary plasmacytoma, extramedullary plasmacytoma, and multiple plasmacytoma), systemic amyloid light chain amyloidosis, and POEMS syndrome (also known as Crow-Fukase syndrome, Takatsuki disease, and PEP syndrome).

In embodiments, a composition described herein can be used to treat a disease including but not limited to a cancer, e.g., a cancer described herein, e.g., a prostate cancer (e.g., castrate-resistant or therapy-resistant prostate cancer, or metastatic prostate cancer), pancreatic cancer, or lung cancer.

The present invention also provides methods for inhibiting the proliferation or reducing a BCMA-expressing cell population, the methods comprising contacting a population of cells comprising a BMCA-expressing cell with an anti-BCMA CAR-expressing cell (e.g., BCMA CART cell or BCMA CAR-expressing NK cell)of the invention that binds to the BCMA-expressing cell. In a specific aspect, the present invention provides methods for inhibiting the proliferation or reducing the population of cancer cells expressing BCMA, the methods comprising contacting the BCMA-expressing cancer cell population with an anti-BCMA CAR-expressing cell (e.g., BCMA CART cell or BCMA CAR-expressing NK cell)of the invention that binds to the BCMA-expressing cell. In one aspect, the present invention provides methods for inhibiting the proliferation or reducing the population of cancer cells expressing BCMA, the methods comprising contacting the BMCA-expressing cancer cell population with an anti-BCMA CAR-expressing cell (e.g., BCMA CART cell or BCMA CAR-expressing NK cell)of the invention that binds to the BCMA-expressing cell. In certain aspects, the anti-BCMA CAR-expressing cell (e.g., BCMA CART cell or BCMA CAR-expressing NK cell)of the invention reduces the quantity, number, amount or percentage of cells and/or cancer cells by at least 25%, at least 30%, at least 40%, at least 50%, at least 65%, at least 75%, at least 85%, at least 95%, or at least 99% in a subject with or animal model for myeloid leukemia or another cancer associated with BCMA-expressing cells relative to a negative control. In one aspect, the subject is a human.

The present invention also provides methods for preventing, treating and/or managing a disease associated with BCMA-expressing cells (e.g., a hematologic cancer or atypical cancer expessing BCMA), the methods comprising administering to a subject in need an anti-BCMA CAR-expressing cell (e.g., BCMA CART cell or BCMA CAR-expressing NK cell)of the invention that binds to the BCMA-expressing cell. In one aspect, the subject is a human. Non-limiting examples of disorders associated with BCMA-expressing cells include viral or fungal infections, and disorders related to mucosal immunity.

The present invention also provides methods for preventing, treating and/or managing a disease associated with BCMA-expressing cells, the methods comprising administering to a subject in need an anti-BCMA CAR-expressing cell (e.g., BCMA CART cell or BCMA CAR-expressing NK cell)of the invention that binds to the BCMA-expressing cell. In one aspect, the subject is a human.

The present invention provides methods for preventing relapse of cancer associated with BCMA-expressing cells, the methods comprising administering to a subject in need thereof an anti-BCMA CAR-expressing cell (e.g., BCMA CART cell or BCMA CAR-expressing NK cell)of the invention that binds to the BCMA-expressing cell. In one aspect, the methods comprise administering to the subject in need thereof an effective amount of an anti-BCMA CAR-expressing cell (e.g., BCMA CART cell or BCMA CAR-expressing NK cell)described herein that binds to the BCMA-expressing cell in combination with an effective amount of another therapy.

Methods using Biomarkers for Evaluating CAR-Effectiveness, Subject Suitability, or Sample Suitability

In another aspect, the invention features a method of evaluating or monitoring the effectiveness of a CAR-expressing cell therapy (e.g., a BCMA CAR therapy), in a subject (e.g., a subject having a cancer, e.g., a hematological cancer), or the suitability of a sample (e.g., an apheresis sample) for a CAR therapy (e.g., a BCMA CAR therapy). The method includes acquiring a value of effectiveness to the CAR therapy, subject suitability, or sample suitability, wherein said value is indicative of the effectiveness or suitability of the CAR-expressing cell therapy.

In some embodiments of any of the methods disclosed herein, the CAR-expressing cell therapy comprises a plurality (e.g., a population) of CAR-expressing immune effector cells, e.g., a plurality (e.g., a population) of T cells or NK cells, or a combination thereof. In one embodiment, the CAR-expressing cell therapy is a BCMACAR therapy.

In some embodiments of any of the methods disclosed herein, the subject is evaluated prior to receiving, during, or after receiving, the CAR-expressing cell therapy.

In some embodiments of any of the methods disclosed herein, a responder (e.g., a complete responder) has, or is identified as having, a greater level or activity of one, two, or more (all) of GZMK, PPF1BP2, or naïve T cells as compared to a non-responder.

In some embodiments of any of the methods disclosed herein, a non-responder has, or is identified as having, a greater level or activity of one, two, three, four, five, six, seven, or more (e.g., all) of IL22, IL-2RA, IL-21, IRF8, IL8, CCL17, CCL22, effector T cells, or regulatory T cells, as compared to a responder.

In an embodiment, a relapser is a patient having, or who is identified as having, an increased level of expression of one or more of (e.g., 2, 3, 4, or all of) the following genes, compared to non relapsers: MIR199A1, MIR1203, uc021ovp, ITM2C, and HLA-DQB1 and/or a decreased levels of expression of one or more of (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or all of) the following genes, compared to non relapsers: PPIAL4D, TTTY10, TXLNG2P, MIR4650-1, KDM5D, USP9Y, PRKY, RPS4Y2, RPS4Y1, NCRNA00185, SULT1E1, and EIF1AY.

In some embodiments of any of the methods disclosed herein, a non-responder has, or is identified as having, a greater percentage of an immune cell exhaustion marker, *e.g.*, one, two or more immune checkpoint inhibitors (e.g., PD-1, PD-L1, TIM-3 and/or LAG-3). In one embodiment, a non-responder has, or is identified as having, a greater percentage of PD-1, PD-L1, or LAG-3 expressing immune effector cells (e.g., CD4+ T cells and/or CD8+ T cells) (e.g., CAR-expressing CD4+ cells and/or CD8+ T cells) compared to the percentage of PD-1 or LAG-3 expressing immune effector cells from a responder.

In one embodiment, a non-responder has, or is identified as having, a greater percentage of immune cells having an exhausted phenotype, *e.g.*, immune cells that co-express at least two exhaustion markers, *e.g.*, co-expresses PD-1, PD-L1 and/or TIM-3. In other embodiments, a non-responder has, or is identified as having, a greater percentage of immune cells having an exhausted phenotype, *e.g.*, immune cells that co-express at least two exhaustion markers, *e.g.*, co-expresses PD-1 and LAG-3.

In some embodiments of any of the methods disclosed herein, a non-responder has, or is identified as having, a greater percentage of PD-1/ PD-L1+/LAG-3+ cells in the CAR-expressing cell population (e.g., a BCMACAR+ cell population) compared to a responder (e.g., a complete responder) to the CAR-expressing cell therapy.

In some embodiments of any of the methods disclosed herein, a partial responder has, or is identified as having, a higher percentages of PD-1/ PD-L1+/LAG-3+ cells, than a responder, in the CAR-expressing cell population (e.g., a BCMACAR+ cell population).

In some embodiments of any of the methods disclosed herein, a non-responder has, or is identified as having, an exhausted phenotype of PD1/ PD-L1+ CAR+ and co-expression of LAG3 in the CAR-expressing cell population (e.g., a BCMACAR + cell population).

In some embodiments of any of the methods disclosed herein, a non-responder has, or is identified as having, a greater percentage of PD-1/ PD-L1+/TIM-3+ cells in the CAR-expressing cell population (e.g., a BCMACAR + cell population) compared to the responder (e.g., a complete responder).

In some embodiments of any of the methods disclosed herein, a partial responders has, or is identified as having, a higher percentage of PD-1/ PD-L1+/TIM-3+ cells, than responders, in the CAR-expressing cell population (e.g., a BCMACAR + cell population).

In some embodiments of any of the methods disclosed herein, the presence of CD8+ CD27+ CD45RO- T cells in an apheresis sample is a positive predictor of the subject response to a CAR-expressing cell therapy (e.g., a BCMACAR therapy).

In some embodiments of any of the methods disclosed herein, a high percentage of PD1+ CAR+ and LAG3+ or TIM3+ T cells in an apheresis sample is a poor prognostic predictor of the subject response to a CAR-expressing cell therapy (e.g., a BCMACAR therapy).

In some embodiments of any of the methods disclosed herein, the responder (e.g., the complete or partial responder) has one, two, three or more (or all) of the following profile:

(i) has a greater number of CD27+ immune effector cells compared to a reference value, e.g., a non-responder number of CD27+ immune effector cells;

(ii) (i) has a greater number of CD8+ T cells compared to a reference value, e.g., a non-responder number of CD8+ T cells;

(iii) has a lower number of immune cells expressing one or more checkpoint inhibitors, e.g., a checkpoint inhibitor chosen from PD-1, PD-L1, LAG-3, TIM-3, or KLRG-1, or a combination, compared to a reference value, e.g., a non-responder number of cells expressing one or more checkpoint inhibitors; or

(iv) has a greater number of one, two, three, four or more (all) of resting T_{EFF} cells, resting T_{REG} cells, naïve CD4 cells, unstimulated memory cells or early memory T cells, or a combination thereof, compared to a reference value, e.g., a non-responder number of resting T_{EFF} cells, resting T_{REG} cells, naïve CD4 cells, unstimulated memory cells or early memory T cells.

In some embodiments of any of the methods disclosed herein, the cytokine level or activity of (vi) is chosen from one, two, three, four, five, six, seven, eight, or more (or all) of cytokine CCL20/MIP3a, IL17A, IL6, GM-CSF, IFN-γ, IL10, IL13, IL2, IL21, IL4, IL5, IL9 or TNFα, or a combination thereof. The cytokine can be chosen from one, two, three, four or more (all) of IL-17a, CCL20, IL2, IL6, or TNFa. In one embodiment, an increased level or activity of a cytokine is chosen from one or both of IL-17a and CCL20, is indicative of increased responsiveness or decreased relapse.

In embodiments, the responder, a non-responder, a relapser or a non-relapser identified by the methods herein can be further evaluated according to clinical criteria. For example, a complete

responder has, or is identified as, a subject having a disease, e.g., a cancer, who exhibits a complete response, e.g., a complete remission, to a treatment. A complete response may be identified, e.g., using the NCCN Guidelines®, or Cheson et al, J Clin Oncol 17:1244 (1999) and Cheson et al., "Revised Response Criteria for Malignant Lymphoma", J Clin Oncol 25:579-586 (2007) (both of which are incorporated by reference herein in their entireties), as described herein. A partial responder has, or is identified as, a subject having a disease, e.g., a cancer, who exhibits a partial response, e.g., a partial remission, to a treatment. A partial response may be identified, e.g., using the NCCN Guidelines®, or Cheson criteria as described herein. A non-responder has, or is identified as, a subject having a disease, e.g., a cancer, who does not exhibit a response to a treatment, e.g., the patient has stable disease or progressive disease. A non-responder may be identified, e.g., using the NCCN Guidelines®, or Cheson criteria as described herein.

Alternatively, or in combination with the methods disclosed herein, responsive to said value, performing one, two, three four or more of:

administering e.g., to a responder or a non-relapser, a CAR-expressing cell therapy;

administered an altered dosing of a CAR-expressing cell therapy;

altering the schedule or time course of a CAR-expressing cell therapy;

administering, e.g., to a non-responder or a partial responder, an additional agent in combination with a CAR-expressing cell therapy, e.g., a checkpoint inhibitor, e.g., a checkpoint inhibitor described herein;

administering to a non-responder or partial responder a therapy that increases the number of younger T cells in the subject prior to treatment with a CAR-expressing cell therapy;

modifying a manufacturing process of a CAR-expressing cell therapy, e.g., enriching for younger T cells prior to introducing a nucleic acid encoding a CAR, or increasing the transduction efficiency, e.g., for a subject identified as a non-responder or a partial responder;

administering an alternative therapy, e.g., for a non-responder or partial responder or relapser; or

if the subject is, or is identified as, a non-responder or a relapser, decreasing the T_{REG} cell population and/or T_{REG} gene signature, *e.g.*, by one or more of CD25 depletion, administration of cyclophosphamide, anti-GITR antibody, or a combination thereof.

In certain embodiments, the subject is pre-treated with an anti-GITR antibody. In certain embodiment, the subject is treated with an anti-GITR antibody prior to infusion or re-infusion.

Combination Therapies

A CAR-expressing cell described herein may be used in combination with other known agents and therapies. Administered "in combination", as used herein, means that two (or more) different treatments are delivered to the subject during the course of the subject's affliction with the disorder, e.g., the two or more treatments are delivered after the subject has been diagnosed with the disorder and before the disorder has been cured or eliminated or treatment has ceased for other reasons. In some embodiments, the delivery of one treatment is still occurring when the delivery of the second begins, so that there is overlap in terms of administration. This is sometimes referred to herein as "simultaneous" or "concurrent delivery". In other embodiments, the delivery of one treatment ends before the delivery of the other treatment begins. In some embodiments of either case, the treatment is more effective because of combined administration. For example, the second treatment is more effective, e.g., an equivalent effect is seen with less of the second treatment, or the second treatment reduces symptoms to a greater extent, than would be seen if the second treatment were administered in the absence of the first treatment, or the analogous situation is seen with the first treatment. In some embodiments, delivery is such that the reduction in a symptom, or other parameter related to the disorder is greater than what would be observed with one treatment delivered in the absence of the other. The effect of the two treatments can be partially additive, wholly additive, or greater than additive. The delivery can be such that an effect of the first treatment delivered is still detectable when the second is delivered.

A CAR-expressing cell described herein and the at least one additional therapeutic agent can be administered simultaneously, in the same or in separate compositions, or sequentially. For sequential administration, the CAR-expressing cell described herein can be administered first, and the additional agent can be administered second, or the order of administration can be reversed.

The CAR therapy and/or other therapeutic agents, procedures or modalities can be administered during periods of active disorder, or during a period of remission or less active disease. The CAR therapy can be administered before the other treatment, concurrently with the treatment, post-treatment, or during remission of the disorder.

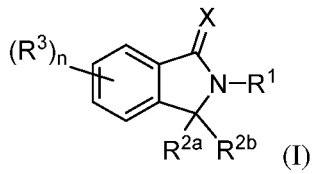
When administered in combination, the CAR therapy and the additional agent (e.g., second or third agent), or all, can be administered in an amount or dose that is higher, lower or the same than the amount or dosage of each agent used individually, e.g., as a monotherapy. In certain embodiments, the administered amount or dosage of the CAR therapy, the additional agent (e.g., second or third agent), or all, is lower (e.g., at least 20%, at least 30%, at least 40%, or at least 50%) than the amount or dosage of each agent used individually, e.g., as a monotherapy. In other embodiments, the amount or dosage of the CAR therapy, the additional agent (e.g., second or third agent), or all, that results in a desired effect (e.g.,

treatment of cancer) is lower (e.g., at least 20%, at least 30%, at least 40%, or at least 50% lower) than the amount or dosage of each agent used individually, e.g., as a monotherapy, required to achieve the same therapeutic effect.

Thalidomide class of compounds

In some embodiments, the BCMA CAR-expressing cell therapy is administered in combination with a member of the thalidomide class of compounds. In some embodiments, members of the thalidomide class of compounds include, but are not limited to, lenalidomide (CC-5013), pomalidomide (CC-4047 or ACTIMID), thalidomide, or salts or derivatives thereof. In some embodiments, the compound can be a mixture of one, two, three, or more members of the thalidomide class of compounds. Thalidomide analogs and immunomodulatory properties of thalidomide analogs are described in Bodera and Stankiewicz, Recent Pat Endocr Metab Immune Drug Discov. 2011 Sep;5(3):192-6, which is hereby incorporated by reference in its entirety. The structural complex of thalidomide analogs and the E3 ubiquitin is described in Gandhi et al., Br J Haematol. 2014 Mar;164(6):811-21, which is hereby incorporated by reference in its entirety. The modulation of the E3 ubiquitin ligase by thalidomide analogs is described in Fischer et al., Nature. 2014 Aug 7;512(7512):49-53, which is hereby incorporated by reference in its entirety.

In some embodiments, the compound comprises a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt, ester, hydrate, solvate, or tautomer thereof, wherein:

X is O or S;

R^1 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted by one or more R^4;

each of R^{2a} and R^{2b} is independently hydrogen or C_1-C_6 alkyl; or R^{2a} and R^{2b} together with the carbon atom to which they are attached form a carbonyl group or a thiocarbonyl group;

each of R^3 is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, halo, cyano, $-C(O)R^A$, $-C(O)OR^B$, $-OR^B$, $-N(R^C)(R^D)$, $-C(O)N(R^C)(R^D)$, $-N(R^C)C(O)R^A$, $-S(O)_xR^E$, $-S(O)_xN(R^C)(R^D)$, or $-N(R^C)S(O)_xR^E$, wherein each alkyl, alkenyl, alkynyl, and heteroalkyl is independently and optionally substituted with one or more R^6;

each R^4 is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, halo, cyano, oxo, $-C(O)R^A$, $-C(O)OR^B$, $-OR^B$, $-N(R^C)(R^D)$, $-C(O)N(R^C)(R^D)$, $-N(R^C)C(O)R^A$, $-S(O)_xR^E$, -

$S(O)_xN(R^C)(R^D)$, -N $(R^C)S(O)_xR^E$, carbocyclyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently and optionally substituted with one or more R^7;

each of R^A, R^B, R^C, R^D, and R^E is independently hydrogen or C_1-C_6 alkyl;

each R^6 is independently C_1-C_6 alkyl, oxo, cyano, -OR^B, -$N(R^C)(R^D)$, -$C(O)N(R^C)(R^D)$, -$N(R^C)C(O)R^A$, aryl, or heteroaryl, wherein each aryl and heteroaryl is independently and optionally substituted with one or more R^8;

each R^7 is independently halo, oxo, cyano, -OR^B, -$N(R^C)(R^D)$, -$C(O)N(R^C)(R^D)$, or -$N(R^C)C(O)R^A$;

each R^8 is independently C_1-C_6 alkyl, cyano, -OR^B, -$N(R^C)(R^D)$, -$C(O)N(R^C)(R^D)$, or -$N(R^C)C(O)R^A$;

n is 0, 1, 2, 3 or 4; and

x is 0, 1, or 2.

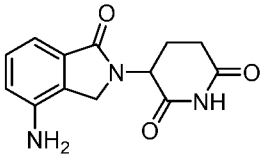
In some embodiments, X is O.

In some embodiments, R^1 is heterocyclyl. In some embodiments, R^1 is a 6-membered heterocyclyl or a 5-membered heterocyclyl. In some embodiments, R^1 is a nitrogen-containing heterocyclyl. In some embodiments, R^1 is piperidinyl (e.g., piperidine-2,6-dionyl).

In some embodiments, each of R^{2a} and R^{2b} is independently hydrogen. In some embodiments, R^{2a} and R^{2b} together with the carbon to which they are attached form a carbonyl group.

In some embodiments, R^3 is C_1-C_6 heteroalkyl, -$N(R^C)(R^D)$ or -$N(R^C)C(O)R^A$. In some embodiments, R^3 is C_1-C_6 heteroalkyl (e.g., $CH_2NHC(O)CH_2$-phenyl-t-butyl), -$N(R^C)(R^D)$ (e.g., NH_2), or -$N(R^C)C(O)R^A$ (e.g., $NHC(O)CH_3$).

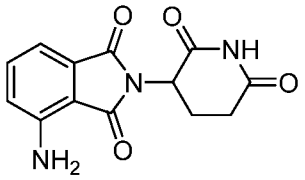
In an embodiment, X is O. In an embodiment, R^1 is heterocyclyl (e.g., piperidine-2,6-dionyl). In an embodiment, each of R^{2a} and R^{2b} is independently hydrogen. In an embodiment, n is 1. In an embodiment, R^3 is -$N(R^C)(R^D)$ (e.g., -NH_2). In an embodiment, the compound comprises lenalidomide, e.g., 3-(4-amino-1-oxoisoindolin-2-yl)piperidine-2,6-dione, or a pharmaceutically acceptable salt thereof. In an embodiment, the compound is lenalidomide, e.g., according to the following formula:



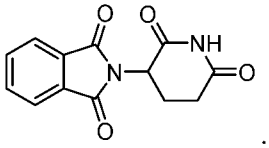
.

In an embodiment, X is O. In an embodiment, R^1 is heterocyclyl (e.g., piperidinyl-2,6-dionyl). In some embodiments, R^{2a} and R^{2b} together with the carbon to which they are attached form a carbonyl

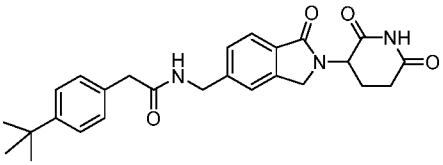
group. In an embodiment, n is 1. In an embodiment, R^3 is $-N(R^C)(R^D)$ (e.g., $-NH_2$). In an embodiment, the compound comprises pomalidomide, e.g., 4-amino-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione, or a pharmaceutically acceptable salt thereof. In an embodiment, the compound is pomalidomide, e.g., according to the following formula:



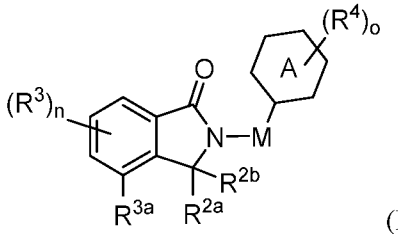
In an embodiment, X is O. In an embodiment, R^1 is heterocyclyl (e.g., piperidinyl-2,6-dionyl). In an embodiment, R^{2a} and R^{2b} together with the carbon to which they are attached form a carbonyl group. In an embodiment, n is 0. In an embodiment, the compound comprises thalidomide, e.g., 2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione, or a pharmaceutically acceptable salt thereof. In an embodiment, the product is thalidomide, e.g., according to the following formula:



In an embodiment, X is O. In an embodiment, R^1 is heterocyclyl (e.g., piperidine-2,6-dionyl). In an embodiment, each of R^{2a} and R^{2b} is independently hydrogen. In an embodiment, n is 1. In an embodiment, R^3 is C_1-C_6 heteroalkyl (e.g., $CH_2NHC(O)CH_2$-phenyl-t-butyl) In an embodiment, the compound comprises 2-(4-(tert-butyl)phenyl)-N-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)methyl)acetamide, or a pharmaceutically acceptable salt thereof. In an embodiment, the compound has the structure as shown in the following formula:



In some embodiments, the compound is a compound of Formula (I-a):



(I-a)

or a pharmaceutically acceptable salt, ester, hydrate, or tautomer thereof, wherein:

Ring A is carbocyclyl, heterocyclyl, aryl, or heteroaryl, each of which optionally substituted with one or more R^4;

M is absent, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 heteroalkyl, wherein each alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one or more R^4;

each of R^{2a} and R^{2b} is independently hydrogen or C_1-C_6 alkyl; or R^{2a} and R^{2b} together with the carbon atom to which they are attached to form a carbonyl group or thiocarbonyl group;

R^{3a} is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, halo, cyano, -$C(O)R^A$, -$C(O)OR^B$, -OR^B, -$N(R^C)(R^D)$, -$C(O)N(R^C)(R^D)$, -$N(R^C)C(O)R^A$, -$S(O)_xR^E$, -$S(O)_xN(R^C)(R^D)$, or -$N(R^C)S(O)_xR^E$, wherein each alkyl, alkenyl, alkynyl, and heteroalkyl is optionally substituted with one or more R^6;

each of R^3 is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, halo, cyano, -$C(O)R^A$, -$C(O)OR^B$, -OR^B, -$N(R^C)(R^D)$, -$C(O)N(R^C)(R^D)$, -$N(R^C)C(O)R^A$, -$S(O)_xR^E$, -$S(O)_xN(R^C)(R^D)$, or -N (R^C)$S(O)_xR^E$, wherein each alkyl, alkenyl, alkynyl, and heteroalkyl is independently and optionally substituted with one or more R^6;

each R^4 is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, halo, cyano, oxo, -$C(O)R^A$, -$C(O)OR^B$, -OR^B, -$N(R^C)(R^D)$, -$C(O)N(R^C)(R^D)$, -$N(R^C)C(O)R^A$, $S(O)_xR^E$, -$S(O)_xN(R^C)(R^D)$, -N (R^C)$S(O)_xR^E$, carbocyclyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is independently and optionally substituted with one or more R^7;

each of R^A, R^B, R^C, R^D, and R^E is independently hydrogen or C_1-C_6 alkyl;

each R^6 is independently C_1-C_6 alkyl, oxo, cyano, -OR^B, -$N(R^C)(R^D)$, -$C(O)N(R^C)(R^D)$, -$N(R^C)C(O)R^A$, aryl, or heteroaryl, wherein each aryl or heteroaryl is independently and optionally substituted with one or more R^8;

each R^7 is independently halo, oxo, cyano, -OR^B, -$N(R^C)(R^D)$, -$C(O)N(R^C)(R^D)$, or -$N(R^C)C(O)R^A$;

each R^8 is independently C_1-C_6 alkyl, cyano, -OR^B, -$N(R^C)(R^D)$, -$C(O)N(R^C)(R^D)$, or -$N(R^C)C(O)R^A$;

n is 0, 1, 2, or 3;

o is 0, 1, 2, 3, 4, or 5; and

x is 0, 1, or 2.

In some embodiments, X is O.

In some embodiments, M is absent.

In some embodiments, Ring A is heterocyclyl. In some embodiments, Ring A is heterocyclyl, e.g., a 6-membered heterocyclyl or a 5-membered heterocyclyl. In some embodiments, Ring A is a

nitrogen-containing heterocyclyl. In some embodiments, Ring A is piperidinyl (e.g., piperidine-2,6-dionyl).

In some embodiments, M is absent and Ring A is heterocyclyl (e.g., piperidinyl, e.g., piperidine-2,6-dionyl).

In some embodiments, each of R^{2a} and R^{2b} is independently hydrogen. In some embodiments, R^{2a} and R^{2b} together with the carbon to which they are attached form a carbonyl group.

In some embodiments, R^{3a} is hydrogen, $-N(R^C)(R^D)$ or $-N(R^C)C(O)R^A$. In some embodiments, R^{3a} is hydrogen. In some embodiments, R^{3a} is $-N(R^C)(R^D)$ (e.g., $-NH_2$). In some embodiments, R^{3a} is $-N(R^C)C(O)R^A$ (e.g, $NHC(O)CH_3$).

In some embodiments, R^3 is C_1-C_6 heteroalkyl (e.g., $CH_2NHC(O)CH_2$-phenyl-t-butyl). In some embodiments, n is 0 or 1. In some embodiments, n is 0. In some embodiments, n is 1.

The compound may comprise one or more chiral centers or exist as one or more stereoisomers. In some embodiments, the compound comprises a single chiral center and is a mixture of stereoisomers, e.g., an R stereoisomer and an S stereoisomer. In some embodiments, the mixture comprises a ratio of R stereoisomers to S stereoisomers, for example, about a 1:1 ratio of R stereoisomers to S stereoisomers (i.e., a racemic mixture). In some embodiments, the mixture comprises a ratio of R stereoisomers to S stereoisomers of about 51:49, about 52: 48, about 53:47, about 54:46, about 55:45, about 60:40, about 65:35, about 70:30, about 75:25, about 80:20, about 85:15, about 90:10, about 95:5, or about 99:1. In some embodiments, the mixture comprises a ratio of S stereoisomers to R stereoisomers of about 51:49, about 52: 48, about 53:47, about 54:46, about 55:45, about 60:40, about 65:35, about 70:30, about 75:25, about 80:20, about 85:15, about 90:10, about 95:5, or about 99:1. In some embodiments, the compound is a single stereoisomer of Formula (I) or Formula (I-a), e.g., a single R stereoisomer or a single S stereoisomer.

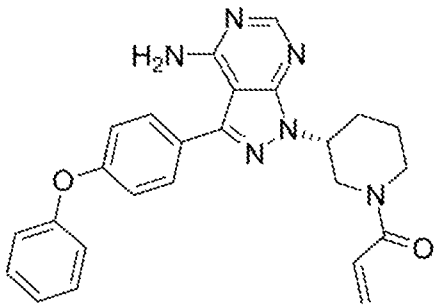
Kinase inhibitors

In some embodiments, the BCMA CAR-expressing cell therapy is administered in combination with a kinase inhibitor. In one embodiment, the kinase inhibitor is a CDK4 inhibitor, e.g., a CDK4 inhibitor described herein, e.g., a CDK4/6 inhibitor, such as, e.g., 6-Acetyl-8-cyclopentyl-5-methyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one, hydrochloride (also referred to as palbociclib or PD0332991). In one embodiment, the kinase inhibitor is a BTK inhibitor, e.g., a BTK inhibitor described herein, such as, e.g., ibrutinib. In one embodiment, the kinase inhibitor is an mTOR inhibitor, e.g., an mTOR inhibitor described herein, such as, e.g., rapamycin, a rapamycin analog, OSI-027. The mTOR inhibitor can be, e.g., an mTORC1 inhibitor and/or an mTORC2 inhibitor, e.g., an

mTORC1 inhibitor and/or mTORC2 inhibitor described herein. In one embodiment, the kinase inhibitor is a MNK inhibitor, e.g., a MNK inhibitor described herein, such as, e.g., 4-amino-5-(4-fluoroanilino)-pyrazolo [3,4-*d*] pyrimidine. The MNK inhibitor can be, e.g., a MNK1a, MNK1b, MNK2a and/or MNK2b inhibitor. In one embodiment, the kinase inhibitor is a dual PI3K/mTOR inhibitor described herein, such as, e.g., PF-04695102. In one embodiment, the kinase inhibitor is a DGK inhibitor, e.g., a DGK inhibitor described herein, such as, e.g., DGKinh1 (D5919) or DGKinh2 (D5794).

In one embodiment, the kinase inhibitor is a BTK inhibitor selected from ibrutinib (PCI-32765); GDC-0834; RN-486; CGI-560; CGI-1764; HM-71224; CC-292; ONO-4059; CNX-774; and LFM-A13. In a preferred embodiment, the BTK inhibitor does not reduce or inhibit the kinase activity of interleukin-2-inducible kinase (ITK), and is selected from GDC-0834; RN-486; CGI-560; CGI-1764; HM-71224; CC-292; ONO-4059; CNX-774; and LFM-A13.

In one embodiment, the kinase inhibitor is a BTK inhibitor, e.g., ibrutinib (PCI-32765). In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with a BTK inhibitor (e.g., ibrutinib). In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with ibrutinib (also called PCI-32765). The structure of ibrutinib (1-[(3*R*)-3-[4-Amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-d]pyrimidin-1-yl]piperidin-1-yl]prop-2-en-1-one) is shown below.



In embodiments, the subject has CLL, mantle cell lymphoma (MCL), or small lymphocytic lymphoma (SLL). For example, the subject has a deletion in the short arm of chromosome 17 (del(17p), e.g., in a leukemic cell). In other examples, the subject does not have a del(17p). In embodiments, the subject has relapsed CLL or SLL, e.g., the subject has previously been administered a cancer therapy (e.g., previously been administered one, two, three, or four prior cancer therapies). In embodiments, the subject has refractory CLL or SLL. In other embodiments, the subject has follicular lymphoma, e.g., relapse or refractory follicular lymphoma. In some embodiments, ibrutinib is administered at a dosage of about 300-600 mg/day (e.g., about 300-350, 350-400, 400-450, 450-500, 500-550, or 550-600 mg/day, e.g., about 420 mg/day or about 560 mg/day), e.g., orally. In embodiments, the ibrutinib is

administered at a dose of about 250 mg, 300 mg, 350 mg, 400 mg, 420 mg, 440 mg, 460 mg, 480 mg, 500 mg, 520 mg, 540 mg, 560 mg, 580 mg, 600 mg (e.g., 250 mg, 420 mg or 560 mg) daily for a period of time, e.g., daily for 21 day cycle cycle, or daily for 28 day cycle. In one embodiment, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or more cycles of ibrutinib are administered. In some embodiments, ibrutinib is administered in combination with rituximab. See, e.g., Burger et al. (2013) Ibrutinib In Combination With Rituximab (iR) Is Well Tolerated and Induces a High Rate Of Durable Remissions In Patients With High-Risk Chronic Lymphocytic Leukemia (CLL): New, Updated Results Of a Phase II Trial In 40 Patients, Abstract 675 presented at 55th ASH Annual Meeting and Exposition, New Orleans, LA 7-10 Dec. Without being bound by theory, it is thought that the addition of ibrutinib enhances the T cell proliferative response and may shift T cells from a T-helper-2 (Th2) to T-helper-1 (Th1) phenotype. Th1 and Th2 are phenotypes of helper T cells, with Th1 versus Th2 directing different immune response pathways. A Th1 phenotype is associated with proinflammatory responses, e.g., for killing cells, such as intracellular pathogens/viruses or cancerous cells, or perpetuating autoimmune responses. A Th2 phenotype is associated with eosinophil accumulation and anti-inflammatory responses.

EGFR Inhibitors

In some embodiments, the BCMA CAR-expressing cell therapy is administered in combination with an inhibitor of Epidermal Growth Factor Receptor (EGFR).

In some embodiments, the EGFR inhibitor is (R,E)-N-(7-chloro-1-(1-(4-(dimethylamino)but-2-enoyl)azepan-3-yl)-1H-benzo[d]imidazol-2-yl)-2-methylisonicotinamide (Compound A40) or a compound disclosed in PCT Publication No. WO 2013/184757.

In some embodiments, the EGFR inhibitor, (R,E)-N-(7-chloro-1-(1-(4-(dimethylamino)but-2-enoyl)azepan-3-yl)-1H-benzo[d]imidazol-2-yl)-2-methylisonicotinamide (Compound A40), or a compound disclosed in PCT Publication No. WO 2013/184757, is a covalent, irreversible tyrosine kinase inhibitor. In certain embodiments, the EGFR inhibitor, (R,E)-N-(7-chloro-1-(1-(4-(dimethylamino)but-2-enoyl)azepan-3-yl)-1H-benzo[d]imidazol-2-yl)-2-methylisonicotinamide (Compound A40), or a compound disclosed in PCT Publication No. WO 2013/184757 inhibits activating EGFR mutations (L858R, ex19del). In other embodiments, the EGFR inhibitor, (R,E)-N-(7-chloro-1-(1-(4-(dimethylamino)but-2-enoyl)azepan-3-yl)-1H-benzo[d]imidazol-2-yl)-2-methylisonicotinamide (Compound A40), or a compound disclosed in PCT Publication No. WO 2013/184757 does not inhibit, or does not substantially inhibit, wild-type (wt) EGFR. Compound A40 has shown efficacy in EGFR mutant NSCLC patients. In some embodiments, the EGFR inhibitor, (R,E)-N-(7-chloro-1-(1-(4-(dimethylamino)but-2-enoyl)azepan-3-yl)-1H-benzo[d]imidazol-2-yl)-2-methylisonicotinamide (Compound A40), or a compound disclosed in PCT Publication No. WO

2013/184757 also inhibits one or more kinases in the TEC family of kinases. The Tec family kinases include, *e.g.,* ITK, BMX, TEC, RLK, and BTK, and are central in the propogation of T-cell receptor and chemokine receptor signaling (Schwartzberg *et al.* (2005) *Nat. Rev. Immunol.* p. 284-95). For example, Compound A40 can inhibit ITK with a biochemical IC50 of 1.3 nM. ITK is a critical enzyme for the survival of Th2 cells and its inhibition results in a shift in the balance between Th2 and Th1 cells.

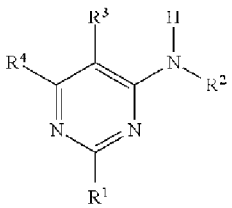
In some embodiments, the EGFR inhibitor is chosen from one of more of erlotinib, gefitinib, cetuximab, panitumumab, necitumumab, PF-00299804, nimotuzumab, or RO5083945.

Adenosine A2A Receptor Inhibitors

In some embodiments, the BCMA CAR-expressing cell therapy is administered in combination with an adenosine A2a receptor (A2aR) antagonist (e.g., an inhibitor of A2aR pathway, e.g., an adenosine inhibitor, e.g., an inhibitor of A2aR or CD-73). In some embodiments, the A2aR antagonist is chosen from PBF509 (Palobiofarma/Novartis), CPI444/V81444 (Corvus/Genentech), AZD4635/HTL-1071 (AstraZeneca/Heptares), Vipadenant (Redox/Juno), GBV-2034 (Globavir), AB928 (Arcus Biosciences), Theophylline, Istradefylline (Kyowa Hakko Kogyo), Tozadenant/SYN-115 (Acorda), KW-6356 (Kyowa Hakko Kogyo), ST-4206 (Leadiant Biosciences), or Preladenant/SCH 420814 (Merck/Schering).

In some embodiments, the A2aR antagonist comprises PBF509 or a compound disclosed in U.S. Patent No. 8,796,284 or in International Application Publication No. WO 2017/025918, herein incorporated by reference in their entirety.

In some embodiments, the A2aR antagonist comprises a compound of formula (I):



wherein

R^1 represents a five-membered heteroaryl ring selected from the group consisting of a pyrazole, a thiazole, and a triazole ring optionally substituted by one or two halogen atoms or by one or two methyl groups;

R^2 represents a hydrogen atom;

R^3 represents bromine or chlorine atom;

R^4 represents independently:

a) a five-membered heteroaryl group optionally substituted by one or more halogen atoms or by one or more groups selected from the group consisting of alkyl, cycloalkyl, alkoxy, alkylthio, amino, mono- or dialkylamino

b) a group —N(R^5)(R^6) in which R^5 and R^6 represent independently:

a hydrogen atom;

an alkyl or cycloalkyl group of 3 to 6 carbon atoms, linear or branched, optionally substituted by one or more halogen atoms or by one or more groups selected from the group consisting of cycloalkyl (3-8 carbon atoms), hydroxy, alkoxy, amino, mono- and dialkylamino (1-8 carbon atoms);

or R^5 and R^6 form together with the nitrogen atom to that they are attached a saturated heterocyclic group of 4 to 6 members in which further heteroatom may be inserted, which is optionally substituted by one or more halogen atoms or by one or more alkyl groups (1-8 carbon atoms), hydroxy, lower alkoxy, amino, mono- or dialkylamino, or

c) a group —OR^7 or —SR^7, where R^7 represents independently:

an alkyl (1-8 carbon atoms) or cycloalkyl (3-8 carbon atoms) group, linear or branched, optionally substituted by one or more halogen atoms or by one or more groups selected from the group consisting of alkyl (1-8 carbon atoms), alkoxy (1-8 carbon atoms), amino, mono- or dialkylamino (1-8 carbon atoms); or

a Phenyl ring optionally substituted with one or more halogen atoms.

In certain embodiments, the A2aR antagonist comprises 5-bromo-2,6-di-(1*H*-pyrazol-1-yl)pyrimidin-4-amine.

In certain embodiments, the A2AR antagonist comprises CPI444/V81444. CPI-444 and other A2aR antagonists are disclosed in International Application Publication No. WO 2009/156737, herein incorporated by reference in its entirety. In certain embodiments, the A2aR antagonist is (*S*)-7-(5-methylfuran-2-yl)-3-((6-(((tetrahydrofuran-3-yl)oxy)methyl)pyridin-2-yl)methyl)-3*H*-[1,2,3]triazolo[4,5-d]pyrimidin-5-amine. In certain embodiments, the A2aR antagonist is (*R*)-7-(5-methylfuran-2-yl)-3-((6-(((tetrahydrofuran-3-yl)oxy)methyl)pyridin-2-yl)methyl)-3*H*-[1,2,3]triazolo[4,5-d]pyrimidin-5-amine, or racemate thereof. In certain embodiments, the A2aR antagonist is 7-(5-methylfuran-2-yl)-3-((6-(((tetrahydrofuran-3-yl)oxy)methyl)pyridin-2-yl)methyl)-3*H*-[1,2,3]triazolo[4,5-d]pyrimidin-5-amine.

In certain embodiments, the A2aR antagonist is AZD4635/HTL-1071. A2aR antagonists are disclosed in International Application Publication No. WO 2011/095625, herein incorporated by reference in its entirety. In certain embodiments, the A2aR antagonist is 6-(2-chloro-6-methylpyridin-4-yl)-5-(4-fluorophenyl)-1,2,4-triazin-3-amine.

In certain embodiments, the A2aR antagonist is ST-4206 (Leadiant Biosciences). In certain embodiments, the A2aR antagonist is an A2aR antagonist described in U.S. Patent No. 9,133,197, herein incorporated by reference in its entirety.

In certain embodiments, the A2AR antagonist is an A2aR antagonist described in U.S. Patent Nos. 8,114,845 and 9,029,393, U.S. Application Publication Nos. 2017/0015758 and 2016/0129108, herein incorporated by reference in their entirety.

In some embodiments, the A2aR antagonist is istradefylline (CAS Registry Number: 155270-99-8). Istradefylline is also known as KW-6002 or 8-[(E)-2-(3,4-dimethoxyphenyl)vinyl]-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione. Istradefylline is disclosed, *e.g.,* in LeWitt *et al.* (2008) *Annals of Neurology* 63 (3): 295–302).

In some embodiments, the A2aR antagonist is tozadenant (Biotie). Tozadenant is also known as SYN115 or 4-hydroxy-N-(4-methoxy-7-morpholin-4-yl-1,3-benzothiazol-2-yl)-4-methylpiperidine-1-carboxamide. Tozadenant blocks the effect of endogenous adenosine at the A2a receptors, resulting in the potentiation of the effect of dopamine at the D2 receptor and inhibition of the effect of glutamate at the mGluR5 receptor. In some embodiments, the A2aR antagonist is preladenant (CAS Registry Number: 377727-87-2). Preladenant is also known as SCH 420814 or 2-(2-Furanyl)-7-[2-[4-[4-(2-methoxyethoxy)phenyl]-1-piperazinyl]ethyl]7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine-5-amine. Preladenant was developed as a drug that acted as a potent and selective antagonist at the adenosine A2A receptor.

In some embodiments, the A2aR antagonist is vipadenan. Vipadenan is also known as BIIB014, V2006, or 3-[(4-amino-3-methylphenyl)methyl]-7-(furan-2-yl)triazolo[4,5-d]pyrimidin-5-amine.

Other exemplary A2aR antagonists include, *e.g.,* ATL-444, MSX-3, SCH-58261, SCH-412,348, SCH-442,416, VER-6623, VER-6947, VER-7835, CGS-15943, or ZM-241,385.

IDO/TDO Inhibitors

In some embodiments, the BCMA CAR-expressing cell therapy is administered in combination with an inhibitor of indoleamine 2,3-dioxygenase (IDO) and/or tryptophan 2,3-dioxygenase (TDO). In some embodiments, the IDO inhibitor is chosen from (4E)-4-[(3-chloro-4-fluoroanilino)-nitrosomethylidene]-1,2,5-oxadiazol-3-amine (also known as epacadostat or INCB24360), indoximod (NLG8189), (1-methyl-D-tryptophan), α-cyclohexyl-5H-Imidazo[5,1-a]isoindole-5-ethanol (also known as NLG919), indoximod, BMS-986205 (formerly F001287).

In some embodiments, the IDO/TDO inhibitor is indoximod (New Link Genetics). Indoximod, the D isomer of 1-methyl-tryptophan, is an orally administered small-molecule indoleamine 2,3-

dioxygenase (IDO) pathway inhibitor that disrupts the mechanisms by which tumors evade immune-mediated destruction.

In some embodiments, the IDO/TDO inhibitor is NLG919 (New Link Genetics). NLG919 is a potent IDO (indoleamine-(2,3)-dioxygenase) pathway inhibitor with Ki/EC50 of 7 nM/75 nM in cell-free assays.

In some embodiments, the IDO/TDO inhibitor is epacadostat (CAS Registry Number: 1204669-58-8). Epacadostat is also known as INCB24360 or INCB024360 (Incyte). Epacadostat is a potent and selective indoleamine 2,3-dioxygenase (IDO1) inhibitor with IC50 of 10 nM, highly selective over other related enzymes such as IDO2 or tryptophan 2,3-dioxygenase (TDO).

In some embodiments, the IDO/TDO inhibitor is F001287 (Flexus/BMS). F001287 is a small molecule inhibitor of indoleamine 2,3-dioxygenase 1 (IDO1).

CD19 CAR

In some embodiments, the BCMA CAR-expressing cell therapy is administered in combination with a CD19 CAR-expressing cell therapy.

In one embodiment, the antigen binding domain of the CD19 CAR has the same or a similar binding specificity as the FMC63 scFv fragment described in Nicholson et al. Mol. Immun. 34 (16-17): 1157-1165 (1997). In one embodiment, the antigen binding domain of the CD19 CAR includes the scFv fragment described in Nicholson et al. *Mol. Immun.* 34 (16-17): 1157-1165 (1997).

In some embodiments, the CD19 CAR includes an antigen binding domain (*e.g.*, a humanized antigen binding domain) according to Table 3 of WO2014/153270, incorporated herein by reference. WO2014/153270 also describes methods of assaying the binding and efficacy of various CAR constructs.

In one aspect, the parental murine scFv sequence is the CAR19 construct provided in PCT publication WO2012/079000 (incorporated herein by reference). In one embodiment, the anti-CD19 binding domain is a scFv described in WO2012/079000.

In one embodiment, the CAR molecule comprises the fusion polypeptide sequence provided as SEQ ID NO: 12 in PCT publication WO2012/079000, which provides an scFv fragment of murine origin that specifically binds to human CD19.

In one embodiment, the CD19 CAR comprises an amino acid sequence provided as SEQ ID NO: 12 in PCT publication WO2012/079000. In embodiment, the amino acid sequence is

(MALPVTALLLPLALLLHAARP)diqmtqttsslsaslgdrvtiscrasqdiskylnwyqqkpdgtvklliyhtsrlhsg vpsrfsgsgsgtdysltisnleqediatyfcqqgntlpytfgggtkleitggggsggggsggggsevklqesgpglvapsqslsvtctvsgvslpdyg vswirqpprkglewlgviwgsettyynsalksrltiikdnsksqvflkmnslqtddtaiyycakhyyyggsyamdywgqgtsvtvsstttpaprp

ptpaptiasqplslrpeacrpaaggavhtrgldfacdiyiwaplagtcgvlllslvitlyckrgrkkllyifkqpfmrpvqttqeedgcscrfpeeeegg celrvkfsrsadapaykqgqnqlynelnlgrreeydvldkrrgrdpemggkprrknpqeglynelqkdkmaeayseigmkgerrrgkghdgl yqglstatkdtydalhmqalppr (SEQ ID NO: 2029), or a sequence substantially homologous thereto. The optional sequence of the signal peptide is shown in capital letters and parenthesis.

In one embodiment, the amino acid sequence is:

Diqmtqttsslsaslgdrvtiscrasqdiskylnwyqqkpdgtvklliyhtsrlhsgvpsrfsgsgsgtdysltisnleqediatyfcqqgn tlpytfgggtkleitggggsggggsggggsevklqesgpglvapsqslsvtctvsgvslpdygvswirqpprkglewlgviwgsettyynsalksr ltiikdnsksqvflkmnslqtddtaiyycakhyyyggsyamdywgqgtsvtvssttpaprpptpaptiasqplslrpeacrpaaggavhtrgldfa cdiyiwaplagtcgvlllslvitlyckrgrkkllyifkqpfmrpvqttqeedgcscrfpeeeggcelrvkfsrsadapaykqgqnqlynelnlgrre eydvldkrrgrdpemggkprrknpqeglynelqkdkmaeayseigmkgerrrgkghdglyqglstatkdtydalhmqalppr (SEQ ID NO: 2030), or a sequence substantially homologous thereto.

In one embodiment, the CD19 CAR has the USAN designation TISAGENLECLEUCEL-T. In embodiments, CTL019 is made by a gene modification of T cells is mediated by stable insertion via transduction with a self-inactivating, replication deficient Lentiviral (LV) vector containing the CTL019 transgene under the control of the EF-1 alpha promoter. CTL019 can be a mixture of transgene positive and negative T cells that are delivered to the subject on the basis of percent transgene positive T cells.

In other embodiments, the CD19 CAR comprises an antigen binding domain (e.g., a humanized antigen binding domain) according to Table 3 of WO2014/153270, incorporated herein by reference.

Humanization of murine CD19 antibody is desired for the clinical setting, where the mouse-specific residues may induce a human-anti-mouse antigen (HAMA) response in patients who receive CART19 treatment, i.e., treatment with T cells transduced with the CAR19 construct. The production, characterization, and efficacy of humanized CD19 CAR sequences is described in International Application WO2014/153270 which is herein incorporated by reference in its entirety, including Examples 1-5 (p. 115-159).

In some embodiments, CD19 CAR constructs are described in PCT publication WO 2012/079000, incorporated herein by reference, and the amino acid sequence of the murine CD19 CAR and scFv constructs are shown in Table 8 below, or a sequence substantially identical to any of the aforesaid sequences (e.g., at least 85%, 90%, 95% or more identical to any of the sequences described herein).

Table 8. CD19 CAR Constructs

SEQ ID NO	**Region**
CTL019	
1300	CTL019 Full amino acid sequence
1301	CTL019 Full nucleotide sequence

1302	CTL019 scFv domain
mCAR1	
1303	mCAR1 scFv
1304	mCAR1 Full amino acid sequence
mCAR2	
1305	mCAR2 scFv
1306	mCAR2 amino acid sequence
1307	mCAR2 full amino acid sequence
mCAR3	
1308	mCAR3 scFv
1309	mCAR3 full amino acid sequence
SSJ25-C1	
1310	SSJ25-C1 VH sequence
1311	SSJ25-C1 VL
Humanized CAR1	
1312	CAR1 scFv domain
1313	CAR 1 – Full - aa
Humanized CAR2	
1314	CAR2 scFv domain - aa (Linker is underlined)
1315	CAR2 scFv domain - nt
1316	CAR 2 - Full - aa
1317	CAR 2 - Full - nt
1318	CAR2 - Soluble scFv - aa
Humanized CAR3	
1319	CAR3 scFv domain
1320	CAR 3 – Full – aa
Humanized CAR4	
1321	CAR4 scFv domain
1322	CAR 4 – Full - aa
Humanized CAR5	
1323	CAR5 scFv domain
1324	CAR 5 – Full - aa
Humanized CAR6	
1325	CAR6 scFv domain
1326	CAR6 –Full – aa
Humanized CAR7	
1327	CAR7 scFv domain
1328	CAR 7 Full - aa
Humanized CAR8	
1329	CAR8 scFv domain
1330	CAR 8 – Full - aa
Humanized CAR9	
1331	CAR9 scFv domain
1332	CAR 9 – Full - aa
Humanized CAR10	
1333	CAR10 scFv domain
1334	CAR 10 Full - aa
Humanized CAR11	
1335	CAR11 scFv domain
1336	CAR 11 Full - aa

Humanized CAR12	
1337	CAR12 scFv domain
1338	CAR 12 – Full - aa
Murine CART19	
1339	HCDR1 (Kabat)
1340	HCDR2 (Kabat)
1341	HCDR3 (Kabat)
1342	LCDR1 (Kabat)
1343	LCDR2 (Kabat)
1344	LCDR3 (Kabat)
Humanized CART19 a	
1345	HCDR1 (Kabat)
1346	HCDR2 (Kabat)
1347	HCDR3 (Kabat)
1348	LCDR1 (Kabat)
1349	LCDR2 (Kabat)
1350	LCDR3 (Kabat)
Humanized CART19 b	
1351	HCDR1 (Kabat)
1352	HCDR2 (Kabat)
1353	HCDR3 (Kabat)
1354	LCDR1 (Kabat)
1355	LCDR2 (Kabat)
1356	LCDR3 (Kabat)
Humanized CART19 c	
1357	HCDR1 (Kabat)
1358	HCDR2 (Kabat)
1359	HCDR3 (Kabat)
1360	LCDR1 (Kabat)
1361	LCDR2 (Kabat)
1362	LCDR3 (Kabat)

CD19 CAR constructs containing humanized anti-CD19 scFv domains are described in PCT publication WO 2014/153270, incorporated herein by reference.

The sequences of murine and humanized CDR sequences of the anti-CD19 scFv domains are shown in Table 9 for the heavy chain variable domains and in Table 10 for the light chain variable domains. The SEQ ID NOs refer to those found in Table 8.

Table 9. Heavy Chain Variable Domain CDR (Kabat) SEQ ID NO's of CD19 Antibodies

Candidate	HCDR1	HCDR2	HCDR3
murine_CART19	SEQ ID NO: 1339	SEQ ID NO: 1340	SEQ ID NO: 1341
humanized_CART19 a	SEQ ID NO: 1345	SEQ ID NO: 1346	SEQ ID NO: 1347
humanized_CART19 b	SEQ ID NO: 1351	SEQ ID NO: 1352	SEQ ID NO: 1353
humanized_CART19 c	SEQ ID NO: 1357	SEQ ID NO: 1358	SEQ ID NO: 1359

Table 10. Light Chain Variable Domain CDR (Kabat) SEQ ID NO's of CD19 Antibodies

Candidate	LCDR1	LCDR2	LCDR3
murine_CART19	SEQ ID NO: 1342	SEQ ID NO: 1343	SEQ ID NO: 1344
humanized_CART19 a	SEQ ID NO: 1348	SEQ ID NO: 1349	SEQ ID NO: 1350
humanized_CART19 b	SEQ ID NO: 1354	SEQ ID NO: 1355	SEQ ID NO: 1356
humanized_CART19 c	SEQ ID NO: 1360	SEQ ID NO: 1361	SEQ ID NO: 1362

Any known CD19 CAR, e.g., the CD19 antigen binding domain of any known CD19 CAR, in the art can be used in accordance with the present disclosure. For example, LG-740; CD19 CAR described in the US Pat. No. 8,399,645; US Pat. No. 7,446,190; Xu et al., Leuk Lymphoma. 2013 54(2):255-260(2012); Cruz et al., Blood 122(17):2965-2973 (2013); Brentjens et al., Blood, 118(18):4817-4828 (2011); Kochenderfer et al., Blood 116(20):4099-102 (2010); Kochenderfer et al., Blood 122 (25):4129-39(2013); and 16th Annu Meet Am Soc Gen Cell Ther (ASGCT) (May 15-18, Salt Lake City) 2013, Abst 10.

Exemplary CD19 CARs include CD19 CARs described herein, e.g., in one or more tables described herein, or an anti-CD19 CAR described in Xu et al. Blood 123.24(2014):3750-9; Kochenderfer et al. Blood 122.25(2013):4129-39, Cruz et al. Blood 122.17(2013):2965-73, NCT00586391, NCT01087294, NCT02456350, NCT00840853, NCT02659943, NCT02650999, NCT02640209, NCT01747486, NCT02546739, NCT02656147, NCT02772198, NCT00709033, NCT02081937, NCT00924326, NCT02735083, NCT02794246, NCT02746952, NCT01593696, NCT02134262, NCT01853631, NCT02443831, NCT02277522, NCT02348216, NCT02614066, NCT02030834, NCT02624258, NCT02625480, NCT02030847, NCT02644655, NCT02349698, NCT02813837, NCT02050347, NCT01683279, NCT02529813, NCT02537977, NCT02799550, NCT02672501, NCT02819583, NCT02028455, NCT01840566, NCT01318317, NCT01864889, NCT02706405, NCT01475058, NCT01430390, NCT02146924, NCT02051257, NCT02431988, NCT01815749, NCT02153580, NCT01865617, NCT02208362, NCT02685670, NCT02535364, NCT02631044, NCT02728882, NCT02735291, NCT01860937, NCT02822326, NCT02737085, NCT02465983, NCT02132624, NCT02782351, NCT01493453, NCT02652910, NCT02247609, NCT01029366, NCT01626495, NCT02721407, NCT01044069, NCT00422383, NCT01680991, NCT02794961, or NCT02456207, each of which is incorporated herein by reference in its entirety.

CD20 CAR

In some embodiments, the BCMA CAR-expressing cell therapy is administered in combination with a CD20 CAR-expressing cell therapy.

In one embodiment, the CD20 CAR comprises one or more of: LC CDR1, LC CDR2, LC

CDR3, HC CDR1, HC CDR2, HC CDR3, VH, VL, an scFv, or full-length sequence of a construct of **Tables 11, 12, 13**, e.g., CAR20-1, CAR20-2, CAR20-3, CAR20-4, CAR20-5, CAR20-6, CAR20-7, CAR20-8, CAR20-9, CAR20-10, CAR20-11, CAR20-12, CAR20-13, CAR20-14, CAR20-15, or CAR20-16, or a sequence substantially identical thereto (e.g., a sequence sharing 80%, 85%, 90%, or 95% identity thereto). Each full CD20 CAR amino acid sequence in Table 11 includes an optional signal peptide sequence of 21 amino acids corresponding to the amino acid sequence: MALPVTALLLPLALLLHAARP (SEQ ID NO: 2031). Each full CAR nucleotide sequence in Table 11 includes an optional nucleotide signal peptide sequence corresponding to the first 63 nucleotides corresponding to the nucleotide sequence: ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGCC C (SEQ ID NO: 2032).

Table 11. CD20 CAR Constructs

SEQ ID NO:	**Ab region**
CD20-C3H2	
1363 (Kabat)	HCDR1
1364 (Kabat)	HCDR2
1365 (Kabat)	HCDR3
1366 (Chothia)	HCDR1
1367 (Chothia)	HCDR2
1368 (Chothia)	HCDR3
1369 (IMGT)	HCDR1
1370 (IMGT)	HCDR2
1371 (IMGT)	HCDR3
1372 (Combined Chothia and Kabat)	HCDR1
1373 (Combined Chothia and Kabat)	HCDR2
1374 (Combined Chothia and Kabat)	HCDR3
1375	VH
1376	DNA VH
1377 (Kabat)	LCDR1
1378 (Kabat)	LCDR2
1379 (Kabat)	LCDR3
1380 (Chothia)	LCDR1
1381 (Chothia)	LCDR2
1382 (Chothia)	LCDR3
1383 (IMGT)	LCDR1
1384 (IMGT)	LCDR2
1385 (IMGT)	LCDR3
1386 (Combined Chothia and Kabat)	LCDR1
1387 (Combined Chothia and Kabat)	LCDR2
1388 (Combined Chothia and Kabat)	LCDR3
1389	VL
1390	DNA VL
1391	Linker

1392	scFv (VH-linker-VL)
1393	DNA scFv (VH-linker-VL)
1394	Full CAR amino acid sequence
1395	Full CAR nucleic acid sequence
CD20-C5H1	
1396 (Kabat)	HCDR1
1397 (Kabat)	HCDR2
1398 (Kabat)	HCDR3
1399 (Chothia)	HCDR1
1400 (Chothia)	HCDR2
1401 (Chothia)	HCDR3
1402 (IMGT)	HCDR1
1403 (IMGT)	HCDR2
1404 (IMGT)	HCDR3
1405 (Combined Chothia and Kabat)	HCDR1
1406 (Combined Chothia and Kabat)	HCDR2
1407 (Combined Chothia and Kabat)	HCDR3
1408	VH
1409	DNA VH
1410 (Kabat)	LCDR1
1411 (Kabat)	LCDR2
1412 (Kabat)	LCDR3
1413 (Chothia)	LCDR1
1414 (Chothia)	LCDR2
1415 (Chothia)	LCDR3
1416 (IMGT)	LCDR1
1417 (IMGT)	LCDR2
1418 (IMGT)	LCDR3
1419 (Combined Chothia and Kabat)	LCDR1
1420 (Combined Chothia and Kabat)	LCDR2
1421 (Combined Chothia and Kabat)	LCDR3
1422	VL
1423	DNA VL
1424	Linker
1425	scFv (VH-linker-VL)
1426	DNA scFv (VH-linker-VL)
1427	Full CAR amino acid sequence
1428	Full CAR nucleic acid sequence
CD20-C2H1	
1429 (Kabat)	HCDR1
1430 (Kabat)	HCDR2
1431 (Kabat)	HCDR3
1432 (Chothia)	HCDR1
1433 (Chothia)	HCDR2
1434 (Chothia)	HCDR3
1435 (IMGT)	HCDR1
1436 (IMGT)	HCDR2
1437 (IMGT)	HCDR3
1438 (Combined Chothia and Kabat)	HCDR1
1439 (Combined Chothia and Kabat)	HCDR2

1440 (Combined Chothia and Kabat)	HCDR3
1441	VH
1442	DNA VH
1443 (Kabat)	LCDR1
1444 (Kabat)	LCDR2
1445 (Kabat)	LCDR3
1446 (Chothia)	LCDR1
1447 (Chothia)	LCDR2
1448 (Chothia)	LCDR3
1449 (IMGT)	LCDR1
1450 (IMGT)	LCDR2
1451 (IMGT)	LCDR3
1452 (Combined Chothia and Kabat)	LCDR1
1453 (Combined Chothia and Kabat)	LCDR2
1454 (Combined Chothia and Kabat)	LCDR3
1455	VL
1456	DNA VL
1457	Linker
1458	scFv (VH-linker-VL)
1459	DNA scFv (VH-linker-VL)
1460	Full CAR amino acid sequence
1461	Full CAR nucleic acid sequence
CD20-C2H2	
1462 (Kabat)	HCDR1
1463 (Kabat)	HCDR2
1464 (Kabat)	HCDR3
1465 (Chothia)	HCDR1
1466 (Chothia)	HCDR2
1467 (Chothia)	HCDR3
1468 (IMGT)	HCDR1
1469 (IMGT)	HCDR2
1470 (IMGT)	HCDR3
1471 (Combined Chothia and Kabat)	HCDR1
1472 (Combined Chothia and Kabat)	HCDR2
1473 (Combined Chothia and Kabat)	HCDR3
1474	VH
1475	DNA VH
1476 (Kabat)	LCDR1
1477 (Kabat)	LCDR2
1478 (Kabat)	LCDR3
1479 (Chothia)	LCDR1
1480 (Chothia)	LCDR2
1481 (Chothia)	LCDR3
1482 (IMGT)	LCDR1
1483 (IMGT)	LCDR2
1484 (IMGT)	LCDR3
1485 (Combined Chothia and Kabat)	LCDR1
1486 (Combined Chothia and Kabat)	LCDR2
1487 (Combined Chothia and Kabat)	LCDR3
1488	VL

1489	DNA VL
1490	Linker
1491	scFv (VH-linker-VL)
1492	DNA scFv (VH-linker-VL)
1493	Full CAR amino acid sequence
1494	Full CAR nucleic acid sequence
CD20-C2H3	
1495 (Kabat)	HCDR1
1496 (Kabat)	HCDR2
1497 (Kabat)	HCDR3
1498 (Chothia)	HCDR1
1499 (Chothia)	HCDR2
1500 (Chothia)	HCDR3
1501 (IMGT)	HCDR1
1502 (IMGT)	HCDR2
1503 (IMGT)	HCDR3
1504 (Combined Chothia and Kabat)	HCDR1
1505 (Combined Chothia and Kabat)	HCDR2
1506 (Combined Chothia and Kabat)	HCDR3
1507	VH
1508	DNA VH
1509 (Kabat)	LCDR1
1510 (Kabat)	LCDR2
1511 (Kabat)	LCDR3
1512 (Chothia)	LCDR1
1513 (Chothia)	LCDR2
1514 (Chothia)	LCDR3
1515 (IMGT)	LCDR1
1516 (IMGT)	LCDR2
1517 (IMGT)	LCDR3
1518 (Combined Chothia and Kabat)	LCDR1
1519 (Combined Chothia and Kabat)	LCDR2
1520 (Combined Chothia and Kabat)	LCDR3
1521	VL
1522	DNA VL
1523	Linker
1524	scFv (VH-linker-VL)
1525	DNA scFv (VH-linker-VL)
1526	Full CAR amino acid sequence
1527	Full CAR nucleic acid sequence
CD20-C2H4	
1528 (Kabat)	HCDR1
1529 (Kabat)	HCDR2
1530 (Kabat)	HCDR3
1531 (Chothia)	HCDR1
1532 (Chothia)	HCDR2
1533 (Chothia)	HCDR3
1534 (IMGT)	HCDR1
1535 (IMGT)	HCDR2

1536 (IMGT)	HCDR3
1537 (Combined Chothia and Kabat)	HCDR1
1538 (Combined Chothia and Kabat)	HCDR2
1539 (Combined Chothia and Kabat)	HCDR3
1540	VH
1541	DNA VH
1542 (Kabat)	LCDR1
1543 (Kabat)	LCDR2
1544 (Kabat)	LCDR3
1545 (Chothia)	LCDR1
1546 (Chothia)	LCDR2
1547 (Chothia)	LCDR3
1548 (IMGT)	LCDR1
1549 (IMGT)	LCDR2
1550 (IMGT)	LCDR3
1551 (Combined Chothia and Kabat)	LCDR1
1552 (Combined Chothia and Kabat)	LCDR2
1553 (Combined Chothia and Kabat)	LCDR3
1554	VL
1555	DNA VL
1556	Linker
1557	scFv (VH-linker-VL)
1558	DNA scFv (VH-linker-VL)
1559	Full CAR amino acid sequence
1560	Full CAR nucleic acid sequence
CD20-C3H1	
1561 (Kabat)	HCDR1
1562 (Kabat)	HCDR2
1563 (Kabat)	HCDR3
1564 (Chothia)	HCDR1
1565 (Chothia)	HCDR2
1566 (Chothia)	HCDR3
1567 (IMGT)	HCDR1
1568 (IMGT)	HCDR2
1569 (IMGT)	HCDR3
1570 (Combined Chothia and Kabat)	HCDR1
1571 (Combined Chothia and Kabat)	HCDR2
1572 (Combined Chothia and Kabat)	HCDR3
1573	VH
1574	DNA VH
1575 (Kabat)	LCDR1
1576 (Kabat)	LCDR2
1577 (Kabat)	LCDR3
1578 (Chothia)	LCDR1
1579 (Chothia)	LCDR2
1580 (Chothia)	LCDR3
1581 (IMGT)	LCDR1
1582 (IMGT)	LCDR2
1583 (IMGT)	LCDR3
1584 (Combined Chothia and Kabat)	LCDR1

1585 (Combined Chothia and Kabat)	LCDR2
1586 (Combined Chothia and Kabat)	LCDR3
1587	VL
1588	DNA VL
1589	Linker
1590	scFv (VH-linker-VL)
1591	DNA scFv (VH-linker-VL)
1592	Full CAR amino acid sequence
1593	Full CAR nucleic acid sequence
CD20-C3H3	
1594 (Kabat)	HCDR1
1595 (Kabat)	HCDR2
1596 (Kabat)	HCDR3
1597 (Chothia)	HCDR1
1598 (Chothia)	HCDR2
1599 (Chothia)	HCDR3
1600 (IMGT)	HCDR1
1601 (IMGT)	HCDR2
1602 (IMGT)	HCDR3
1603	VH
1604	DNA VH
1605 (Kabat)	LCDR1
1606 (Kabat)	LCDR2
1607 (Kabat)	LCDR3
1608 (Chothia)	LCDR1
1609 (Chothia)	LCDR2
1610 (Chothia)	LCDR3
1611 (IMGT)	LCDR1
1612 (IMGT)	LCDR2
1613 (IMGT)	LCDR3
1614 (Combined Chothia and Kabat)	LCDR1
1615 (Combined Chothia and Kabat)	LCDR2
1616 (Combined Chothia and Kabat)	LCDR3
1617	VL
1618	DNA VL
1619	Linker
1620	scFv (VH-linker-VL)
1621	DNA scFv (VH-linker-VL)
1622	Full CAR amino acid sequence
1623	Full CAR nucleic acid sequence
CD20-C3H4	
1624 (Kabat)	HCDR1
1625 (Kabat)	HCDR2
1626 (Kabat)	HCDR3
1627 (Chothia)	HCDR1
1628 (Chothia)	HCDR2
1629 (Chothia)	HCDR3
1630 (IMGT)	HCDR1
1631 (IMGT)	HCDR2
1632 (IMGT)	HCDR3

1633 (Combined Chothia and Kabat)	HCDR1
1634 (Combined Chothia and Kabat)	HCDR2
1635 (Combined Chothia and Kabat)	HCDR3
1636	VH
1637	DNA VH
1638 (Kabat)	LCDR1
1639 (Kabat)	LCDR2
1640 (Kabat)	LCDR3
1641 (Chothia)	LCDR1
1642 (Chothia)	LCDR2
1643 (Chothia)	LCDR3
1644 (IMGT)	LCDR1
1645 (IMGT)	LCDR2
1646 (IMGT)	LCDR3
1647 (Combined Chothia and Kabat)	LCDR1
1648 (Combined Chothia and Kabat)	LCDR2
1649 (Combined Chothia and Kabat)	LCDR3
1650	VL
1651	DNA VL
1652	Linker
1653	scFv (VH-linker-VL)
1654	DNA scFv (VH-linker-VL)
1655	Full CAR amino acid sequence
1656	Full CAR nucleic acid sequence
CD20-C5H2	
1657 (Kabat)	HCDR1
1658 (Kabat)	HCDR2
1659 (Kabat)	HCDR3
1660 (Chothia)	HCDR1
1661 (Chothia)	HCDR2
1662 (Chothia)	HCDR3
1663 (IMGT)	HCDR1
1664 (IMGT)	HCDR2
1665 (IMGT)	HCDR3
1666 (Combined Chothia and Kabat)	HCDR1
1667 (Combined Chothia and Kabat)	HCDR2
1668 (Combined Chothia and Kabat)	HCDR3
1669	VH
1670	DNA VH
1671 (Kabat)	LCDR1
1672 (Kabat)	LCDR2
1673 (Kabat)	LCDR3
1674 (Chothia)	LCDR1
1675 (Chothia)	LCDR2
1676 (Chothia)	LCDR3
1677 (IMGT)	LCDR1
1678 (IMGT)	LCDR2
1679 (IMGT)	LCDR3
1680 (Combined Chothia and Kabat)	LCDR1
1681 (Combined Chothia and Kabat)	LCDR2

1682 (Combined Chothia and Kabat)	LCDR3
1683	VL
1684	DNA VL
1685	Linker
1686	scFv (VH-linker-VL)
1687	DNA scFv (VH-linker-VL)
1688	Full CAR amino acid sequence
1689	Full CAR nucleic acid sequence
CD20-C5H3	
1690 (Kabat)	HCDR1
1691 (Kabat)	HCDR2
1692 (Kabat)	HCDR3
1693 (Chothia)	HCDR1
1694 (Chothia)	HCDR2
1695 (Chothia)	HCDR3
1696 (IMGT)	HCDR1
1697 (IMGT)	HCDR2
1698 (IMGT)	HCDR3
1699 (Combined Chothia and Kabat)	HCDR1
1700 (Combined Chothia and Kabat)	HCDR2
1701 (Combined Chothia and Kabat)	HCDR3
1702	VH
1703	DNA VH
1704 (Kabat)	LCDR1
1705 (Kabat)	LCDR2
1706 (Kabat)	LCDR3
1707 (Chothia)	LCDR1
1708 (Chothia)	LCDR2
1709 (Chothia)	LCDR3
1710 (IMGT)	LCDR1
1711 (IMGT)	LCDR2
1712 (IMGT)	LCDR3
1713 (Combined Chothia and Kabat)	LCDR1
1714 (Combined Chothia and Kabat)	LCDR2
1715 (Combined Chothia and Kabat)	LCDR3
1716	VL
1717	DNA VL
1718	Linker
1719	scFv (VH-linker-VL)
1720	DNA scFv (VH-linker-VL)
1721	Full CAR amino acid sequence
1722	Full CAR nucleic acid sequence
CD20-C5H4	
1723 (Kabat)	HCDR1
1724 (Kabat)	HCDR2
1725 (Kabat)	HCDR3
1726 (Chothia)	HCDR1
1727 (Chothia)	HCDR2
1728 (Chothia)	HCDR3
1729 (IMGT)	HCDR1

1730 (IMGT)	HCDR2
1731 (IMGT)	HCDR3
1732 (Combined Chothia and Kabat)	HCDR1
1733 (Combined Chothia and Kabat)	HCDR2
1734 (Combined Chothia and Kabat)	HCDR3
1735	VH
1736	DNA VH
1737 (Kabat)	LCDR1
1738 (Kabat)	LCDR2
1739 (Kabat)	LCDR3
1740 (Chothia)	LCDR1
1741 (Chothia)	LCDR2
1742 (Chothia)	LCDR3
1743 (IMGT)	LCDR1
1744 (IMGT)	LCDR2
1745 (IMGT)	LCDR3
1746 (Combined Chothia and Kabat)	LCDR1
1747 (Combined Chothia and Kabat)	LCDR2
1748 (Combined Chothia and Kabat)	LCDR3
1749	VL
1750	DNA VL
1751	Linker
1752	scFv (VH-linker-VL)
1753	DNA scFv (VH-linker-VL)
1754	Full CAR amino acid sequence
1755	Full CAR nucleic acid sequence
CD20-C8H1	
1756 (Kabat)	HCDR1
1757 (Kabat)	HCDR2
1758 (Kabat)	HCDR3
1759 (Chothia)	HCDR1
1760 (Chothia)	HCDR2
1761 (Chothia)	HCDR3
1762 (IMGT)	HCDR1
1763 (IMGT)	HCDR2
1764 (IMGT)	HCDR3
1765 (Combined Chothia and Kabat)	HCDR1
1766 (Combined Chothia and Kabat)	HCDR2
1767 (Combined Chothia and Kabat)	HCDR3
1768	VH
1769	DNA VH
1770 (Kabat)	LCDR1
1771 (Kabat)	LCDR2
1772 (Kabat)	LCDR3
1773 (Chothia)	LCDR1
1774 (Chothia)	LCDR2
1775 (Chothia)	LCDR3
1776 (IMGT)	LCDR1
1777 (IMGT)	LCDR2
1778 (IMGT)	LCDR3

1779 (Combined Chothia and Kabat)	LCDR1
1780 (Combined Chothia and Kabat)	LCDR2
1781 (Combined Chothia and Kabat)	LCDR3
1782	VL
1783	DNA VL
1784	Linker
1785	scFv (VH-linker-VL)
1786	DNA scFv (VH-linker-VL)
1787	Full CAR amino acid sequence
1788	Full CAR nucleic acid sequence
CD20-C8H2	
1789 (Kabat)	HCDR1
1790 (Kabat)	HCDR2
1791 (Kabat)	HCDR3
1792 (Chothia)	HCDR1
1793 (Chothia)	HCDR2
1794 (Chothia)	HCDR3
1795 (IMGT)	HCDR1
1796 (IMGT)	HCDR2
1797 (IMGT)	HCDR3
1798 (Combined Chothia and Kabat)	HCDR1
1799 (Combined Chothia and Kabat)	HCDR2
1800 (Combined Chothia and Kabat)	HCDR3
1801	VH
1802	DNA VH
1803 (Kabat)	LCDR1
1804 (Kabat)	LCDR2
1805 (Kabat)	LCDR3
1806 (Chothia)	LCDR1
1807 (Chothia)	LCDR2
1808 (Chothia)	LCDR3
1809 (IMGT)	LCDR1
1810 (IMGT)	LCDR2
1811 (IMGT)	LCDR3
1812 (Combined Chothia and Kabat)	LCDR1
1813 (Combined Chothia and Kabat)	LCDR2
1814 (Combined Chothia and Kabat)	LCDR3
1815	VL
1816	DNA VL
1817	Linker
1818	scFv (VH-linker-VL)
1819	DNA scFv (VH-linker-VL)
1820	Full CAR amino acid sequence
1821	Full CAR nucleic acid sequence
CD20-C8H3	
1822 (Kabat)	HCDR1
1823 (Kabat)	HCDR2
1824 (Kabat)	HCDR3
1825 (Chothia)	HCDR1

1826 (Chothia)	HCDR2
1827 (Chothia)	HCDR3
1828 (IMGT)	HCDR1
1829 (IMGT)	HCDR2
1830 (IMGT)	HCDR3
1831 (Combined Chothia and Kabat)	HCDR1
1832 (Combined Chothia and Kabat)	HCDR2
1833 (Combined Chothia and Kabat)	HCDR3
1834	VH
1835	DNA VH
1836 (Kabat)	LCDR1
1837 (Kabat)	LCDR2
1838 (Kabat)	LCDR3
1839 (Chothia)	LCDR1
1840 (Chothia)	LCDR2
1841 (Chothia)	LCDR3
1842 (IMGT)	LCDR1
1843 (IMGT)	LCDR2
1844 (IMGT)	LCDR3
1845 (Combined Chothia and Kabat)	LCDR1
1846 (Combined Chothia and Kabat)	LCDR2
1847 (Combined Chothia and Kabat)	LCDR3
1848	VL
1849	DNA VL
1850	Linker
1851	scFv (VH-linker-VL)
1852	DNA scFv (VH-linker-VL)
1853	Full CAR amino acid sequence
1854	Full CAR nucleic acid sequence
CD20-C8H4	
1855 (Kabat)	HCDR1
1856 (Kabat)	HCDR2
1857 (Kabat)	HCDR3
1858 (Chothia)	HCDR1
1859 (Chothia)	HCDR2
1860 (Chothia)	HCDR3
1861 (IMGT)	HCDR1
1862 (IMGT)	HCDR2
1863 (IMGT)	HCDR3
1864 (Combined Chothia and Kabat)	HCDR1
1865 (Combined Chothia and Kabat)	HCDR2
1866 (Combined Chothia and Kabat)	HCDR3
1867	VH
1868	DNA VH
1869 (Kabat)	LCDR1
1870 (Kabat)	LCDR2
1871 (Kabat)	LCDR3
1872 (Chothia)	LCDR1
1873 (Chothia)	LCDR2
1874 (Chothia)	LCDR3

1875 (IMGT)	LCDR1
1876 (IMGT)	LCDR2
1877 (IMGT)	LCDR3
1878 (Combined Chothia and Kabat)	LCDR1
1879 (Combined Chothia and Kabat)	LCDR2
1880 (Combined Chothia and Kabat)	LCDR3
1881	VL
1882	DNA VL
1883	Linker
1884	scFv (VH-linker-VL)
1885	DNA scFv (VH-linker-VL)
1886	Full CAR amino acid sequence
1887	Full CAR nucleic acid sequence
CD20-C2	
1888	VH
1889	DNA VH
1890	VL
1891	DNA VL
CD20-C3	
1892	VH
1893	DNA VH
1894	VL
1895	DNA VL
CD20-C5	
1896	VH
1897	DNA VH
1898	VL
1899	DNA VL
CD20-C6	
1900	VH
1901	DNA VH
1902	VL
1903	DNA VL
CD20-C7	
1904	VH
1905	DNA VH
1906	VL
1907	DNA VL
CD20-C8	
1908	VH
1909	DNA VH
1910	VL
1911	DNA VL
CD20-3m	
1912	VH
1913	DNA VH
1914	VL
1915	DNA VL
1916	Linker
1917	scFv (VH-linker-VL)

CD20-3J	
1918	VH
1919	DNA VH
1920	VL
1921	DNA VL
1922	Linker
1923	scFv (VH-linker-VL)
CD20-3H5k1	
1924	VH
1925	DNA VH
1926	VL
1927	DNA VL
1928	Linker
1929	scFv (VH-linker-VL)
CD20-3H5k3	
1930	VH
1931	DNA VH
1932	VL
1933	DNA VL
1934	Linker
1935	scFv (VH-linker-VL)
CD20-Ofa	
1936 (Kabat)	HCDR1
1937 (Kabat)	HCDR2
1938 (Kabat)	HCDR3
1939 (Chothia)	HCDR1
1940 (Chothia)	HCDR2
1941 (Chothia)	HCDR3
1942 (IMGT)	HCDR1
1943 (IMGT)	HCDR2
1944 (IMGT)	HCDR3
1945	VH
1946	DNA VH
1947 (Kabat)	LCDR1
1948 (Kabat)	LCDR2
1949 (Kabat)	LCDR3
1950 (Chothia)	LCDR1
1951 (Chothia)	LCDR2
1952 (Chothia)	LCDR3
1953 (IMGT)	LCDR1
1954 (IMGT)	LCDR2
1955 (IMGT)	LCDR3
1956	VL
1957	DNA VL
1958	Linker
1959	scFv (VH-linker-VL)
1960	DNA scFv (VH-linker-VL)
CD20-3	
1961	VH
1962	VL

1963	Linker
1964	scFv (VH-linker-VL)
CD20-8aBBz	
1965	VH
1966	DNA VH
1967	VL
1968	DNA VL
1969	Linker
1970	scFv (VH-linker-VL)
1971	DNA scFv (VH-linker-VL)

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An overview of the sequences identifications of CDR (Kabat) sequences of the CD20 scFv domains of Table 11 are shown in Table 12 for the heavy chain variable domains and in Table 13 for the light chain variable domains. The SEQ ID NOs refer to those found in Table 11.

Table 12. Heavy Chain Variable Domain CDR (Kabat) SEQ ID NO's of CD20 CAR molecules

Candidate	**HCDR1**	**HCDR2**	**HCDR3**
CD20-C3H2	1363	1364	1365
CD20-C5H1	1396	1397	1398
CD20-C2H1	1429	1430	1431
CD20-C2H2	1462	1463	1464
CD20-C2H3	1495	1496	1497
CD20-C2H4	1528	1529	1530
CD20-C3H1	1561	1562	1563
CD20-C3H3	1594	1595	1596
CD20-C3H4	1624	1625	1626
CD20-C5H2	1657	1658	1659
CD20-C5H3	1690	1691	1692
CD20-C5H4	1723	1724	1725
CD20-C8H1	1756	1757	1758
CD20-C8H2	1789	1790	1791
CD20-C8H3	1822	1823	1824
CD20-C8H4	1855	1856	1857

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Table 13. Light Chain Variable Domain CDR (Kabat) SEQ ID NO's of CD20 Antibody Molecules

Candidate	**LCDR1**	**LCDR2**	**LCDR3**
CD20-C3H2	1377	1378	1379
CD20-C5H1	1410	1411	1412
CD20-C2H1	1443	1444	1445
CD20-C2H2	1476	1477	1478
CD20-C2H3	1509	1510	1511
CD20-C2H4	1542	1543	1544
CD20-C3H1	1575	1576	1577

CD20-C3H3	1605	1606	1607
CD20-C3H4	1638	1639	1640
CD20-C5H2	1671	1672	1673
CD20-C5H3	1704	1705	1706
CD20-C5H4	1737	1738	1739
CD20-C8H1	1770	1771	1772
CD20-C8H2	1803	1804	1805
CD20-C8H3	1836	1837	1838
CD20-C8H4	1869	1870	1871

Additional CD20 inhibitors

In some embodiments, the BCMA CAR-expressing cell therapy is administered in combination with a CD20 inhibitor.

In one embodiment, the CD20 inhibitor is an anti-CD20 antibody or fragment thereof. In an embodiment, the antibody is a monospecific antibody and in another embodiment the antibody is a bispecific antibody. In an embodiment, the CD20 inhibitor is a chimeric mouse/human monoclonal antibody, e.g., rituximab. In an embodiment, the CD20 inhibitor is a human monoclonal antibody such as ofatumumab. In an embodiment, the CD20 inhibitor is a humanized antibody such as ocrelizumab, veltuzumab, obinutuzumab, ocaratuzumab, or PRO131921 (Genentech). In an embodiment, the CD20 inhibitor is a fusion protein comprising a portion of an anti-CD20 antibody, such as TRU-015 (Trubion Pharmaceuticals).

CD22 CAR

In some embodiments, the BCMA CAR-expressing cell therapy is administered in combination with a CD22 CAR-expressing cell therapy (e.g., cells expressing a CAR that binds to human CD22).

In some embodiments, the CD22 CAR-expressing cell therapy includes an antigen binding domain according to WO2016/164731, incorporated herein by reference.

The sequences of CD22 CAR are provided below. In some embodiments, the CD22 CAR is CD22-65. In some embodiments, the CD22 CAR is CD22-65s. In some embodiments, the CD22 CAR is CD22-65ss.

Human CD22 CAR CD22-65 scFv sequence

EVQLQQSGPGLVKPSQTLSLTCAISGDSMLSNSDTWNWIRQSPSRGLEWLGRTYHRSTWYDDY
ASSVRGRVSINVDTSKNQYSLQLNAVTPEDTGVYYCARVRLQDGNSWSDAFDVWGQGTMVT
VSSGGGGSGGGGSGGGGSQSALTQPASASGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGK

APKLMIYDVSNRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTLYVFGTGTQLT VL (SEQ ID NO: 1972)

Human CD22 CAR CD22-65s scFc sequence (linker shown by italics and underline)

EVQLQQSGPGLVKPSQTLSLTCAISGDSMLSNSDTWNWIRQSPSRGLEWLGRTYHRSTWYDDY ASSVRGRVSINVDTSKNQYSLQLNAVTPEDTGVYYCARVRLQDGNSWSDAFDVWGQGTMVT VSS*GGGGS*QSALTQPASASGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSN RPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTLYVFGTGTQLTVL (SEQ ID NO: 2036)

Human CD22 CAR CD22-65ss scFc sequence

EVQLQQSGPGLVKPSQTLSLTCAISGDSMLSNSDTWNWIRQSPSRGLEWLGRTYHRSTWYDDY ASSVRGRVSINVDTSKNQYSLQLNAVTPEDTGVYYCARVRLQDGNSWSDAFDVWGQGTMVT VSSQSALTQPASASGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSNRPSGV SNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTLYVFGTGTQLTVL (SEQ ID NO: 1973)

Human CD22 CAR heavy chain variable region

EVQLQQSGPGLVKPSQTLSLTCAISGDSMLSNSDTWNWIRQSPSRGLEWLGRTYHRSTWYDDY ASSVRGRVSINVDTSKNQYSLQLNAVTPEDTGVYYCARVRLQDGNSWSDAFDVWGQGTMVT VSS (SEQ ID NO: 1974)

Human CD22 CAR light chain variable region

QSALTQPASASGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSNRPSGVSNR FSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTLYVFGTGTQLTVL (SEQ ID NO: 1975)

Table 14. Heavy Chain Variable Domain CDRs of CD22 CAR (CD22-65)

Candidate	HCDR1	SEQ ID NO:	HCDR2	SEQ ID NO:	HCDR3	SEQ ID NO:
CD22-65 Combined	GDSML SNSDT WN	1976	RTYHRSTWYDDYA SSVRG	1978	VRLQDGNSWSD AFDV	1980
CD22-65 Kabat	SNSDT WN	1977	RTYHRSTWYDDYA SSVRG	1979	VRLQDGNSWSD AFDV	1981

Table 15. Light Chain Variable Domain CDRs of CD22 CAR (CD22-65). The LC CDR sequences in this table have the same sequence under the Kabat or combined definitions.

Candidate	LCDR1	SEQ ID NO:	LCDR2	SEQ ID NO:	LCDR3	SEQ ID NO:
CD22-65 Combined	TGTSSDVGGYNYVS	1982	DVSNRPS	1983	SSYTSSSTLYV	1984

In some embodiments, the antigen binding domain comprises a HC CDR1, a HC CDR2, and a HC CDR3 of any heavy chain binding domain amino acid sequences listed in **Table 14**. In embodiments, the antigen binding domain further comprises a LC CDR1, a LC CDR2, and a LC CDR3. In embodiments, the antigen binding domain comprises a LC CDR1, a LC CDR2, and a LC CDR3 amino acid sequences listed in **Table 15.**

In some embodiments, the antigen binding domain comprises one, two or all of LC CDR1, LC CDR2, and LC CDR3 of any light chain binding domain amino acid sequences listed in **Table 15**, and one, two or all of HC CDR1, HC CDR2, and HC CDR3 of any heavy chain binding domain amino acid sequences listed in **Table 14**.

In some embodiments, the CDRs are defined according to the Kabat numbering scheme, the Chothia numbering scheme, or a combination thereof.

The order in which the VL and VH domains appear in the scFv can be varied (i.e., VL-VH, or VH-VL orientation), and where any of one, two, three or four copies of the "G4S" (SEQ ID NO: 1032) subunit, in which each subunit comprises the sequence GGGGS (SEQ ID NO: 1032) (e.g., $(G4S)_3$ (SEQ ID NO: 1040) or $(G4S)_4$ (SEQ ID NO: 1039)), can connect the variable domains to create the entirety of the scFv domain. Alternatively, the CAR construct can include, for example, a linker including the sequence GSTSGSGKPGSGEGSTKG (SEQ ID NO: 1985). Alternatively, the CAR construct can include, for example, a linker including the sequence LAEAAAK (SEQ ID NO: 2033). In an embodiment, the CAR construct does not include a linker between the VL and VH domains.

These clones all contained a Q/K residue change in the signal domain of the co-stimulatory domain derived from CD3zeta chain.

Additional CD22 inhibitors

In some embodiments, the BCMA CAR-expressing cell therapy is administered in combination with a CD20 inhibitor. In some embodiments, the CD20 inhibitor is a small molecule or an anti-CD20 antibody molecule.

In an embodiment, the antibody is a monospecific antibody, optionally conjugated to a second agent such as a chemotherapeutic agent. For instance, in an embodiment the antibody is an anti-CD22 monoclonal antibody-MMAE conjugate (e.g., DCDT2980S). In an embodiment, the antibody is an scFv of an anti-CD22 antibody, e.g., an scFv of antibody RFB4. This scFv can be fused to all of or a fragment of Pseudomonas exotoxin-A (e.g., BL22). In an embodiment, the antibody is a humanized anti-CD22 monoclonal antibody (e.g., epratuzumab). In an embodiment, the antibody or fragment

thereof comprises the Fv portion of an anti-CD22 antibody, which is optionally covalently fused to all or a fragment or (e.g., a 38 KDa fragment of) Pseudomonas exotoxin-A (e.g., moxetumomab pasudotox). In an embodiment, the anti-CD22 antibody is an anti-CD19/CD22 bispecific antibody, optionally conjugated to a toxin. For instance, in one embodiment, the anti-CD22 antibody comprises an anti-CD19/CD22 bispecific portion, (e.g., two scFv ligands, recognizing human CD19 and CD22) optionally linked to all of or a portion of diphtheria toxin (DT), e.g., first 389 amino acids of diphtheria toxin (DT), DT 390, e.g., a ligand-directed toxin such as DT2219ARL). In another embodiment, the bispecific portion (e.g., anti-CD19/anti-CD22) is linked to a toxin such as deglycosylated ricin A chain (e.g., Combotox).

In some embodiments, the CD22 inhibitor is a multispecific antibody molecule, e.g., a bispecific antibody molecule, e.g., a bispecific antibody molecule that binds to CD20 and CD3. Exemplary bispecific antibody molecules that bind to CD20 and CD3 are disclosed in WO2016086189 and WO2016182751, herein incorporated by reference in their entirety. In some embodiments, the bispecific antibody molecule that binds to CD20 and CD3 is XENP13676 as disclosed in Figure 74, SEQ ID NOs: 323, 324, and 325 of WO2016086189.

Multispecific CAR

In some embodiments, the CAR molecule disclosed herein is a multispecific, e.g., bispecific, CAR molecule comprising one, two, or more binding specificities, e.g., a first binding specificity for a first antigen, e.g., a B-cell epitope, and a second binding specificity for the same or a different antigen, e.g., B cell epitope.

In one embodiment, the first and second binding specificity is an antibody molecule, e.g., an antigen binding domain (e.g., a scFv). Within each antibody molecule (e.g., scFv) of a bispecific CAR molecule, the VH can be upstream or downstream of the VL. In some embodiments, the upstream antibody or antibody fragment (e.g., scFv) is arranged with its VH (VH_1) upstream of its VL (VL_1) and the downstream antibody or antibody fragment (e.g., scFv) is arranged with its VL (VL_2) upstream of its VH (VH_2), such that the overall bispecific CAR molecule has the arrangement VH_1-VL_1-VL_2-VH_2, from an N- to C-terminal orientation.

In some embodiments, the upstream antibody or antibody fragment or antigen binding domain (e.g., scFv) is arranged with its VL (VL_1) upstream of its VH (VH_1) and the downstream antibody or antibody fragment (e.g., scFv) is arranged with its VH (VH_2) upstream of its VL (VL_2), such that the overall bispecific CAR molecule has the arrangement VL_1-VH_1-VH_2-VL_2, from an N- to C-terminal orientation.

In some embodiments, the upstream antibody or antibody fragment (e.g., scFv) is arranged with its VL (VL_1) upstream of its VH (VH_1) and the downstream antibody or antibody fragment or antigen binding domain (e.g., scFv) is arranged with its VL (VL_2) upstream of its VH (VH_2), such that the overall bispecific CAR molecule has the arrangement VL_1-VH_1-VL_2-VH_2, from an N- to C-terminal orientation.

In some embodiments, the upstream antibody or antibody fragment or antigen binding domain (e.g., scFv) is arranged with its VH (VH_1) upstream of its VL (VL_1) and the downstream antibody or antibody fragment (e.g., scFv) is arranged with its VH (VH_2) upstream of its VL (VL_2), such that the overall bispecific CAR molecule has the arrangement VH_1-VL_1-VH_2-VL_2, from an N- to C-terminal orientation.

In any of the aforesaid configurations, optionally, a linker is disposed between the two antibodies or antibody fragments or antigen binding domains (e.g., scFvs), e.g., between VL_1 and VL_2 if the construct is arranged as VH_1-VL_1-VL_2-VH_2; between VH_1 and VH_2 if the construct is arranged as VL_1-VH_1-VH_2-VL_2; between VH_1 and VL_2 if the construct is arranged as VL_1-VH_1-VL_2-VH_2; or between VL_1 and VH_2 if the construct is arranged as VH_1-VL_1-VH_2-VL_2. In general, the linker between the two antibody fragments or antigen binding domains, e.g.,scFvs, should be long enough to avoid mispairing between the domains of the two scFvs. The linker may be a linker as described herein. In some embodiments, the linker is a $(Gly_4\text{-}Ser)_n$ linker (SEQ ID NO: 2034), wherein n is 1, 2, 3, 4, 5, or 6. In some embodiments, the linker is $(Gly_4\text{-}Ser)_n$, wherein n = 1 (SEQ ID NO: 1032), e.g., the linker has the amino acid sequence Gly_4-Ser (SEQ ID NO: 1032). In some embodiments, the linker is $(Gly_4\text{-}Ser)_n$, wherein n = 3 (SEQ ID NO: 1040). In some embodiments, the linker is $(Gly_4\text{-}Ser)_n$, wherein n= 4 (SEQ ID NO: 1039). In some embodiments, the linker comprises, e.g., consists of, the amino acid sequence: LAEAAAK (SEQ ID NO: 2033).

In any of the aforesaid configurations, optionally, a linker is disposed between the VL and VH of the first antigen binding domains, e.g., scFv. Optionally, a linker is disposed between the VL and VH of the second antigen binding domains, e.g., scFv. In constructs that have multiple linkers, any two or more of the linkers can be the same or different. Accordingly, in some embodiments, a bispecific CAR comprises VLs, VHs, and optionally one or more linkers in an arrangement as described herein.

In some embodiments, each antibody molecule, e.g., each antigen binding domain (e.g., each scFv) comprises a linker between the VH and the VL regions. In some embodiments, the linker between the VH and the VL regions is a $(Gly_4\text{-}Ser)_n$ linker (SEQ ID NO: 2034), wherein n is 1, 2, 3, 4, 5, or 6. In some embodiments, the linker is $(Gly_4\text{-}Ser)_n$, wherein n = 1 (SEQ ID NO: 1032), e.g., the linker has the amino acid sequence Gly_4-Ser (SEQ ID NO: 1032). In other embodiments, the linker is

$(Gly_4\text{-}Ser)_n$, wherein n= 3 (SEQ ID NO: 1040). In some embodiments, the linker is $(Gly_4\text{-}Ser)_n$, wherein n= 4 (SEQ ID NO: 1039). In some embodiments, the VH and VL regions are connected without a linker.

In certain embodiments, the CAR molecule is a bispecific CAR molecule having a first binding specificity for a first B-cell epitope and a second binding specificity for the same or a different B-cell antigen. For instance, in some embodiments the bispecific CAR molecule has a first binding specificity for BCMA and a second binding specificity for one or more of BCMA, CD10, CD19, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, or CD79a. In some embodiments the bispecific CAR molecule has a first binding specificity for BCMA and a second binding specificity for CD19. In some embodiments the bispecific CAR molecule has a first binding specificity for BCMA and a second binding specificity for CD20. In some embodiments the bispecific CAR molecule has a first binding specificity for BCMA and a second binding specificity for CD22.

In one embodiment, the CAR molecule is a bispecific CAR molecule having a binding specificity, e.g., a first and/or second binding specificity, to BCMA, CD19, CD20, and/or CD22. In one embodiment, the binding specificity is configured with its VL (VL_1) upstream of its VH (VH_1) and the downstream antibody or antibody fragment or antigen binding domains (e.g., scFv) is arranged with its VL (VL_2) upstream of its VH (VH_2), such that the overall bispecific CAR molecule has the arrangement $VL_1\text{-}VH_1\text{-}VL_2\text{-}VH_2$, from an N- to C-terminal orientation. In some embodiments, the first and/or second binding specificity, to BCMA, CD19, CD20, and/or CD22 (e.g., first and/or second scFv to BCMA, CD19, CD20, and/or CD22) comprises a linker between the VH and the VL regions. In some embodiments, the linker between the VH and the VL regions is a $(Gly_4\text{-}Ser)_n$ linker (SEQ ID NO: 2034), wherein n is 1, 2, 3, 4, 5, or 6. In some embodiments, the linker is $(Gly_4\text{-}Ser)_n$, wherein n = 1 (SEQ ID NO: 1032), e.g., the linker has the amino acid sequence Gly_4-Ser (SEQ ID NO: 1032). In some embodiments, the linker is $(Gly_4\text{-}Ser)_n$, wherein n= 3 (SEQ ID NO: 1040). In some embodiments, the linker is $(Gly_4\text{-}Ser)_n$, wherein n= 4 (SEQ ID NO: 1039). In some embodiments, the VH and VL regions are connected without a linker.

In another embodiment, the binding specificity, e.g., a first and/or second binding specificity, to BCMA, CD19, CD20, and/or CD22 is configured with its VL (VL_1) upstream of its VH (VH_1) and the downstream antibody or antibody fragment or antigen binding domains (e.g., scFv) is arranged with its VH (VH_2) upstream of its VL (VL_2), such that the overall bispecific CAR molecule has the arrangement $VL_1\text{-}VH_1\text{-}VH_2\text{-}VL_2$, from an N- to C-terminal orientation. In some embodiments, the first and/or second binding specificity, to BCMA, CD19, CD20, and/or CD22 (e.g., first and/or second scFv to BCMA, CD19, CD20, and/or CD22) comprises a linker between the VH and the VL regions. In some embodiments, the linker between the VH and the VL regions is a $(Gly_4\text{-}Ser)_n$ linker

(SEQ ID NO: 2034), wherein n is 1, 2, 3, 4, 5, or 6. In some embodiments, the linker is $(Gly_4\text{-}Ser)_n$, wherein n = 1 (SEQ ID NO: 1032), e.g., the linker has the amino acid sequence Gly_4-Ser (SEQ ID NO: 1032). In some embodiments, the linker is $(Gly_4\text{-}Ser)_n$, wherein n= 3 (SEQ ID NO: 1040). In some embodiments, the linker is $(Gly_4\text{-}Ser)_n$, wherein n= 4 (SEQ ID NO: 1039). In some embodiments, the VH and VL regions are connected without a linker.

In another embodiment, the binding specificity, e.g., a first and/or second binding specificity, to BCMA, CD19, CD20, and/or CD22 is configured with its VH (VH_1) upstream of its VL (VL_1) and the downstream antibody or antibody fragment or antigen binding domain (e.g., scFv) is arranged with its VL (VL_2) upstream of its VH (VH_2), such that the overall bispecific CAR molecule has the arrangement VH_1-VL_1-VL_2-VH_2, from an N- to C-terminal orientation. In some embodiments, the first and/or second binding specificity, to BCMA, CD19, CD20, and/or CD22 (e.g., first and/or second scFv to BCMA, CD19, CD20, and/or CD22) comprises a linker between the VH and the VL regions. In some embodiments, the linker between the VH and the VL regions is a $(Gly_4\text{-}Ser)_n$ linker (SEQ ID NO: 2034), wherein n is 1, 2, 3, 4, 5, or 6. In some embodiments, the linker is $(Gly_4\text{-}Ser)_n$, wherein n = 1 (SEQ ID NO: 1032), e.g., the linker has the amino acid sequence Gly_4-Ser (SEQ ID NO: 1032). In some embodiments, the linker is $(Gly_4\text{-}Ser)_n$, wherein n= 3 (SEQ ID NO: 1040). In some embodiments, the linker is $(Gly_4\text{-}Ser)_n$, wherein n= 4 (SEQ ID NO: 1039). In some embodiments, the VH and VL regions are connected without a linker.

In another embodiment, the binding specificity, e.g., a first and/or second binding specificity, to BCMA, CD19, CD20, and/or CD22 is configured with its VH (VH_1) upstream of its VL (VL_1) and the downstream antibody or antibody fragment or antigen binding domain (e.g., scFv) is arranged with its VH (VH_2) upstream of its VL (VL_2), such that the overall bispecific CAR molecule has the arrangement VH_1-VL_1-VH_2-VL_2, from an N- to C-terminal orientation. In some embodiments, the first and/or second binding specificity, to BCMA, CD19, CD20, and/or CD22 (e.g., first and/or second scFv to BCMA, CD19, CD20, and/or CD22) comprises a linker between the VH and the VL regions. In some embodiments, the linker between the VH and the VL regions is a $(Gly_4\text{-}Ser)_n$ linker (SEQ ID NO: 2034), wherein n is 1, 2, 3, 4, 5, or 6. In some embodiments, the linker is $(Gly_4\text{-}Ser)_n$, wherein n = 1 (SEQ ID NO: 1032), e.g., the linker has the amino acid sequence Gly_4-Ser (SEQ ID NO: 1032). In some embodiments, the linker is $(Gly_4\text{-}Ser)_n$, wherein n= 3 (SEQ ID NO: 1040). In some embodiments, the linker is $(Gly_4\text{-}Ser)_n$, wherein n= 4 (SEQ ID NO: 1039). In some embodiments, the VH and VL regions are connected without a linker.

In some embodiments, the bispecific CAR molecule comprises a first binding specificity to BCMA, e.g., any of the binding specificities to BCMA described herein, and a second binding specificity to CD19, e.g., any of the binding specificities to CD19 as described herein. In some

embodiments, the bispecific CAR molecule comprises a first binding specificity to BCMA, e.g., any of the binding specificities to BCMA described herein, and a second binding specificity to CD20, e.g., any of the binding specificities to CD20 as described herein. In some embodiments, the bispecific CAR molecule comprises a first binding specificity to BCMA, e.g., any of the binding specificities to BCMA described herein, and a second binding specificity to CD22, e.g., any of the binding specificities to CD22 as described herein. In one embodiment, the first and second binding specificity are in a contiguous polypeptide chain, e.g., a single chain. In some embodiments, the first and second binding specificities, optionally, comprise a linker as described herein. In some embodiments, the linker is a $(Gly_4\text{-}Ser)_n$ linker (SEQ ID NO: 2034), wherein n is 1, 2, 3, 4, 5, or 6. In some embodiments, the linker is $(Gly_4\text{-}Ser)_n$, wherein n = 1 (SEQ ID NO: 1032), e.g., the linker has the amino acid sequence Gly_4-Ser (SEQ ID NO: 1032). In some embodiments, the linker is $(Gly_4\text{-}Ser)_n$, wherein n = 3 (SEQ ID NO: 1040). In some embodiments, the linker is $(Gly_4\text{-}Ser)_n$, wherein n= 4 (SEQ ID NO: 1039). In some embodiments, the linker comprises, e.g., consists of, the amino acid sequence: LAEAAAK (SEQ ID NO: 2033).

In some embodiments, the CAR molecule disclosed herein comprises a bispecific CAR comprising a fist and second binding specificities, e.g., as described herein (e.g., two antibody molecules, e.g., two scFvs as described herein). In some embodiments, the bispecific CAR comprises two antibody molecules, wherein the first binding specificity, e.g., the first antibody molecule (e.g., the first antigen binding domain, e.g., the first scFv) is closer to the transmembrane domain, also referred to herein as the proximal antibody molecule (e.g., proximal antigen binding domain) and the second binding specificity, e.g., the second antibody molecule (e.g., second antigen binding domain, e.g., the second scFv) is further away from the membrane, also referred to herein as the distal antibody molecule (e.g., the distal antigen binding domain). Thus, from N-to-C-terminus, the CAR molecule comprises a distal binding specificity, e.g., a distal antibody molecule (e.g., a distal antigen binding domain, e.g., a distal scFV or scFv2), optionally, a linker, followed by a proximal binding specificity, e.g., a proximal antibody molecule (e.g., a proximal antigen binding domain, e.g., a proximal scFv or scFv1), optionally via a linker, to a transmembrane domain and an intracellular domain, e.g., as described herein. In some embodiments, the CAR molecule comprises a proximal or distal binding specificity for BCMA, e.g., a BCMA binding specificity as described herein. In one embodiment, the CAR molecule comprises a proximal binding specificity for BCMA, e.g., a BCMA binding specificity as described herein, and a distal binding specificity for CD19, e.g., a CD19 binding specificity as described herein. In one embodiment, the CAR molecule comprises a proximal binding specificity for BCMA, e.g., a BCMA binding specificity as described herein, and a distal binding specificity for CD20, e.g., a CD20 binding specificity as described herein. In one embodiment, the CAR molecule comprises a proximal binding

specificity for BCMA, e.g., a BCMA binding specificity as described herein, and a distal binding specificity for CD22, e.g., a CD22 binding specificity as described herein. In one embodiment, the CAR molecule comprises a distal binding specificity for BCMA, e.g., a BCMA binding specificity as described herein, and a proximal binding specificity for CD19, e.g., a CD19 binding specificity as described herein. In one embodiment, the CAR molecule comprises a distal binding specificity for BCMA, e.g., a BCMA binding specificity as described herein, and a proximal binding specificity for CD20, e.g., a CD20 binding specificity as described herein. In one embodiment, the CAR molecule comprises a distal binding specificity for BCMA, e.g., a BCMA binding specificity as described herein, and a proximal binding specificity for CD22, e.g., a CD22 binding specificity as described herein.

In one embodiment, the CAR molecule comprises a distal to the membrane binding specificity to BCMA, e.g., a VL1-VH1 binding specificity to BCMA, and a proximal to the membrane binding specificity to CD19, CD20, or CD22, e.g., a VL2-VH2 or VH2-VL1 binding specificity to CD19. In one embodiment, the first and second binding specificity are in a contiguous polypeptide chain, e.g., a single chain. In some embodiments, the first and second binding specificities, optionally, comprise a linker as described herein. In some embodiments, the linker is a $(Gly_4\text{-}Ser)_n$ linker (SEQ ID NO: 2034), wherein n is 1, 2, 3, 4, 5, or 6. In some embodiments, the linker is $(Gly_4\text{-}Ser)_n$, wherein n = 1 (SEQ ID NO: 1032), e.g., the linker has the amino acid sequence Gly_4-Ser (SEQ ID NO: 1032). In some embodiments, the linker is $(Gly_4\text{-}Ser)_n$, wherein n = 3 (SEQ ID NO: 1040). In some embodiments, the linker is $(Gly_4\text{-}Ser)_n$, wherein n= 4 (SEQ ID NO: 1039). In some embodiments, the linker comprises, e.g., consists of, the amino acid sequence: LAEAAAK (SEQ ID NO: 2033).

In one embodiment, the CAR molecule comprises a proximal to the membrane binding specificity to BCMA, e.g., a VL1-VH1 binding specificity to BCMA, and a distal to the membrane binding specificity to CD19, CD20, or CD22, e.g., a VL2-VH2 or VH2-VL1 binding specificity to CD19, CD20, or CD22. In one embodiment, the first and second binding specificity are in a contiguous polypeptide chain, e.g., a single chain. In some embodiments, the first and second binding specificities, optionally, comprise a linker as described herein. In some embodiments, the linker is a $(Gly_4\text{-}Ser)_n$ linker (SEQ ID NO: 2034), wherein n is 1, 2, 3, 4, 5, or 6. In some embodiments, the linker is $(Gly_4\text{-}Ser)_n$, wherein n = 1 (SEQ ID NO: 1032), e.g., the linker has the amino acid sequence Gly_4-Ser (SEQ ID NO: 1032). In some embodiments, the linker is $(Gly_4\text{-}Ser)_n$, wherein n = 3 (SEQ ID NO: 1040). In some embodiments, the linker is $(Gly_4\text{-}Ser)_n$, wherein n= 4 (SEQ ID NO: 1039). In some embodiments, the linker comprises, e.g., consists of, the amino acid sequence: LAEAAAK (SEQ ID NO: 2033).

FCRL2 or FCRL5 inhibitor

In some embodiments, the BCMA CAR-expressing cell therapy is administered in combination with a FCRL2 or FCRL5 inhibitor. In some embodiments, the FCRL2 or FCRL5 inhibitor is an anti-FCRL2 antibody molecule, e.g., a bispecific antibody molecule, e.g., a bispecific antibody that binds to FCRL2 and CD3. In some embodiments, the FCRL2 or FCRL5 inhibitor is an anti-FCRL5 antibody molecule, e.g., a bispecific antibody molecule, e.g., a bispecific antibody that binds to FCRL5 and CD3. In some embodiments, the FCRL2 or FCRL5 inhibitor is a FCRL2 CAR-expressing cell therapy. In some embodiments, the FCRL2 or FCRL5 inhibitor is a FCRL5 CAR-expressing cell therapy.

Exemplary anti-FCRL5 antibody molecules are disclosed in US20150098900, US20160368985, WO2017096120 (e.g., antibodies ET200-001, ET200-002, ET200-003, ET200-006, ET200-007, ET200-008, ET200-009, ET200-010, ET200-011, ET200-012, ET200-013, ET200-014, ET200-015, ET200-016, ET200-017, ET200-018, ET200-019, ET200-020, ET200-021, ET200-022, ET200-023, ET200-024, ET200-025, ET200-026, ET200-027, ET200-028, ET200-029, ET200-030, ET200-031, ET200-032, ET200-033, ET200-034, ET200-035, ET200-037, ET200-038, ET200-039, ET200-040, ET200-041, ET200-042, ET200-043, ET200-044, ET200-045, ET200-069, ET200-078, ET200-079, ET200-081, ET200-097, ET200-098, ET200-099, ET200-100, ET200-101, ET200-102, ET200-103, ET200-104, ET200-105, ET200-106, ET200-107, ET200-108, ET200-109, ET200-110, ET200-111, ET200-112, ET200-113, ET200-114, ET200-115, ET200-116, ET200-117, ET200-118, ET200-119, ET200-120, ET200-121, ET200-122, ET200-123, ET200-125, ET200-005 and ET200-124 disclosed in WO2017096120), herein incorporated by reference in their entirety.

Exemplary FCRL5 CAR molecules are disclosed in WO2016090337, herein incorporated by reference in its entirety.

IL-15 and/or IL-15Ra

In some embodiments, the BCMA CAR-expressing cell therapy is administered in combination with IL-15. In some embodiments, the BCMA CAR-expressing cell therapy is administered in combination with an IL15/IL-15Ra complex. In some embodiments, the IL-15/IL-15Ra complex is chosen from NIZ985 (Novartis), ATL-803 (Altor) or CYP0150 (Cytune).

Exemplary IL-15/IL-15Ra complexes

In one embodiment, the IL-15/IL-15Ra complex comprises human IL-15 complexed with a soluble form of human IL-15Ra. The complex may comprise IL-15 covalently or noncovalently bound

to a soluble form of IL-15Ra. In a particular embodiment, the human IL-15 is noncovalently bonded to a soluble form of IL-15Ra. In a particular embodiment, the human IL-15 of the composition comprises an amino acid sequence of SEQ ID NO: 1001 in Table 16 and the soluble form of human IL-15Ra comprises an amino acid sequence of SEQ ID NO:1002 in Table 16, as described in WO 2014/066527, incorporated by reference in its entirety. The molecules described herein can be made by vectors, host cells, and methods described in WO 2007/084342, incorporated by reference in its entirety.

Table 16. Amino acid and nucleotide sequences of exemplary IL-15/IL-15Ra complexes

NIZ985		
SEQ ID NO: 1001	Human IL-15	NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAM KCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE SGCKECEELEEKNIKEFLQSFVHIVQMFINTS
SEQ ID NO: 1002	Human Soluble IL-15Ra	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSS LTECVLNKATNVAHWTTPSLKCIRDPALVHQRPAPPSTVT TAGVTPQPESLSPSGKEPAASSPSSNNTAATTAAIVPGSQL MPSKSPSTGTTEISSHESSHGTPSQTTAKNWELTASASHQP PGVYPQG

Other exemplary IL-15/IL-15Ra complexes

In one embodiment, the IL-15/IL-15Ra complex is ALT-803, an IL-15/IL-15Ra Fc fusion protein (IL-15N72D:IL-15RaSu/Fc soluble complex). ALT-803 is disclosed in WO 2008/143794, incorporated by reference in its entirety. In one embodiment, the IL-15/IL-15Ra Fc fusion protein comprises the sequences as disclosed in Table 17.

In one embodiment, the IL-15/IL-15Ra complex comprises IL-15 fused to the sushi domain of IL-15Ra (CYP0150, Cytune). The sushi domain of IL-15Ra refers to a domain beginning at the first cysteine residue after the signal peptide of IL-15Ra, and ending at the fourth cysteine residue after said signal peptide. The complex of IL-15 fused to the sushi domain of IL-15Ra is disclosed in WO 2007/04606 and WO 2012/175222, incorporated by reference in their entirety. In one embodiment, the IL-15/IL-15Ra sushi domain fusion comprises the sequences as disclosed in Table 17.

Table 17. Amino acid sequences of other exemplary IL-15/IL-15Ra complexes

ALT-803 (Altor)		
SEQ ID NO: 1003	IL-15N72D	NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMK CFLLELQVISLESGDASIHDTVENLIILANDSLSSNGNVTESG CKECEELEEKNIKEFLQSFVHIVQMFINTS
SEQ ID NO: 1004	IL-15RaSu/ Fc	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSL TECVLNKATNVAHWTTPSLKCIREPKSCDKTHTCPPCPAPE LLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW

		LNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS RDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK
IL-15 / IL-15Ra sushi domain fusion (Cytune)		
SEQ ID NO:1005	Human IL-15	NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMK CFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTESG CKECEELEXKNIKEFLQSFVHIVQMFINTS Where X is E or K
SEQ ID NO:1006	Human IL-15Ra sushi and hinge domains	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSL TECVLNKATNVAHWTTPSLKCIRDPALVHQRPAPP

PD-1 inhibitor

In some embodiments, the BCMA CAR-expressing cell therapy is administered in combination with a PD-1 inhibitor. In some embodiments, the PD-1 inhibitor is chosen from PDR001 (Novartis), Nivolumab (Bristol-Myers Squibb), Pembrolizumab (Merck & Co), Pidilizumab (CureTech), MEDI0680 (Medimmune), REGN2810 (Regeneron), TSR-042 (Tesaro), PF-06801591 (Pfizer), BGB-A317 (Beigene), BGB-108 (Beigene), INCSHR1210 (Incyte), or AMP-224 (Amplimmune).

Exemplary PD-1 Inhibitors

In one embodiment, the PD-1 inhibitor is an anti-PD-1 antibody molecule. In one embodiment, the PD-1 inhibitor is an anti-PD-1 antibody molecule as described in US 2015/0210769, published on July 30, 2015, entitled "Antibody Molecules to PD-1 and Uses Thereof," incorporated by reference in its entirety.

In one embodiment, the anti-PD-1 antibody molecule comprises at least one, two, three, four, five or six complementarity determining regions (CDRs) (or collectively all of the CDRs) from a heavy and light chain variable region comprising an amino acid sequence shown in Table 18 (*e.g.*, from the heavy and light chain variable region sequences of BAP049-Clone-E or BAP049-Clone-B disclosed in Table 18), or encoded by a nucleotide sequence shown in Table 18. In some embodiments, the CDRs are according to the Kabat definition (*e.g.*, as set out in Table 18). In some embodiments, the CDRs are according to the Chothia definition (*e.g.*, as set out in Table 18). In some embodiments, the CDRs are according to the combined CDR definitions of both Kabat and Chothia (*e.g.*, as set out in Table 18). In one embodiment, the combination of Kabat and Chothia CDR of VH CDR1 comprises the amino acid sequence GYTFTTYWMH (SEQ ID NO: 541). In one embodiment, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five, six or more changes, *e.g.*, amino acid substitutions (*e.g.*, conservative amino acid substitutions) or deletions, relative to an amino acid sequence shown in Table 18, or encoded by a nucleotide sequence shown in Table 18.

In one embodiment, the anti-PD-1 antibody molecule comprises a heavy chain variable region (VH) comprising a VHCDR1 amino acid sequence of SEQ ID NO: 501, a VHCDR2 amino acid sequence of SEQ ID NO: 502, and a VHCDR3 amino acid sequence of SEQ ID NO: 503; and a light chain variable region (VL) comprising a VLCDR1 amino acid sequence of SEQ ID NO: 510, a VLCDR2 amino acid sequence of SEQ ID NO: 511, and a VLCDR3 amino acid sequence of SEQ ID NO: 512, each disclosed in Table 18.

In one embodiment, the antibody molecule comprises a VH comprising a VHCDR1 encoded by the nucleotide sequence of SEQ ID NO: 524, a VHCDR2 encoded by the nucleotide sequence of SEQ ID NO: 525, and a VHCDR3 encoded by the nucleotide sequence of SEQ ID NO: 526; and a VL comprising a VLCDR1 encoded by the nucleotide sequence of SEQ ID NO: 529, a VLCDR2 encoded by the nucleotide sequence of SEQ ID NO: 530, and a VLCDR3 encoded by the nucleotide sequence of SEQ ID NO: 531, each disclosed in Table 18.

In one embodiment, the anti-PD-1 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 506, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 506. In one embodiment, the anti-PD-1 antibody molecule comprises a VL comprising the amino acid sequence of SEQ ID NO: 520, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 520. In one embodiment, the anti-PD-1 antibody molecule comprises a VL comprising the amino acid sequence of SEQ ID NO: 516, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 516. In one embodiment, the anti-PD-1 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 506 and a VL comprising the amino acid sequence of SEQ ID NO: 520. In one embodiment, the anti-PD-1 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 506 and a VL comprising the amino acid sequence of SEQ ID NO: 516.

In one embodiment, the antibody molecule comprises a VH encoded by the nucleotide sequence of SEQ ID NO: 507, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 507. In one embodiment, the antibody molecule comprises a VL encoded by the nucleotide sequence of SEQ ID NO: 521 or 517, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 521 or 517. In one embodiment, the antibody molecule comprises a VH encoded by the nucleotide sequence of SEQ ID NO: 507 and a VL encoded by the nucleotide sequence of SEQ ID NO: 521 or 517.

In one embodiment, the anti-PD-1 antibody molecule comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 508, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 508. In one embodiment, the anti-PD-1 antibody molecule comprises a light chain comprising the amino acid sequence of SEQ ID NO: 522, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 522. In one embodiment,

the anti-PD-1 antibody molecule comprises a light chain comprising the amino acid sequence of SEQ ID NO: 518, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 518. In one embodiment, the anti-PD-1 antibody molecule comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 508 and a light chain comprising the amino acid sequence of SEQ ID NO: 522. In one embodiment, the anti-PD-1 antibody molecule comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 508 and a light chain comprising the amino acid sequence of SEQ ID NO: 518.

In one embodiment, the antibody molecule comprises a heavy chain encoded by the nucleotide sequence of SEQ ID NO: 509, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 509. In one embodiment, the antibody molecule comprises a light chain encoded by the nucleotide sequence of SEQ ID NO: 523 or 519, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 523 or 519. In one embodiment, the antibody molecule comprises a heavy chain encoded by the nucleotide sequence of SEQ ID NO: 509 and a light chain encoded by the nucleotide sequence of SEQ ID NO: 523 or 519.

The antibody molecules described herein can be made by vectors, host cells, and methods described in US 2015/0210769, incorporated by reference in its entirety.

Table 18. Amino acid and nucleotide sequences of exemplary anti-PD-1 antibody molecules

BAP049-Clone-B HC	
SEQ ID NO: 501 (Kabat)	HCDR1
SEQ ID NO: 502 (Kabat)	HCDR2
SEQ ID NO: 503 (Kabat)	HCDR3
SEQ ID NO: 504 (Chothia)	HCDR1
SEQ ID NO: 505 (Chothia)	HCDR2
SEQ ID NO: 503 (Chothia)	HCDR3
SEQ ID NO: 506	VH
SEQ ID NO: 507	DNA VH
SEQ ID NO: 508	Heavy chain
SEQ ID NO: 509	DNA heavy chain
BAP049-Clone-B LC	
SEQ ID NO: 510 (Kabat)	LCDR1
SEQ ID NO: 511 (Kabat)	LCDR2
SEQ ID NO: 512 (Kabat)	LCDR3
SEQ ID NO: 513 (Chothia)	LCDR1
SEQ ID NO: 514 (Chothia)	LCDR2
SEQ ID NO: 515 (Chothia)	LCDR3
SEQ ID NO: 516	VL
SEQ ID NO: 517	DNA VL
SEQ ID NO: 518	Light chain
SEQ ID NO: 519	DNA light chain
BAP049-Clone-E HC	

SEQ ID NO: 501 (Kabat)	HCDR1
SEQ ID NO: 502 (Kabat)	HCDR2
SEQ ID NO: 503 (Kabat)	HCDR3
SEQ ID NO: 504 (Chothia)	HCDR1
SEQ ID NO: 505 (Chothia)	HCDR2
SEQ ID NO: 503 (Chothia)	HCDR3
SEQ ID NO: 506	VH
SEQ ID NO: 507	DNA VH
SEQ ID NO: 508	Heavy chain
SEQ ID NO: 509	DNA heavy chain
BAP049-Clone-E LC	
SEQ ID NO: 510 (Kabat)	LCDR1
SEQ ID NO: 511 (Kabat)	LCDR2
SEQ ID NO: 512 (Kabat)	LCDR3
SEQ ID NO: 513 (Chothia)	LCDR1
SEQ ID NO: 514 (Chothia)	LCDR2
SEQ ID NO: 515 (Chothia)	LCDR3
SEQ ID NO: 520	VL
SEQ ID NO: 521	DNA VL
SEQ ID NO: 522	Light chain
SEQ ID NO: 523	DNA light chain
BAP049-Clone-B HC	
SEQ ID NO: 524 (Kabat)	HCDR1
SEQ ID NO: 525 (Kabat)	HCDR2
SEQ ID NO: 526 (Kabat)	HCDR3
SEQ ID NO: 527 (Chothia)	HCDR1
SEQ ID NO: 528 (Chothia)	HCDR2
SEQ ID NO: 526 (Chothia)	HCDR3
BAP049-Clone-B LC	
SEQ ID NO: 529 (Kabat)	LCDR1
SEQ ID NO: 530 (Kabat)	LCDR2
SEQ ID NO: 531 (Kabat)	LCDR3
SEQ ID NO: 532 (Chothia)	LCDR1
SEQ ID NO: 533 (Chothia)	LCDR2
SEQ ID NO: 534 (Chothia)	LCDR3
BAP049-Clone-E HC	
SEQ ID NO: 524 (Kabat)	HCDR1
SEQ ID NO: 525 (Kabat)	HCDR2
SEQ ID NO: 526 (Kabat)	HCDR3
SEQ ID NO: 527 (Chothia)	HCDR1
SEQ ID NO: 528 (Chothia)	HCDR2
SEQ ID NO: 526 (Chothia)	HCDR3
BAP049-Clone-E LC	
SEQ ID NO: 529 (Kabat)	LCDR1
SEQ ID NO: 530 (Kabat)	LCDR2
SEQ ID NO: 531 (Kabat)	LCDR3
SEQ ID NO: 532 (Chothia)	LCDR1
SEQ ID NO: 533 (Chothia)	LCDR2
SEQ ID NO: 534 (Chothia)	LCDR3

Other Exemplary PD-1 Inhibitors

In one embodiment, the anti-PD-1 antibody molecule is Nivolumab (Bristol-Myers Squibb), also known as MDX-1106, MDX-1106-04, ONO-4538, BMS-936558, or OPDIVO®. Nivolumab (clone 5C4) and other anti-PD-1 antibodies are disclosed in US 8,008,449 and WO 2006/121168, incorporated by reference in their entirety. In one embodiment, the anti-PD-1 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of Nivolumab, *e.g.*, as disclosed in Table 19.

In one embodiment, the anti-PD-1 antibody molecule is Pembrolizumab (Merck & Co), also known as Lambrolizumab, MK-3475, MK03475, SCH-900475, or KEYTRUDA®. Pembrolizumab and other anti-PD-1 antibodies are disclosed in Hamid, O. *et al.* (2013) *New England Journal of Medicine* 369 (2): 134–44, US 8,354,509, and WO 2009/114335, incorporated by reference in their entirety. In one embodiment, the anti-PD-1 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of Pembrolizumab, *e.g.*, as disclosed in Table 19.

In one embodiment, the anti-PD-1 antibody molecule is Pidilizumab (CureTech), also known as CT-011. Pidilizumab and other anti-PD-1 antibodies are disclosed in Rosenblatt, J. *et al.* (2011) *J Immunotherapy* 34(5): 409-18, US 7,695,715, US 7,332,582, and US 8,686,119, incorporated by reference in their entirety. In one embodiment, the anti-PD-1 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of Pidilizumab, *e.g.*, as disclosed in Table 19.

In one embodiment, the anti-PD-1 antibody molecule is MEDI0680 (Medimmune), also known as AMP-514. MEDI0680 and other anti-PD-1 antibodies are disclosed in US 9,205,148 and WO 2012/145493, incorporated by reference in their entirety. In one embodiment, the anti-PD-1 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of MEDI0680.

In one embodiment, the anti-PD-1 antibody molecule is REGN2810 (Regeneron). In one embodiment, the anti-PD-1 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of REGN2810.

In one embodiment, the anti-PD-1 antibody molecule is PF-06801591 (Pfizer). In one embodiment, the anti-PD-1 antibody molecule comprises one or more of the CDR sequences (or

collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of PF-06801591.

In one embodiment, the anti-PD-1 antibody molecule is BGB-A317 or BGB-108 (Beigene). In one embodiment, the anti-PD-1 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of BGB-A317 or BGB-108.

In one embodiment, the anti-PD-1 antibody molecule is INCSHR1210 (Incyte), also known as INCSHR01210 or SHR-1210. In one embodiment, the anti-PD-1 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of INCSHR1210.

In one embodiment, the anti-PD-1 antibody molecule is TSR-042 (Tesaro), also known as ANB011. In one embodiment, the anti-PD-1 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of TSR-042.

Further known anti-PD-1 antibodies include those described, *e.g.*, in WO 2015/112800, WO 2016/092419, WO 2015/085847, WO 2014/179664, WO 2014/194302, WO 2014/209804, WO 2015/200119, US 8,735,553, US 7,488,802, US 8,927,697, US 8,993,731, and US 9,102,727, incorporated by reference in their entirety.

In one embodiment, the anti-PD-1 antibody is an antibody that competes for binding with, and/or binds to the same epitope on PD-1 as, one of the anti-PD-1 antibodies described herein.

In one embodiment, the PD-1 inhibitor is a peptide that inhibits the PD-1 signaling pathway, *e.g.*, as described in US 8,907,053, incorporated by reference in its entirety. In one embodiment, the PD-1 inhibitor is an immunoadhesin (*e.g.*, an immunoadhesin comprising an extracellular or PD-1 binding portion of PD-L1 or PD-L2 fused to a constant region (*e.g.*, an Fc region of an immunoglobulin sequence). In one embodiment, the PD-1 inhibitor is AMP-224 (B7-DCIg (Amplimmune), *e.g.*, disclosed in WO 2010/027827 and WO 2011/066342, incorporated by reference in their entirety).

Table 19. Amino acid sequences of other exemplary anti-PD-1 antibody molecules

Nivolumab	
SEQ ID NO: 535	Heavy chain
SEQ ID NO: 536	Light chain
Pembrolizumab	
SEQ ID NO: 537	Heavy chain
SEQ ID NO: 538	Light chain
Pidilizumab	

SEQ ID NO: 539	Heavy chain
SEQ ID NO: 540	Light chain

PD-L1 Inhibitors

In some embodiments, the BCMA CAR-expressing cell therapy is administered in combination with a PD-L1 inhibitor. In some embodiments, the PD-L1 inhibitor is chosen from FAZ053 (Novartis), Atezolizumab (Genentech/Roche), Avelumab (Merck Serono and Pfizer), Durvalumab (MedImmune/AstraZeneca), or BMS-936559 (Bristol-Myers Squibb).

Exemplary PD-L1 Inhibitors

In one embodiment, the PD-L1 inhibitor is an anti-PD-L1 antibody molecule. In one embodiment, the PD-L1 inhibitor is an anti-PD-L1 antibody molecule as disclosed in US 2016/0108123, published on April 21, 2016, entitled "Antibody Molecules to PD-L1 and Uses Thereof," incorporated by reference in its entirety.

In one embodiment, the anti-PD-L1 antibody molecule comprises at least one, two, three, four, five or six complementarity determining regions (CDRs) (or collectively all of the CDRs) from a heavy and light chain variable region comprising an amino acid sequence shown in Table 20 (*e.g.*, from the heavy and light chain variable region sequences of BAP058-Clone O or BAP058-Clone N disclosed in Table 20), or encoded by a nucleotide sequence shown in Table 20. In some embodiments, the CDRs are according to the Kabat definition (*e.g.*, as set out in Table 20). In some embodiments, the CDRs are according to the Chothia definition (*e.g.*, as set out in Table 20). In some embodiments, the CDRs are according to the combined CDR definitions of both Kabat and Chothia (*e.g.*, as set out in Table 20). In one embodiment, the combination of Kabat and Chothia CDR of VH CDR1 comprises the amino acid sequence GYTFTSYWMY (SEQ ID NO: 647). In one embodiment, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five, six or more changes, *e.g.*, amino acid substitutions (*e.g.,* conservative amino acid substitutions) or deletions, relative to an amino acid sequence shown in Table 20, or encoded by a nucleotide sequence shown in Table 20.

In one embodiment, the anti-PD-L1 antibody molecule comprises a heavy chain variable region (VH) comprising a VHCDR1 amino acid sequence of SEQ ID NO: 601, a VHCDR2 amino acid sequence of SEQ ID NO: 602, and a VHCDR3 amino acid sequence of SEQ ID NO: 603; and a light chain variable region (VL) comprising a VLCDR1 amino acid sequence of SEQ ID NO: 609, a VLCDR2 amino acid sequence of SEQ ID NO: 610, and a VLCDR3 amino acid sequence of SEQ ID NO: 611, each disclosed in Table 20.

In one embodiment, the anti-PD-L1 antibody molecule comprises a VH comprising a VHCDR1 encoded by the nucleotide sequence of SEQ ID NO: 628, a VHCDR2 encoded by the nucleotide sequence of SEQ ID NO: 629, and a VHCDR3 encoded by the nucleotide sequence of SEQ ID NO: 630; and a VL comprising a VLCDR1 encoded by the nucleotide sequence of SEQ ID NO: 633, a VLCDR2 encoded by the nucleotide sequence of SEQ ID NO: 634, and a VLCDR3 encoded by the nucleotide sequence of SEQ ID NO: 635, each disclosed in Table 20.

In one embodiment, the anti-PD-L1 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 606, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 606. In one embodiment, the anti-PD-L1 antibody molecule comprises a VL comprising the amino acid sequence of SEQ ID NO: 616, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 616. In one embodiment, the anti-PD-L1 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 620, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 620. In one embodiment, the anti-PD-L1 antibody molecule comprises a VL comprising the amino acid sequence of SEQ ID NO: 624, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 624. In one embodiment, the anti-PD-L1 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 606 and a VL comprising the amino acid sequence of SEQ ID NO: 616. In one embodiment, the anti-PD-L1 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 620 and a VL comprising the amino acid sequence of SEQ ID NO: 624.

In one embodiment, the antibody molecule comprises a VH encoded by the nucleotide sequence of SEQ ID NO: 607, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 607. In one embodiment, the antibody molecule comprises a VL encoded by the nucleotide sequence of SEQ ID NO: 617, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 617. In one embodiment, the antibody molecule comprises a VH encoded by the nucleotide sequence of SEQ ID NO: 621, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 621. In one embodiment, the antibody molecule comprises a VL encoded by the nucleotide sequence of SEQ ID NO: 625, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 625. In one embodiment, the antibody molecule comprises a VH encoded by the nucleotide sequence of SEQ ID NO: 607 and a VL encoded by the nucleotide sequence of SEQ ID NO: 617. In one embodiment, the antibody molecule comprises a VH encoded by the nucleotide sequence of SEQ ID NO: 621 and a VL encoded by the nucleotide sequence of SEQ ID NO: 625.

In one embodiment, the anti-PD-L1 antibody molecule comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 608, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 608. In one embodiment, the anti-PD-L1 antibody molecule

comprises a light chain comprising the amino acid sequence of SEQ ID NO: 618, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 618. In one embodiment, the anti-PD-L1 antibody molecule comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 622, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 622. In one embodiment, the anti-PD-L1 antibody molecule comprises a light chain comprising the amino acid sequence of SEQ ID NO: 626, or an amino acid sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 626. In one embodiment, the anti-PD-L1 antibody molecule comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 608 and a light chain comprising the amino acid sequence of SEQ ID NO: 618. In one embodiment, the anti-PD-L1 antibody molecule comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 622 and a light chain comprising the amino acid sequence of SEQ ID NO: 626.

In one embodiment, the antibody molecule comprises a heavy chain encoded by the nucleotide sequence of SEQ ID NO: 615, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 615. In one embodiment, the antibody molecule comprises a light chain encoded by the nucleotide sequence of SEQ ID NO: 619, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 619. In one embodiment, the antibody molecule comprises a heavy chain encoded by the nucleotide sequence of SEQ ID NO: 623, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 623. In one embodiment, the antibody molecule comprises a light chain encoded by the nucleotide sequence of SEQ ID NO: 627, or a nucleotide sequence at least 85%, 90%, 95%, or 99% identical or higher to SEQ ID NO: 627. In one embodiment, the antibody molecule comprises a heavy chain encoded by the nucleotide sequence of SEQ ID NO: 615 and a light chain encoded by the nucleotide sequence of SEQ ID NO: 619. In one embodiment, the antibody molecule comprises a heavy chain encoded by the nucleotide sequence of SEQ ID NO: 623 and a light chain encoded by the nucleotide sequence of SEQ ID NO: 627.

The antibody molecules described herein can be made by vectors, host cells, and methods described in US 2016/0108123, incorporated by reference in its entirety.

Table 20. Amino acid and nucleotide sequences of exemplary anti-PD-L1 antibody molecules

BAP058-Clone O HC	
SEQ ID NO: 601 (Kabat)	HCDR1
SEQ ID NO: 602 (Kabat)	HCDR2
SEQ ID NO: 603 (Kabat)	HCDR3
SEQ ID NO: 604 (Chothia)	HCDR1
SEQ ID NO: 605 (Chothia)	HCDR2
SEQ ID NO: 603 (Chothia)	HCDR3
SEQ ID NO: 606	VH
SEQ ID NO: 607	DNA VH

SEQ ID NO: 608	Heavy chain
SEQ ID NO: 615	DNA heavy chain
BAP058-Clone O LC	
SEQ ID NO: 609 (Kabat)	LCDR1
SEQ ID NO: 610 (Kabat)	LCDR2
SEQ ID NO: 611(Kabat)	LCDR3
SEQ ID NO: 612 (Chothia)	LCDR1
SEQ ID NO: 613 (Chothia)	LCDR2
SEQ ID NO: 614 (Chothia)	LCDR3
SEQ ID NO: 616	VL
SEQ ID NO: 617	DNA VL
SEQ ID NO: 618	Light chain
SEQ ID NO: 619	DNA light chain
BAP058-Clone N HC	
SEQ ID NO: 601 (Kabat)	HCDR1
SEQ ID NO: 602 (Kabat)	HCDR2
SEQ ID NO: 603 (Kabat)	HCDR3
SEQ ID NO: 604 (Chothia)	HCDR1
SEQ ID NO: 605 (Chothia)	HCDR2
SEQ ID NO: 603 (Chothia)	HCDR3
SEQ ID NO: 620	VH
SEQ ID NO: 621	DNA VH
SEQ ID NO: 622	Heavy chain
SEQ ID NO: 623	DNA heavy chain
BAP058-Clone N LC	
SEQ ID NO: 609 (Kabat)	LCDR1
SEQ ID NO: 610 (Kabat)	LCDR2
SEQ ID NO: 611(Kabat)	LCDR3
SEQ ID NO: 612 (Chothia)	LCDR1
SEQ ID NO: 613 (Chothia)	LCDR2
SEQ ID NO: 614 (Chothia)	LCDR3
SEQ ID NO: 624	VL
SEQ ID NO: 625	DNA VL
SEQ ID NO: 626	Light chain
SEQ ID NO: 627	DNA light chain
BAP058-Clone O HC	
SEQ ID NO: 628 (Kabat)	HCDR1
SEQ ID NO: 629 (Kabat)	HCDR2
SEQ ID NO: 630 (Kabat)	HCDR3
SEQ ID NO: 631 (Chothia)	HCDR1
SEQ ID NO: 632 (Chothia)	HCDR2
SEQ ID NO: 630 (Chothia)	HCDR3
BAP058-Clone O LC	
SEQ ID NO: 633 (Kabat)	LCDR1
SEQ ID NO: 634 (Kabat)	LCDR2
SEQ ID NO: 635 (Kabat)	LCDR3
SEQ ID NO: 636 (Chothia)	LCDR1
SEQ ID NO: 637 (Chothia)	LCDR2
SEQ ID NO: 638 (Chothia)	LCDR3
BAP058-Clone N HC	

SEQ ID NO: 628 (Kabat)	HCDR1
SEQ ID NO: 629 (Kabat)	HCDR2
SEQ ID NO: 630 (Kabat)	HCDR3
SEQ ID NO: 631 (Chothia)	HCDR1
SEQ ID NO: 632 (Chothia)	HCDR2
SEQ ID NO: 630 (Chothia)	HCDR3
BAP058-Clone N LC	
SEQ ID NO: 633 (Kabat)	LCDR1
SEQ ID NO: 634 (Kabat)	LCDR2
SEQ ID NO: 635 (Kabat)	LCDR3
SEQ ID NO: 636 (Chothia)	LCDR1
SEQ ID NO: 637 (Chothia)	LCDR2
SEQ ID NO: 638 (Chothia)	LCDR3

Other Exemplary PD-L1 Inhibitors

In one embodiment, the anti-PD-L1 antibody molecule is Atezolizumab (Genentech/Roche), also known as MPDL3280A, RG7446, RO5541267, YW243.55.S70, or TECENTRIQ™. Atezolizumab and other anti-PD-L1 antibodies are disclosed in US 8,217,149, incorporated by reference in its entirety. In one embodiment, the anti-PD-L1 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of Atezolizuma, *e.g.*, as disclosed in Table 21.

In one embodiment, the anti-PD-L1 antibody molecule is Avelumab (Merck Serono and Pfizer), also known as MSB0010718C. Avelumab and other anti-PD-L1 antibodies are disclosed in WO 2013/079174, incorporated by reference in its entirety. In one embodiment, the anti-PD-L1 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of Avelumab, *e.g.*, as disclosed in Table 21.

In one embodiment, the anti-PD-L1 antibody molecule is Durvalumab (MedImmune/AstraZeneca), also known as MEDI4736. Durvalumab and other anti-PD-L1 antibodies are disclosed in US 8,779,108, incorporated by reference in its entirety. In one embodiment, the anti-PD-L1 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of Durvalumab, *e.g.*, as disclosed in Table 21.

In one embodiment, the anti-PD-L1 antibody molecule is BMS-936559 (Bristol-Myers Squibb), also known as MDX-1105 or 12A4. BMS-936559 and other anti-PD-L1 antibodies are disclosed in US 7,943,743 and WO 2015/081158, incorporated by reference in their entirety. In one embodiment, the anti-PD-L1 antibody molecule comprises one or more of the CDR sequences (or collectively all of the

CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of BMS-936559, *e.g.*, as disclosed in Table 21.

Further known anti-PD-L1 antibodies include those described, *e.g.*, in WO 2015/181342, WO 2014/100079, WO 2016/000619, WO 2014/022758, WO 2014/055897, WO 2015/061668, WO 2013/079174, WO 2012/145493, WO 2015/112805, WO 2015/109124, WO 2015/195163, US 8,168,179, US 8,552,154, US 8,460,927, and US 9,175,082, incorporated by reference in their entirety.

In one embodiment, the anti-PD-L1 antibody is an antibody that competes for binding with, and/or binds to the same epitope on PD-L1 as, one of the anti-PD-L1 antibodies described herein.

Table 21. Amino acid sequences of other exemplary anti-PD-L1 antibody molecules

Atezolizumab	
SEQ ID NO: 639	Heavy chain
SEQ ID NO: 640	Light chain
Avelumab	
SEQ ID NO: 641	Heavy chain
SEQ ID NO: 642	Light chain
Durvalumab	
SEQ ID NO: 643	Heavy chain
SEQ ID NO: 644	Light chain
BMS-936559	
SEQ ID NO: 645	VH
SEQ ID NO: 646	VL

LAG-3 Inhibitors

In some embodiments, the BCMA CAR-expressing cell therapy is administered in combination with a LAG-3 inhibitor. In some embodiments, the LAG-3 inhibitor is chosen from LAG525 (Novartis), BMS-986016 (Bristol-Myers Squibb), or TSR-033 (Tesaro).

Exemplary LAG-3 Inhibitors

In one embodiment, the LAG-3 inhibitor is an anti-LAG-3 antibody molecule. In one embodiment, the LAG-3 inhibitor is an anti-LAG-3 antibody molecule as disclosed in US 2015/0259420, published on September 17, 2015, entitled "Antibody Molecules to LAG-3 and Uses Thereof," incorporated by reference in its entirety.

In one embodiment, the anti-LAG-3 antibody molecule comprises at least one, two, three, four, five or six complementarity determining regions (CDRs) (or collectively all of the CDRs) from a heavy and light chain variable region comprising an amino acid sequence shown in Table 22 (*e.g.*, from the heavy and light chain variable region sequences of BAP050-Clone I or BAP050-Clone J disclosed in

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What is claimed is:

1. A method of evaluating or predicting a subject's responsiveness to a BCMA CAR-expressing cell therapy, wherein the subject has a disease associated with the expression of BCMA, comprising:

acquiring a value for one, two, three, four, five, or all of:

(i) the level or activity of CD4+ immune effector cells (e.g., CD4+ T cells) relative to the level or activity of CD8+ immune effector cells (e.g., CD8+ T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample), in a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or in the subject's peripheral blood and/or bone marrow prior to the administration of the BCMA CAR-expressing cell therapy,

(ii) the level or activity of CD8+ Tscm (stem cell memory T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(iii) the level or activity of HLADR-CD95+CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(iv) the level or activity of CD45RO-CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(v) the level or activity of CCR7+CD45RO-CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or

(vi) the proliferation of seeded cells from the subject during manufacturing of the BCMA CAR-expressing cell therapy, e.g., as measured by population doublings by day 9 (PDL9), wherein:

(a) an increase in the value of one, two, three, four, five, or all of (i)-(vi), as compared to a reference value, e.g., a non-responder reference value, is indicative or predictive of increased responsiveness of the subject to the BCMA CAR-expressing cell therapy; or

(b) a decrease in the value of one, two, three, four, five, or all of (i)-(vi), as compared to a reference value, e.g., a responder reference value, is indicative or predictive of decreased responsiveness of the subject to the BCMA CAR-expressing cell therapy,

thereby evaluating or predicting the subject's responsiveness to the BCMA CAR-expressing cell therapy.

2. The method of claim 1, wherein the increase in the value of one, two, three, four, five, or all of (i)-(vi), as compared to a reference value, e.g., a non-responder reference value, is indicative or predictive of one, two, three, or all of:

(a) increased responsiveness of the subject to the BCMA CAR-expressing cell therapy;

(b) the subject as a responder of the BCMA CAR-expressing cell therapy;

(c) the subject as suitable for the BCMA CAR-expressing cell therapy; or

(d) increased expansion of the BCMA CAR-expressing cell therapy in the subject, e.g., as measured by an assay disclosed herein, e.g., as measured by the copy number of CAR transgenes per µg DNA using qPCR.

3. The method of claim 1 or 2, wherein the decrease in the value of one, two, three, four, five, or all of (i)-(vi), as compared to a reference value, e.g., a responder reference value, is indicative or predictive of one, two, or all of:

(a) decreased responsiveness of the subject to the BCMA CAR-expressing cell therapy;

(b) the subject as a non-responder of the BCMA CAR-expressing cell therapy; or

(c) decreased expansion of the BCMA CAR-expressing cell therapy in the subject, e.g., as measured by an assay disclosed herein, e.g., as measured by the copy number of CAR transgenes per µg DNA using qPCR.

4. The method of any one of claims 1-3, wherein the value for the level or activity of CD4+ immune effector cells (e.g., CD4+ T cells) relative to the level or activity of CD8+ immune effector cells (e.g., CD8+ T cells) comprises a ratio of the amount of CD4+ immune effector cells (e.g., CD4+ T cells) to the amount of CD8+ immune effector cells (e.g., CD8+ T cells), e.g., as measured by an assay disclosed herein, e.g., flow cytometry.

5. The method of claim 4, wherein the ratio being:

(1) greater than or equal to 1 (e.g., between 1 and 5, e.g., between 1 and 3.5); or

(2) greater than or equal to 1.6 (e.g., between 1.6 and 5, e.g., between 1.6 and 3.5),

is indicative or predictive of one, two, three, or all of:

(a) increased responsiveness of the subject to the BCMA CAR-expressing cell therapy;

(b) the subject as a responder of the BCMA CAR-expressing cell therapy;

(c) the subject as suitable for the BCMA CAR-expressing cell therapy; or

(d) increased expansion of the BCMA CAR-expressing cell therapy in the subject, e.g., as measured by an assay disclosed herein, e.g., as measured by the copy number of CAR transgenes per µg DNA using qPCR.

6. The method of claim 4 or 5, wherein the ratio being less than 1 (e.g., between 0.001 and 1) is indicative or predictive of one, two, or all of:

(a) decreased responsiveness of the subject to the BCMA CAR-expressing cell therapy;

(b) the subject as a non-responder of the BCMA CAR-expressing cell therapy; or

(c) decreased expansion of the BCMA CAR-expressing cell therapy in the subject, e.g., as measured by an assay disclosed herein, e.g., as measured by the copy number of CAR transgenes per µg DNA using qPCR.

7. The method of any one of claims 1-6, wherein the value for the level or activity of CD8+ Tscm (stem cell memory T cells) comprises the percentage of CD8+ Tscm (stem cell memory T cells) among CD8+ T cells, e.g., as measured by an assay disclosed herein, e.g., flow cytometry.

8. The method of any one of claims 1-7, wherein the value for the level or activity of HLADR-CD95+CD27+CD8+ cells comprises the percentage of HLADR-CD95+CD27+CD8+ cells among CD8+ T cells, e.g., as measured by an assay disclosed herein, e.g., flow cytometry.

9. The method of claim 8, wherein the percentage of HLADR-CD95+CD27+CD8+ cells among CD8+ T cells being greater than or equal to 25% (e.g., between 30% and 90%, e.g., between 35% and 85%, e.g., between 40% and 80%, e.g., between 45% and 75%, e.g., between 50% and 75%) is indicative or predictive of one, two, three, or all of:

(a) increased responsiveness of the subject to the BCMA CAR-expressing cell therapy;

(b) the subject as a responder of the BCMA CAR-expressing cell therapy;

(c) the subject as suitable for the BCMA CAR-expressing cell therapy; or

(d) increased expansion of the BCMA CAR-expressing cell therapy in the subject, e.g., as measured by an assay disclosed herein, e.g., as measured by the copy number of CAR transgenes per µg DNA using qPCR.

10. The method of claim 8 or 9, wherein the percentage of HLADR-CD95+CD27+CD8+ cells among CD8+ T cells being less than 25% (e.g., between 0.1% and 25%, e.g., between 0.1% and 22%, e.g., between 0.1% and 20%, e.g., between 0.1% and 18%, e.g., between 0.1% and 15%)) is indicative or predictive of one, two, or all of:

(a) decreased responsiveness of the subject to the BCMA CAR-expressing cell therapy;

(b) the subject as a non-responder of the BCMA CAR-expressing cell therapy; or

(c) decreased expansion of the BCMA CAR-expressing cell therapy in the subject, e.g., as measured by an assay disclosed herein, e.g., as measured by the copy number of CAR transgenes per µg DNA using qPCR.

11. The method of any one of claims 1-10, wherein the value for the level or activity of CD45RO-CD27+CD8+ cells comprises the percentage of CD45RO-CD27+CD8+ cells among CD8+ T cells, e.g., as measured by an assay disclosed herein, e.g., flow cytometry.

12. The method of claim 11, wherein the percentage of CD45RO-CD27+CD8+ cells among CD8+ T cells being greater than or equal to 20% (e.g., between 20% and 90%, e.g., between 20% and 80%, e.g., between 20% and 70%, e.g., between 20% and 60%) is indicative or predictive of one, two, three, or all of:

(a) increased responsiveness of the subject to the BCMA CAR-expressing cell therapy;

(b) the subject as a responder of the BCMA CAR-expressing cell therapy;

(c) the subject as suitable for the BCMA CAR-expressing cell therapy; or

(d) increased expansion of the BCMA CAR-expressing cell therapy in the subject, e.g., as measured by an assay disclosed herein, e.g., as measured by the copy number of CAR transgenes per µg DNA using qPCR.

13. The method of claim 11 or 12, wherein the percentage of CD45RO-CD27+CD8+ cells among CD8+ T cells being less than 20% (e.g., between 0.1% and 20%, e.g., between 0.1% and 18%, e.g., between 0.1% and 15%, e.g., between 0.1% and 12%, e.g., between 0.1% and 10%) is indicative or predictive of one, two, or all of:

(a) decreased responsiveness of the subject to the BCMA CAR-expressing cell therapy;

(b) the subject as a non-responder of the BCMA CAR-expressing cell therapy; or

(c) decreased expansion of the BCMA CAR-expressing cell therapy in the subject, e.g., as measured by an assay disclosed herein, e.g., as measured by the copy number of CAR transgenes per µg DNA using qPCR.

14. The method of any one of claims 1-13, wherein the value for the level or activity of CCR7+CD45RO-CD27+CD8+ cells comprises the percentage of CCR7+CD45RO-CD27+CD8+ cells among CD8+ T cells, e.g., as measured by an assay disclosed herein, e.g., flow cytometry.

15. The method of claim 14, wherein the percentage of CCR7+CD45RO-CD27+CD8+ cells among CD8+ T cells being greater than or equal to 15% (e.g., between 15% and 90%, e.g., between 15% and 80%, e.g., between 15% and 70%, e.g., between 15% and 60%, e.g., between 15% and 50%) is indicative or predictive of one, two, three, or all of:

(a) increased responsiveness of the subject to the BCMA CAR-expressing cell therapy;

(b) the subject as a responder of the BCMA CAR-expressing cell therapy;

(c) the subject as suitable for the BCMA CAR-expressing cell therapy; or

(d) increased expansion of the BCMA CAR-expressing cell therapy in the subject, e.g., as measured by an assay disclosed herein, e.g., as measured by the copy number of CAR transgenes per µg DNA using qPCR.

16. The method of claim 14 or 15, wherein the percentage of CCR7+CD45RO-CD27+CD8+ cells among CD8+ T cells being less than 15% (e.g., between 0.1% and 15%, e.g., between 0.1% and 12%, e.g., between 0.1% and 10%, e.g., between 0.1% and 8%) is indicative or predictive of one, two, or all of:

(a) decreased responsiveness of the subject to the BCMA CAR-expressing cell therapy;

(b) the subject as a non-responder of the BCMA CAR-expressing cell therapy; or

(c) decreased expansion of the BCMA CAR-expressing cell therapy in the subject, e.g., as measured by an assay disclosed herein, e.g., as measured by the copy number of CAR transgenes per µg DNA using qPCR.

17. The method of any one of claims 1-16, wherein the value for the proliferation of seeded cells from the subject during manufacturing of the BCMA CAR-expressing cell therapy comprises the fold expansion of seeded cells from the subject during manufacturing (e.g., total cell counts at the end of manufacturing relative to at the start of manufacturing) of the BCMA CAR-expressing cell therapy, e.g., as measured by an assay disclosed herein, e.g., as measured by cell counting.

18. The method of any one of claims 1-17, further comprising performing:

manufacturing the BCMA CAR-expressing cell therapy using cells (e.g., T cells) from the subject and administering the BCMA CAR-expressing cell therapy to the subject; or

administering, e.g., initiating administering or continuing administering, the BCMA CAR-expressing cell therapy to the subject, when:

(a) the subject was indicated or predicted to have increased responsiveness to the BCMA CAR-expressing cell therapy;

(b) the subject was indicated or predicted as a responder of the BCMA CAR-expressing cell therapy;

(c) the subject was indicated or predicted as suitable for the BCMA CAR-expressing cell therapy; or

(d) the BCMA CAR-expressing cell therapy was indicated or predicted to have increased expansion in the subject, e.g., as measured by an assay disclosed herein, e.g., as measured by the copy number of CAR transgenes per μg DNA using qPCR.

19. The method of any one of claims 1-17, further comprising performing one, two, three, four, five, six, seven, or all of:

administering an altered dosing regimen of the BCMA CAR-expressing cell therapy (e.g., a dosing regimen with a higher dose and/or more frequent administration than a reference dosing regimen) to the subject;

administering a second therapy (e.g., a second therapy that is not the BCMA CAR-expressing cell therapy) to the subject;

administering the BCMA CAR-expressing cell therapy and a second therapy to the subject;

discontinuing administration of the BCMA CAR-expressing cell therapy and optionally administering a second therapy to the subject;

modifying a manufacturing process of the BCMA CAR-expressing cell therapy, e.g., enriching for CD4+ immune effector cells (e.g., CD4+ T cells) relative to CD8+ immune effector cells (CD8+ T cells) prior to introducing a nucleic acid encoding a BCMA CAR, and administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject;

modifying a manufacturing process of the BCMA CAR-expressing cell therapy, e.g., enriching for CD8+ Tscm (e.g., HLADR-CD95+CD27+CD8+ cells, CD45RO-CD27+CD8+ cells, or CCR7+CD45RO-CD27+CD8+ cells) prior to introducing a nucleic acid encoding a BCMA CAR, and

administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject;

modifying a manufacturing process of the BCMA CAR-expressing cell therapy, e.g., increasing the proliferation of seeded cells from the subject during the manufacturing of the BCMA CAR-expressing cell therapy, and administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject; or

administering a pretreatment to the subject, wherein the pretreatment increases the ratio of the amount of CD4+ immune effector cells (e.g., CD4+ T cells) to the amount of CD8+ immune effector cells (e.g., CD8+ T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample), in a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or in the subject's peripheral blood and/or bone marrow prior to the administration of the BCMA CAR-expressing cell therapy, e.g., the pretreatment increases the ratio to greater than or equal to 1.6 (e.g., between 1.6 and 5, e.g., between 1.6 and 3.5), manufacturing the BCMA CAR-expressing cell therapy using cells (e.g., T cells) from the subject, and administering the BCMA CAR-expressing cell therapy to the subject, when:

(a) the subject was indicated or predicted to have decreased responsiveness to the BCMA CAR-expressing cell therapy;

(b) the subject was indicated or predicted as a non-responder of the BCMA CAR-expressing cell therapy; or

(c) the BCMA CAR-expressing cell therapy was indicated or predicted to have decreased expansion in the subject, e.g., as measured by an assay disclosed herein, e.g., as measured by the copy number of CAR transgenes per μg DNA using qPCR.

20. A method of treating a subject having a disease associated with the expression of BCMA, comprising:

responsive to an increased value for one, two, three, four, five, or all of:

(i) the level or activity of CD4+ immune effector cells (e.g., CD4+ T cells) relative to the level or activity of CD8+ immune effector cells (e.g., CD8+ T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample), in a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or in the subject's peripheral blood and/or bone marrow prior to the administration of the BCMA CAR-expressing cell therapy,

(ii) the level or activity of CD8+ Tscm (stem cell memory T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(iii) the level or activity of HLADR-CD95+CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(iv) the level or activity of CD45RO-CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(v) the level or activity of CCR7+CD45RO-CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or

(vi) the proliferation of seeded cells from the subject during manufacturing of a BCMA CAR-expressing cell therapy,

as compared to a reference value, e.g., a non-responder reference value, performing:

manufacturing a BCMA CAR-expressing cell therapy using cells (e.g., T cells) from the subject and administering the BCMA CAR-expressing cell therapy to the subject; or

administering, e.g., initiating administering or continuing administering, a BCMA CAR-expressing cell therapy to the subject,

thereby treating the subject having the disease associated with the expression of BCMA.

21. A method of treating a subject having a disease associated with the expression of BCMA, comprising:

responsive to a decreased value for one, two, three, four, five, or all of:

(i) the level or activity of CD4+ immune effector cells (e.g., CD4+ T cells) relative to the level or activity of CD8+ immune effector cells (e.g., CD8+ T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample), in a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or in the subject's peripheral blood and/or bone marrow prior to the administration of the BCMA CAR-expressing cell therapy,

(ii) the level or activity of CD8+ Tscm (stem cell memory T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(iii) the level or activity of HLADR-CD95+CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(iv) the level or activity of CD45RO-CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(v) the level or activity of CCR7+CD45RO-CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or

(vi) the proliferation of seeded cells from the subject during manufacturing of a BCMA CAR-expressing cell therapy,

as compared to a reference value, e.g., a responder reference value, performing one, two, three, four, five, six, seven, or all of:

administering an altered dosing regimen of a BCMA CAR-expressing cell therapy (e.g., a dosing regimen with a higher dose and/or more frequent administration than a reference dosing regimen) to the subject;

administering a second therapy (e.g., a second therapy that is not a BCMA CAR-expressing cell therapy) to the subject;

administering a BCMA CAR-expressing cell therapy and a second therapy to the subject;

discontinuing administration of a BCMA CAR-expressing cell therapy and optionally administering a second therapy to the subject;

modifying a manufacturing process of a BCMA CAR-expressing cell therapy, e.g., enriching for CD4+ immune effector cells (e.g., CD4+ T cells) relative to CD8+ immune effector cells (CD8+ T cells) prior to introducing a nucleic acid encoding a BCMA CAR, and administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject;

modifying a manufacturing process of a BCMA CAR-expressing cell therapy, e.g., enriching for CD8+ Tscm (e.g., HLADR-CD95+CD27+CD8+ cells, CD45RO-CD27+CD8+ cells, or

CCR7+CD45RO-CD27+CD8+ cells) prior to introducing a nucleic acid encoding a BCMA CAR, and administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject;

modifying a manufacturing process of the BCMA CAR-expressing cell therapy, e.g., increasing the proliferation of seeded cells from the subject during the manufacturing of the BCMA CAR-expressing cell therapy, and administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject; or

administering a pretreatment to the subject, wherein the pretreatment increases the ratio of the amount of CD4+ immune effector cells (e.g., CD4+ T cells) to the amount of CD8+ immune effector cells (e.g., CD8+ T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample), a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or in the subject's peripheral blood and/or bone marrow prior to the administration of the BCMA CAR-expressing cell therapy, e.g., the pretreatment increases the ratio to greater than or equal to 1.6 (e.g., between 1.6 and 5, e.g., between 1.6 and 3.5), manufacturing the BCMA CAR-expressing cell therapy using cells (e.g., T cells) from the subject, and administering the BCMA CAR-expressing cell therapy to the subject,

thereby treating the subject having the disease associated with the expression of BCMA.

22. The method of claim 20, comprising: responsive to an increased value for one, two, three, four, five, or all of (i)-(vi), identifying or predicting one, two, three, or all of:

(a) the subject as having increased responsiveness to the BCMA CAR-expressing cell therapy;

(b) the subject as a responder of the BCMA CAR-expressing cell therapy;

(c) the subject as suitable for the BCMA CAR-expressing cell therapy; or

(d) the BCMA CAR-expressing cell therapy as having increased expansion in the subject, e.g., as measured by an assay disclosed herein, e.g., as measured by the copy number of CAR transgenes per µg DNA using qPCR.

23. The method of claim 21, comprising: response to a decreased value for one, two, three, four, five, or all of (i)-(vi), identifying or predicting one, two, or all of:

(a) the subject as having decreased responsiveness to the BCMA CAR-expressing cell therapy;

(b) the subject as a non-responder of the BCMA CAR-expressing cell therapy; or

(c) the BCMA CAR-expressing cell therapy as having decreased expansion in the subject, e.g., as measured by an assay disclosed herein, e.g., as measured by the copy number of CAR transgenes per µg DNA using qPCR.

24. The method of any one of claims 20-23, wherein the value for the level or activity of CD4+ immune effector cells (e.g., CD4+ T cells) relative to the level or activity of CD8+ immune effector cells (e.g., CD8+ T cells) comprises a ratio of the amount of CD4+ immune effector cells (e.g., CD4+ T cells) to the amount of CD8+ immune effector cells (e.g., CD8+ T cells), e.g., as measured by an assay disclosed herein, e.g., flow cytometry.

25. The method of claim 24, comprising:

responsive to the ratio being:

(1) greater than or equal to 1 (e.g., between 1 and 5, e.g., between 1 and 3.5); or

(2) greater than or equal to 1.6 (e.g., between 1.6 and 5, e.g., between 1.6 and 3.5), performing:

manufacturing a BCMA CAR-expressing cell therapy using cells (e.g., T cells) from the subject and administering the BCMA CAR-expressing cell therapy to the subject; or

administering, e.g., initiating administering or continuing administering, a BCMA CAR-expressing cell therapy to the subject.

26. The method of claim 24 or 25, comprising:

responsive to the ratio being less than 1 (e.g., between 0.001 and 1), performing one, two, three, four, five, six, seven, or all of:

administering an altered dosing regimen of a BCMA CAR-expressing cell therapy (e.g., a dosing regimen with a higher dose and/or more frequent administration than a reference dosing regimen) to the subject;

administering a second therapy (e.g., a second therapy that is not a BCMA CAR-expressing cell therapy) to the subject;

administering a BCMA CAR-expressing cell therapy and a second therapy to the subject;

discontinuing administration of a BCMA CAR-expressing cell therapy and optionally administering a second therapy to the subject;

modifying a manufacturing process of a BCMA CAR-expressing cell therapy, e.g., enriching for CD4+ immune effector cells (e.g., CD4+ T cells) relative to CD8+ immune effector cells (CD8+ T cells) prior to introducing a nucleic acid encoding a BCMA CAR, and administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject;

modifying a manufacturing process of a BCMA CAR-expressing cell therapy, e.g., enriching for CD8+ Tscm (e.g., HLADR-CD95+CD27+CD8+ cells, CD45RO-CD27+CD8+ cells, or CCR7+CD45RO-CD27+CD8+ cells) prior to introducing a nucleic acid encoding a BCMA CAR, and administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject;

modifying a manufacturing process of the BCMA CAR-expressing cell therapy, e.g., increasing the proliferation of seeded cells from the subject during the manufacturing of the BCMA CAR-expressing cell therapy, and administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject; or

administering a pretreatment to the subject, wherein the pretreatment increases the ratio of the amount of CD4+ immune effector cells (e.g., CD4+ T cells) to the amount of CD8+ immune effector cells (e.g., CD8+ T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample), in a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or in the subject's peripheral blood and/or bone marrow prior to the administration of the BCMA CAR-expressing cell therapy, e.g., the pretreatment increases the ratio to greater than or equal to 1.6 (e.g., between 1.6 and 5, e.g., between 1.6 and 3.5), manufacturing the BCMA CAR-expressing cell therapy using cells (e.g., T cells) from the subject, and administering the BCMA CAR-expressing cell therapy to the subject.

27. The method of any one of claims 20-26, wherein the value for the level or activity of CD8+ Tscm (stem cell memory T cells) comprises the percentage of CD8+ Tscm (stem cell memory T cells) among CD8+ T cells, e.g., as measured by an assay disclosed herein, e.g., flow cytometry.

28. The method of any one of claims 20-27, wherein the value for the level or activity of HLADR-CD95+CD27+CD8+ cells comprises the percentage of HLADR-CD95+CD27+CD8+ cells among CD8+ T cells, e.g., as measured by an assay disclosed herein, e.g., flow cytometry.

29. The method of claim 28, comprising:

responsive to the percentage of HLADR-CD95+CD27+CD8+ cells among CD8+ T cells being greater than or equal to 25% (e.g., between 30% and 90%, e.g., between 35% and 85%, e.g., between 40% and 80%, e.g., between 45% and 75%, e.g., between 50% and 75%), performing:

manufacturing a BCMA CAR-expressing cell therapy using cells (e.g., T cells) from the subject and administering the BCMA CAR-expressing cell therapy to the subject; or

administering, e.g., initiating administering or continuing administering, a BCMA CAR-expressing cell therapy to the subject.

30. The method of claim 28 or 29, comprising:

responsive to the percentage of HLADR-CD95+CD27+CD8+ cells among CD8+ T cells being less than 25% (e.g., between 0.1% and 25%, e.g., between 0.1% and 22%, e.g., between 0.1% and 20%, e.g., between 0.1% and 18%, e.g., between 0.1% and 15%), performing one, two, three, four, five, six, seven, or all of:

administering an altered dosing regimen of a BCMA CAR-expressing cell therapy (e.g., a dosing regimen with a higher dose and/or more frequent administration than a reference dosing regimen) to the subject;

administering a second therapy (e.g., a second therapy that is not a BCMA CAR-expressing cell therapy) to the subject;

administering a BCMA CAR-expressing cell therapy and a second therapy to the subject;

discontinuing administration of a BCMA CAR-expressing cell therapy and optionally administering a second therapy to the subject;

modifying a manufacturing process of a BCMA CAR-expressing cell therapy, e.g., enriching for CD4+ immune effector cells (e.g., CD4+ T cells) relative to CD8+ immune effector cells (CD8+ T cells) prior to introducing a nucleic acid encoding a BCMA CAR, and administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject;

modifying a manufacturing process of a BCMA CAR-expressing cell therapy, e.g., enriching for CD8+ Tscm (e.g., HLADR-CD95+CD27+CD8+ cells, CD45RO-CD27+CD8+ cells, or CCR7+CD45RO-CD27+CD8+ cells) prior to introducing a nucleic acid encoding a BCMA CAR, and administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject;

modifying a manufacturing process of the BCMA CAR-expressing cell therapy, e.g., increasing the proliferation of seeded cells from the subject during the manufacturing of the BCMA CAR-expressing cell therapy, and administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject; or

administering a pretreatment to the subject, wherein the pretreatment increases the ratio of the amount of CD4+ immune effector cells (e.g., CD4+ T cells) to the amount of CD8+ immune effector cells (e.g., CD8+ T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample), in a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or

in the subject's peripheral blood and/or bone marrow prior to the administration of the BCMA CAR-expressing cell therapy, e.g., the pretreatment increases the ratio to greater than or equal to 1.6 (e.g., between 1.6 and 5, e.g., between 1.6 and 3.5), manufacturing the BCMA CAR-expressing cell therapy using cells (e.g., T cells) from the subject, and administering the BCMA CAR-expressing cell therapy to the subject.

31. The method of any one of claims 20-30, wherein the value for the level or activity of CD45RO-CD27+CD8+ cells comprises the percentage of CD45RO-CD27+CD8+ cells among CD8+ T cells, e.g., as measured by an assay disclosed herein, e.g., flow cytometry.

32. The method of claim 31, comprising:

responsive to the percentage of CD45RO-CD27+CD8+ cells among CD8+ T cells being greater than or equal to 20% (e.g., between 20% and 90%, e.g., between 20% and 80%, e.g., between 20% and 70%, e.g., between 20% and 60%), performing:

manufacturing a BCMA CAR-expressing cell therapy using cells (e.g., T cells) from the subject and administering the BCMA CAR-expressing cell therapy to the subject; or

administering, e.g., initiating administering or continuing administering, a BCMA CAR-expressing cell therapy to the subject.

33. The method of claim 31 or 32, comprising:

responsive to the percentage of CD45RO-CD27+CD8+ cells among CD8+ T cells being less than 20% (e.g., between 0.1% and 20%, e.g., between 0.1% and 18%, e.g., between 0.1% and 15%, e.g., between 0.1% and 12%, e.g., between 0.1% and 10%), performing one, two, three, four, five, six, seven, or all of:

administering an altered dosing regimen of a BCMA CAR-expressing cell therapy (e.g., a dosing regimen with a higher dose and/or more frequent administration than a reference dosing regimen) to the subject;

administering a second therapy (e.g., a second therapy that is not a BCMA CAR-expressing cell therapy) to the subject;

administering a BCMA CAR-expressing cell therapy and a second therapy to the subject;

discontinuing administration of a BCMA CAR-expressing cell therapy and optionally administering a second therapy to the subject;

modifying a manufacturing process of a BCMA CAR-expressing cell therapy, e.g., enriching for CD4+ immune effector cells (e.g., CD4+ T cells) relative to CD8+ immune effector cells (CD8+ T

cells) prior to introducing a nucleic acid encoding a BCMA CAR, and administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject;

modifying a manufacturing process of a BCMA CAR-expressing cell therapy, e.g., enriching for CD8+ Tscm (e.g., HLADR-CD95+CD27+CD8+ cells, CD45RO-CD27+CD8+ cells, or CCR7+CD45RO-CD27+CD8+ cells) prior to introducing a nucleic acid encoding a BCMA CAR, and administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject;

modifying a manufacturing process of the BCMA CAR-expressing cell therapy, e.g., increasing the proliferation of seeded cells from the subject during the manufacturing of the BCMA CAR-expressing cell therapy, and administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject; or

administering a pretreatment to the subject, wherein the pretreatment increases the ratio of the amount of CD4+ immune effector cells (e.g., CD4+ T cells) to the amount of CD8+ immune effector cells (e.g., CD8+ T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample), in a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or in the subject's peripheral blood and/or bone marrow prior to the administration of the BCMA CAR-expressing cell therapy, e.g., the pretreatment increases the ratio to greater than or equal to 1.6 (e.g., between 1.6 and 5, e.g., between 1.6 and 3.5), manufacturing the BCMA CAR-expressing cell therapy using cells (e.g., T cells) from the subject, and administering the BCMA CAR-expressing cell therapy to the subject.

34. The method of any one of claims 20-33, wherein the value for the level or activity of CCR7+CD45RO-CD27+CD8+ cells comprises the percentage of CCR7+CD45RO-CD27+CD8+ cells among CD8+ T cells, e.g., as measured by an assay disclosed herein, e.g., flow cytometry.

35. The method of claim 34, comprising:

responsive to the percentage of CCR7+CD45RO-CD27+CD8+ cells among CD8+ T cells being greater than or equal to 15% (e.g., between 15% and 90%, e.g., between 15% and 80%, e.g., between 15% and 70%, e.g., between 15% and 60%, e.g., between 15% and 50%), performing:

manufacturing a BCMA CAR-expressing cell therapy using cells (e.g., T cells) from the subject and administering the BCMA CAR-expressing cell therapy to the subject; or

administering, e.g., initiating administering or continuing administering, a BCMA CAR-expressing cell therapy to the subject.

36. The method of claim 34 or 35, comprising:

responsive to the percentage of CCR7+CD45RO-CD27+CD8+ cells among CD8+ T cells being less than 15% (e.g., between 0.1% and 15%, e.g., between 0.1% and 12%, e.g., between 0.1% and 10%, e.g., between 0.1% and 8%), performing one, two, three, four, five, six, seven, or all of:

administering an altered dosing regimen of a BCMA CAR-expressing cell therapy (e.g., a dosing regimen with a higher dose and/or more frequent administration than a reference dosing regimen) to the subject;

administering a second therapy (e.g., a second therapy that is not a BCMA CAR-expressing cell therapy) to the subject;

administering a BCMA CAR-expressing cell therapy and a second therapy to the subject;

discontinuing administration of a BCMA CAR-expressing cell therapy and optionally administering a second therapy to the subject;

modifying a manufacturing process of a BCMA CAR-expressing cell therapy, e.g., enriching for CD4+ immune effector cells (e.g., CD4+ T cells) relative to CD8+ immune effector cells (CD8+ T cells) prior to introducing a nucleic acid encoding a BCMA CAR, and administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject;

modifying a manufacturing process of a BCMA CAR-expressing cell therapy, e.g., enriching for CD8+ Tscm (e.g., HLADR-CD95+CD27+CD8+ cells, CD45RO-CD27+CD8+ cells, or CCR7+CD45RO-CD27+CD8+ cells) prior to introducing a nucleic acid encoding a BCMA CAR, and administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject;

modifying a manufacturing process of the BCMA CAR-expressing cell therapy, e.g., increasing the proliferation of seeded cells from the subject during the manufacturing of the BCMA CAR-expressing cell therapy, and administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject; or

administering a pretreatment to the subject, wherein the pretreatment increases the ratio of the amount of CD4+ immune effector cells (e.g., CD4+ T cells) to the amount of CD8+ immune effector cells (e.g., CD8+ T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample), in a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or in the subject's peripheral blood and/or bone marrow prior to the administration of the BCMA CAR-expressing cell therapy, e.g., the pretreatment increases the ratio to greater than or equal to 1.6 (e.g., between 1.6 and 5, e.g., between 1.6 and 3.5), manufacturing the BCMA CAR-expressing cell therapy

using cells (e.g., T cells) from the subject, and administering the BCMA CAR-expressing cell therapy to the subject.

37. The method of any one of claims 20-36, wherein the value for the proliferation of seeded cells from the subject during manufacturing of the BCMA CAR-expressing cell therapy comprises the fold expansion of seeded cells from the subject during manufacturing (e.g., total cell counts at the end of manufacturing relative to at the start of manufacturing) of the BCMA CAR-expressing cell therapy, e.g., as measured by an assay disclosed herein, e.g., as measured by cell counting.

38. A method of evaluating or predicting the potency of a BCMA CAR-expressing cell therapy in a subject, wherein the subject has a disease associated with the expression of BCMA and wherein the BCMA CAR-expressing cell therapy is manufactured using cells (e.g., T cells) from the subject, comprising:

acquiring a value for one, two, three, four, five, or all of:

(i) the level or activity of CD4+ immune effector cells (e.g., CD4+ T cells) relative to the level or activity of CD8+ immune effector cells (e.g., CD8+ T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample), in a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or in the subject's peripheral blood and/or bone marrow prior to the administration of the BCMA CAR-expressing cell therapy,

(ii) the level or activity of CD8+ Tscm (stem cell memory T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(iii) the level or activity of HLADR-CD95+CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(iv) the level or activity of CD45RO-CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(v) the level or activity of CCR7+CD45RO-CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of

the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or

(vi) the proliferation of seeded cells from the subject during manufacturing of the BCMA CAR-expressing cell therapy, e.g., as measured by population doublings by day 9 (PDL9), wherein:

(a) an increase in the value of one, two, three, four, five, or all of (i)-(vi), as compared to a reference value, e.g., a non-responder reference value, is indicative or predictive of increased potency of the BCMA CAR-expressing cell therapy in the subject; or

(b) a decrease in the value of one, two, three, four, five, or all of (i)-(vi), as compared to a reference value, e.g., a responder reference value, is indicative or predictive of decreased potency of the BCMA CAR-expressing cell therapy in the subject,

thereby evaluating or predicting the potency of the BCMA CAR-expressing cell therapy.

39. The method of claim 38, wherein the increase in the value of one, two, three, four, five, or all of (i)-(vi), as compared to a reference value, e.g., a non-responder reference value, is indicative or predictive of increased expansion of the BCMA CAR-expressing cell therapy in the subject, e.g., as measured by an assay disclosed herein, e.g., as measured by the copy number of CAR transgenes per µg DNA using qPCR.

40. The method of claim 38 or 39, wherein the decrease in the value of one, two, three, four, five, or all of (i)-(vi), as compared to a reference value, e.g., a responder reference value, is indicative or predictive of decreased expansion of the BCMA CAR-expressing cell therapy in the subject, e.g., as measured by an assay disclosed herein, e.g., as measured by the copy number of CAR transgenes per µg DNA using qPCR.

41. A method of manufacturing a BCMA CAR-expressing cell therapy, wherein the BCMA CAR-expressing cell therapy is manufactured using cells (e.g., T cells) from a subject, comprising:

acquiring a value for one, two, three, four, five, or all of:

(i) the level or activity of CD4+ immune effector cells (e.g., CD4+ T cells) relative to the level or activity of CD8+ immune effector cells (e.g., CD8+ T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample), in a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or in the subject's peripheral blood and/or bone marrow prior to the administration of the BCMA CAR-expressing cell therapy,

(ii) the level or activity of CD8+ Tscm (stem cell memory T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(iii) the level or activity of HLADR-CD95+CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(iv) the level or activity of CD45RO-CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(v) the level or activity of CCR7+CD45RO-CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or

(vi) the proliferation of seeded cells from the subject during manufacturing of the BCMA CAR-expressing cell therapy, e.g., as measured by population doublings by day 9 (PDL9), wherein:

responsive to an increase in the value of one, two, three, four, five, or all of (i)-(vi), as compared to a reference value, e.g., a non-responder reference value, manufacturing the BCMA CAR-expressing cell therapy using cells from the subject.

42. A method of manufacturing a BCMA CAR-expressing cell therapy, wherein the BCMA CAR-expressing cell therapy is manufactured using cells (e.g., T cells) from a subject, comprising:

acquiring a value for one, two, three, four, five, or all of:

(i) the level or activity of CD4+ immune effector cells (e.g., CD4+ T cells) relative to the level or activity of CD8+ immune effector cells (e.g., CD8+ T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample), in a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or in the subject's peripheral blood and/or bone marrow prior to the administration of the BCMA CAR-expressing cell therapy,

(ii) the level or activity of CD8+ Tscm (stem cell memory T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the

start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(iii) the level or activity of HLADR-CD95+CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(iv) the level or activity of CD45RO-CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(v) the level or activity of CCR7+CD45RO-CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or

(vi) the proliferation of seeded cells from the subject during manufacturing of the BCMA CAR-expressing cell therapy, e.g., as measured by population doublings by day 9 (PDL9), wherein:

responsive to a decrease in the value of one, two, three, four, five, or all of (i)-(vi), as compared to a reference value, e.g., a responder reference value, performing one, two, three, or all of:

modifying a manufacturing process of the BCMA CAR-expressing cell therapy, e.g., enriching for CD4+ immune effector cells (e.g., CD4+ T cells) relative to CD8+ immune effector cells (CD8+ T cells) prior to introducing a nucleic acid encoding a BCMA CAR;

modifying a manufacturing process of the BCMA CAR-expressing cell therapy, e.g., enriching for CD8+ Tscm (e.g., HLADR-CD95+CD27+CD8+ cells, CD45RO-CD27+CD8+ cells, or CCR7+CD45RO-CD27+CD8+ cells) prior to introducing a nucleic acid encoding a BCMA CAR;

modifying a manufacturing process of the BCMA CAR-expressing cell therapy, e.g., increasing the proliferation of seeded cells from the subject during the manufacturing of the BCMA CAR-expressing cell therapy; or

administering a pretreatment to the subject, wherein the pretreatment increases the ratio of the amount of CD4+ immune effector cells (e.g., CD4+ T cells) to the amount of CD8+ immune effector cells (e.g., CD8+ T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample), in a seed culture at the start of the manufacturing of the BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or in the subject's peripheral blood and/or bone marrow prior to the administration of the BCMA CAR-expressing cell therapy, e.g., the pretreatment increases the ratio to greater than or equal to 1.6 (e.g.,

between 1.6 and 5, e.g., between 1.6 and 3.5), and manufacturing the BCMA CAR-expressing cell therapy using cells (e.g., T cells) from the subject.

43. The method of any one of claims 38-42, wherein the value for the level or activity of CD4+ immune effector cells (e.g., CD4+ T cells) relative to the level or activity of CD8+ immune effector cells (e.g., CD8+ T cells) comprises a ratio of the amount of CD4+ immune effector cells (e.g., CD4+ T cells) to the amount of CD8+ immune effector cells (e.g., CD8+ T cells), e.g., as measured by an assay disclosed herein, e.g., flow cytometry.

44. The method of any one of claims 38-43, wherein the value for the level or activity of CD8+ Tscm (stem cell memory T cells) comprises the percentage of CD8+ Tscm (stem cell memory T cells) among CD8+ T cells, e.g., as measured by an assay disclosed herein, e.g., flow cytometry.

45. The method of any one of claims 38-44, wherein the value for the level or activity of HLADR-CD95+CD27+CD8+ cells comprises the percentage of HLADR-CD95+CD27+CD8+ cells among CD8+ T cells, e.g., as measured by an assay disclosed herein, e.g., flow cytometry.

46. The method of any one of claims 38-45, the value for the level or activity of CD45RO-CD27+CD8+ cells comprises the percentage of CD45RO-CD27+CD8+ cells among CD8+ T cells, e.g., as measured by an assay disclosed herein, e.g., flow cytometry.

47. The method of any one of claims 38-46, wherein the value for the level or activity of CCR7+CD45RO-CD27+CD8+ cells comprises the percentage of CCR7+CD45RO-CD27+CD8+ cells among CD8+ T cells, e.g., as measured by an assay disclosed herein, e.g., flow cytometry.

48. The method of any one of claims 38-47, the value for the proliferation of seeded cells from the subject during manufacturing of the BCMA CAR-expressing cell therapy comprises the fold expansion of seeded cells from the subject during manufacturing (e.g., total cell counts at the end of manufacturing relative to at the start of manufacturing) of the BCMA CAR-expressing cell therapy, e.g., as measured by an assay disclosed herein, e.g., as measured by cell counting.

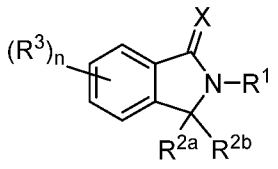
49. The method of any one of claims 1-48, comprising administering the BCMA CAR-expressing cell therapy to the subject in combination with one, two, or all of:

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

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

(3) an agent that treats the disease associated with the expression of BCMA.

50. The method of any one of claims 1-49, comprising administering the BCMA CAR-expressing cell therapy to the subject in combination with a compound of Formula (I) (COF1), wherein the COF1 is:



(I)

or a pharmaceutically acceptable salt, ester, hydrate, solvate, or tautomer thereof, wherein:

X is O or S;

R^1 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted by one or more R^4;

each of R^{2a} and R^{2b} is independently hydrogen or C_1-C_6 alkyl; or R^{2a} and R^{2b} together with the carbon atom to which they are attached form a carbonyl group or a thiocarbonyl group;

each of R^3 is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, halo, cyano, $-C(O)R^A$, $-C(O)OR^B$, $-OR^B$, $-N(R^C)(R^D)$, $-C(O)N(R^C)(R^D)$, $-N(R^C)C(O)R^A$, $-S(O)_xR^E$, $-S(O)_xN(R^C)(R^D)$, or $-N(R^C)S(O)_xR^E$, wherein each alkyl, alkenyl, alkynyl, and heteroalkyl is independently and optionally substituted with one or more R^6;

each R^4 is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, halo, cyano, oxo, $-C(O)R^A$, $-C(O)OR^B$, $-OR^B$, $-N(R^C)(R^D)$, $-C(O)N(R^C)(R^D)$, $-N(R^C)C(O)R^A$, $-S(O)_xR^E$, $-S(O)_xN(R^C)(R^D)$, $-N(R^C)S(O)_xR^E$, carbocyclyl, heterocyclyl, aryl, or heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently and optionally substituted with one or more R^7;

each of R^A, R^B, R^C, R^D, and R^E is independently hydrogen or C_1-C_6 alkyl;

each R^6 is independently C_1-C_6 alkyl, oxo, cyano, $-OR^B$, $-N(R^C)(R^D)$, $-C(O)N(R^C)(R^D)$, $-N(R^C)C(O)R^A$, aryl, or heteroaryl, wherein each aryl and heteroaryl is independently and optionally substituted with one or more R^8;

each R^7 is independently halo, oxo, cyano, $-OR^B$, $-N(R^C)(R^D)$, $-C(O)N(R^C)(R^D)$, or $-N(R^C)C(O)R^A$;

each R^8 is independently C_1-C_6 alkyl, cyano, -OR^B, -$N(R^C)(R^D)$, -$C(O)N(R^C)(R^D)$, or -$N(R^C)C(O)R^A$;

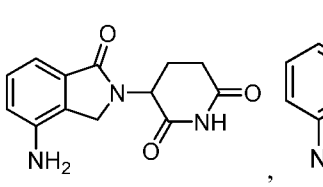
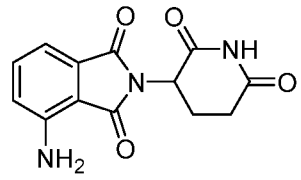
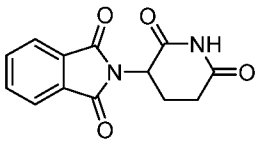
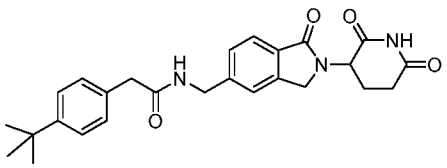
n is 0, 1, 2, 3 or 4; and

x is 0, 1, or 2, optionally wherein:

(1) the COF1 is an immunomodulatory imide drug (IMiD), or a pharmaceutically acceptable salt thereof;

(2) the COF1 is selected from the group consisting of lenalidomide, pomalidomide, thalidomide, and 2-(4-(tert-butyl)phenyl)-N-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)methyl)acetamide, or a pharmaceutically acceptable salt thereof;

(3) the COF1 is selected from the group consisting of:


, 
, 
, and 
, or a pharmaceutically acceptable salt thereof; or

(4) the COF1 is lenalidomide, or a pharmaceutically acceptable salt thereof.

51. The method of any one of claims 1-50, comprising administering the BCMA CAR-expressing cell therapy to the subject in combination with a kinase inhibitor, e.g., a BTK inhibitor, e.g., ibrutinib.

52. The method of any one of claims 1-51, comprising administering the BCMA CAR-expressing cell therapy to the subject in combination with a second CAR-expressing cell therapy, optionally wherein the second CAR-expressing cell therapy is:

(1) a CD19 CAR-expressing cell therapy, e.g., a CD19 CAR-expressing cell therapy disclosed herein, e.g., CTL119 or CTL019, optionally wherein the CD19 CAR-expressing cell therapy is administered after the administration of the BCMA CAR-expressing cell therapy, e.g., after CD19 expression is increased in the subject following the administration of the BCMA CAR-expressing cell therapy;

(2) a CD20 CAR-expressing cell therapy, e.g., a CD20 CAR-expressing cell therapy disclosed herein, optionally wherein the CD20 CAR-expressing cell therapy is administered after the

administration of the BCMA CAR-expressing cell therapy, e.g., after CD20 expression is increased in the subject following the administration of the BCMA CAR-expressing cell therapy;

(3) a CD22 CAR-expressing cell therapy, e.g., a CD22 CAR-expressing cell therapy disclosed herein, optionally wherein the CD22 CAR-expressing cell therapy is administered after the administration of the BCMA CAR-expressing cell therapy, e.g., after CD22 expression is increased in the subject following the administration of the BCMA CAR-expressing cell therapy;

(4) a CAR-expressing cell therapy comprising a cell expressing a first CAR and a second CAR, wherein the first CAR is a BCMA CAR (e.g., a BCMA CAR disclosed herein), optionally wherein the second CAR is selected from the group consisting of a CD19 CAR (e.g., a CD19 CAR disclosed herein), a CD20 CAR (e.g., a CD20 CAR disclosed herein), and a CD22 CAR (e.g., a CD22 CAR disclosed herein); or

(5) a CAR-expressing cell therapy comprising a cell expressing a multispecific CAR, e.g., a bispecific CAR, that binds to a first antigen and a second antigen, wherein the first antigen is BCMA, optionally wherein the second antigen is selected from the group consisting of CD19, CD20, and CD22.

53. The method of any one of claims 1-52, comprising administering the BCMA CAR-expressing cell therapy to the subject in combination with a CD19 inhibitor, e.g., a CD19 inhibitor disclosed herein, optionally wherein the CD19 inhibitor is administered after the administration of the BCMA CAR-expressing cell therapy, e.g., after CD19 expression is increased in the subject following the administration of the BCMA CAR-expressing cell therapy.

54. The method of any one of claims 1-53, comprising administering the BCMA CAR-expressing cell therapy to the subject in combination with a CD20 inhibitor, e.g., a CD20 inhibitor disclosed herein, optionally wherein the CD20 inhibitor is a multispecific antibody molecule, e.g., a bispecific antibody molecule, that binds to CD20 and CD3, e.g., THG338, optionally wherein the CD20 inhibitor is administered after the administration of the BCMA CAR-expressing cell therapy, e.g., after CD20 expression is increased in the subject following the administration of the BCMA CAR-expressing cell therapy.

55. The method of any one of claims 1-54, comprising administering the BCMA CAR-expressing cell therapy to the subject in combination with a CD22 inhibitor, e.g., a CD22 inhibitor disclosed herein, optionally wherein the CD22 inhibitor is administered after the administration of the BCMA CAR-expressing cell therapy, e.g., after CD22 expression is increased in the subject following the administration of the BCMA CAR-expressing cell therapy.

56. The method of any one of claims 1-55, comprising administering the BCMA CAR-expressing cell therapy to the subject in combination with a molecule that binds to Fc receptor like 2 (FCRL2) or Fc receptor like 5 (FCRL5), optionally wherein the molecule is:

(1) a CAR-expressing cell therapy comprising a cell expressing a CAR that binds to FCRL2 or FCRL5; or

(2) a multispecific antibody molecule, e.g., a bispecific antibody molecule, that binds to a first antigen and a second antigen, wherein the first antigen is FCRL2 or FCRL5, optionally wherein the second antigen is CD3.

57. The method of any one of claims 1-56, comprising administering the BCMA CAR-expressing cell therapy to the subject in combination with an interleukin-15 (IL-15) polypeptide, an interleukin-15 receptor alpha (IL-15Ra) polypeptide, or a combination of both an IL-15 polypeptide and an IL-15Ra polypeptide, e.g., hetIL-15.

58. The method of any one of claims 1-57, comprising administering the BCMA CAR-expressing cell therapy to the subject in combination with an inhibitor of TGF beta.

59. The method of any one of claims 1-58, comprising administering the BCMA CAR-expressing cell therapy to the subject in combination with an $EGFR^{mut}$-tyrosine kinase inhibitor (TKI), e.g., EGF816.

60. The method of any one of claims 1-59, comprising administering the BCMA CAR-expressing cell therapy to the subject in combination with an adenosine A2AR antagonist, optionally wherein:

(1) the adenosine A2AR antagonist is selected from the group consisting of PBF509, CPI444, AZD4635, Vipadenant, GBV-2034, and AB928; or

(2) the adenosine A2AR antagonist is selected from the group consisting of 5-bromo-2,6-di-(1H-pyrazol-1-yl)pyrimidine-4-amine; (S)-7-(5-methylfuran-2-yl)-3-((6-(((tetrahydrofuran-3-yl)oxy)methyl)pyridin-2-yl)methyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-amine; (R)-7-(5-methylfuran-2-yl)-3-((6-(((tetrahydrofuran-3-yl)oxy)methyl)pyridin-2-yl)methyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-amine, or racemate thereof; 7-(5-methylfuran-2-yl)-3-((6-(((tetrahydrofuran-3-yl)oxy)methyl)pyridin-2-yl)methyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-amine; and 6-(2-chloro-6-methylpyridin-4-yl)-5-(4-fluorophenyl)-1,2,4-triazin-3-amine.

61. The method of any one of claims 1-60, comprising administering the BCMA CAR-expressing cell therapy to the subject in combination with an anti-CD73 antibody molecule, e.g., an anti-CD73 antibody molecule disclosed herein.

62. The method of any one of claims 1-61, comprising administering the BCMA CAR-expressing cell therapy to the subject in combination with a check point inhibitor, optionally wherein the check point inhibitor is:

(1) a PD-1 inhibitor, optionally wherein the PD-1 inhibitor is selected from the group consisting of PDR001, Nivolumab, Pembrolizumab, Pidilizumab, MEDI0680, REGN2810, TSR-042, PF-06801591, and AMP-224, optionally wherein the PD-1 inhibitor increases expansion of BCMA CAR-expressing cells in the subject;

(2) a PD-L1 inhibitor, optionally wherein the PD-L1 inhibitor is selected from the group consisting of FAZ053, Atezolizumab, Avelumab, Durvalumab, and BMS-936559, optionally wherein the PD-L1 inhibitor increases expansion of BCMA CAR-expressing cells in the subject;

(3) a LAG-3 inhibitor, optionally wherein the LAG-3 inhibitor is selected from the group consisting of LAG525, BMS-986016, TSR-033, MK-4280 and REGN3767; or

(4) a TIM-3 inhibitor, optionally wherein the TIM-3 inhibitor is selected from the group consisting of MGB453, TSR-022, and LY3321367.

63. The method of any one of claims 1-62, comprising administering the BCMA CAR-expressing cell therapy to the subject in combination with an antibody molecule that binds to CD32B.

64. The method of any one of claims 1-63, comprising administering the BCMA CAR-expressing cell therapy to the subject in combination with an antibody molecule that binds to IL-17, e.g., an antagonistic antibody molecule that binds to IL-17, e.g., CJM112.

65. The method of any one of claims 1-64, comprising administering the BCMA CAR-expressing cell therapy to the subject in combination with an antibody molecule that binds to IL-1 beta.

66. The method of any one of claims 1-65, comprising administering the BCMA CAR-expressing cell therapy to the subject in combination with an inhibitor of indoleamine 2,3-dioxygenase (IDO) and/or tryptophan 2,3-dioxygenase (TDO), e.g., an IDO1 inhibitor, optionally wherein the inhibitor of IDO and/or TDO is chosen from:

(1) INCB24360, indoximod, NLG919, epacadostat, NLG919, or F001287; or

(2) (4E)-4-[(3-chloro-4-fluoroanilino)-nitrosomethylidene]-1,2,5-oxadiazol-3-amine, 1-methyl-D-tryptophan, α-cyclohexyl-5H-Imidazo[5,1-a]isoindole-5-ethanol, or the D isomer of 1-methyl-tryptophan.

67. A method of treating a subject having a disease associated with the expression of BCMA, comprising administering a BCMA CAR-expressing cell therapy and a second therapy to the subject, wherein the second therapy is:

(1) a CD19 CAR-expressing cell therapy, e.g., a CD19 CAR-expressing cell therapy disclosed herein, e.g., CTL119 or CTL019, optionally wherein the CD19 CAR-expressing cell therapy is administered after the administration of the BCMA CAR-expressing cell therapy, e.g., after CD19 expression is increased in the subject following the administration of the BCMA CAR-expressing cell therapy;

(2) a CD20 CAR-expressing cell therapy, e.g., a CD20 CAR-expressing cell therapy disclosed herein, optionally wherein the CD20 CAR-expressing cell therapy is administered after the administration of the BCMA CAR-expressing cell therapy, e.g., after CD20 expression is increased in the subject following the administration of the BCMA CAR-expressing cell therapy;

(3) a CD22 CAR-expressing cell therapy, e.g., a CD22 CAR-expressing cell therapy disclosed herein, optionally wherein the CD22 CAR-expressing cell therapy is administered after the administration of the BCMA CAR-expressing cell therapy, e.g., after CD22 expression is increased in the subject following the administration of the BCMA CAR-expressing cell therapy;

(4) a CAR-expressing cell therapy comprising a cell expressing a first CAR and a second CAR, wherein the first CAR is a BCMA CAR (e.g., a BCMA CAR disclosed herein), optionally wherein the second CAR is selected from the group consisting of a CD19 CAR (e.g., a CD19 CAR disclosed herein), a CD20 CAR (e.g., a CD20 CAR disclosed herein), and a CD22 CAR (e.g., a CD22 CAR disclosed herein); or

(5) a CAR-expressing cell therapy comprising a cell expressing a multispecific CAR, e.g., a bispecific CAR that binds to a first antigen and a second antigen, wherein the first antigen is BCMA, optionally wherein the second antigen is selected from the group consisting of CD19, CD20, and CD22.

68. A method of treating a subject having a disease associated with the expression of BCMA, comprising administering a BCMA CAR-expressing cell therapy and a second therapy to the subject, wherein the second therapy is:

(1) a CD19 inhibitor, e.g., a CD19 inhibitor disclosed herein, optionally wherein the CD19 inhibitor is administered after the administration of the BCMA CAR-expressing cell therapy, e.g., after

CD19 expression is increased in the subject following the administration of the BCMA CAR-expressing cell therapy;

(2) a CD20 inhibitor, e.g., a CD20 inhibitor disclosed herein, optionally wherein the CD20 inhibitor is a multispecific antibody molecule, e.g., a bispecific antibody molecule that binds to CD20 and CD3, e.g., THG338, optionally wherein the CD20 inhibitor is administered after the administration of the BCMA CAR-expressing cell therapy, e.g., after CD20 expression is increased in the subject following the administration of the BCMA CAR-expressing cell therapy; or

(3) a CD22 inhibitor, e.g., a CD22 inhibitor disclosed herein, optionally wherein the CD22 inhibitor is administered after the administration of the BCMA CAR-expressing cell therapy, e.g., after CD22 expression is increased in the subject following the administration of the BCMA CAR-expressing cell therapy.

69. A method of treating a subject having a disease associated with the expression of BCMA, comprising administering a BCMA CAR-expressing cell therapy and a second therapy to the subject, wherein the second therapy is a molecule that binds to Fc receptor like 2 (FCRL2) or Fc receptor like 5 (FCRL5), optionally wherein the molecule is:

(1) a CAR-expressing cell therapy comprising a cell expressing a CAR that binds to FCRL2 or FCRL5; or

(2) a multispecific antibody molecule, e.g., a bispecific antibody molecule, that binds to a first antigen and a second antigen, wherein the first antigen is FCRL2 or FCRL5, optionally wherein the second antigen is CD3.

70. A method of treating a subject having a disease associated with the expression of BCMA, comprising administering a BCMA CAR-expressing cell therapy and a second therapy to the subject, wherein the second therapy is an inhibitor of TGF beta.

71. A method of treating a subject having a disease associated with the expression of BCMA, comprising administering a BCMA CAR-expressing cell therapy and a second therapy to the subject, wherein the second therapy is an $EGFR^{mut}$-tyrosine kinase inhibitor (TKI), e.g., EGF816.

72. A method of treating a subject having a disease associated with the expression of BCMA, comprising administering a BCMA CAR-expressing cell therapy and a second therapy to the subject, wherein the second therapy is an adenosine A2AR antagonist, optionally wherein:

(1) the adenosine A2AR antagonist is selected from the group consisting of PBF509, CPI444, AZD4635, Vipadenant, GBV-2034, and AB928; or

(2) the adenosine A2AR antagonist is selected from the group consisting of 5-bromo-2,6-di-(1H-pyrazol-1-yl)pyrimidine-4-amine; (S)-7-(5-methylfuran-2-yl)-3-((6-(((tetrahydrofuran-3-yl)oxy)methyl)pyridin-2-yl)methyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-amine; (R)-7-(5-methylfuran-2-yl)-3-((6-(((tetrahydrofuran-3-yl)oxy)methyl)pyridin-2-yl)methyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-amine, or racemate thereof; 7-(5-methylfuran-2-yl)-3-((6-(((tetrahydrofuran-3-yl)oxy)methyl)pyridin-2-yl)methyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-amine; and 6-(2-chloro-6-methylpyridin-4-yl)-5-(4-fluorophenyl)-1,2,4-triazin-3-amine.

73. A method of treating a subject having a disease associated with the expression of BCMA, comprising administering a BCMA CAR-expressing cell therapy and a second therapy to the subject, wherein the second therapy is an anti-CD73 antibody molecule, e.g., an anti-CD73 antibody molecule disclosed herein.

74. A method of treating a subject having a disease associated with the expression of BCMA, comprising administering a BCMA CAR-expressing cell therapy and a second therapy to the subject, wherein the second therapy is a check point inhibitor, optionally wherein the check point inhibitor is:

(1) a PD-1 inhibitor, optionally wherein the PD-1 inhibitor is selected from the group consisting of PDR001, Nivolumab, Pembrolizumab, Pidilizumab, MEDI0680, REGN2810, TSR-042, PF-06801591, and AMP-224, optionally wherein the PD-1 inhibitor is administered after the administration of the BCMA CAR-expressing cell therapy, e.g., after the expression of PD-1 or PD-L1 is increased in the subject following the administration of the BCMA CAR-expressing cell therapy, optionally wherein the PD-1 inhibitor increases expansion of BCMA CAR-expressing cells in the subject;

(2) a PD-L1 inhibitor, optionally wherein the PD-L1 inhibitor is selected from the group consisting of FAZ053, Atezolizumab, Avelumab, Durvalumab, and BMS-936559, optionally wherein the PD-L1 inhibitor is administered after the administration of the BCMA CAR-expressing cell therapy, e.g., after the expression of PD-1 or PD-L1 is increased in the subject following the administration of the BCMA CAR-expressing cell therapy, optionally wherein the PD-L1 inhibitor increases expansion of BCMA CAR-expressing cells in the subject;

(3) a LAG-3 inhibitor, optionally wherein the LAG-3 inhibitor is selected from the group consisting of LAG525, BMS-986016, TSR-033, MK-4280 and REGN3767, optionally wherein the LAG-3 inhibitor is administered after the administration of the BCMA CAR-expressing cell therapy,

e.g., after the expression of LAG-3 is increased in the subject following the administration of the BCMA CAR-expressing cell therapy; or

(4) a TIM-3 inhibitor, optionally wherein the TIM-3 inhibitor is selected from the group consisting of MGB453, TSR-022, and LY3321367, optionally wherein the TIM-3 inhibitor is administered after the administration of the BCMA CAR-expressing cell therapy, e.g., after the expression of TIM-3 is increased in the subject following the administration of the BCMA CAR-expressing cell therapy.

75. A method of treating a subject having a disease associated with the expression of BCMA, comprising administering a BCMA CAR-expressing cell therapy and a second therapy to the subject, wherein the second therapy is an antibody molecule that binds to CD32B.

76. A method of treating a subject having a disease associated with the expression of BCMA, comprising administering a BCMA CAR-expressing cell therapy and a second therapy to the subject, wherein the second therapy is an antibody molecule that binds to IL-17, e.g., an antagonistic antibody molecule that binds to IL-17, e.g., CJM112.

77. A method of treating a subject having a disease associated with the expression of BCMA, comprising administering a BCMA CAR-expressing cell therapy and a second therapy to the subject, wherein the second therapy is an antibody molecule that binds to IL-1 beta.

78. A method of treating a subject having a disease associated with the expression of BCMA, comprising administering a BCMA CAR-expressing cell therapy and a second therapy to the subject, wherein the second therapy is an inhibitor of indoleamine 2,3-dioxygenase (IDO) and/or tryptophan 2,3-dioxygenase (TDO), e.g., an IDO1 inhibitor, optionally wherein the inhibitor of IDO and/or TDO is chosen from:

(1) INCB24360, indoximod, NLG919, epacadostat, NLG919, or F001287; or

(2) (4E)-4-[(3-chloro-4-fluoroanilino)-nitrosomethylidene]-1,2,5-oxadiazol-3-amine, 1-methyl-D-tryptophan, α-cyclohexyl-5H-Imidazo[5,1-a]isoindole-5-ethanol, or the D isomer of 1-methyl-tryptophan, optionally wherein:

the inhibitor of IDO and/or TDO is administered after the administration of the BCMA CAR-expressing cell therapy, e.g., after IDO and/or TDO expression is increased in the subject following the administration of the BCMA CAR-expressing cell therapy.

79. The method of any one of claims 67-78, wherein the second therapy is administered prior to, concurrently with, or subsequent to the administration of the BCMA CAR-expressing cell therapy.

80. A method of treating a subject having a disease associated with the expression of BCMA, wherein the subject has received or is receiving a BCMA CAR-expressing cell therapy, comprising:

responsive to an increase in a value of the level or activity of an antigen in the subject, e.g., in a sample from the subject (e.g., a biopsy sample, e.g., a bone marrow biopsy sample), at at least one time point after the subject began receiving the BCMA CAR-expressing cell therapy, relative to a reference value, wherein the reference value is:

(i) the level or activity of the antigen in the subject, e.g., in a sample from the subject (e.g., a biopsy sample, e.g., a bone marrow biopsy sample), prior to the at least one time point (e.g., the level or activity of the antigen in the subject before the subject began receiving the BCMA CAR-expressing cell therapy, or the level or activity of the antigen in the subject after the subject began receiving the BCMA CAR-expressing cell therapy but prior to the at least one time point);

(ii) the level or activity of the antigen in a different subject having the disease associated with the expression of BCMA; or

(iii) an average level or activity of the antigen in a population of subjects having the disease associated with the expression of BCMA,

administering an inhibitor of the antigen to the subject, wherein:

(1) the antigen is CD19 and the inhibitor of the antigen is a CD19 inhibitor, optionally wherein the CD19 inhibitor is:

(a) a CD19 CAR-expressing cell therapy, e.g., a CD19 CAR-expressing cell therapy disclosed herein, e.g., CTL119 or CTL019;

(b) a CAR-expressing cell therapy comprising a cell expressing a first CAR and a second CAR, wherein the first CAR is a BCMA CAR (e.g., a BCMA CAR disclosed herein) and the second CAR is a CD19 CAR (e.g., a CD19 CAR disclosed herein); or

(c) a CAR-expressing cell therapy comprising a cell expressing a multispecific CAR, e.g., a bispecific CAR, that binds to BCMA and CD19,

(2) the antigen is CD20 and the inhibitor of the antigen is a CD20 inhibitor, optionally wherein the CD20 inhibitor is:

(d) a CD20 CAR-expressing cell therapy, e.g., a CD20 CAR-expressing cell therapy disclosed herein;

(e) a CAR-expressing cell therapy comprising a cell expressing a first CAR and a second CAR, wherein the first CAR is a BCMA CAR (e.g., a BCMA CAR disclosed herein) and the second CAR is a CD20 CAR (e.g., a CD20 CAR disclosed herein);

(f) a CAR-expressing cell therapy comprising a cell expressing a multispecific CAR, e.g., a bispecific CAR, that binds to BCMA and CD20; or

(g) a multispecific antibody molecule, e.g., a bispecific antibody molecule, that binds to CD20 and CD3, e.g., THG338,

(3) the antigen is CD22 and the inhibitor of the antigen is a CD22 inhibitor, optionally wherein the CD22 inhibitor is:

(h) a CD22 CAR-expressing cell therapy, e.g., a CD22 CAR-expressing cell therapy disclosed herein;

(i) a CAR-expressing cell therapy comprising a cell expressing a first CAR and a second CAR, wherein the first CAR is a BCMA CAR (e.g., a BCMA CAR disclosed herein) and the second CAR is a CD22 CAR (e.g., a CD22 CAR disclosed herein); or

(j) a CAR-expressing cell therapy comprising a cell expressing a multispecific CAR, e.g., a bispecific CAR, that binds to BCMA and CD22,

(4) the antigen is PD1 or PD-L1 and the inhibitor of the antigen is an anti-PD1 antibody molecule or an anti-PD-L1 antibody molecule, optionally wherein the inhibitor of the antigen is:

(k) PDR001, Nivolumab, Pembrolizumab, Pidilizumab, MEDI0680, REGN2810, TSR-042, PF-06801591, or AMP-224; or

(l) FAZ053, Atezolizumab, Avelumab, Durvalumab, or BMS-936559,

(5) the antigen is IDO or TDO and the inhibitor of the antigen is an inhibitor of IDO and/or TDO, optionally wherein the inhibitor of IDO and/or TDO is:

(m) INCB24360, indoximod, NLG919, epacadostat, NLG919, or F001287; or

(n) (4E)-4-[(3-chloro-4-fluoroanilino)-nitrosomethylidene]-1,2,5-oxadiazol-3-amine, 1-methyl-D-tryptophan, α-cyclohexyl-5H-Imidazo[5,1-a]isoindole-5-ethanol, or the D isomer of 1-methyl-tryptophan, or

(6) the antigen is TGF-beta and the inhibitor of the antigen is a TGF beta inhibitor.

81. A method of treating a subject having a disease associated with the expression of BCMA, wherein the subject has received or is receiving a BCMA CAR-expressing cell therapy, comprising:

acquiring a value of the level or activity of an antigen in the subject, e.g., in a sample from the subject (e.g., a biopsy sample, e.g., a bone marrow biopsy sample), at at least one time point after the subject began receiving the BCMA CAR-expressing cell therapy,

responsive to an increase in the value relative to a reference value, wherein the reference value is:

(i) the level or activity of the antigen in the subject, e.g., in a sample from the subject (e.g., a biopsy sample, e.g., a bone marrow biopsy sample), prior to the at least one time point (e.g., the level or activity of the antigen in the subject before the subject began receiving the BCMA CAR-expressing cell therapy, or the level or activity of the antigen in the subject after the subject began receiving the BCMA CAR-expressing cell therapy but prior to the at least one time point);

(ii) the level or activity of the antigen in a different subject having the disease associated with the expression of BCMA; or

(iii) an average level or activity of the antigen in a population of subjects having the disease associated with the expression of BCMA,

administering an inhibitor of the antigen to the subject, wherein:

(1) the antigen is CD19 and the inhibitor of the antigen is a CD19 inhibitor, optionally wherein the CD19 inhibitor is:

(a) a CD19 CAR-expressing cell therapy, e.g., a CD19 CAR-expressing cell therapy disclosed herein, e.g., CTL119 or CTL019;

(b) a CAR-expressing cell therapy comprising a cell expressing a first CAR and a second CAR, wherein the first CAR is a BCMA CAR (e.g., a BCMA CAR disclosed herein) and the second CAR is a CD19 CAR (e.g., a CD19 CAR disclosed herein); or

(c) a CAR-expressing cell therapy comprising a cell expressing a multispecific CAR, e.g., a bispecific CAR, that binds to BCMA and CD19,

(2) the antigen is CD20 and the inhibitor of the antigen is a CD20 inhibitor, optionally wherein the CD20 inhibitor is:

(d) a CD20 CAR-expressing cell therapy, e.g., a CD20 CAR-expressing cell therapy disclosed herein;

(e) a CAR-expressing cell therapy comprising a cell expressing a first CAR and a second CAR, wherein the first CAR is a BCMA CAR (e.g., a BCMA CAR disclosed herein) and the second CAR is a CD20 CAR (e.g., a CD20 CAR disclosed herein);

(f) a CAR-expressing cell therapy comprising a cell expressing a multispecific CAR, e.g., a bispecific CAR, that binds to BCMA and CD20; or

(g) a multispecific antibody molecule, e.g., a bispecific antibody molecule, that binds to CD20 and CD3, e.g., THG338,

(3) the antigen is CD22 and the inhibitor of the antigen is a CD22 inhibitor, optionally wherein the CD22 inhibitor is:

(h) a CD22 CAR-expressing cell therapy, e.g., a CD22 CAR-expressing cell therapy disclosed herein;

(i) a CAR-expressing cell therapy comprising a cell expressing a first CAR and a second CAR, wherein the first CAR is a BCMA CAR (e.g., a BCMA CAR disclosed herein) and the second CAR is a CD22 CAR (e.g., a CD22 CAR disclosed herein); or

(j) a CAR-expressing cell therapy comprising a cell expressing a multispecific CAR, e.g., a bispecific CAR, that binds to BCMA and CD22,

(4) the antigen is PD1 or PD-L1 and the inhibitor of the antigen is an anti-PD1 antibody molecule or an anti-PD-L1 antibody molecule, optionally wherein the inhibitor of the antigen is:

(k) PDR001, Nivolumab, Pembrolizumab, Pidilizumab, MEDI0680, REGN2810, TSR-042, PF-06801591, or AMP-224; or

(l) FAZ053, Atezolizumab, Avelumab, Durvalumab, or BMS-936559,

(5) the antigen is IDO or TDO and the inhibitor of the antigen is an inhibitor of IDO and/or TDO, optionally wherein the inhibitor of IDO and/or TDO is:

(m) INCB24360, indoximod, NLG919, epacadostat, NLG919, or F001287; or

(n) (4E)-4-[(3-chloro-4-fluoroanilino)-nitrosomethylidene]-1,2,5-oxadiazol-3-amine, 1-methyl-D-tryptophan, α-cyclohexyl-5H-Imidazo[5,1-a]isoindole-5-ethanol, or the D isomer of 1-methyl-tryptophan, or

(6) the antigen is TGF-beta and the inhibitor of the antigen is a TGF beta inhibitor.

82. A method of treating a subject having a disease associated with the expression of BCMA, comprising:

administering a BCMA CAR-expressing cell therapy to the subject,

responsive to an increase in a value of the level or activity of an antigen in the subject, e.g., in a sample from the subject (e.g., a biopsy sample, e.g., a bone marrow biopsy sample), at at least one time point after the subject began receiving the BCMA CAR-expressing cell therapy, relative to a reference value, wherein the reference value is:

(i) the level or activity of the antigen in the subject, e.g., in a sample from the subject (e.g., a biopsy sample, e.g., a bone marrow biopsy sample), prior to the at least one time point (e.g., the level or activity of the antigen in the subject before the subject began receiving the BCMA CAR-expressing cell therapy, or the level or activity of the antigen in the subject after the subject began receiving the BCMA CAR-expressing cell therapy but prior to the at least one time point);

(ii) the level or activity of the antigen in a different subject having the disease associated with the expression of BCMA; or

(iii) an average level or activity of the antigen in a population of subjects having the disease associated with the expression of BCMA,

administering an inhibitor of the antigen to the subject, wherein:

(1) the antigen is CD19 and the inhibitor of the antigen is a CD19 inhibitor, optionally wherein the CD19 inhibitor is:

(a) a CD19 CAR-expressing cell therapy, e.g., a CD19 CAR-expressing cell therapy disclosed herein, e.g., CTL119 or CTL019;

(b) a CAR-expressing cell therapy comprising a cell expressing a first CAR and a second CAR, wherein the first CAR is a BCMA CAR (e.g., a BCMA CAR disclosed herein) and the second CAR is a CD19 CAR (e.g., a CD19 CAR disclosed herein); or

(c) a CAR-expressing cell therapy comprising a cell expressing a multispecific CAR, e.g., a bispecific CAR, that binds to BCMA and CD19,

(2) the antigen is CD20 and the inhibitor of the antigen is a CD20 inhibitor, optionally wherein the CD20 inhibitor is:

(d) a CD20 CAR-expressing cell therapy, e.g., a CD20 CAR-expressing cell therapy disclosed herein;

(e) a CAR-expressing cell therapy comprising a cell expressing a first CAR and a second CAR, wherein the first CAR is a BCMA CAR (e.g., a BCMA CAR disclosed herein) and the second CAR is a CD20 CAR (e.g., a CD20 CAR disclosed herein);

(f) a CAR-expressing cell therapy comprising a cell expressing a multispecific CAR, e.g., a bispecific CAR, that binds to BCMA and CD20; or

(g) a multispecific antibody molecule, e.g., a bispecific antibody molecule, that binds to CD20 and CD3, e.g., THG338,

(3) the antigen is CD22 and the inhibitor of the antigen is a CD22 inhibitor, optionally wherein the CD22 inhibitor is:

(h) a CD22 CAR-expressing cell therapy, e.g., a CD22 CAR-expressing cell therapy disclosed herein;

(i) a CAR-expressing cell therapy comprising a cell expressing a first CAR and a second CAR, wherein the first CAR is a BCMA CAR (e.g., a BCMA CAR disclosed herein) and the second CAR is a CD22 CAR (e.g., a CD22 CAR disclosed herein); or

(j) a CAR-expressing cell therapy comprising a cell expressing a multispecific CAR, e.g., a bispecific CAR, that binds to BCMA and CD22,

(4) the antigen is PD1 or PD-L1 and the inhibitor of the antigen is an anti-PD1 antibody molecule or an anti-PD-L1 antibody molecule, optionally wherein the inhibitor of the antigen is:

(k) PDR001, Nivolumab, Pembrolizumab, Pidilizumab, MEDI0680, REGN2810, TSR-042, PF-06801591, or AMP-224; or

(l) FAZ053, Atezolizumab, Avelumab, Durvalumab, or BMS-936559,

(5) the antigen is IDO or TDO and the inhibitor of the antigen is an inhibitor of IDO and/or TDO, optionally wherein the inhibitor of IDO and/or TDO is:

(m) INCB24360, indoximod, NLG919, epacadostat, NLG919, or F001287; or

(n) (4E)-4-[(3-chloro-4-fluoroanilino)-nitrosomethylidene]-1,2,5-oxadiazol-3-amine, 1-methyl-D-tryptophan, α-cyclohexyl-5H-Imidazo[5,1-a]isoindole-5-ethanol, or the D isomer of 1-methyl-tryptophan, or

(6) the antigen is TGF-beta and the inhibitor of the antigen is a TGF beta inhibitor.

83. A method of treating a subject having a disease associated with the expression of BCMA, comprising:

administering a BCMA CAR-expressing cell therapy to the subject,

acquiring a value of the level or activity of an antigen in the subject, e.g., in a sample from the subject (e.g., a biopsy sample, e.g., a bone marrow biopsy sample), at at least one time point after the subject began receiving the BCMA CAR-expressing cell therapy,

responsive to an increase in the value relative to a reference value, wherein the reference value is:

(i) the level or activity of the antigen in the subject, e.g., in a sample from the subject (e.g., a biopsy sample, e.g., a bone marrow biopsy sample), prior to the at least one time point (e.g., the level or activity of the antigen in the subject before the subject began receiving the BCMA CAR-expressing cell therapy, or the level or activity of the antigen in the subject after the subject began receiving the BCMA CAR-expressing cell therapy but prior to the at least one time point);

(ii) the level or activity of the antigen in a different subject having the disease associated with the expression of BCMA; or

(iii) an average level or activity of the antigen in a population of subjects having the disease associated with the expression of BCMA,

administering an inhibitor of the antigen to the subject, wherein:

(1) the antigen is CD19 and the inhibitor of the antigen is a CD19 inhibitor, optionally wherein the CD19 inhibitor is:

(a) a CD19 CAR-expressing cell therapy, e.g., a CD19 CAR-expressing cell therapy disclosed herein, e.g., CTL119 or CTL019;

(b) a CAR-expressing cell therapy comprising a cell expressing a first CAR and a second CAR, wherein the first CAR is a BCMA CAR (e.g., a BCMA CAR disclosed herein) and the second CAR is a CD19 CAR (e.g., a CD19 CAR disclosed herein); or

(c) a CAR-expressing cell therapy comprising a cell expressing a multispecific CAR, e.g., a bispecific CAR, that binds to BCMA and CD19,

(2) the antigen is CD20 and the inhibitor of the antigen is a CD20 inhibitor, optionally wherein the CD20 inhibitor is:

(d) a CD20 CAR-expressing cell therapy, e.g., a CD20 CAR-expressing cell therapy disclosed herein;

(e) a CAR-expressing cell therapy comprising a cell expressing a first CAR and a second CAR, wherein the first CAR is a BCMA CAR (e.g., a BCMA CAR disclosed herein) and the second CAR is a CD20 CAR (e.g., a CD20 CAR disclosed herein);

(f) a CAR-expressing cell therapy comprising a cell expressing a multispecific CAR, e.g., a bispecific CAR, that binds to BCMA and CD20; or

(g) a multispecific antibody molecule, e.g., a bispecific antibody molecule, that binds to CD20 and CD3, e.g., THG338,

(3) the antigen is CD22 and the inhibitor of the antigen is a CD22 inhibitor, optionally wherein the CD22 inhibitor is:

(h) a CD22 CAR-expressing cell therapy, e.g., a CD22 CAR-expressing cell therapy disclosed herein;

(i) a CAR-expressing cell therapy comprising a cell expressing a first CAR and a second CAR, wherein the first CAR is a BCMA CAR (e.g., a BCMA CAR disclosed herein) and the second CAR is a CD22 CAR (e.g., a CD22 CAR disclosed herein); or

(j) a CAR-expressing cell therapy comprising a cell expressing a multispecific CAR, e.g., a bispecific CAR, that binds to BCMA and CD22,

(4) the antigen is PD1 or PD-L1 and the inhibitor of the antigen is an anti-PD1 antibody molecule or an anti-PD-L1 antibody molecule, optionally wherein the inhibitor of the antigen is:

(k) PDR001, Nivolumab, Pembrolizumab, Pidilizumab, MEDI0680, REGN2810, TSR-042, PF-06801591, or AMP-224; or

(l) FAZ053, Atezolizumab, Avelumab, Durvalumab, or BMS-936559,

(5) the antigen is IDO or TDO and the inhibitor of the antigen is an inhibitor of IDO and/or TDO, optionally wherein the inhibitor of IDO and/or TDO is:

(m) INCB24360, indoximod, NLG919, epacadostat, NLG919, or F001287; or

(n) (4E)-4-[(3-chloro-4-fluoroanilino)-nitrosomethylidene]-1,2,5-oxadiazol-3-amine, 1-methyl-D-tryptophan, α-cyclohexyl-5H-Imidazo[5,1-a]isoindole-5-ethanol, or the D isomer of 1-methyl-tryptophan, or

(6) the antigen is TGF-beta and the inhibitor of the antigen is a TGF beta inhibitor.

84. The method of any one of claims 80-83, wherein the value of the level or activity of the antigen comprises the expression level of the antigen in the subject, e.g., in a sample from the subject (e.g., a biopsy sample, e.g., a bone marrow biopsy sample), as measured by an assay described herein, e.g., immunohistochemistry.

85. The method of any one of claims 80-84, wherein the at least one time point is 5, 10, 15, 20, 25, 28, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, or 90 days after the subject began receiving the BCMA CAR-expressing cell therapy.

86. The method of any one of claims 80-85, wherein the subject experiences a decrease in BCMA expression after the subject began receiving the BCMA CAR-expressing cell therapy.

87. The method of any one of claims 1-86, wherein the BCMA CAR-expressing cell therapy comprises a cell expressing a BCAM CAR, wherein:

(i) the BCMA CAR comprises one or more of (e.g., all three of) heavy chain complementary determining region 1 (HCDR1), HCDR2, and HCDR3 listed in Table 3 or 5 and/or one or more of (e.g., all three of) light chain complementary determining region 1 (LCDR1), LCDR2, and LCDR3 listed in Table 4 or 5, or a sequence with 95-99% identify thereof;

(ii) the BCMA CAR comprises a heavy chain variable region (VH) listed in Table 2 or 5 and/or a light chain variable region (VL) listed in Table 2 or 5, or a sequence with 95-99% identify thereof;

(iii) the BCMA CAR comprises a BCMA scFv domain amino acid sequence listed in Table 2 or 5 (e.g., SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 135, SEQ ID NO: 136, SEQ ID NO: 137, SEQ ID NO: 138, SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, SEQ ID NO: 143, SEQ ID NO: 144, SEQ ID NO: 145, SEQ ID NO: 146, SEQ ID NO: 147, SEQ ID NO: 148, and SEQ ID NO: 149), or a sequence with 95-99% identify thereof;

(iv) the BCMA CAR comprises a full-length BCMA CAR amino acid sequence listed in Table 2 or 5 (e.g., residues 22-483 of SEQ ID NO: 109, residues 22-490 of SEQ ID NO: 99, residues 22-488 of SEQ ID NO: 100, residues 22-487 of SEQ ID NO: 101, residues 22-493 of SEQ ID NO: 102, residues 22-490 of SEQ ID NO: 103, residues 22-491 of SEQ ID NO: 104, residues 22-482 of SEQ ID NO: 105, residues 22-483 of SEQ ID NO: 106, residues 22-485 of SEQ ID NO: 107, residues 22-483 of SEQ ID NO: 108, residues 22-490 of SEQ ID NO: 110, residues 22-483 of SEQ ID NO: 111, residues 22-484 of SEQ ID NO: 112, residues 22-485 of SEQ ID NO: 113, residues 22-487 of SEQ ID NO: 213, residues 23-489 of SEQ ID NO: 214, residues 22-490 of SEQ ID NO: 215, residues 22-484 of SEQ ID NO: 216, residues 22-485 of SEQ ID NO: 217, residues 22-489 of SEQ ID NO: 218, residues 22-497 of SEQ ID NO: 219, residues 22-492 of SEQ ID NO: 220, residues 22-490 of SEQ ID NO: 221, residues 22-485 of SEQ ID NO: 222, residues 22-492 of SEQ ID NO: 223, residues 22-492 of SEQ ID NO: 224, residues 22-483 of SEQ ID NO: 225, residues 22-490 of SEQ ID NO: 226, residues 22-485 of SEQ ID NO: 227, residues 22-486 of SEQ ID NO: 228, residues 22-492 of SEQ ID NO: 229, residues 22-488 of SEQ ID NO: 230, residues 22-488 of SEQ ID NO: 231, residues 22-495 of SEQ ID NO: 232, residues 22-490 of SEQ ID NO: 233), or a sequence with 95-99% identify thereof; or

(v) the BCMA CAR is encoded by a nucleic acid sequence listed in Table 2 or 5 (e.g., SEQ ID NO: 54, SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 150, SEQ ID NO: 151, SEQ ID NO: 152, SEQ ID NO: 153, SEQ ID NO: 154, SEQ ID NO: 155, SEQ ID NO: 156, SEQ ID NO: 157, SEQ ID NO: 158, SEQ ID NO: 159, SEQ ID NO: 160, SEQ ID NO: 161, SEQ ID NO: 162, SEQ ID NO: 163, SEQ ID NO: 164, SEQ ID NO: 165, SEQ ID NO: 166, SEQ ID NO: 167, SEQ ID NO: 168, SEQ ID NO: 169, SEQ ID NO: 170), or a sequence with 95-99% identify thereof.

88. The method of any one of claims 1-87, wherein the disease associated with the expression of BCMA is cancer, optionally wherein the cancer is a hematological cancer.

89. The method of any one of claims 1-88, wherein the disease associated with the expression of BCMA is an acute leukemia chosen from one or more of B-cell acute lymphoid leukemia ("BALL"), T-cell acute lymphoid leukemia ("TALL"), acute lymphoid leukemia (ALL); chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL); B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B cell lymphoma, follicular lymphoma, hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant

lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, Marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia; a prostate cancer (e.g., castrate-resistant or therapy-resistant prostate cancer, or metastatic prostate cancer), pancreatic cancer, lung cancer; or a plasma cell proliferative disorder (e.g., asymptomatic myeloma (smoldering multiple myeloma or indolent myeloma), monoclonal gammapathy of undetermined significance (MGUS), Waldenstrom's macroglobulinemia, plasmacytomas (e.g., plasma cell dyscrasia, solitary myeloma, solitary plasmacytoma, extramedullary plasmacytoma, and multiple plasmacytoma), systemic amyloid light chain amyloidosis, and POEMS syndrome (also known as Crow-Fukase syndrome, Takatsuki disease, and PEP syndrome)), or a combination thereof.

90. The method of any one of claims 1-89, wherein the disease associated with the expression of BCMA is ALL, CLL, DLBCL, or multiple myeloma.

91. The method of any one of claims 1-90, wherein the subject is a human patient.

92. A BCMA CAR-expressing cell therapy for use in a method of treatment of a subject having a disease associated with the expression of BCMA, the method comprising:

responsive to an increased value for one, two, three, four, five, or all of:

(i) the level or activity of CD4+ immune effector cells (e.g., CD4+ T cells) relative to the level or activity of CD8+ immune effector cells (e.g., CD8+ T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample), in a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or in the subject's peripheral blood and/or bone marrow prior to the administration of the BCMA CAR-expressing cell therapy,

(ii) the level or activity of CD8+ Tscm (stem cell memory T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(iii) the level or activity of HLADR-CD95+CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(iv) the level or activity of CD45RO-CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(v) the level or activity of CCR7+CD45RO-CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or

(vi) the proliferation of seeded cells from the subject during manufacturing of a BCMA CAR-expressing cell therapy,

as compared to a reference value, e.g., a non-responder reference value, performing:

manufacturing a BCMA CAR-expressing cell therapy using cells (e.g., T cells) from the subject and administering the BCMA CAR-expressing cell therapy to the subject; or

administering, e.g., initiating administering or continuing administering, a BCMA CAR-expressing cell therapy to the subject,

thereby treating the subject having the disease associated with the expression of BCMA.

93. A BCMA CAR-expressing cell therapy for use in a method of treatment of a subject having a disease associated with the expression of BCMA, the method comprising:

responsive to a decreased value for one, two, three, four, five, or all of:

(i) the level or activity of CD4+ immune effector cells (e.g., CD4+ T cells) relative to the level or activity of CD8+ immune effector cells (e.g., CD8+ T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample), in a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or in the subject's peripheral blood and/or bone marrow prior to the administration of the BCMA CAR-expressing cell therapy,

(ii) the level or activity of CD8+ Tscm (stem cell memory T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(iii) the level or activity of HLADR-CD95+CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(iv) the level or activity of CD45RO-CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)),

(v) the level or activity of CCR7+CD45RO-CD27+CD8+ cells in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample) or a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or

(vi) the proliferation of seeded cells from the subject during manufacturing of a BCMA CAR-expressing cell therapy,

as compared to a reference value, e.g., a responder reference value, performing one, two, three, four, five, six, seven, or all of:

administering an altered dosing regimen of a BCMA CAR-expressing cell therapy (e.g., a dosing regimen with a higher dose and/or more frequent administration than a reference dosing regimen) to the subject;

administering a second therapy (e.g., a second therapy that is not a BCMA CAR-expressing cell therapy) to the subject;

administering a BCMA CAR-expressing cell therapy and a second therapy to the subject;

discontinuing administration of a BCMA CAR-expressing cell therapy and optionally administering a second therapy to the subject;

modifying a manufacturing process of a BCMA CAR-expressing cell therapy, e.g., enriching for CD4+ immune effector cells (e.g., CD4+ T cells) relative to CD8+ immune effector cells (CD8+ T cells) prior to introducing a nucleic acid encoding a BCMA CAR, and administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject;

modifying a manufacturing process of a BCMA CAR-expressing cell therapy, e.g., enriching for CD8+ Tscm (e.g., HLADR-CD95+CD27+CD8+ cells, CD45RO-CD27+CD8+ cells, or CCR7+CD45RO-CD27+CD8+ cells) prior to introducing a nucleic acid encoding a BCMA CAR, and administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject;

modifying a manufacturing process of the BCMA CAR-expressing cell therapy, e.g., increasing the proliferation of seeded cells from the subject during the manufacturing of the BCMA CAR-expressing cell therapy, and administering the BCMA CAR-expressing cell therapy generated by the modified manufacturing process to the subject; or

administering a pretreatment to the subject, wherein the pretreatment increases the ratio of the amount of CD4+ immune effector cells (e.g., CD4+ T cells) to the amount of CD8+ immune effector cells (e.g., CD8+ T cells) in the subject, e.g., in a sample from the subject (e.g., an apheresis sample (e.g., a leukapheresis sample), a seed culture at the start of the manufacturing of a BCMA CAR-expressing cell therapy (e.g., a leukapheresis sample after monocytes are removed using elutriation)), or in the subject's peripheral blood and/or bone marrow prior to the administration of the BCMA CAR-expressing cell therapy, e.g., the pretreatment increases the ratio to greater than or equal to 1.6 (e.g., between 1.6 and 5, e.g., between 1.6 and 3.5), manufacturing the BCMA CAR-expressing cell therapy using cells (e.g., T cells) from the subject, and administering the BCMA CAR-expressing cell therapy to the subject,

thereby treating the subject having the disease associated with the expression of BCMA.

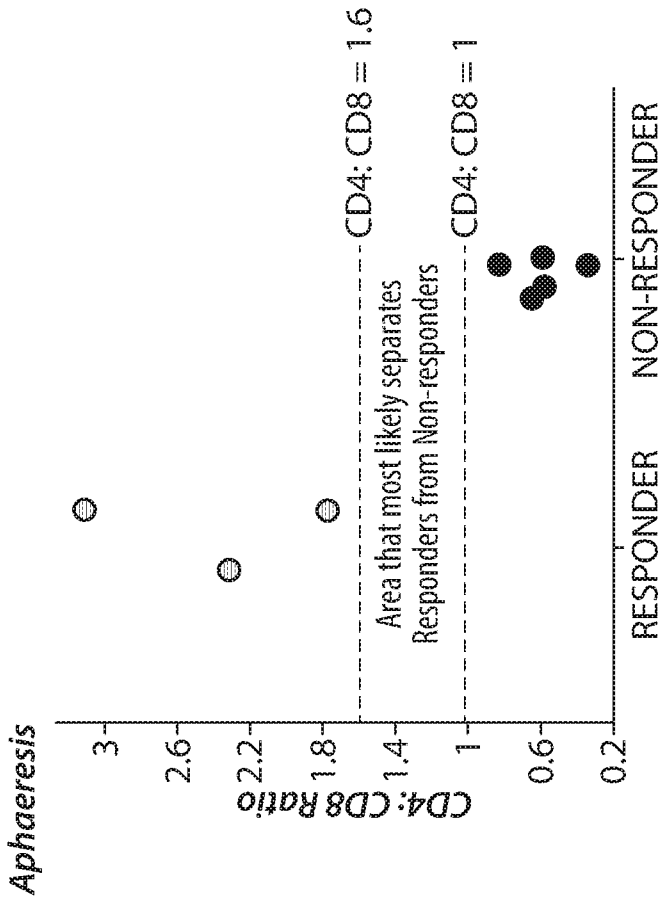

Aphaeresis
CD4: CD8 Ratio
3
2.6
2.2
1.8
1.4
1
0.6
0.2
CD4; CD8 = 1.6
Area that most likely separates
Responders from Non-responders
CD4; CD8 = 1
RESPONDER
NON-RESPONDER

FIG. 1B

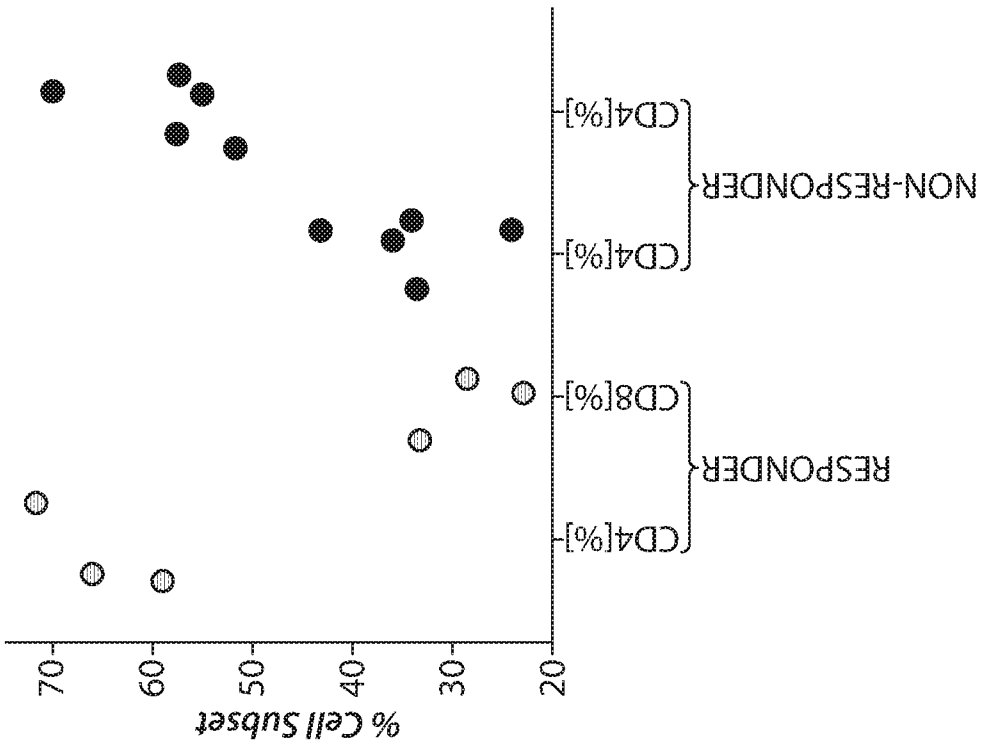

% Cell Subset
70
60
50
40
30
20
RESPONDER
NON-RESPONDER
CD4[%]
CD8[%]
CD4[%]
CD4[%]

FIG. 1A

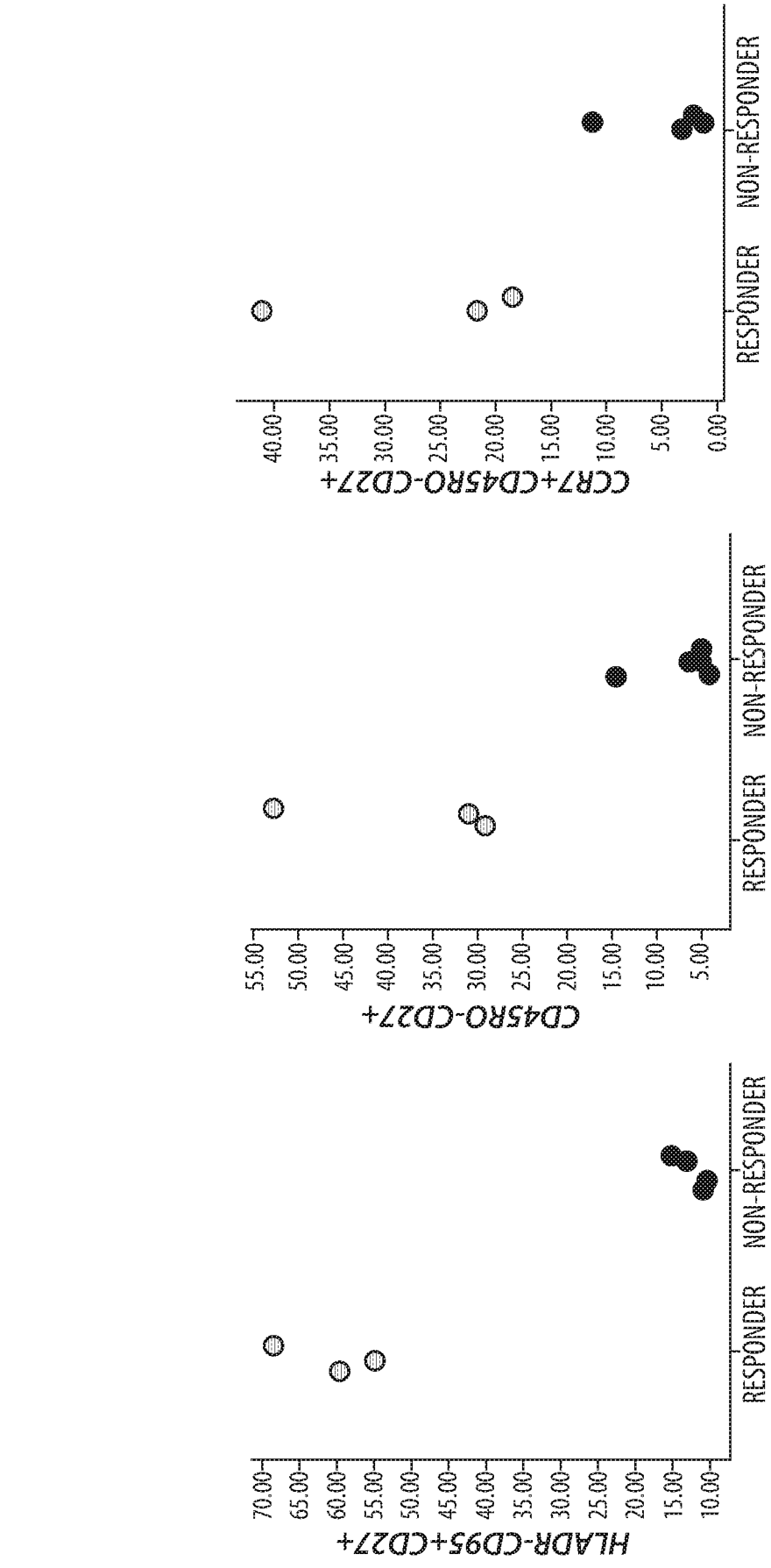


FIG. 2A

FIG. 2B

FIG. 2C

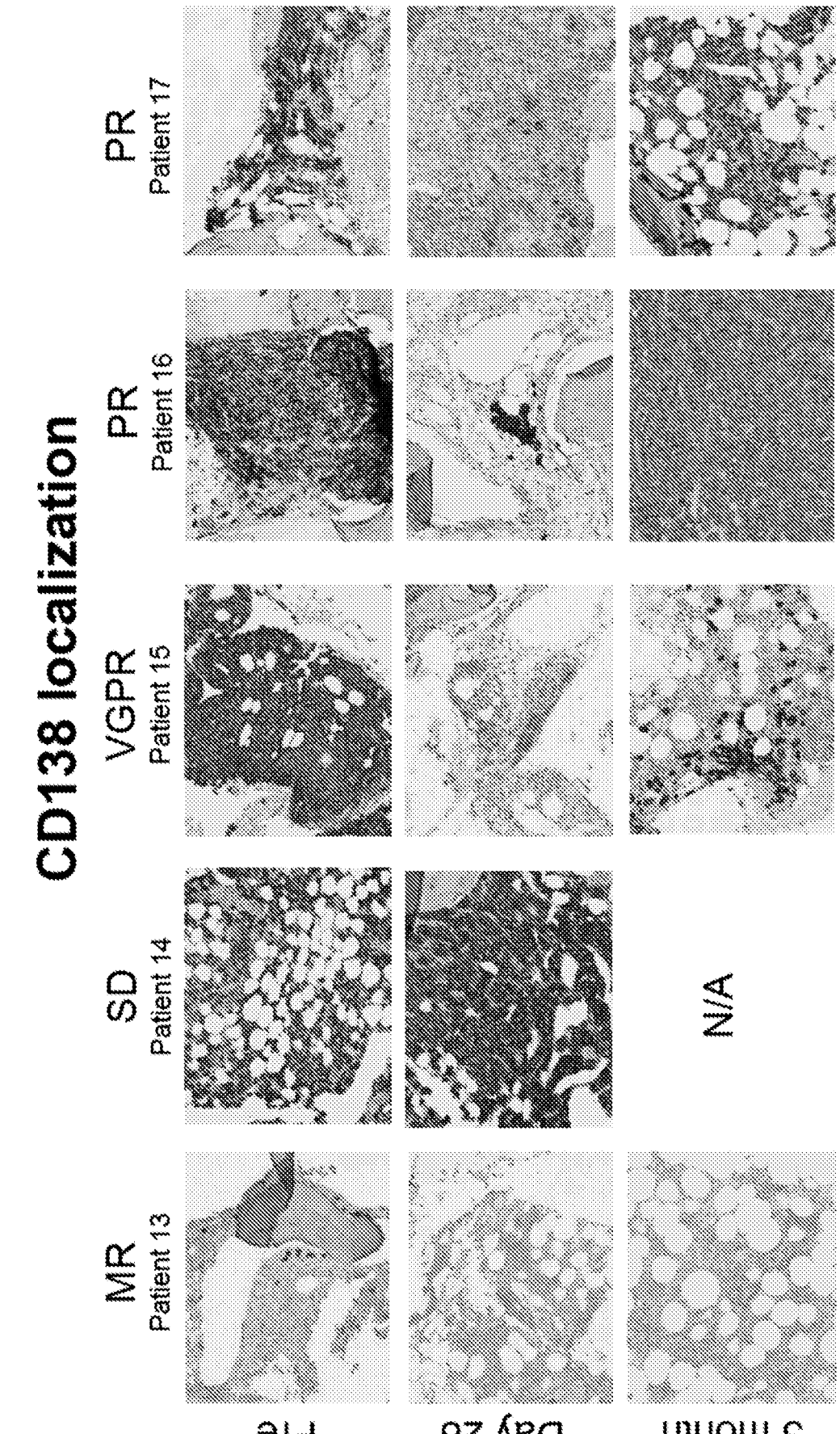

CD138 localization
MR
Patient 13
SD
Patient 14
VGPR
Patient 15
PR
Patient 16
PR
Patient 17
Pre
Day 28
3 month
Minimal CD138 expression detected at all time points in patient 13
Increased numbers of CD138 MM cells were observed at 28 days in patient 14
N/A
Extensive infiltration of CD138 MM cells at base line was observed in patients 15, 16 and 17 followed by reductions at 28 days and increased numbers at 3 months

FIG. 3

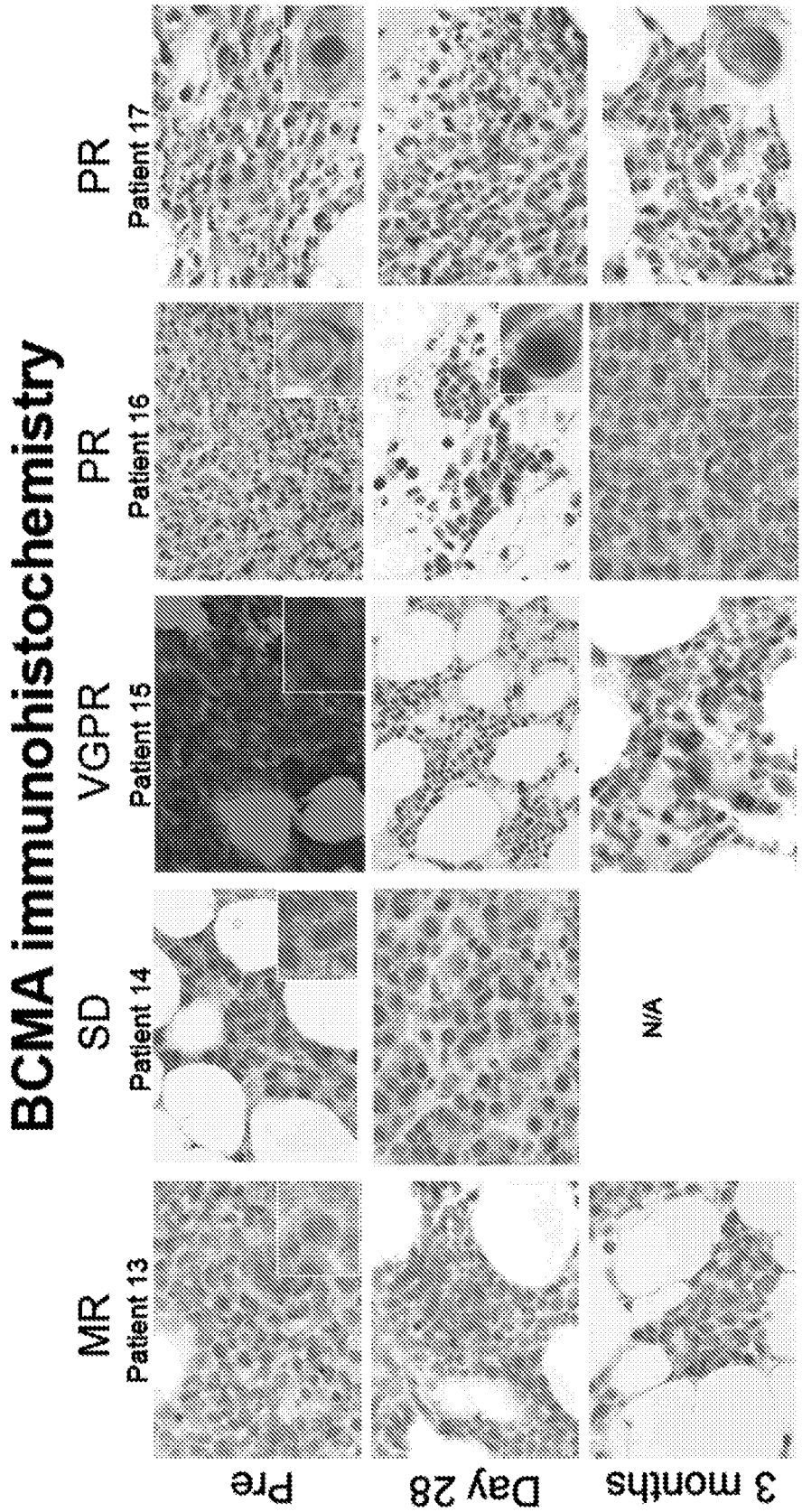

BCMA immunohistochemistry
MR
SD
VGPR
PR
PR
Patient 13
Patient 14
Patient 15
Patient 16
Patient 17
N/A
Pre
Day 28
3 months

FIG. 4

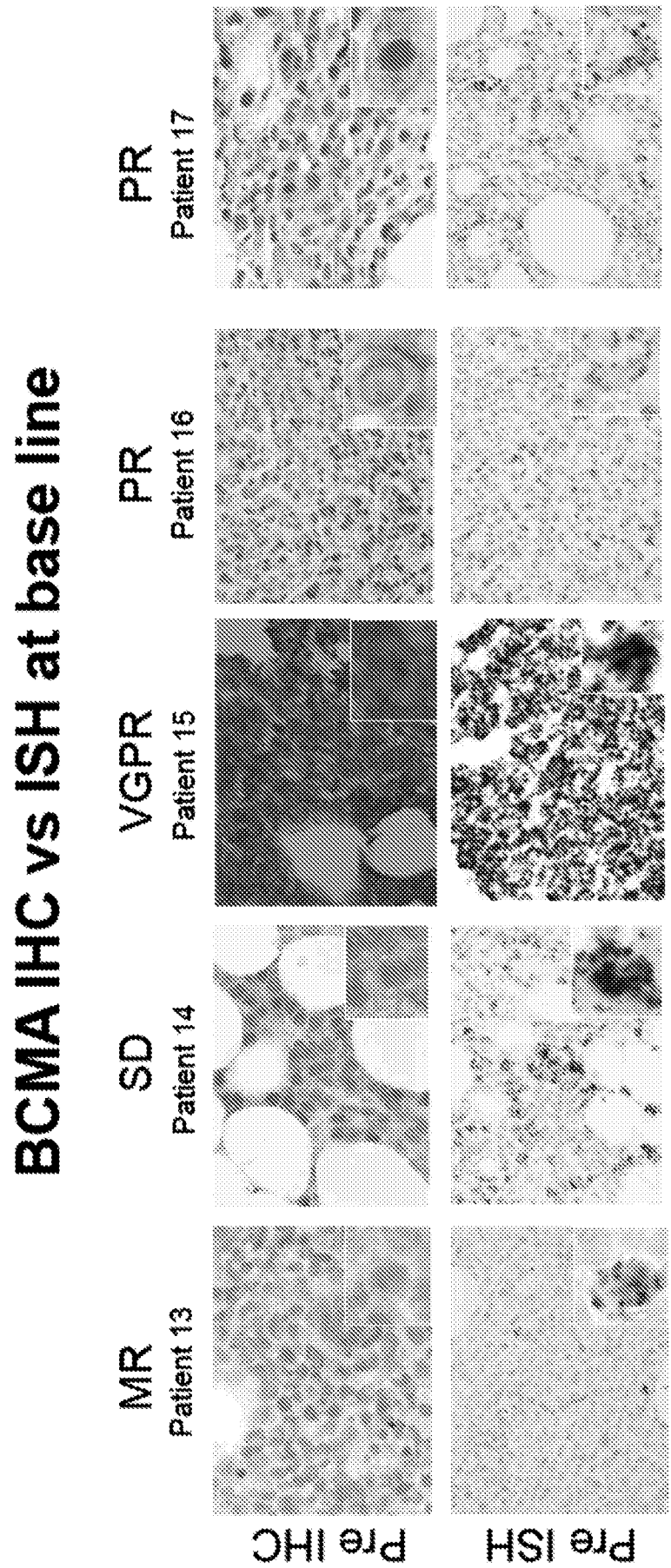

BCMA IHC vs ISH at base line
MR
Patient 13
SD
Patient 14
VGPR
Patient 15
PR
Patient 16
PR
Patient 17
Pre IHC
Pre ISH
• Discordance between BCMA surface protein and mRNA expression observed in patients 13 and 14

FIG. 5

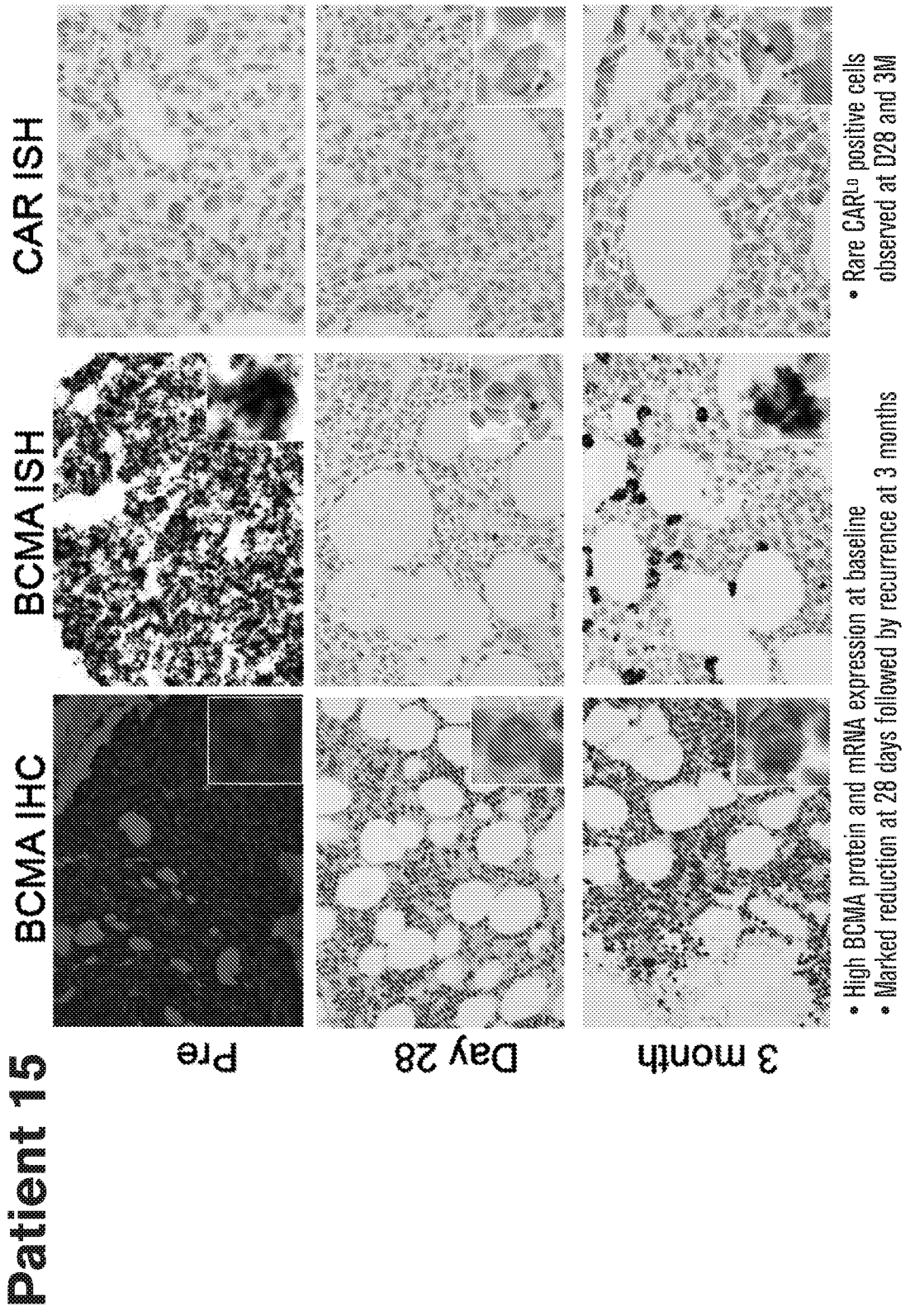

Patient 15
BCMA IHC
BCMA ISH
CAR ISH
Pre
Day 28
3 month
• High BCMA protein and mRNA expression at baseline
• Marked reduction at 28 days followed by recurrence at 3 months
• Rare CAR^{Lo} positive cells observed at D28 and 3M

FIG. 6A

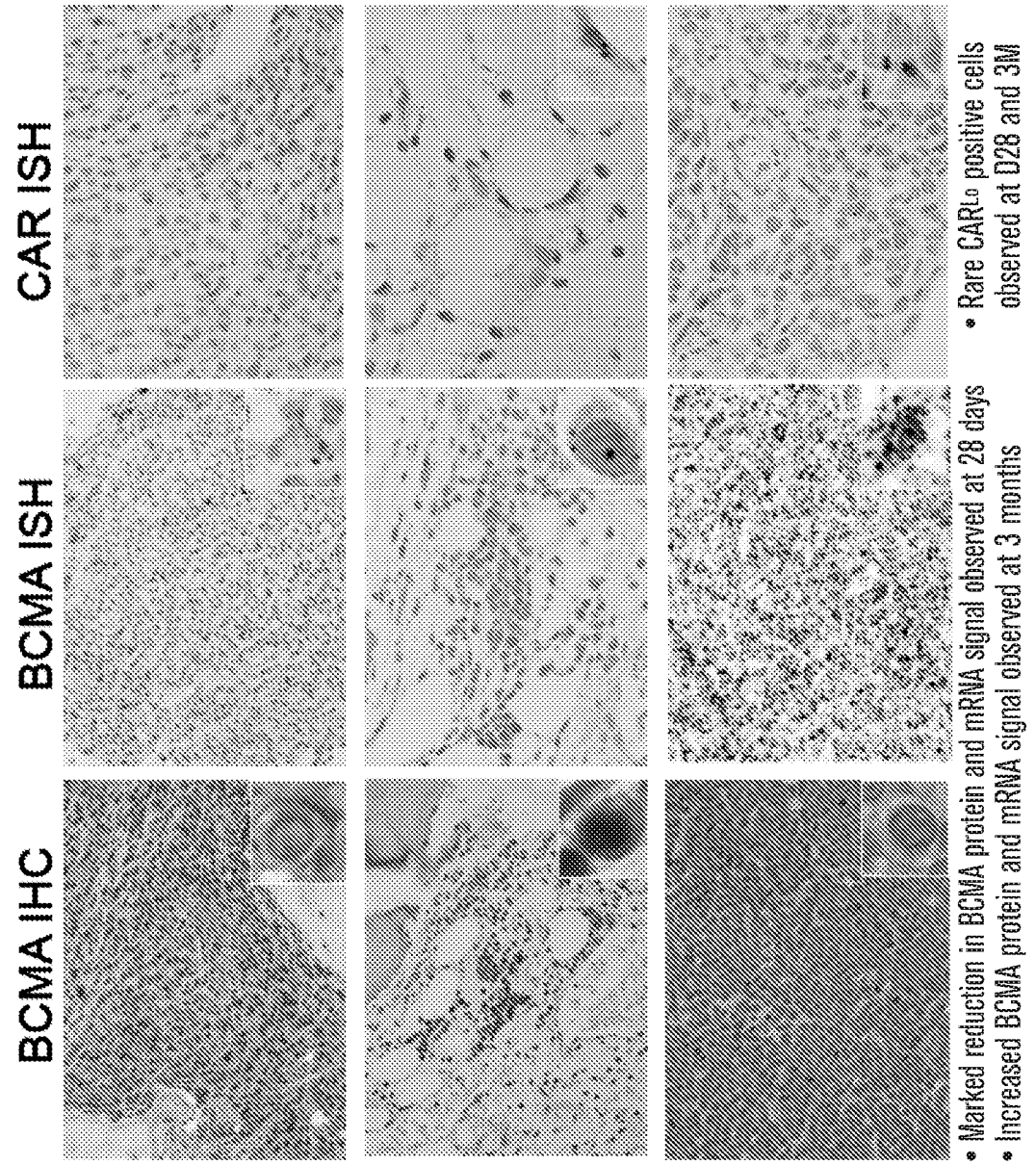

Patient 16
BCMA IHC
BCMA ISH
CAR ISH
Pre
Day 28
3 month
• Marked reduction in BCMA protein and mRNA signal observed at 28 days
• Increased BCMA protein and mRNA signal observed at 3 months
• Rare CAR^{Lo} positive cells observed at D28 and 3M

FIG. 6B

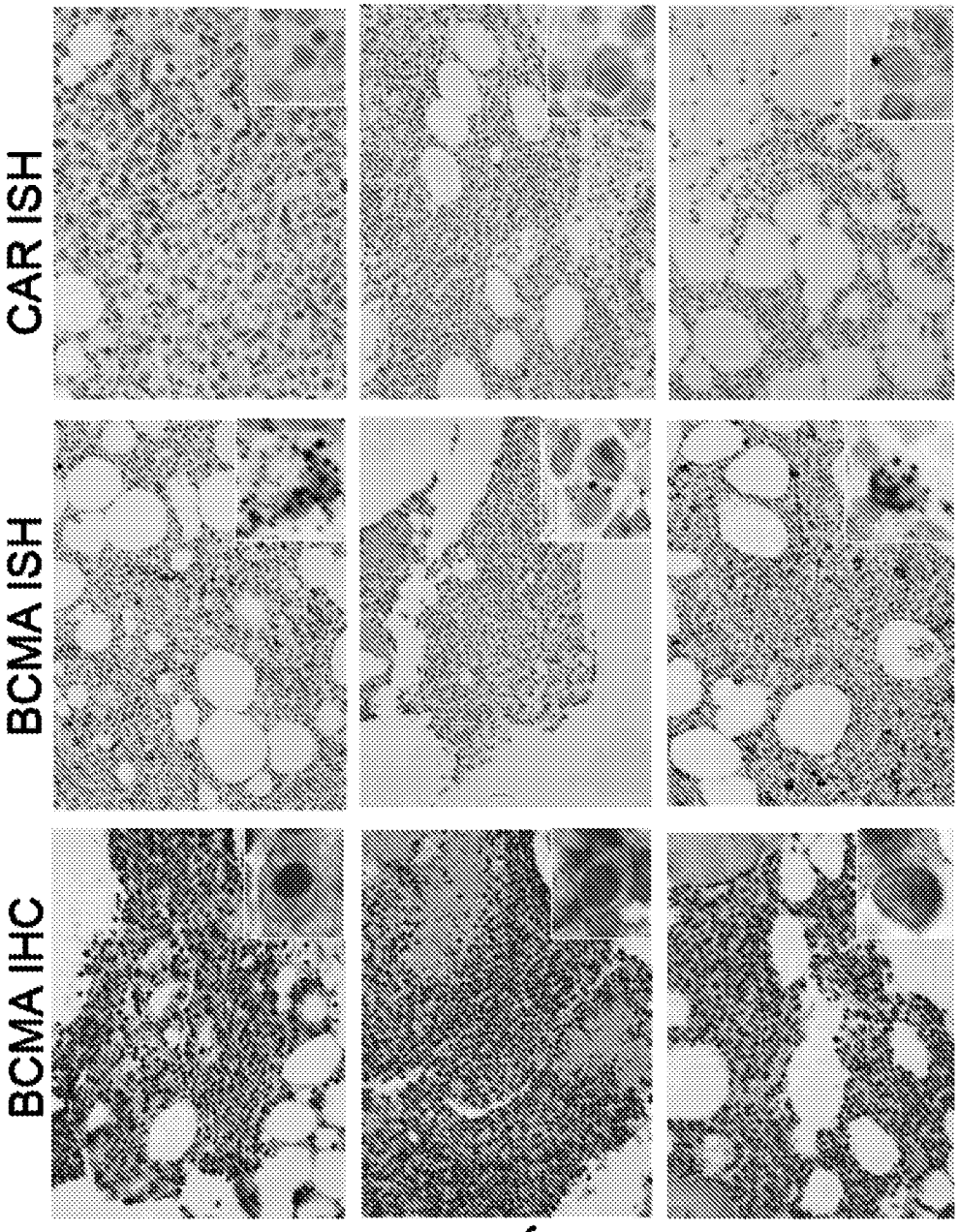

Patient 17
BCMA IHC
BCMA ISH
CAR ISH
Pre
Day 28
3 month
• Reduction in number of BCMA positive cells observed at D28 and reduction in BCMA mRNA signal/cell
• BCMA mRNA signal/cell returns to base line at 3M
• Equivocal CARLo mRNA signal detected at 3M

FIG. 6C

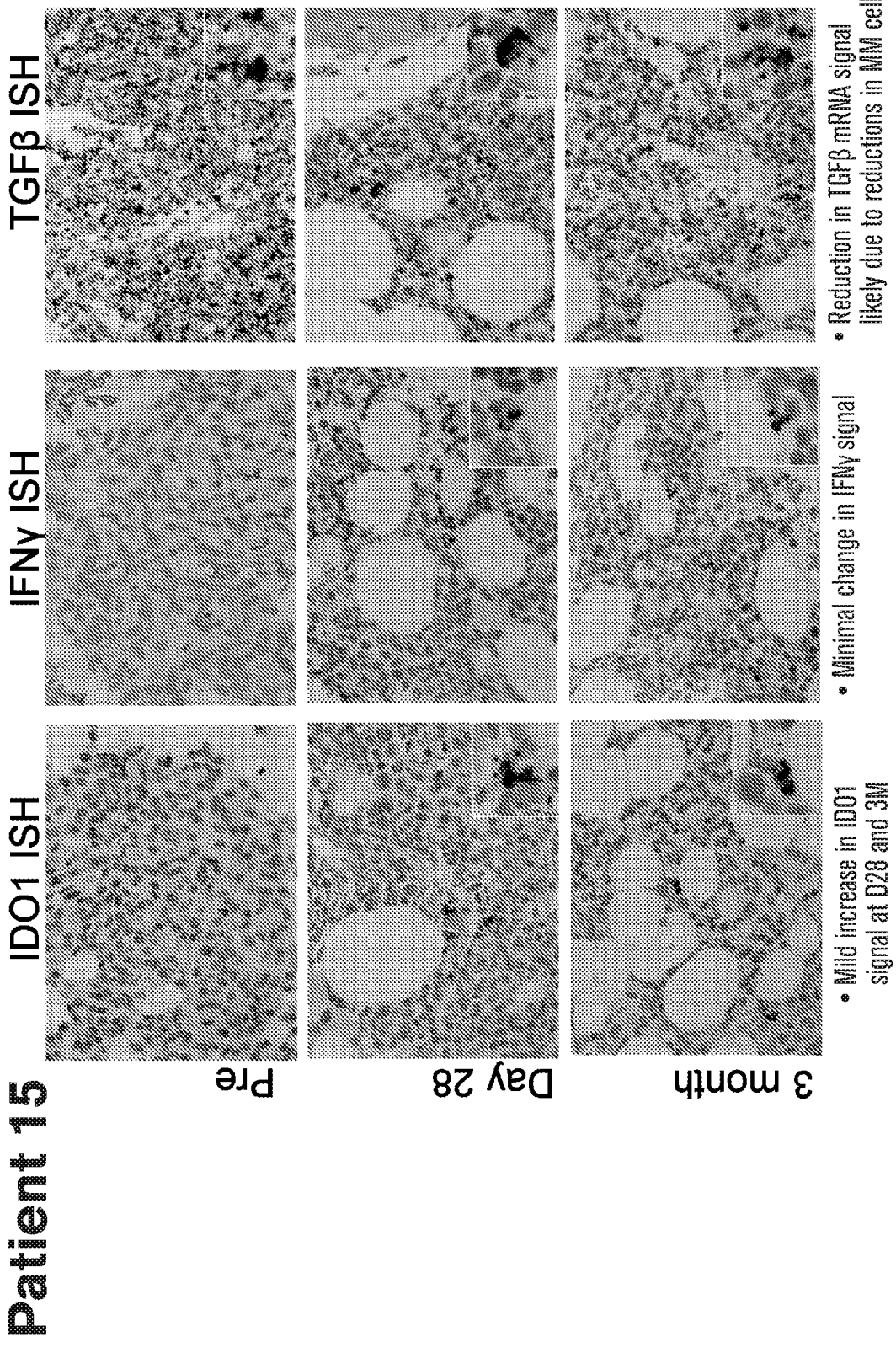

Patient 15
IDO1 ISH
IFNγ ISH
TGFβ ISH
Pre
Day 28
3 month
• Mild increase in IDO1 signal at D28 and 3M
• Minimal change in IFNγ signal
• Reduction in TGFβ mRNA signal likely due to reductions in MM cells

FIG. 7A

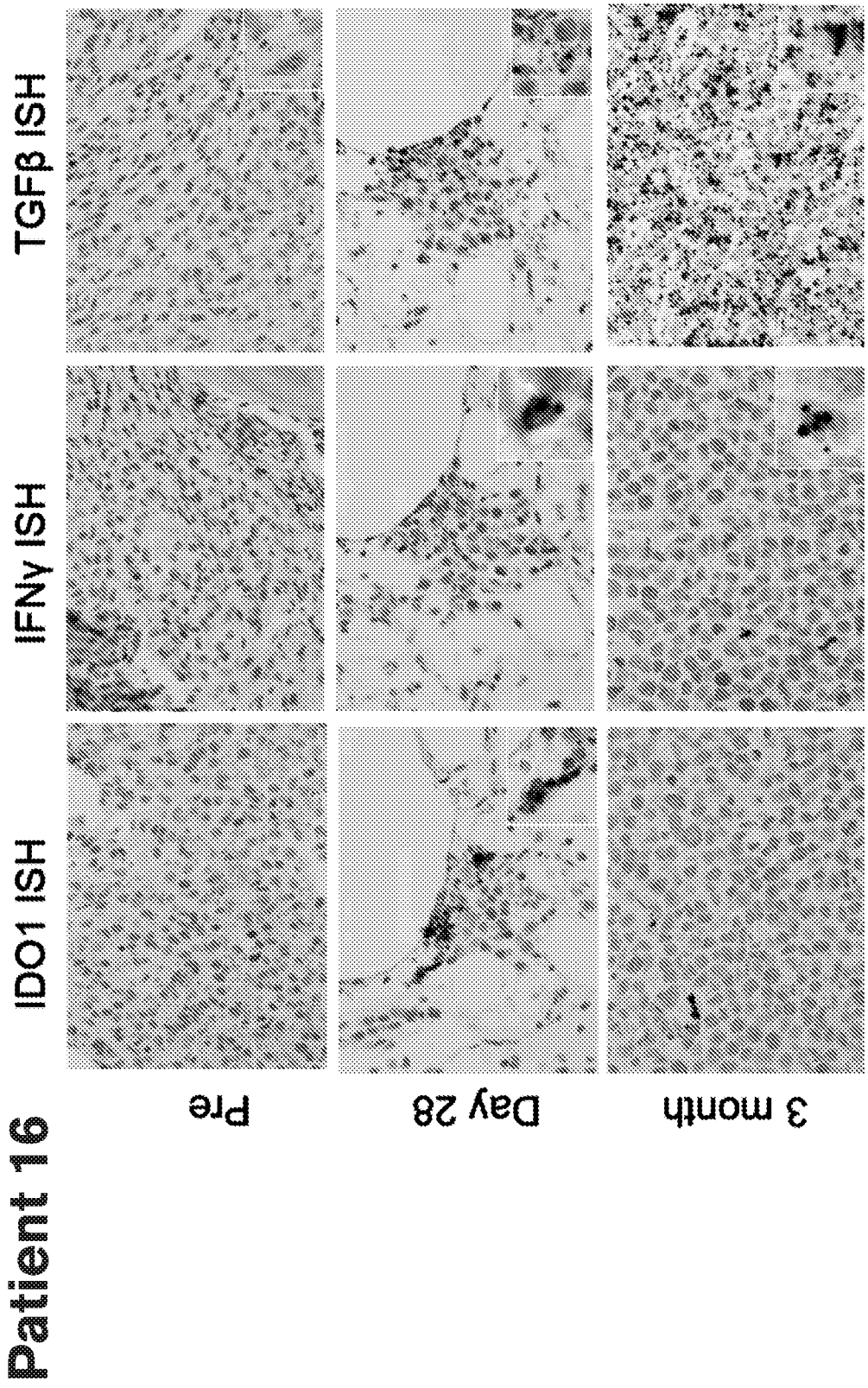

Patient 16
IDO1 ISH
IFNγ ISH
TGFβ ISH
Pre
Day 28
3 month
• Increased IDO1 mRNA expression observed at site of persistent MM cells
• Rare IFNγ mRNA positive cells observed at D28 and 3M
• Marked increase in TGFβ signal in MM cells over base line

FIG. 7B

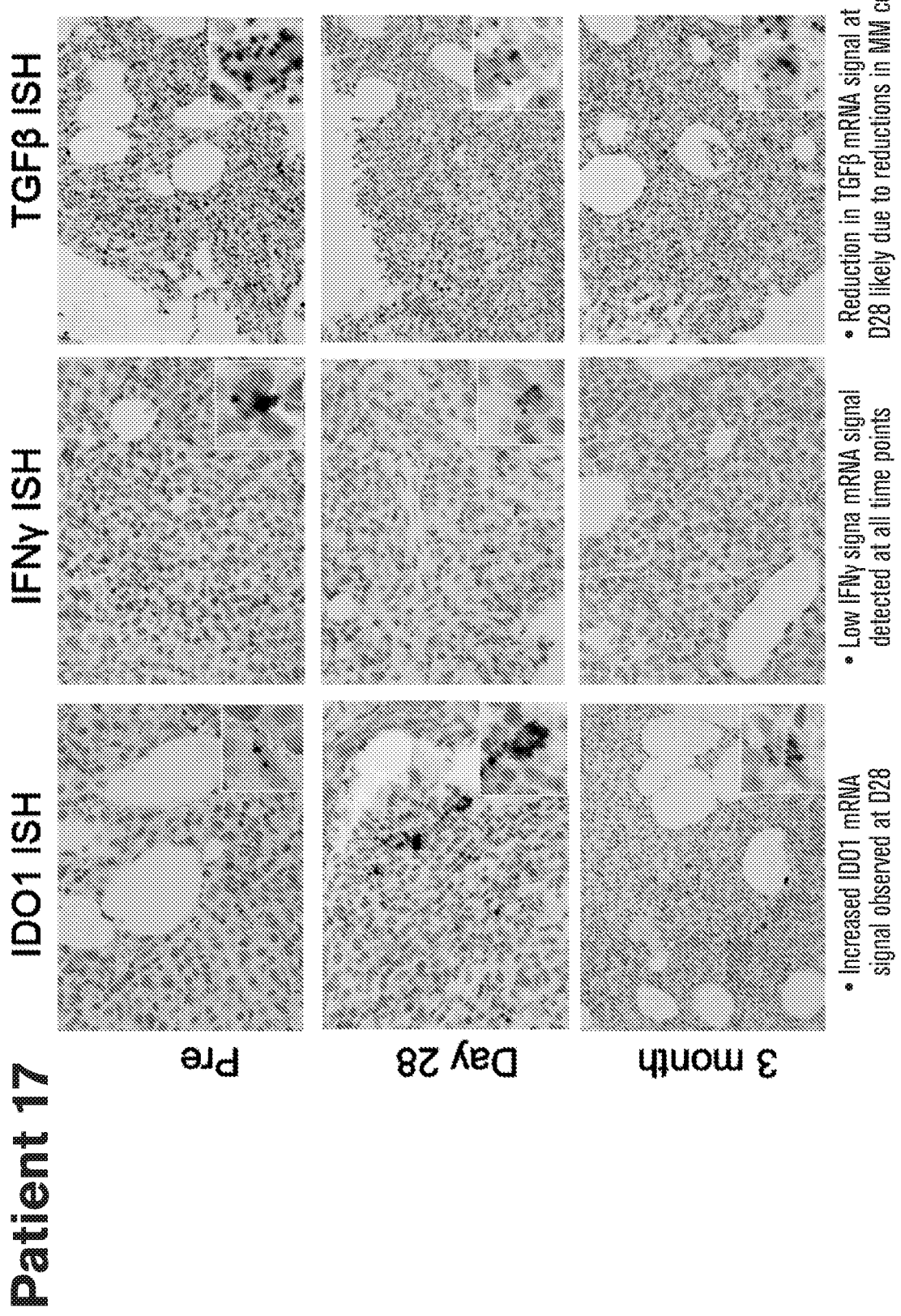

Patient 17
IDO1 ISH
IFNγ ISH
TGFβ ISH
Pre
Day 28
3 month
• Increased IDO1 mRNA signal observed at D28
• Low IFNγ signa mRNA signal detected at all time points
• Reduction in TGFβ mRNA signal at D28 likely due to reductions in MM cells.

FIG. 7C

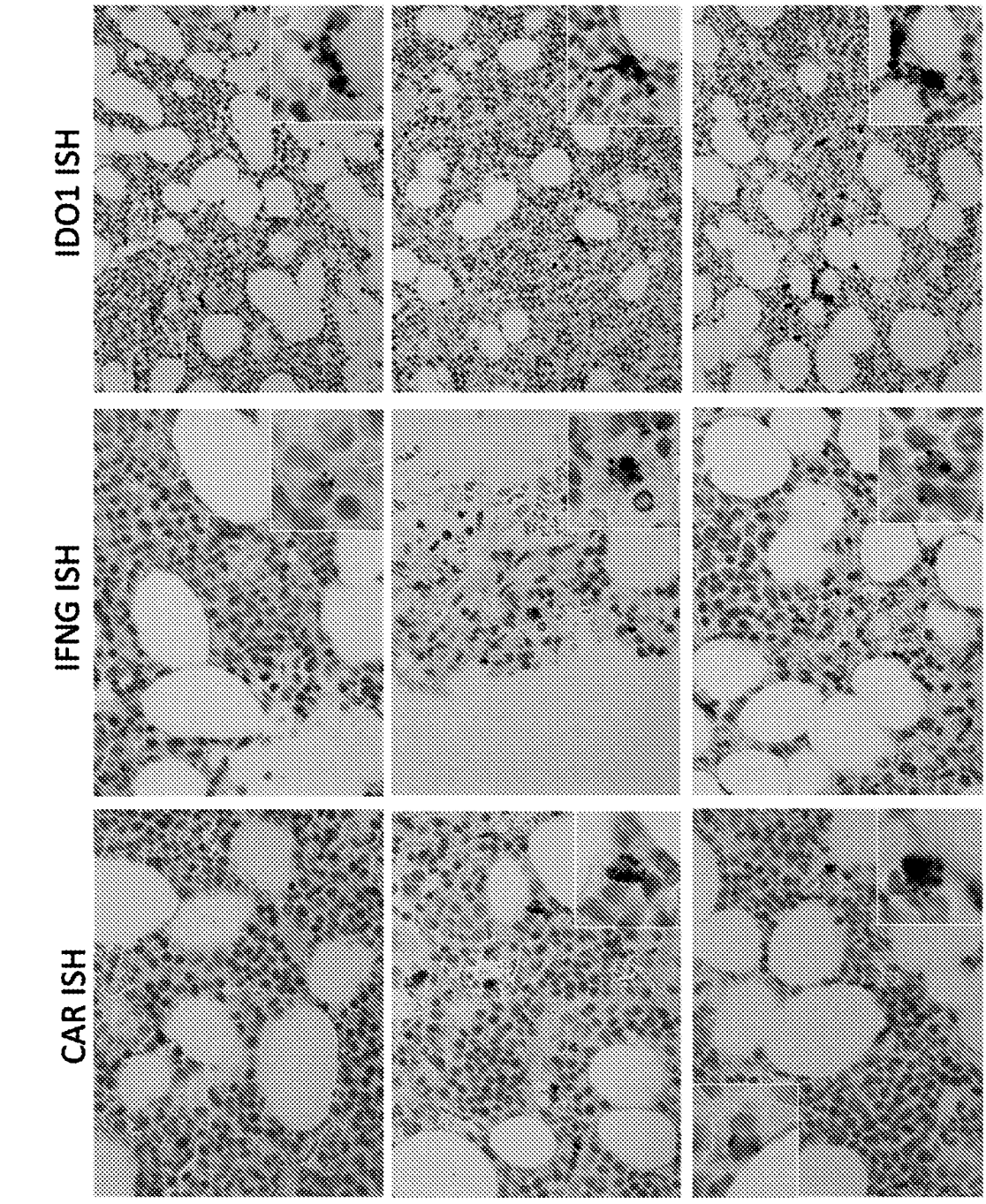


FIG. 7D

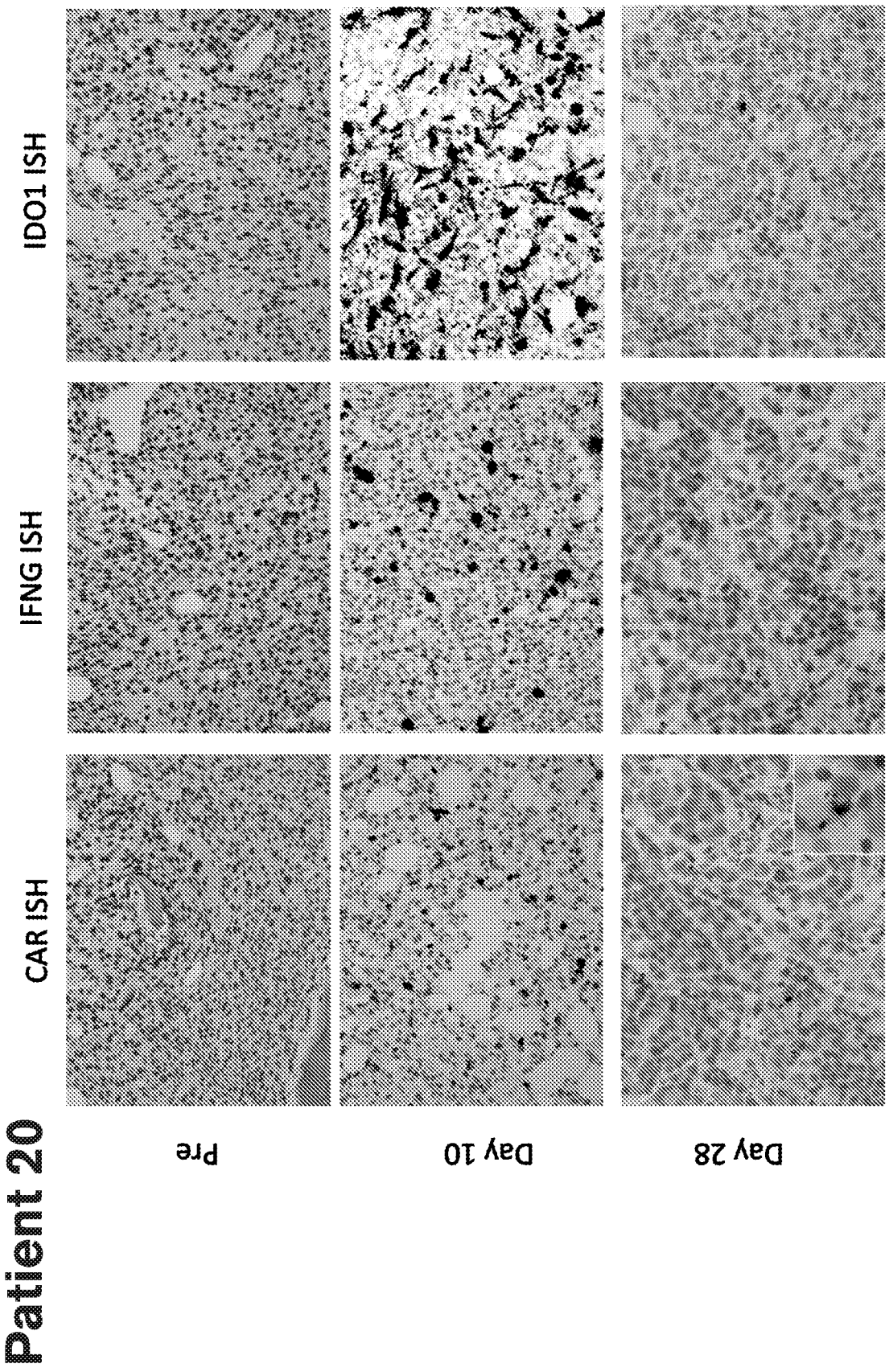


FIG. 7E

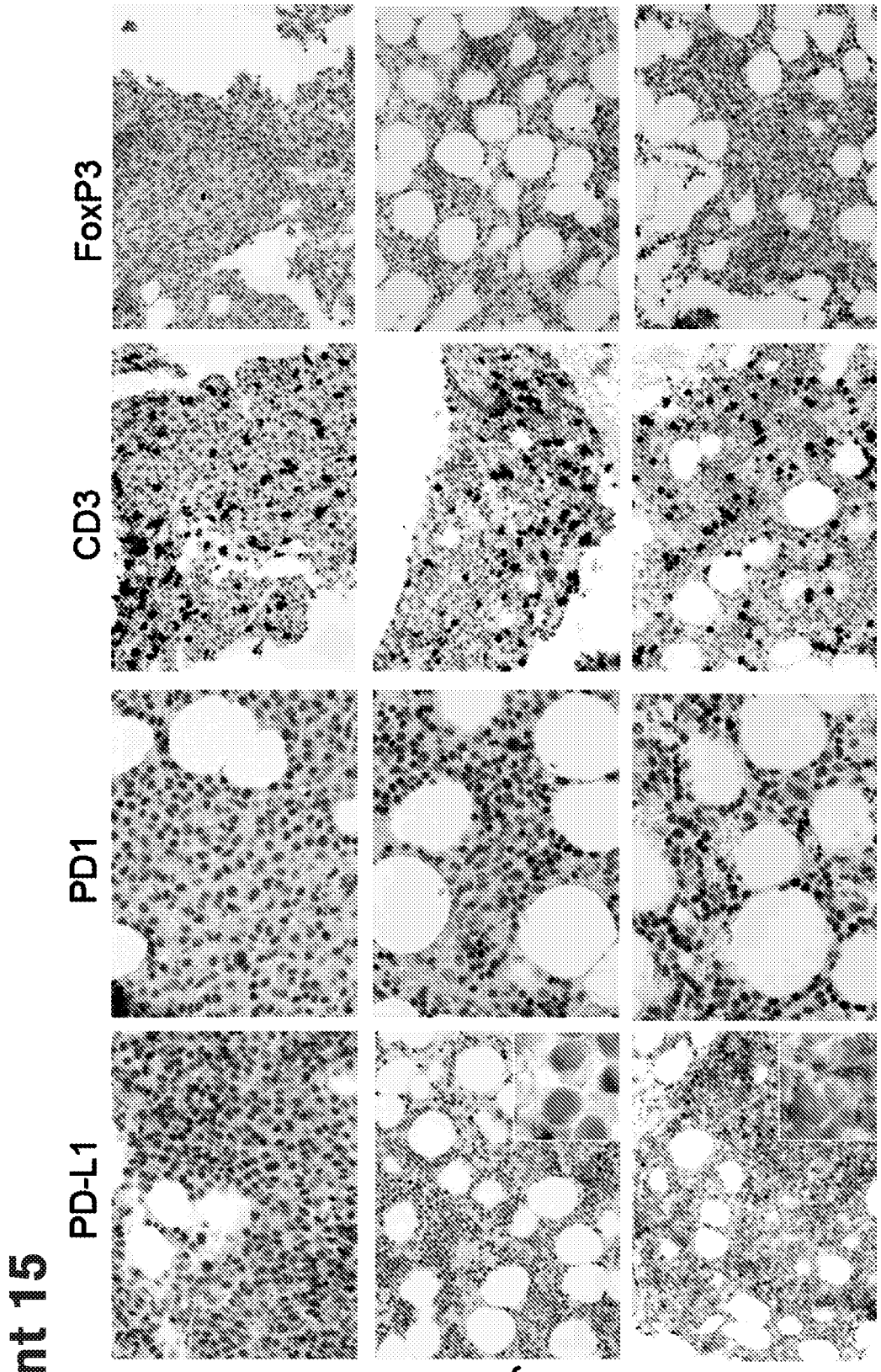

Patient 15
PD-L1
PD1
CD3
FoxP3
Pre
Day 28
3 month
• Increase in PD-L1 stromal cell signal at 3M
• No change in PD1, CD3 or FoxP3 signal observed

FIG. 8A

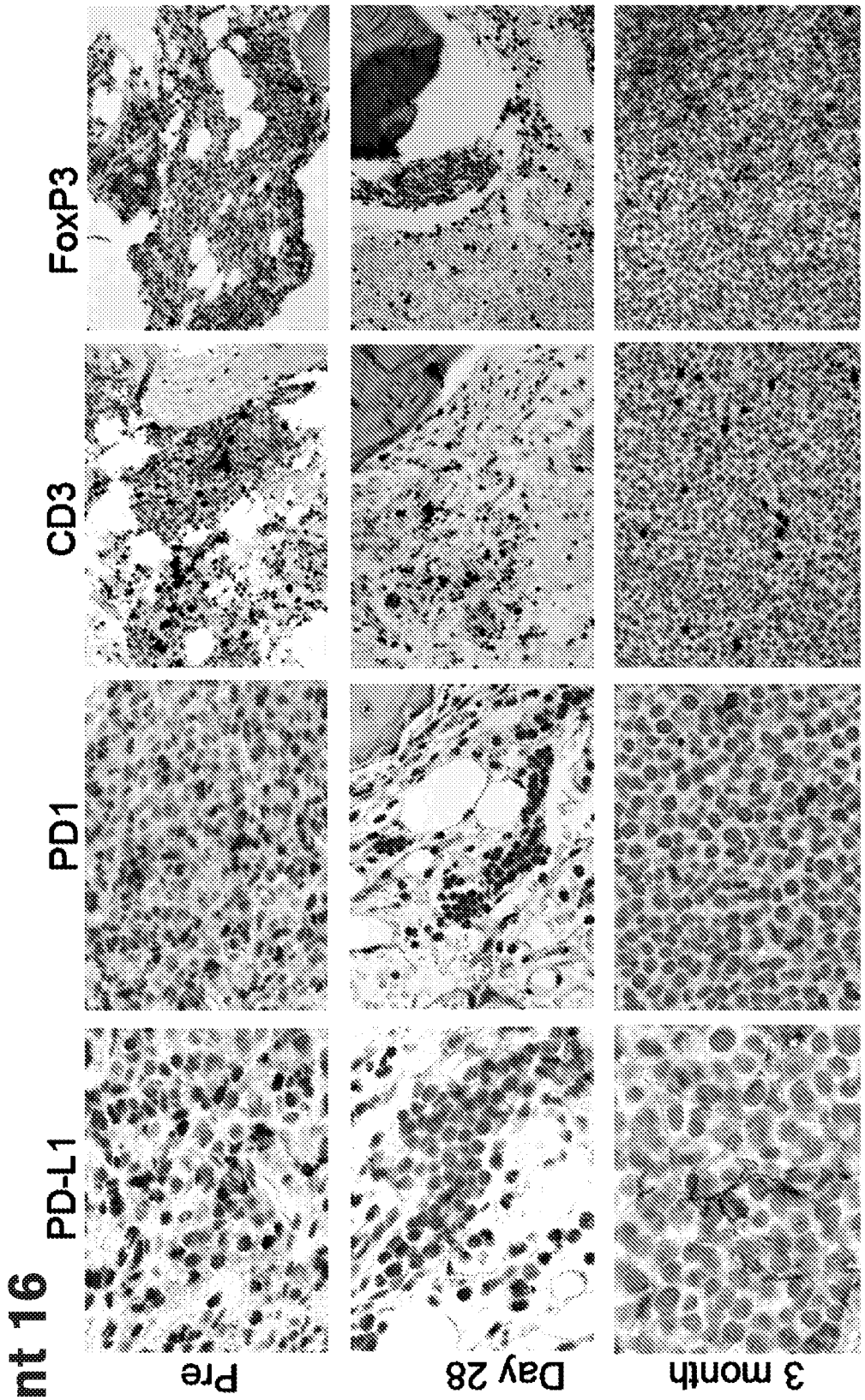

Patient 16
PD-L1
PD1
CD3
FoxP3
Pre
Day 28
3 month
• Increase in PD-L1 expresssion on stromal cells at 3M
• No PD1 infiltration detected
• No change in CD3 or FoxP3 cell number

FIG. 8B

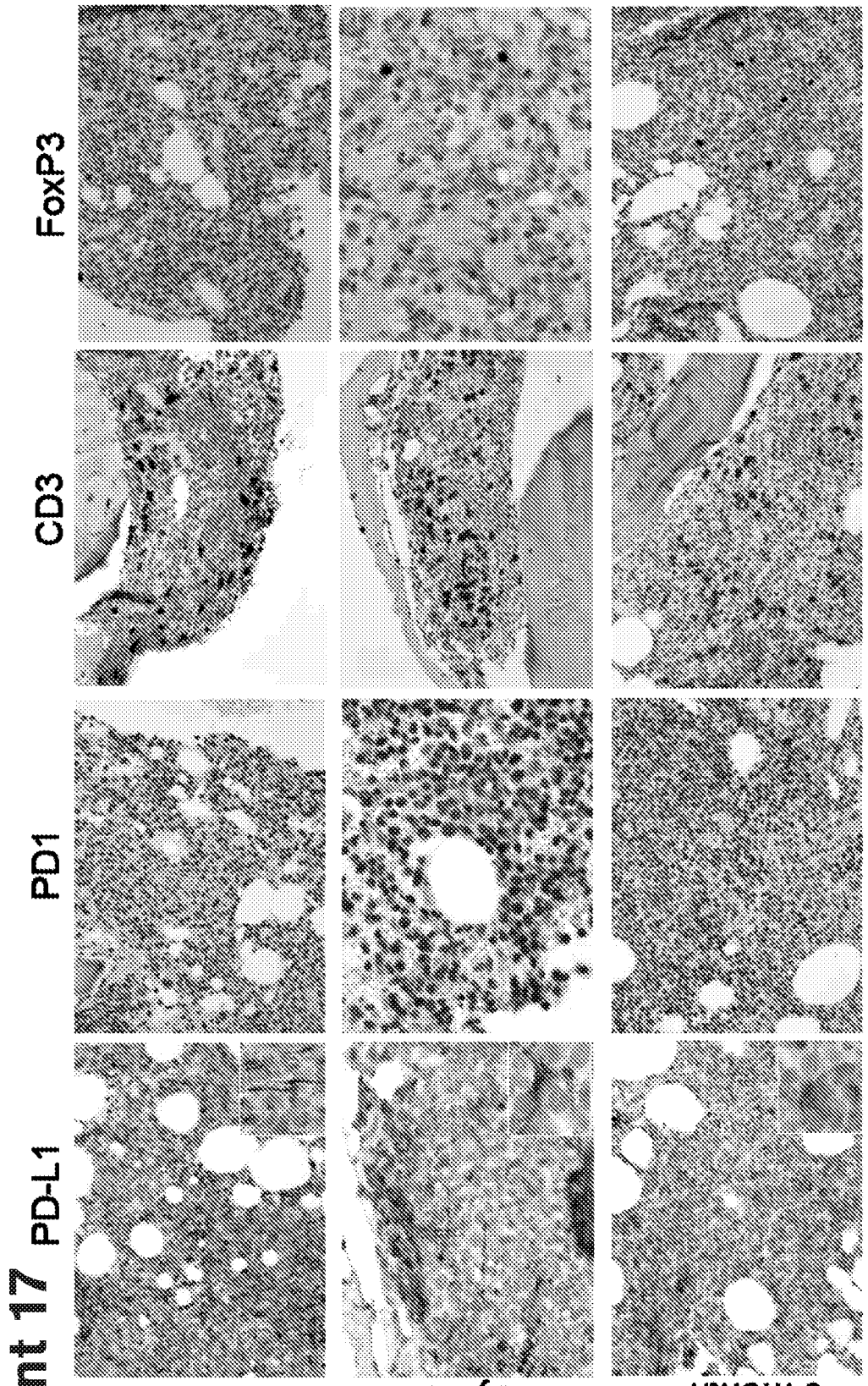

Patient 17
PD-L1
PD1
CD3
FoxP3
Pre
Day 28
3 month
• PD-L1 expresssion detected on stromal cells at all time points
• No PD1 infiltration detected at any time point
• No change in CD3 or FoxP3 infiltration

FIG. 8C

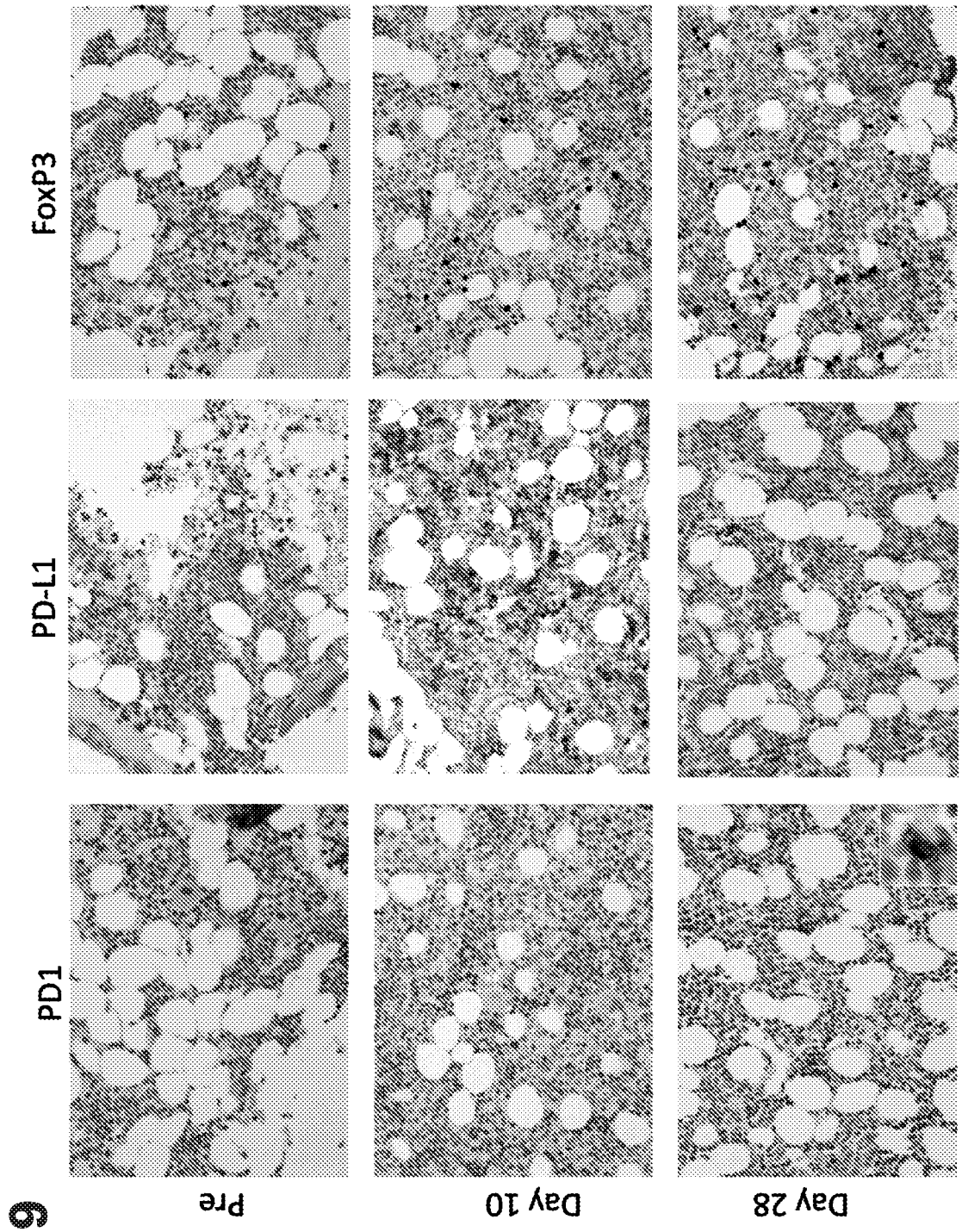


FIG. 8D

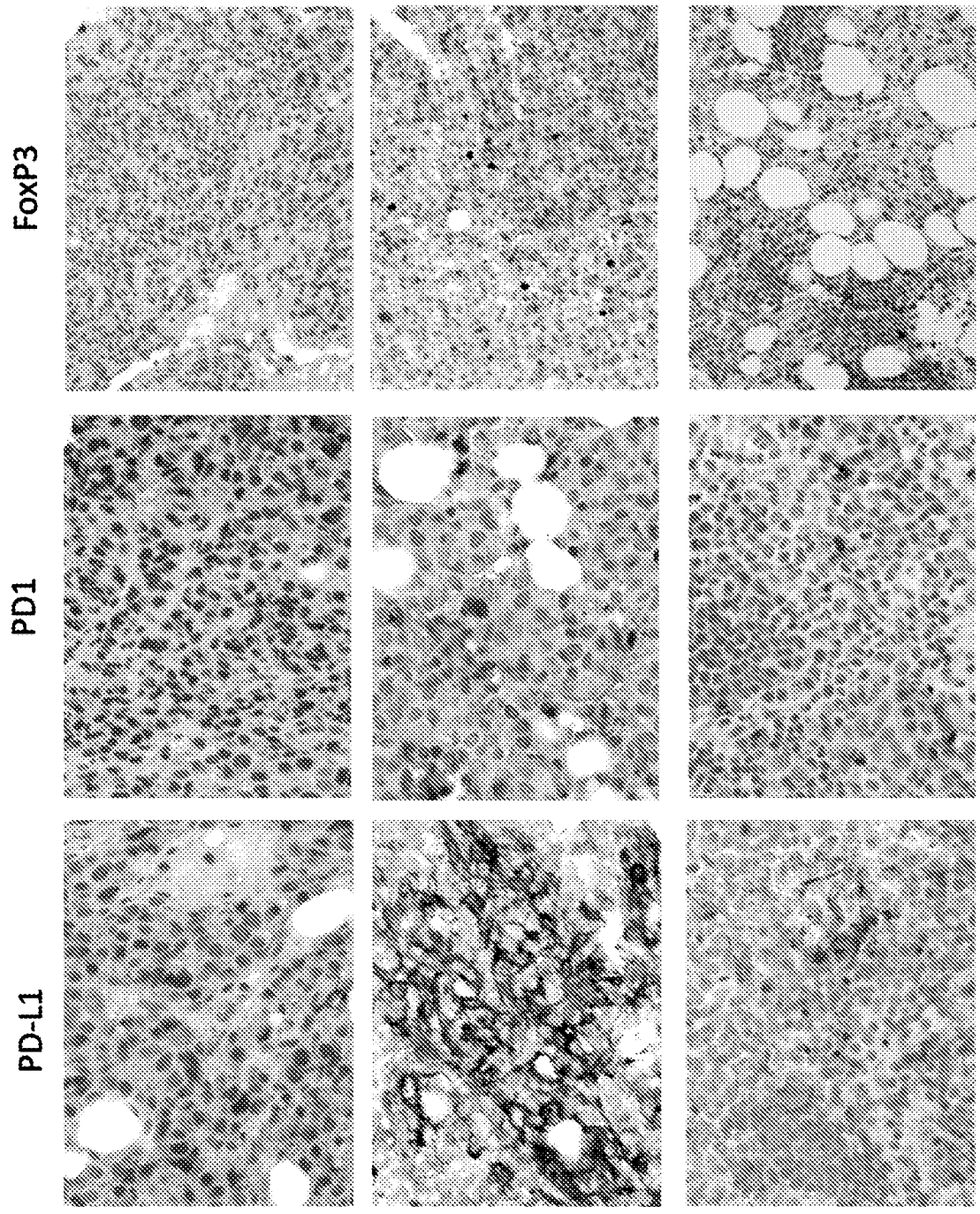


FIG. 8E

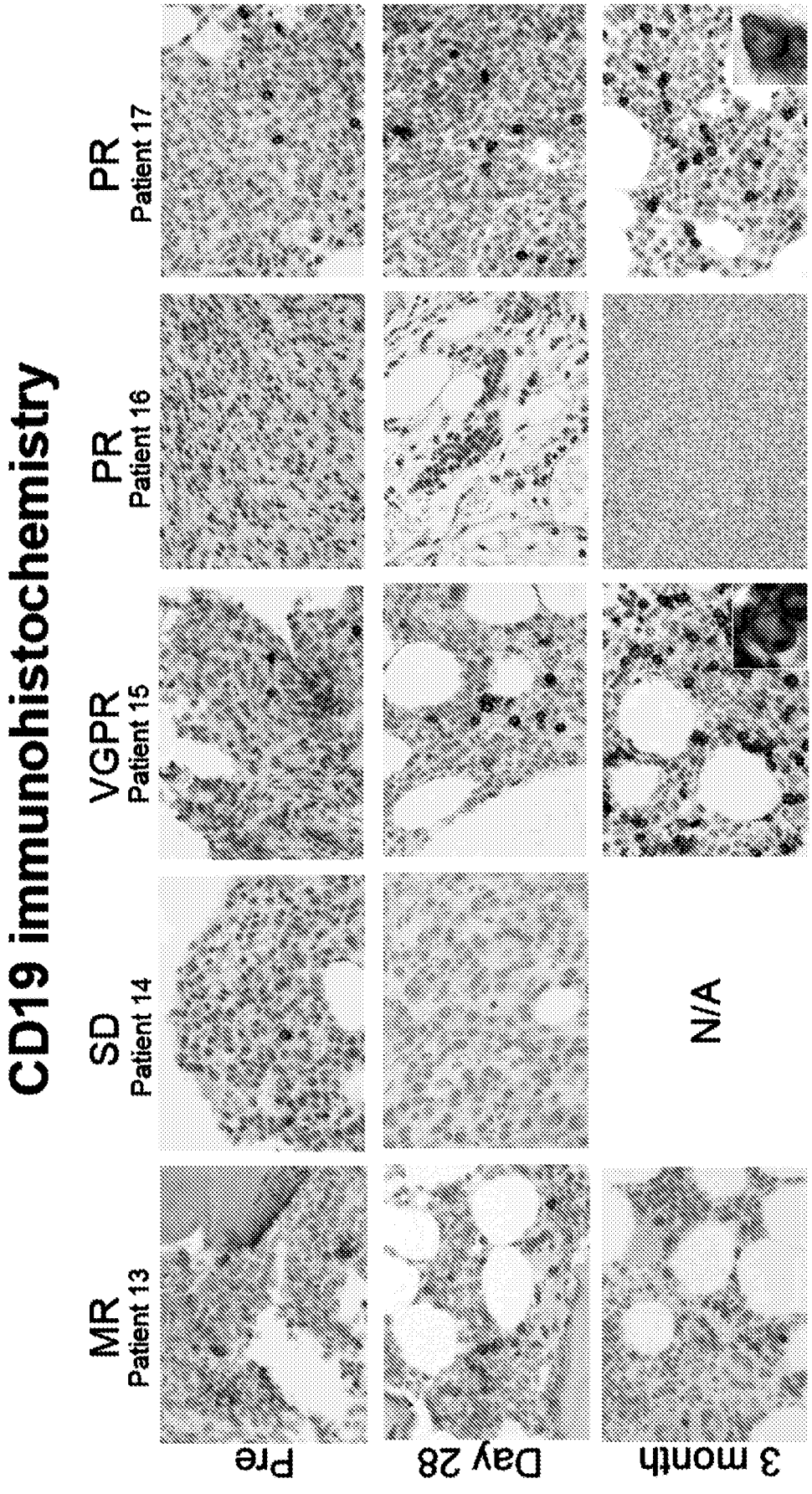

CD19 immunohistochemistry
MR
Patient 13
SD
Patient 14
VGPR
Patient 15
PR
Patient 16
PR
Patient 17
Pre
Day 28
3 month
N/A

FIG. 9

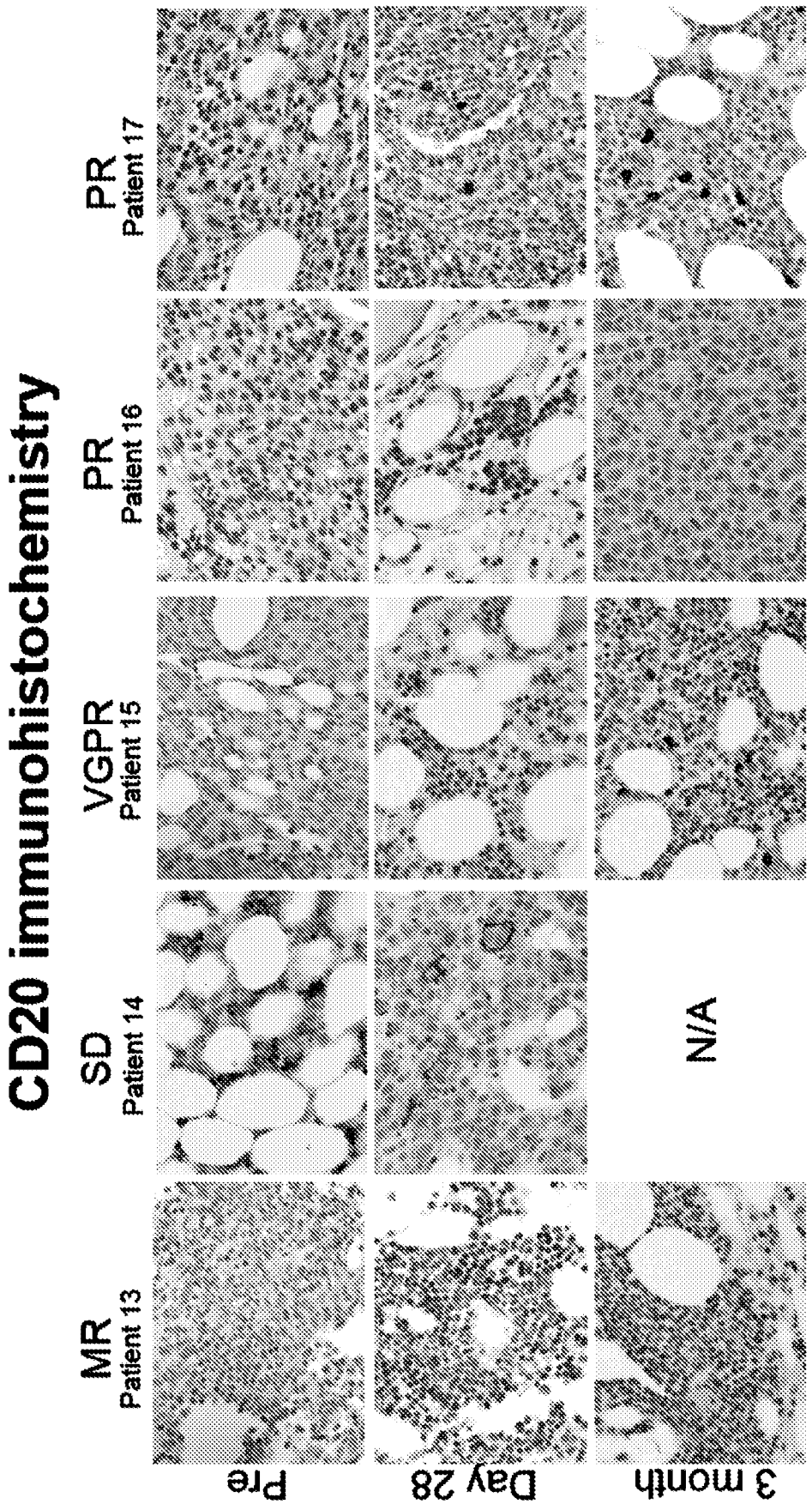

CD20 immunohistochemistry
MR
Patient 13
SD
Patient 14
VGPR
Patient 15
PR
Patient 16
PR
Patient 17
Pre
Day 28
3 month
N/A

FIG. 10

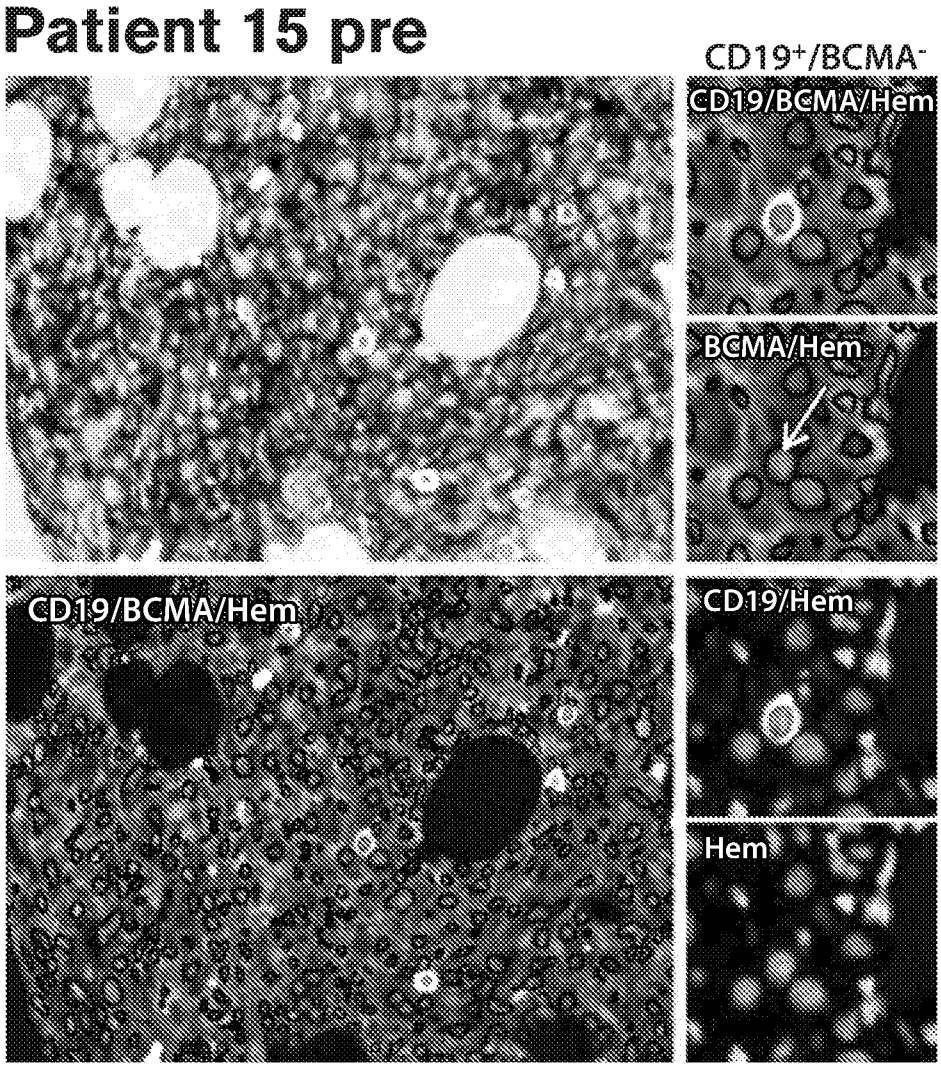

Patient 15 pre
CD19+/BCMA-
CD19/BCMA/Hem
BCMA/Hem
CD19/BCMA/Hem
CD19/Hem
Hem

FIG. 11A

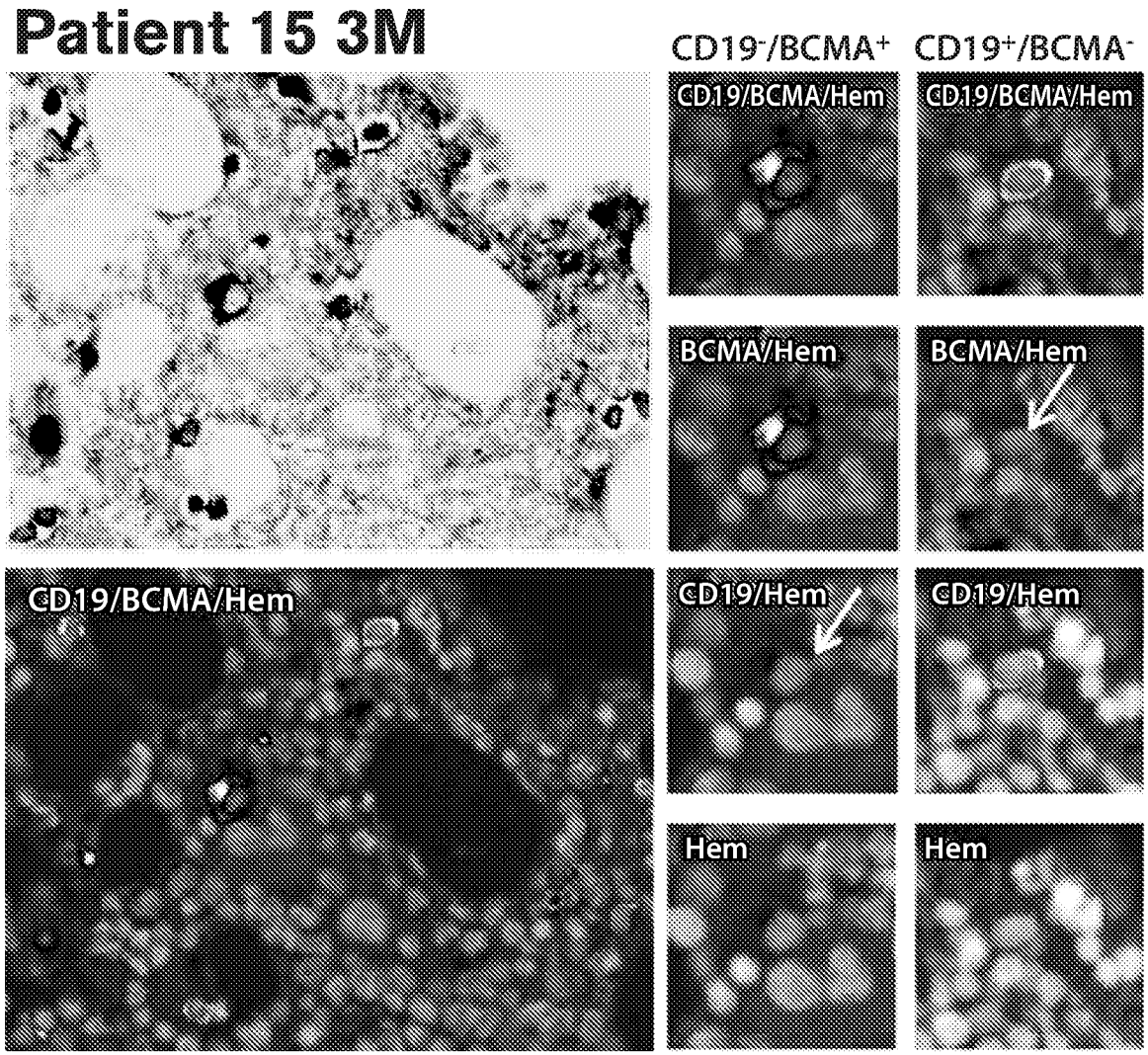

Patient 15 3M
CD19-/BCMA+
CD19+/BCMA-
CD19/BCMA/Hem
CD19/BCMA/Hem
CD19/BCMA/Hem
BCMA/Hem
BCMA/Hem
CD19/Hem
CD19/Hem
Hem
Hem

FIG. 11B

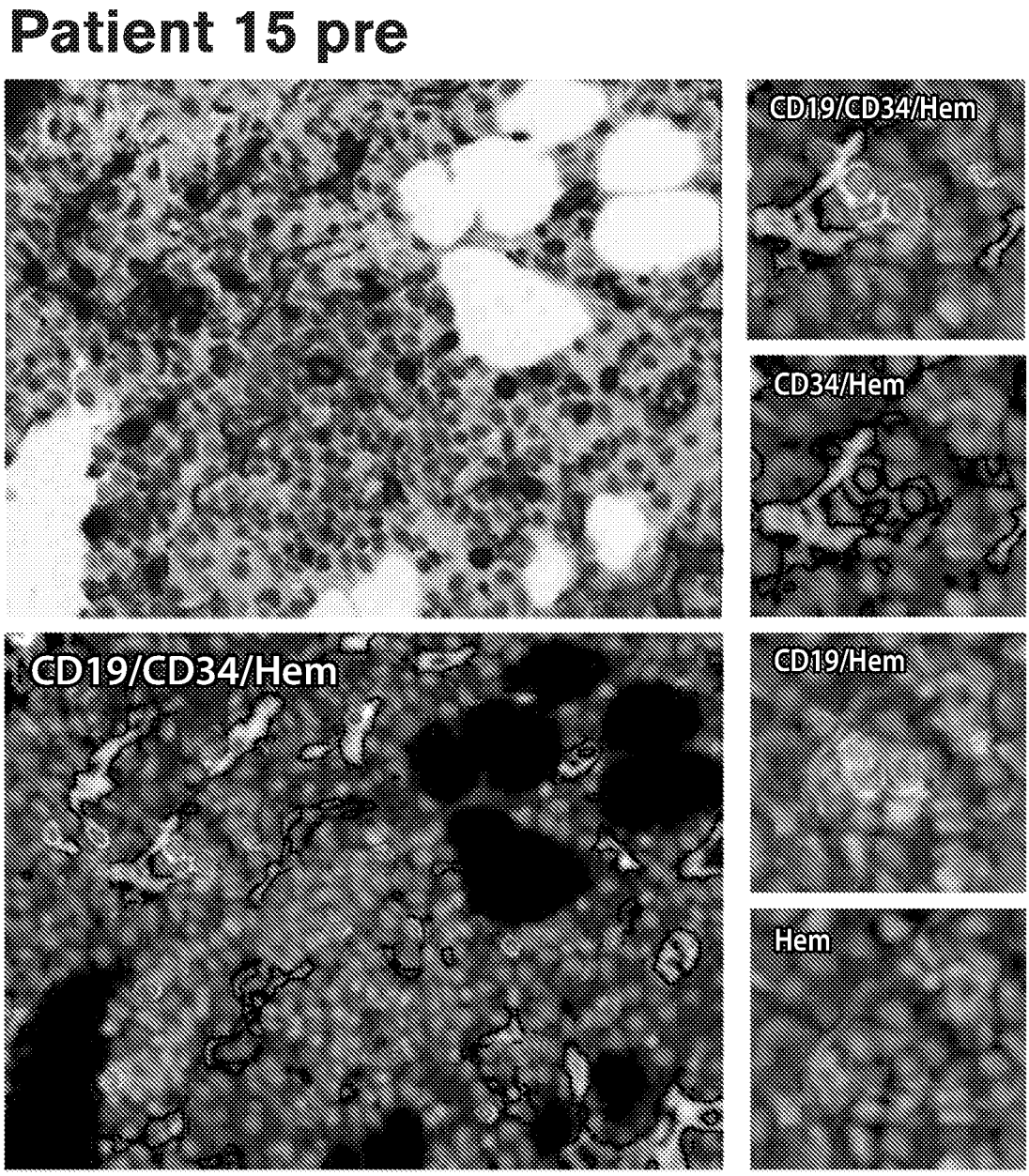

Patient 15 pre
CD19/CD34/Hem
CD34/Hem
CD19/CD34/Hem
CD19/Hem
Hem

FIG. 12A

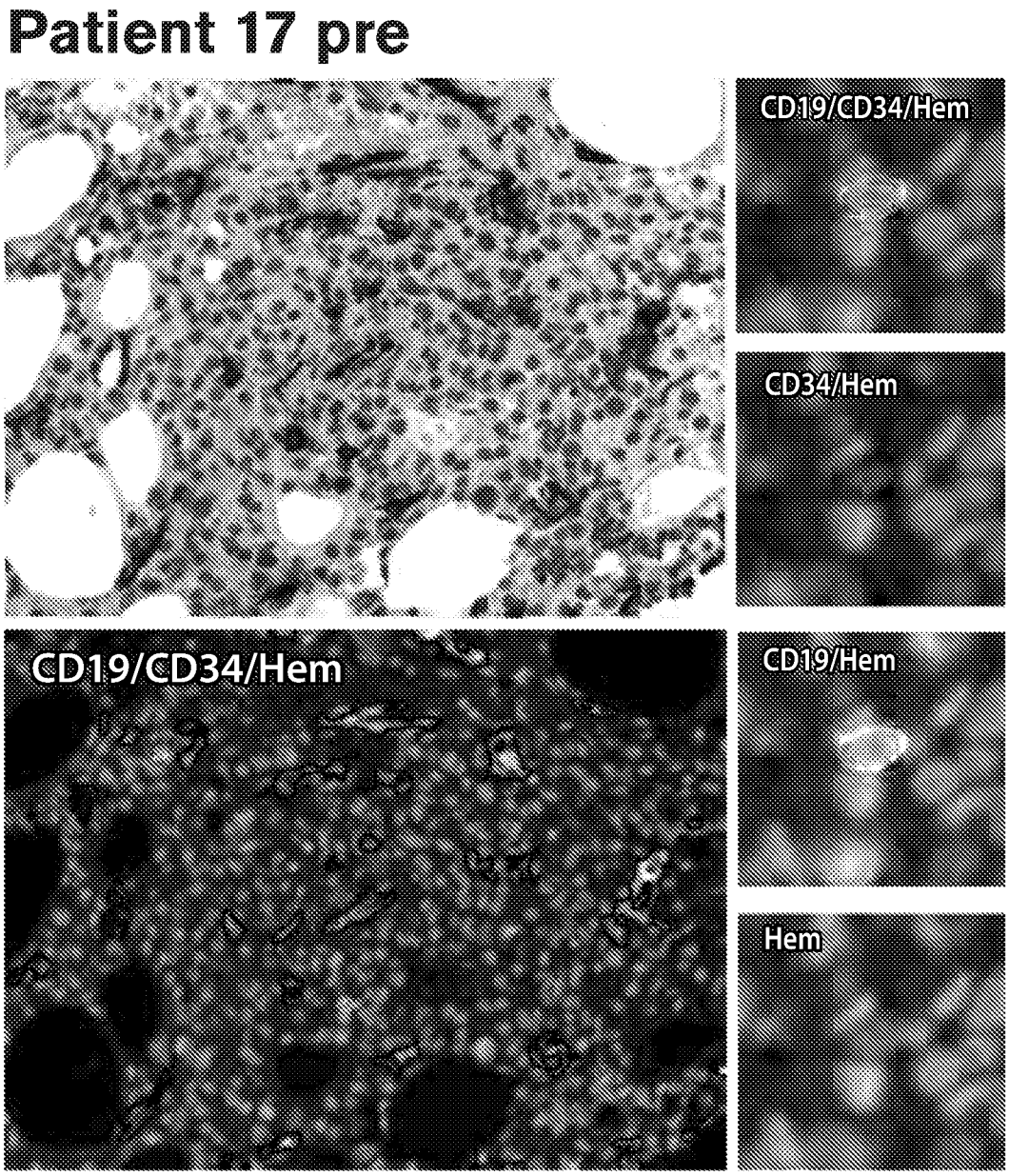

Patient 17 pre
CD19/CD34/Hem
CD34/Hem
CD19/CD34/Hem
CD19/Hem
Hem

FIG. 12B

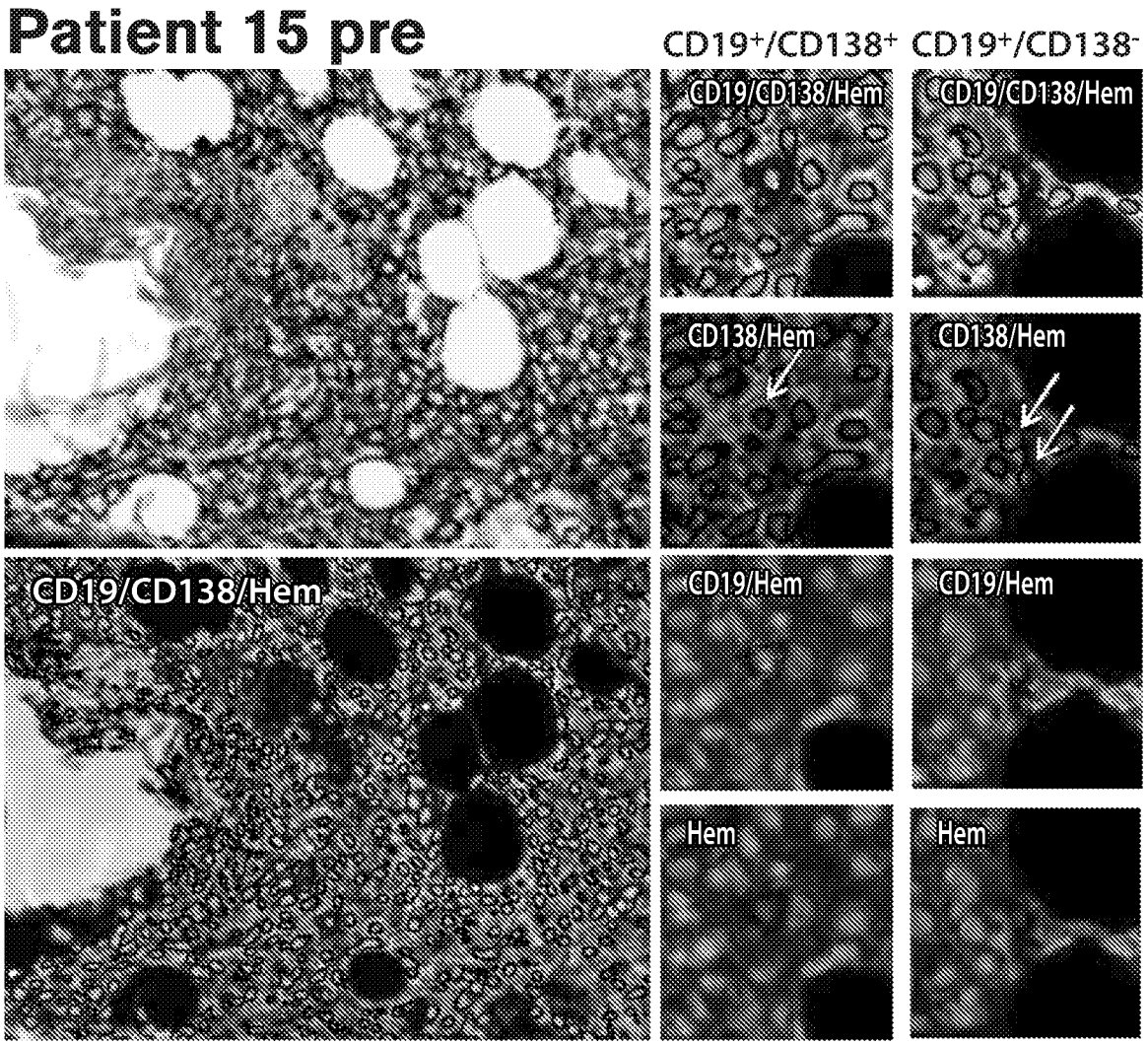

Patient 15 pre
CD19+/CD138+
CD19+/CD138-
CD19/CD138/Hem
CD19/CD138/Hem
CD138/Hem
CD138/Hem
CD19/CD138/Hem
CD19/Hem
CD19/Hem
Hem
Hem

FIG. 13

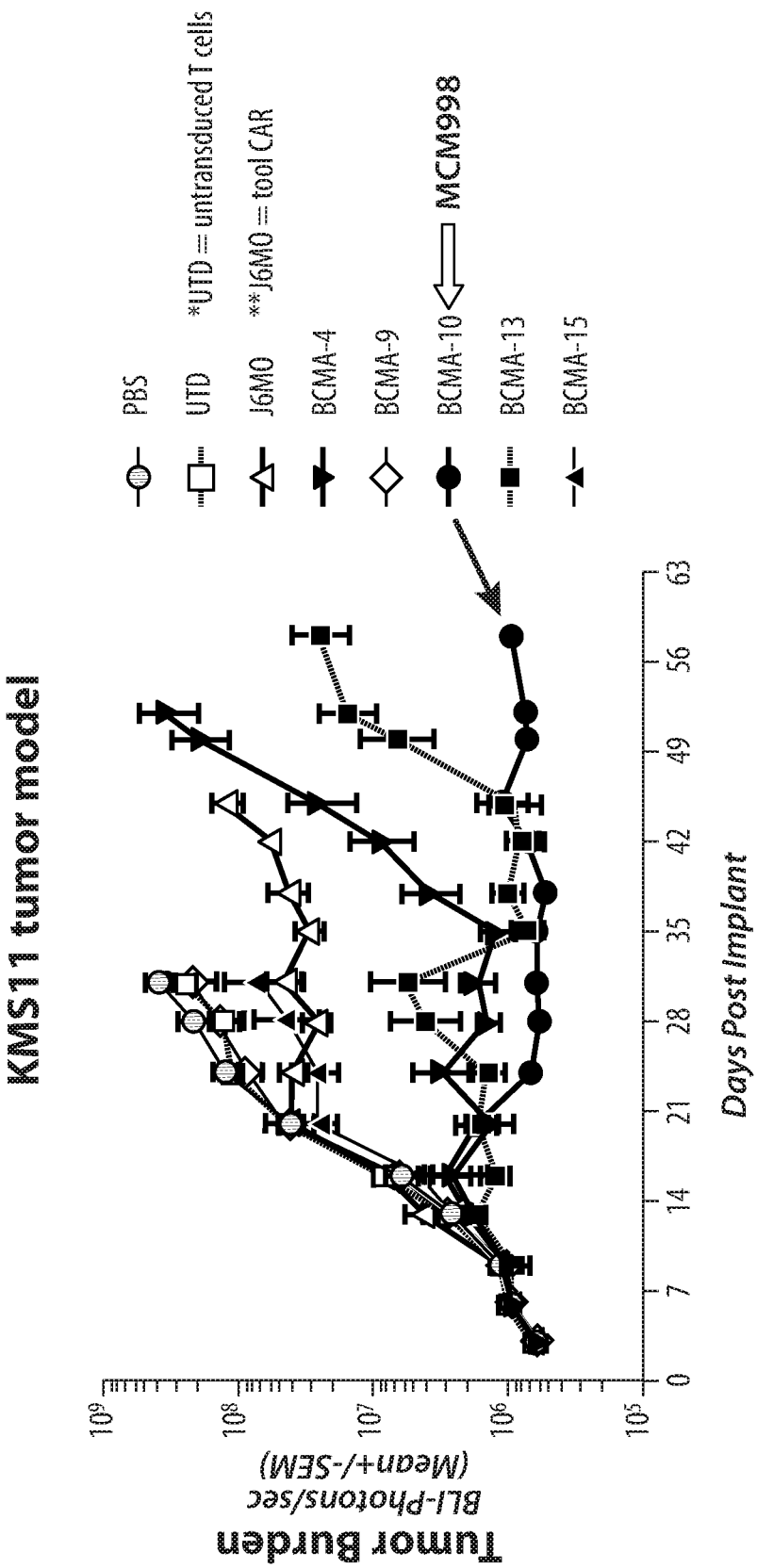

KMS11 tumor model
Tumor Burden
BLI-Photons/sec
(Mean+/-SEM)
Days Post Implant
PBS
UTD
J6MO
BCMA-4
BCMA-9
BCMA-10
BCMA-13
BCMA-15
*UTD = untransduced T cells
**J6MO = tool CAR
MCM998

FIG. 14

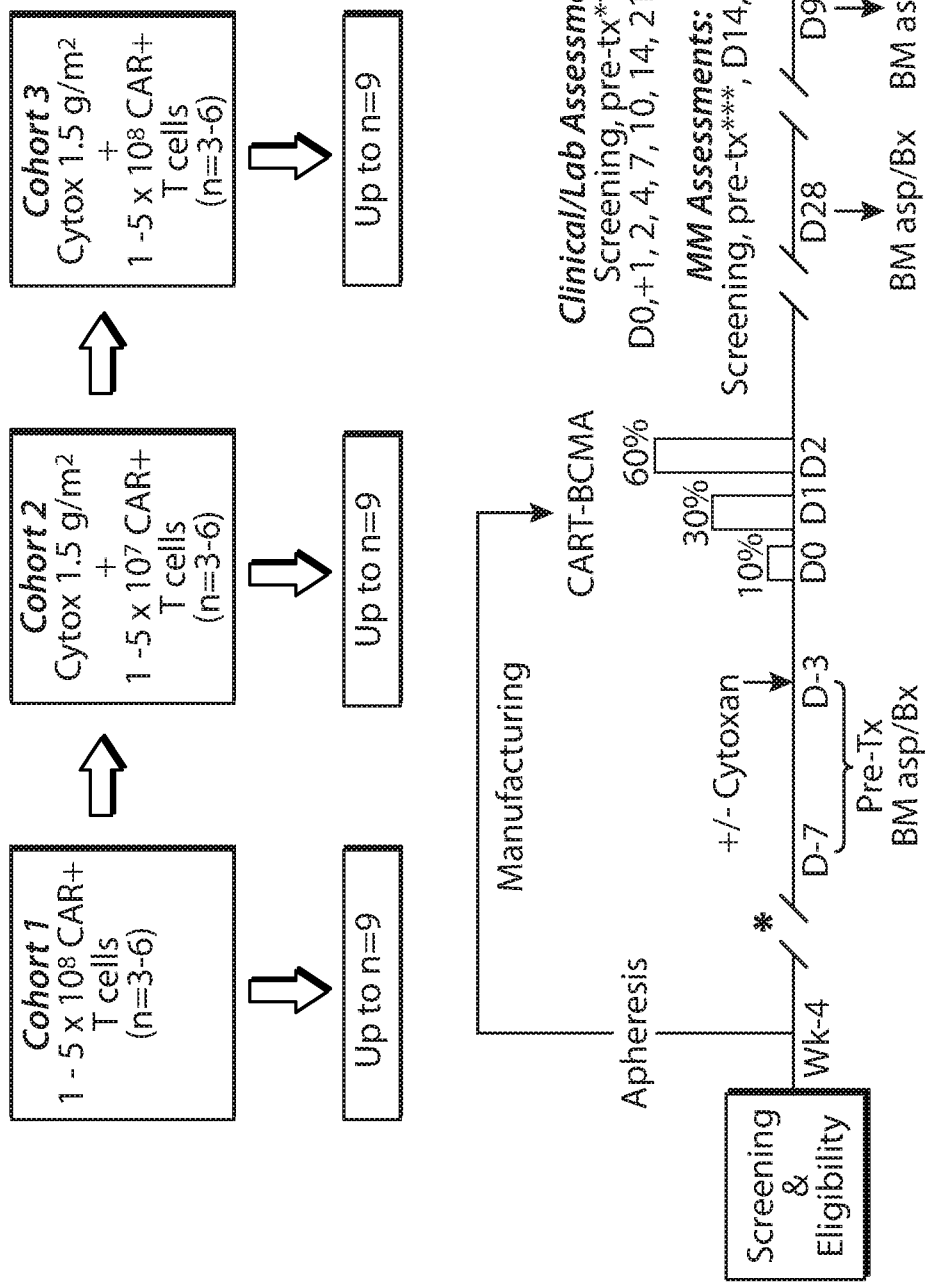

Cohort 1
1 - 5 x 10⁸ CAR+ T cells (n=3-6)
Cohort 2
Cytox 1.5 g/m²
+
1 -5 x 10⁷ CAR+ T cells (n=3-6)
Cohort 3
Cytox 1.5 g/m²
+
1 -5 x 10⁸ CAR+ T cells (n=3-6)
Up to n=9
Up to n=9
Up to n=9
Screening & Eligibility
Wk-4
Apheresis
Manufacturing
CART-BCMA
*
D-7
D-3
Pre-Tx
BM asp/Bx
+/- Cytoxan
10%
30%
60%
D0 D1D2
Clinical/Lab Assessments:
Screening, pre-tx***
D0,+1, 2, 4, 7, 10, 14, 21, 28**
MM Assessments:
Screening, pre-tx***, D14, D28**
D28
BM asp/Bx
D90
BM asp/Bx

FIG. 15

	All patients (n=14)	Cohort 1 (n=9)	Cohort 2/3 (n=5)
Age	55.5 (44-70)	57 (44-70)	54 (51-64)
Gender	57% M; 43% F	67% male; 33% female	40% M; 60% F
Years from diagnosis	4.9 (1.8-9.6)	4.9 (1.8-9.6)	4.9 (2.9-9.4)
Isotype	IgG (42%), IgA (42%) LC (14%)	IgG (33%), IgA (44%) LC (22%)	IgG (60%), IgA (40%)
Prior lines of therapy	7 (4-11)	9 (4-11)	7 (5-10)
Lenalidomide	100% (ref 86%)	100% (refractory: 78%)	100% (ref 80%)
Bortezomib	100% (ref 86%)	100% (refr: 89%)	100% (ref 80%)
Pomalidomide	100% (ref 93%)	100% (refr: 89%)	100% (ref 100%)
Carfilzomib	93%* (ref 92%)	100%* (refr: 89%)	80%* (ref 80%)
Autologous SCT	86%	78%	100%
Cyclophosphamide	100% (ref 71%)	100% (refr: 67%)	100% (ref 80%)
Daratumumab	57% (ref 57%)	44% (refr: 44%)	80% (ref 80%)
Anti-PD1	29% (ref 29%)	33% (refr: 33%)	20% (ref 20%)
High-risk genetics -17P or *TP53* mutation	100% 64%	100% 67%	100% 60%
Extramededullary dz	35%	33%	40%
% BM plasma cells	65% (0-95)	80 (15-95)	45% (0-95%)

FIG. 16A

Median peripheral T cell counts (cells/μL)

	Cohort 1 (n=9)	Cohort 2/3 (n=5)
Pre-pheresis	CD3: 325 (171 - 1134) CD4: 182 (42 - 519) CD8: 149 (80 - 600)	CD3: 633 (295 - 1231) CD4: 371 (129 - 518) CD8: 395 (168 - 706)
Pre-Cytoxan		CD3: 423 (237 - 646) CD4: 158 (95 - 296) CD8: 277 (140 - 343)
Day 0	CD3: 258 (117 - 1354) CD4: 169 (36 - 497) CD8: 126 (66 - 832)	CD3: 138 (79 - 261) CD4: 62 (42 - 131) CD8: 84 (37 - 161)

FIG. 16B

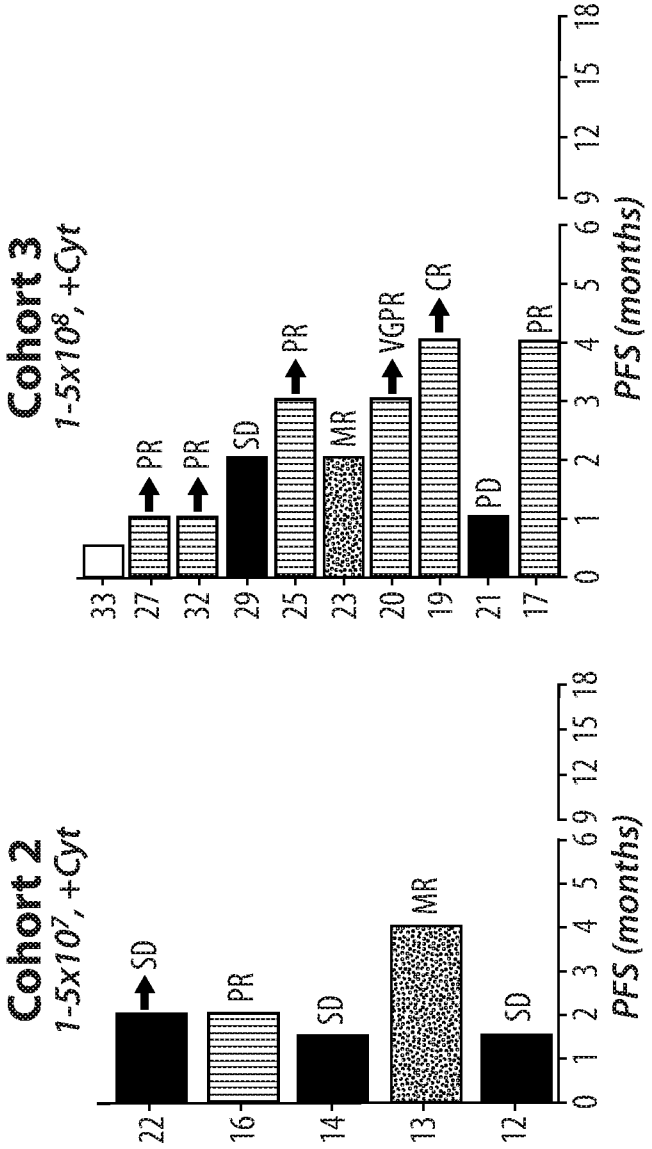


FIG. 17A

FIG. 17B

FIG. 17C

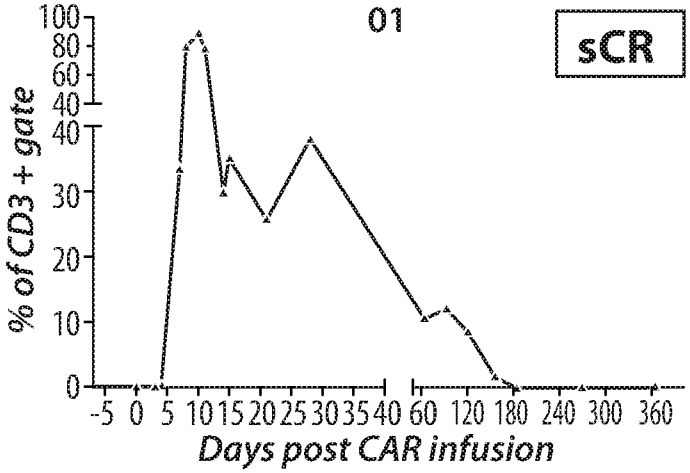


FIG. 18A-1

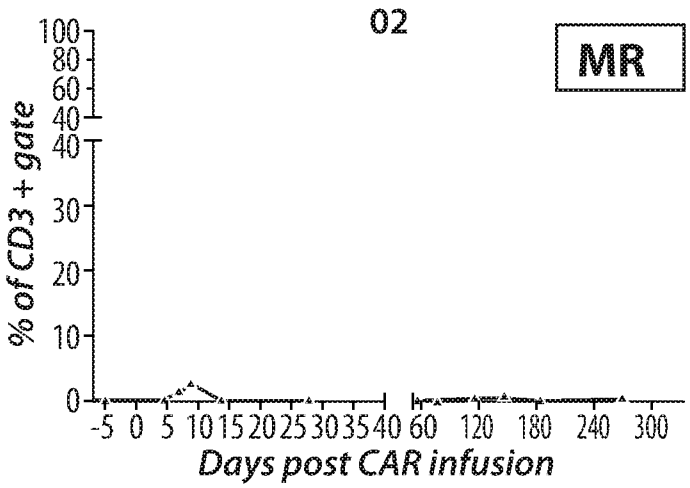


FIG. 18A-2

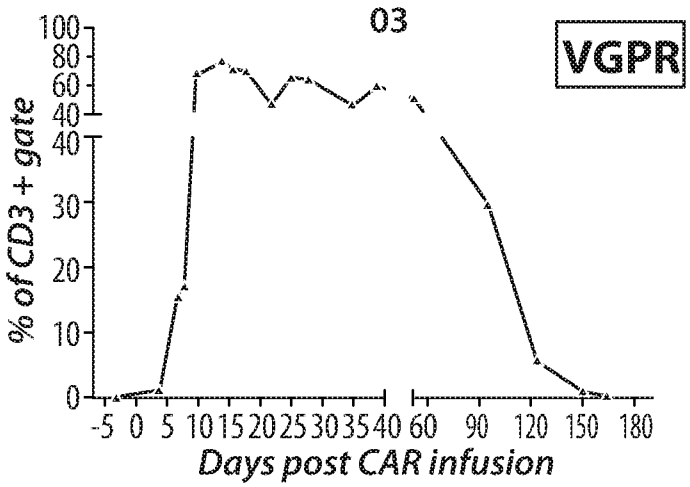


FIG. 18A-3

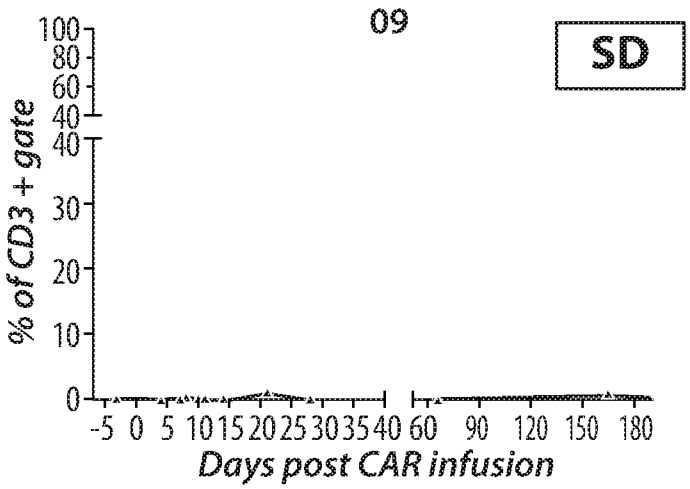


FIG. 18A-4

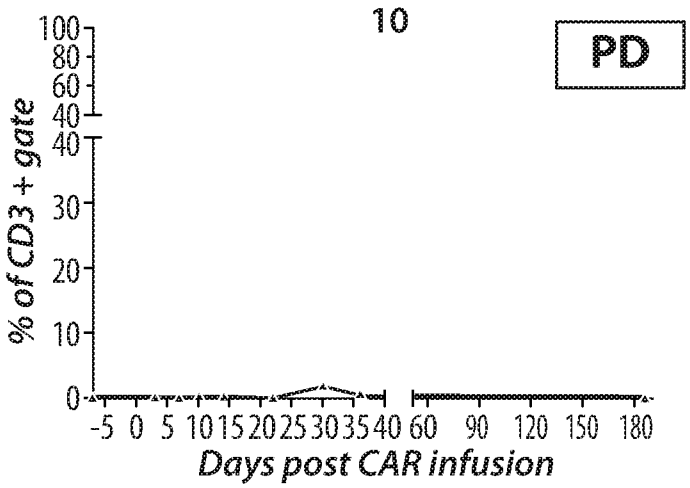


FIG. 18A-5

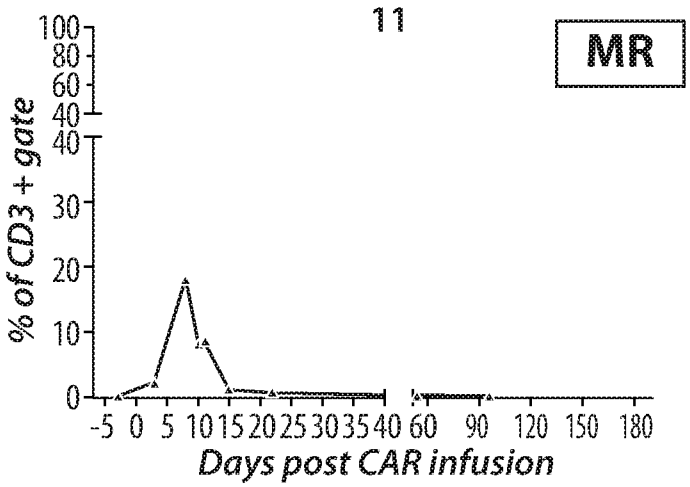


FIG. 18A-6

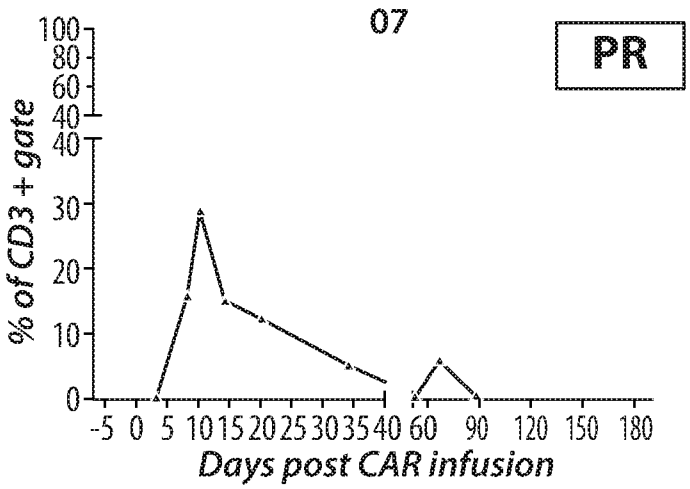


FIG. 18A-7

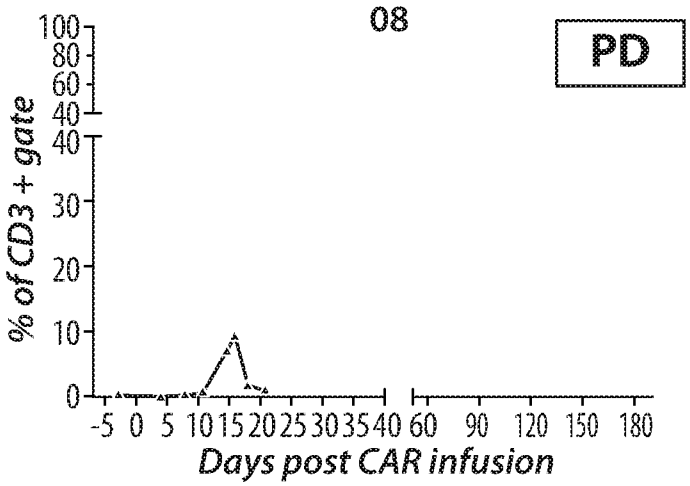


FIG. 18A-8

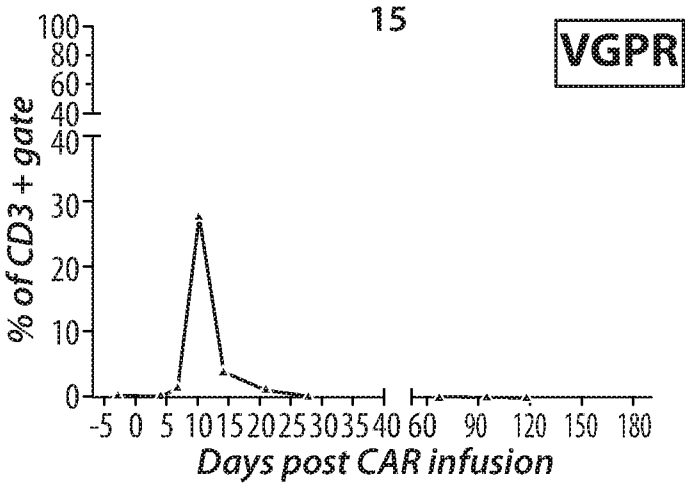


FIG. 18A-9

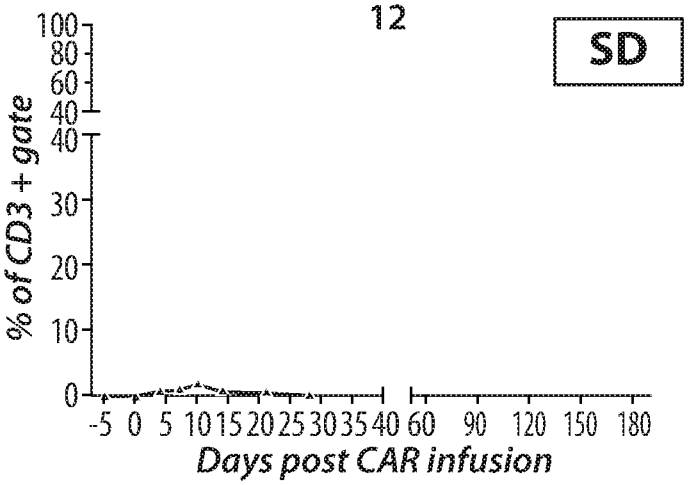


FIG. 18B-1

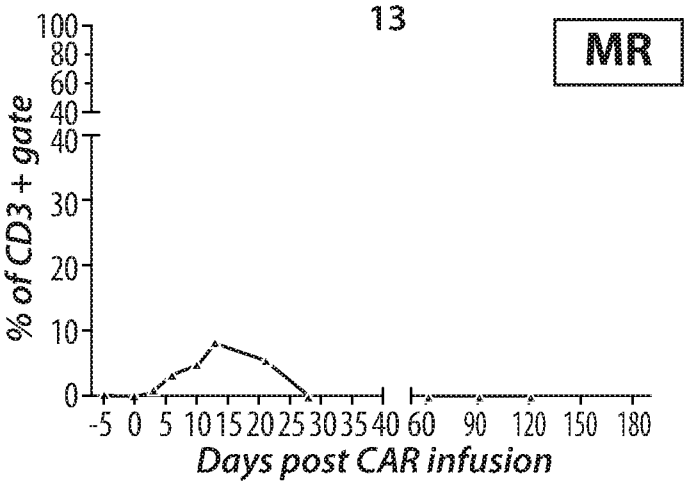


FIG. 18B-2

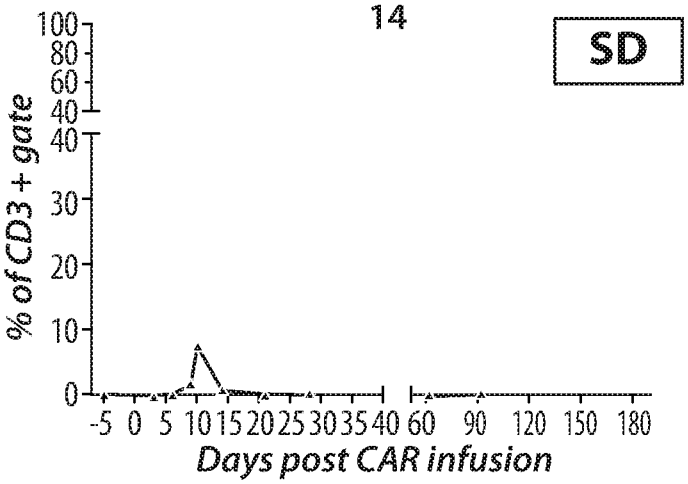


FIG. 18B-3

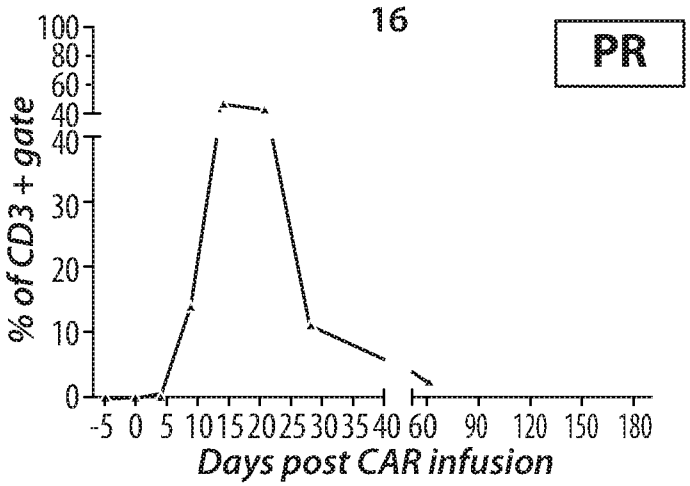


FIG. 18B-4

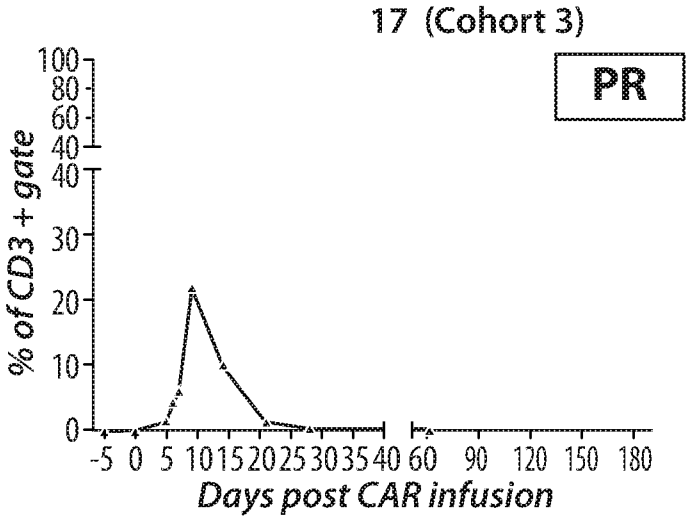


FIG. 18B-5

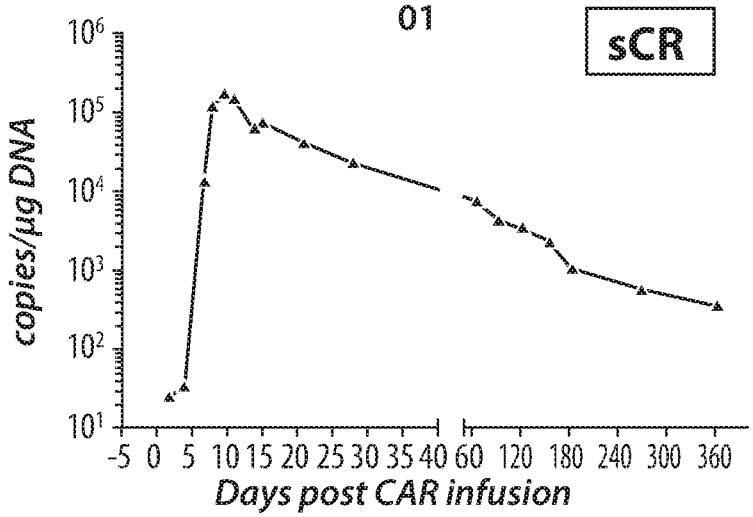


FIG. 19A-1

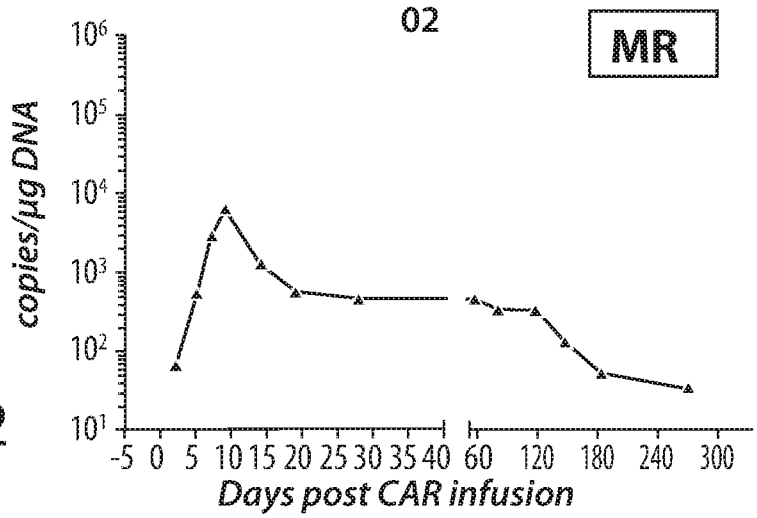


FIG. 19A-2

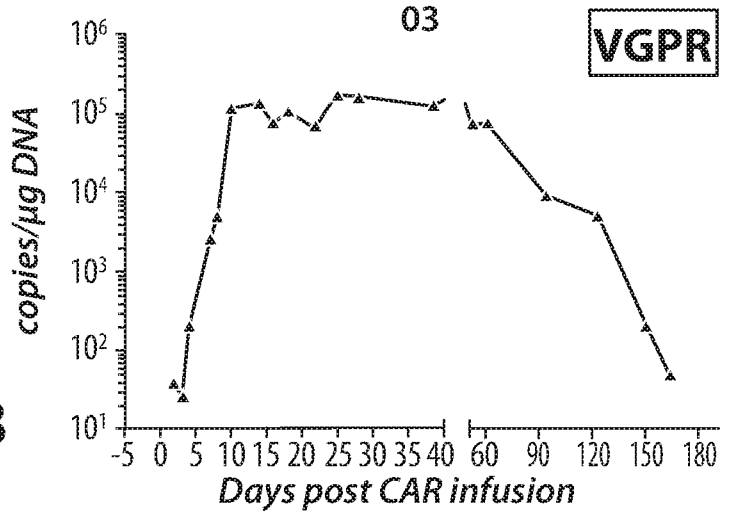


FIG. 19A-3

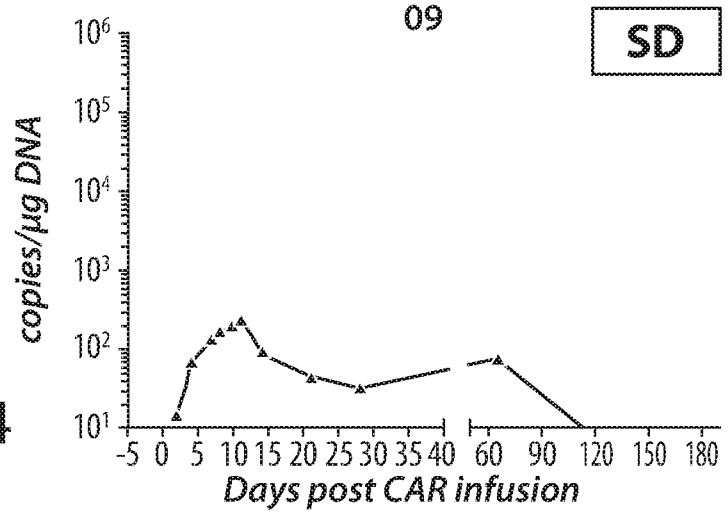


FIG. 19A-4

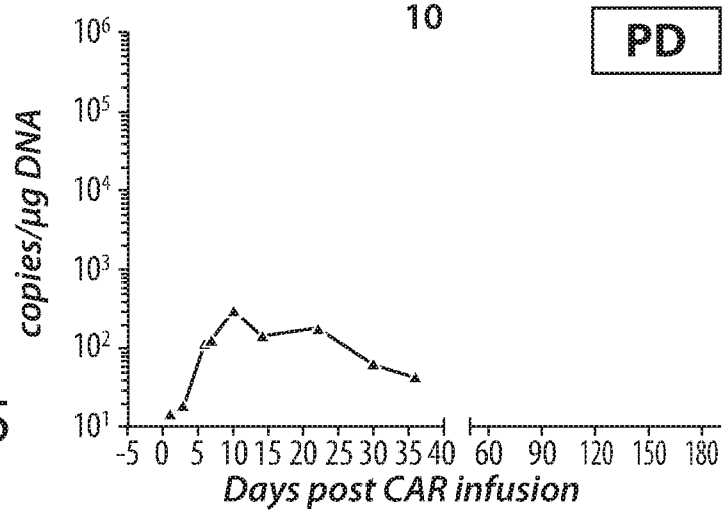


FIG. 19A-5

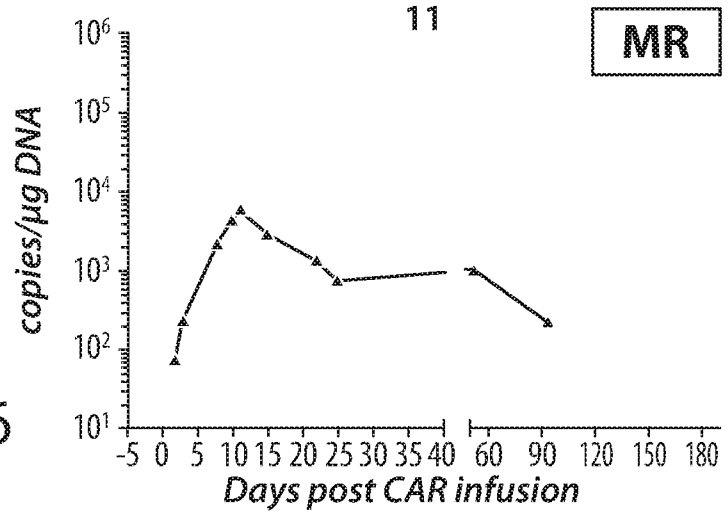


FIG. 19A-6

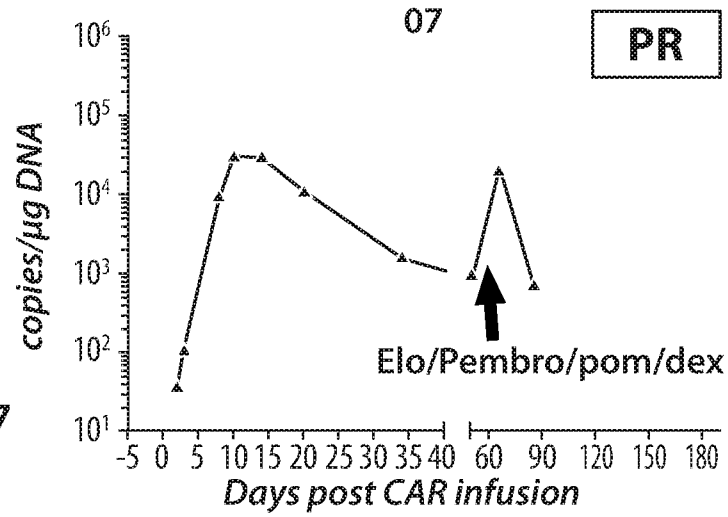


FIG. 19A-7

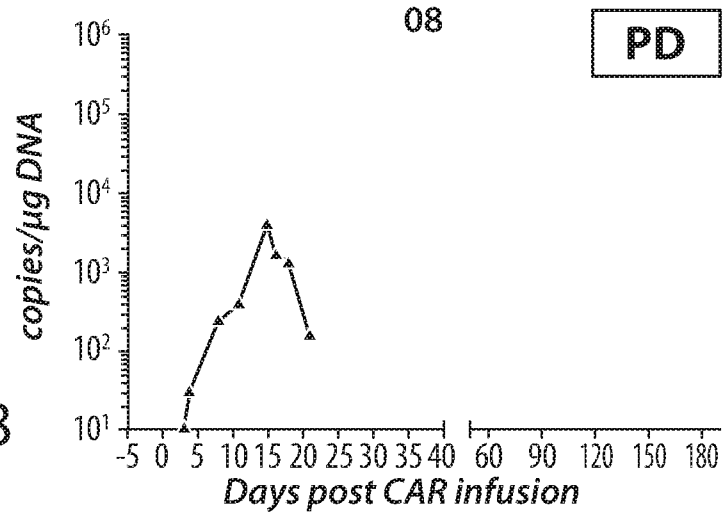


FIG. 19A-8

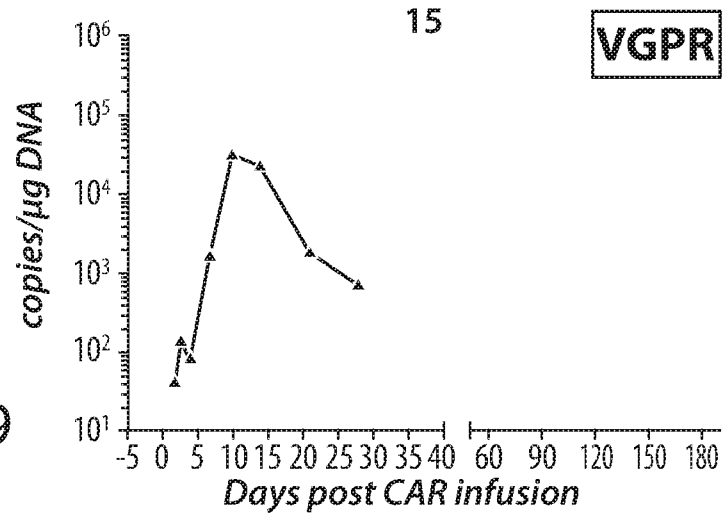


FIG. 19A-9

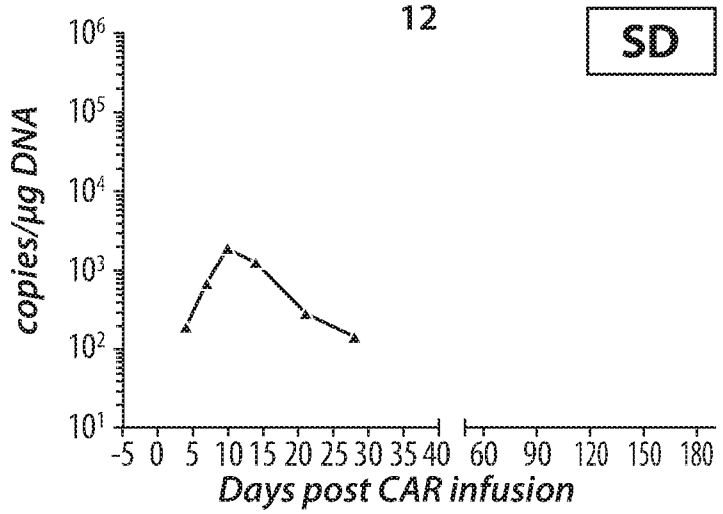


FIG. 19B-1

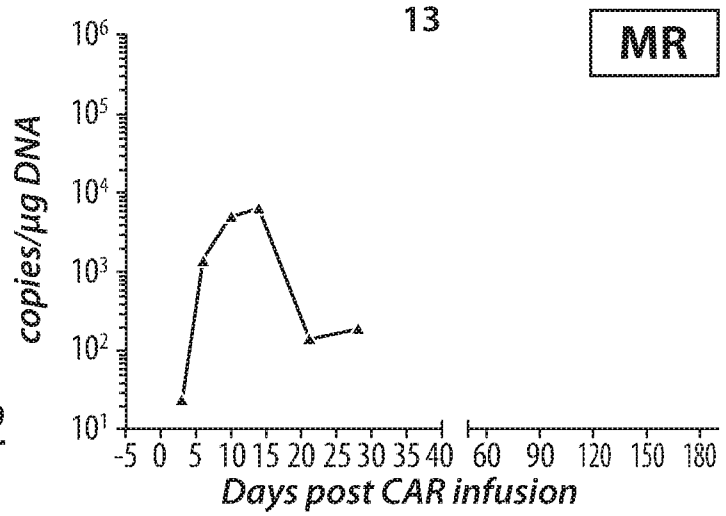


FIG. 19B-2

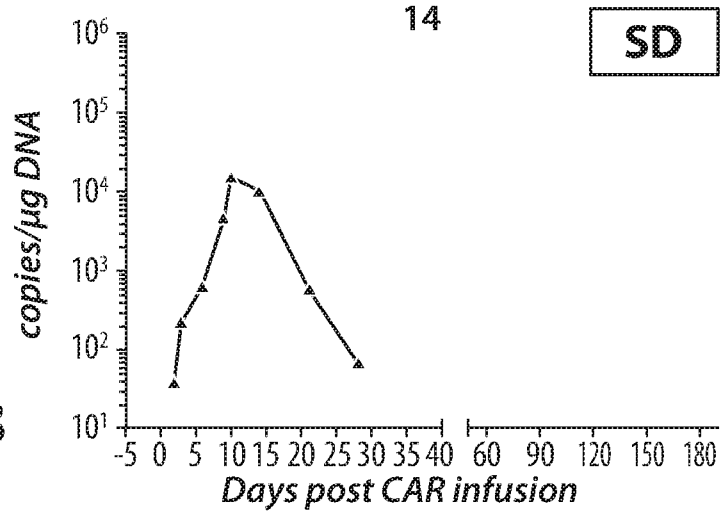


FIG. 19B-3

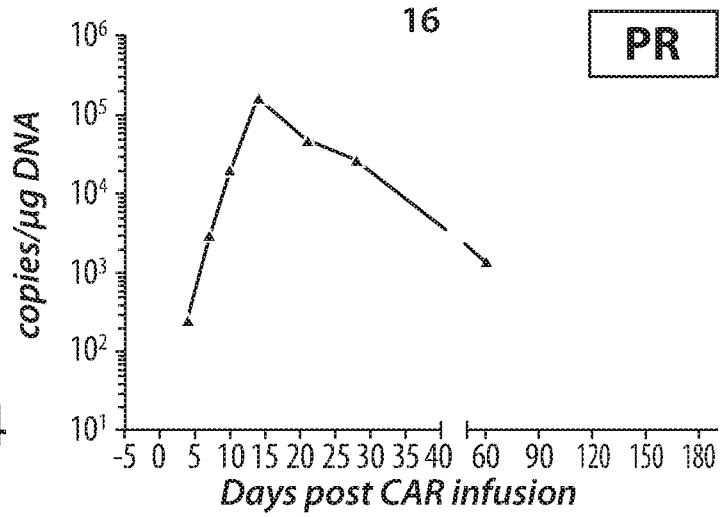


FIG. 19B-4

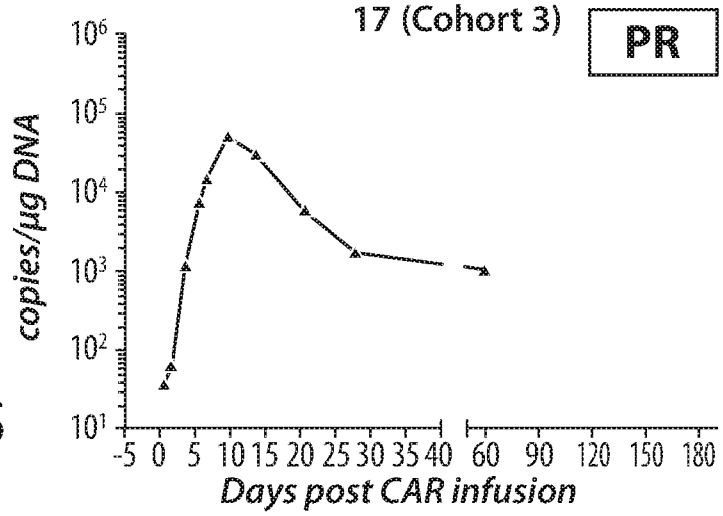


FIG. 19B-5

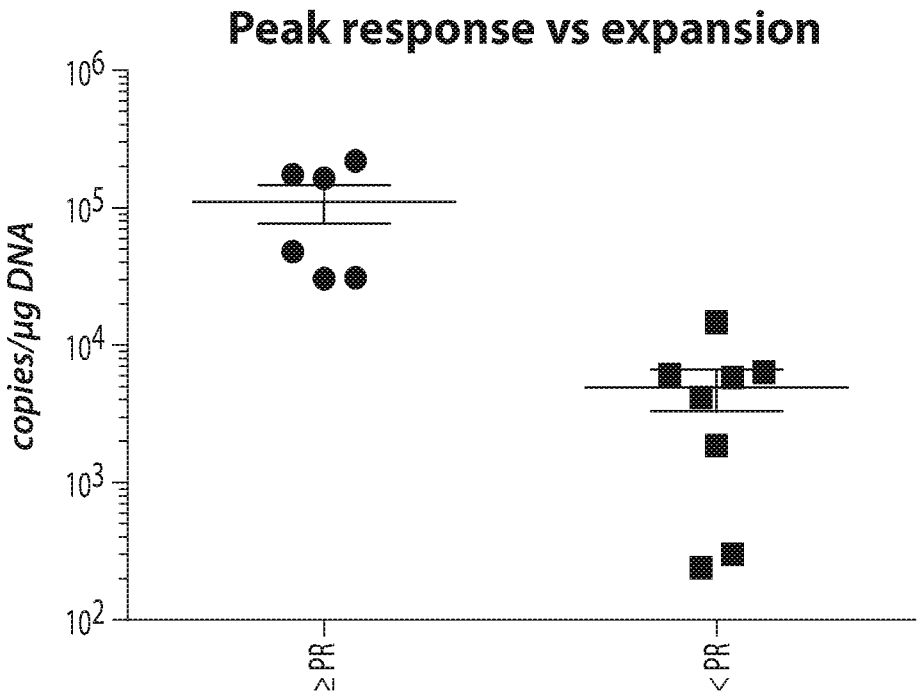


FIG. 20A

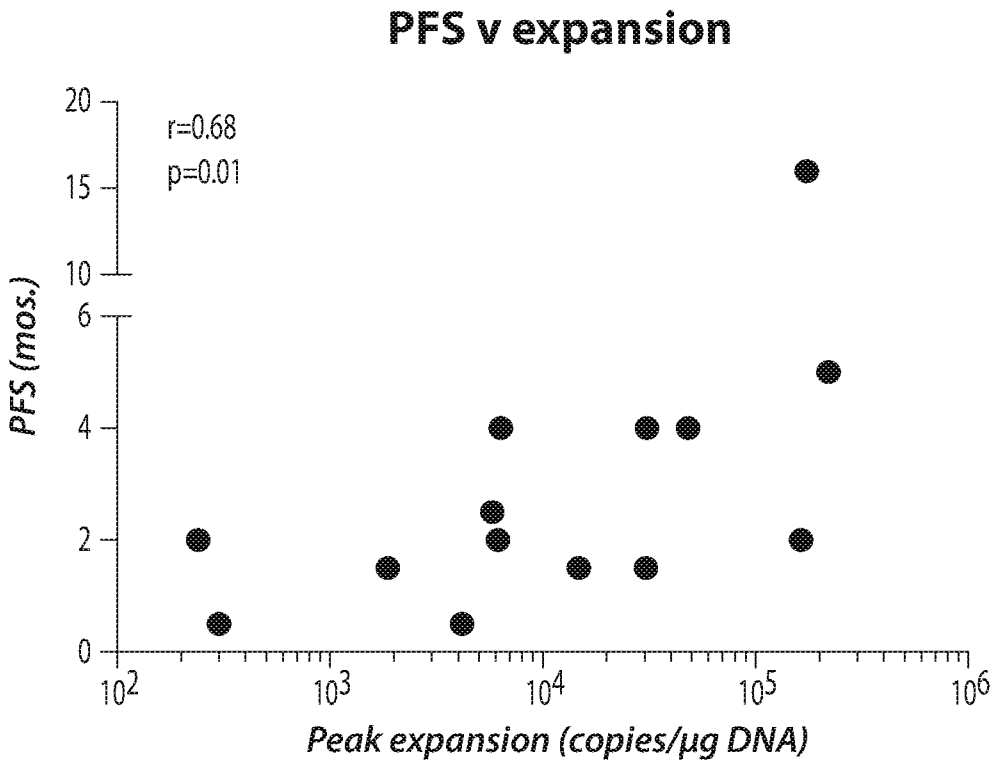


FIG. 20B

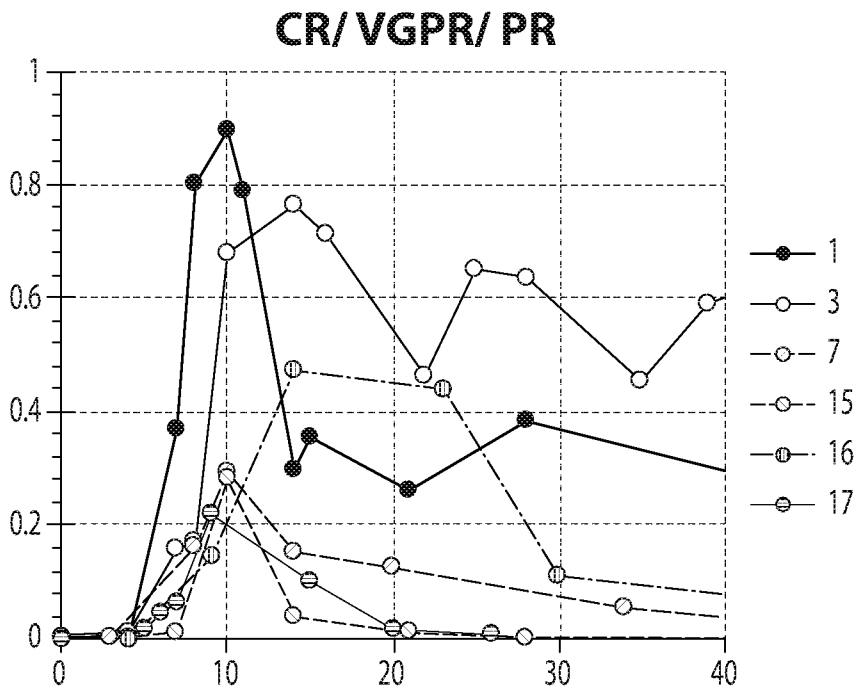
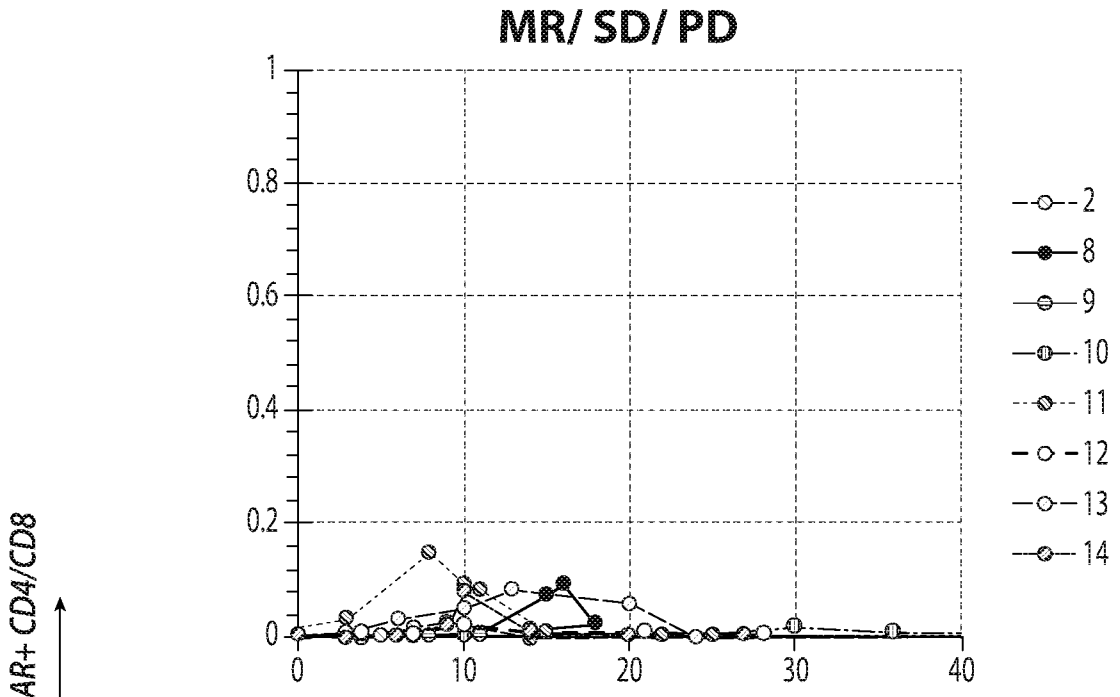


FIG. 21A



CR	VGPR	PR	MR	SD	PD
1	3, 15	7	2, 11, 13	9, 12, 14	8, 10
Unknown: 16, 17					

FIG. 21B

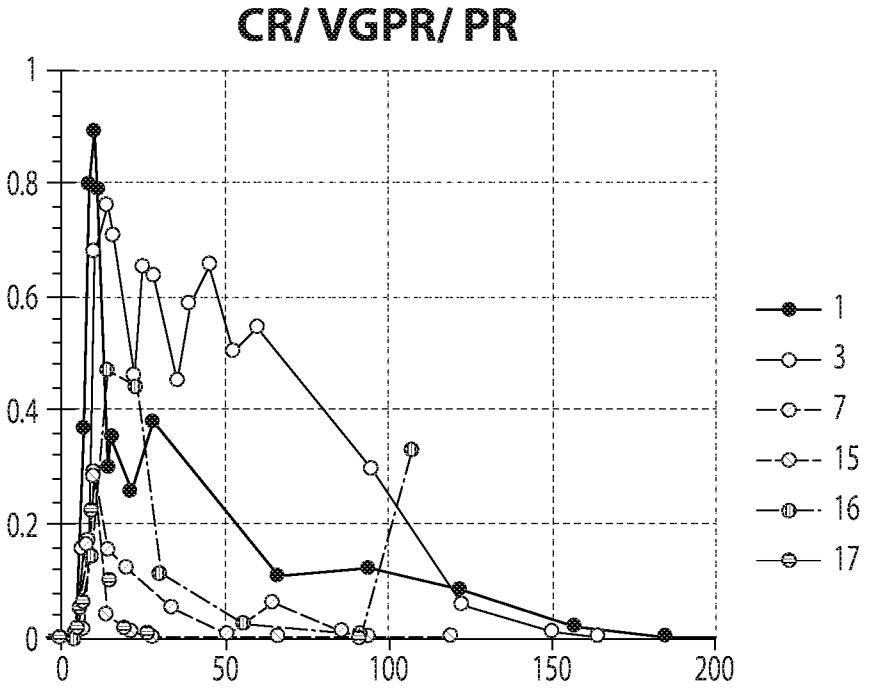
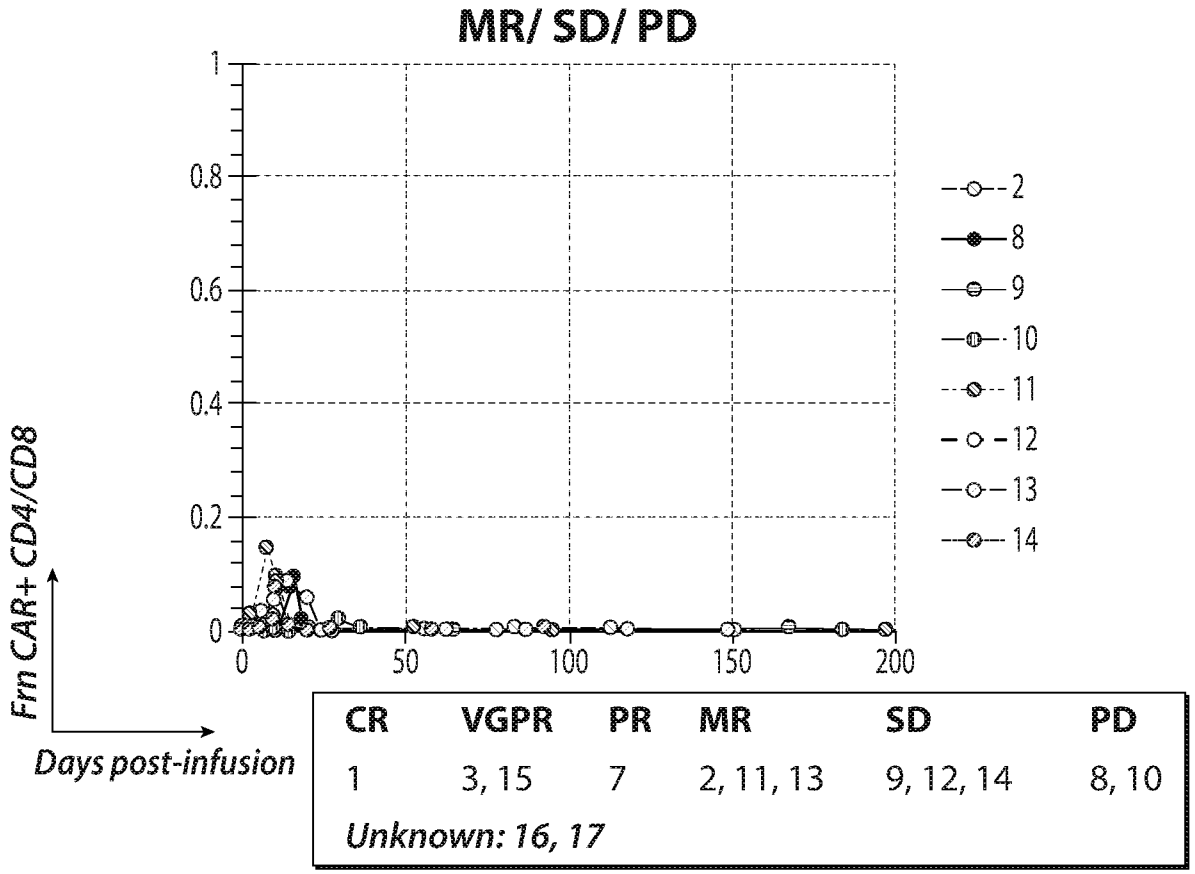


FIG. 21C



CR	VGPR	PR	MR	SD	PD
1	3, 15	7	2, 11, 13	9, 12, 14	8, 10
Unknown: 16, 17					

FIG. 21D

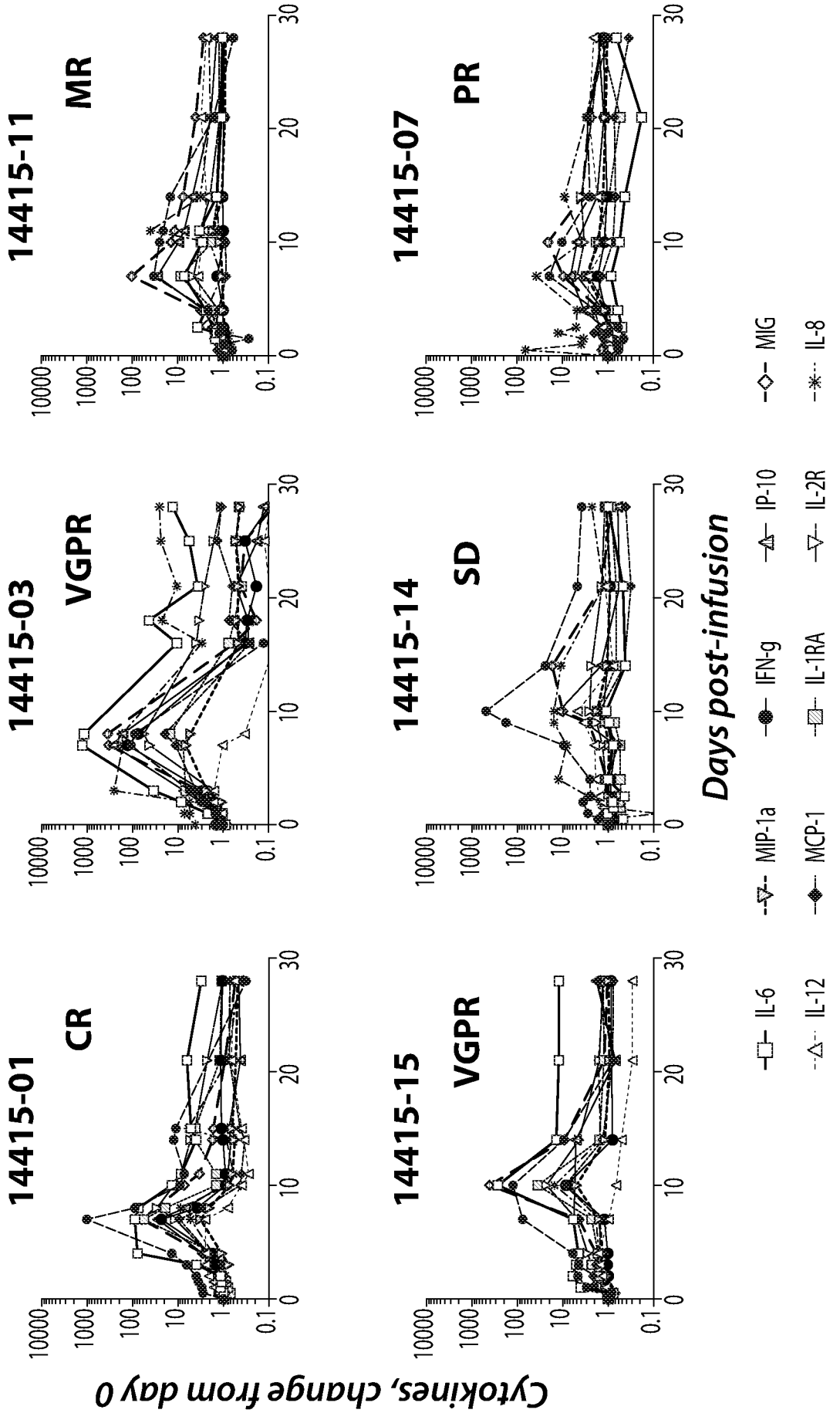

14415-01
CR
14415-03
VGPR
14415-11
MR
14415-15
VGPR
14415-14
SD
14415-07
PR
Cytokines, change from day 0
Days post-infusion
IL-6
MIP-1a
IFN-g
IP-10
MIG
IL-12
MCP-1
IL-1RA
IL-2R
IL-8

Fig. 22-1

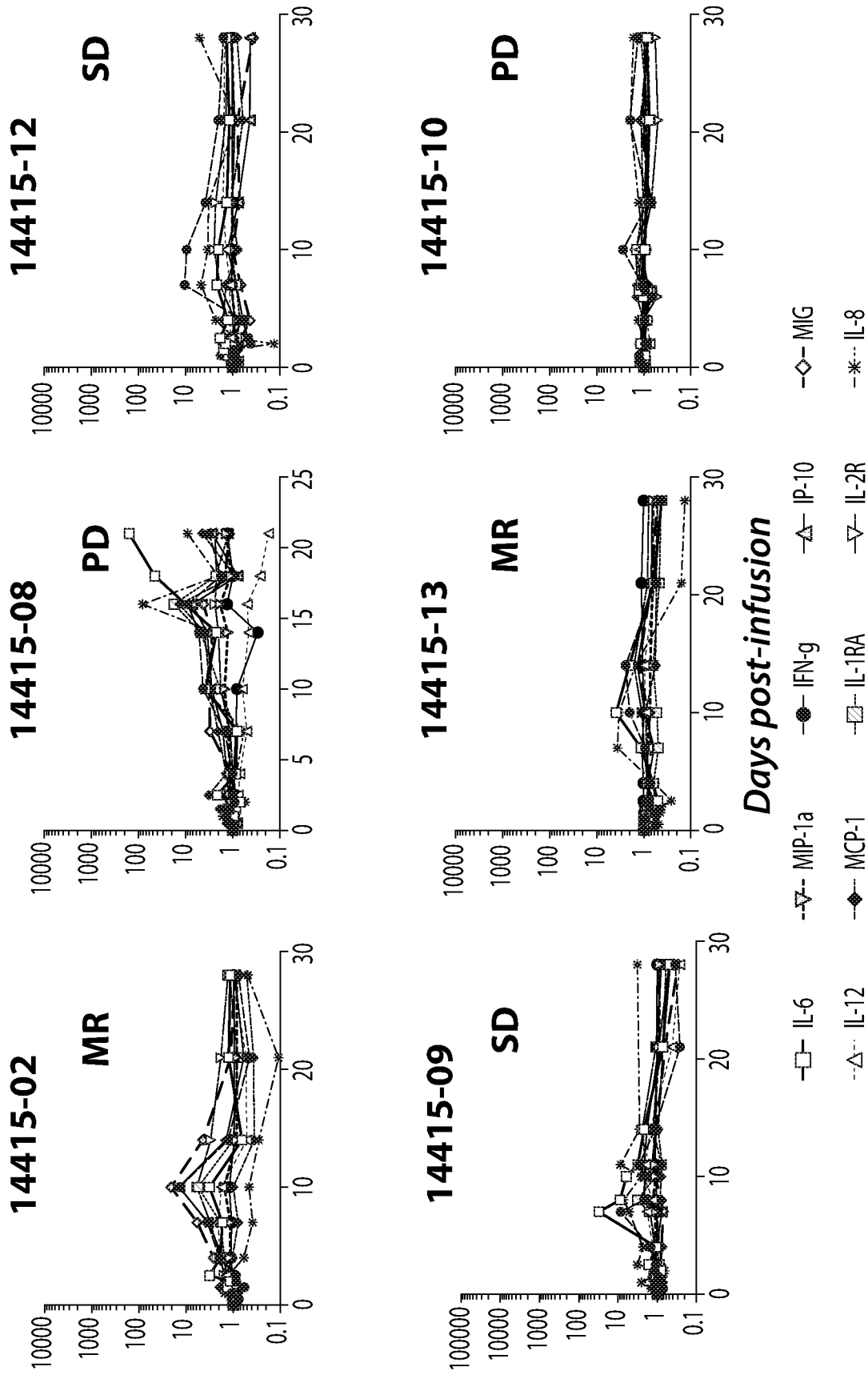

14415-02
MR
14415-08
PD
14415-12
SD
14415-09
SD
14415-13
MR
14415-10
PD
Cytokines, change from day 0
Days post-infusion
IL-6
MIP-1a
IFN-g
IP-10
MIG
IL-12
MCP-1
IL-1RA
IL-2R
IL-8

Fig. 22-2

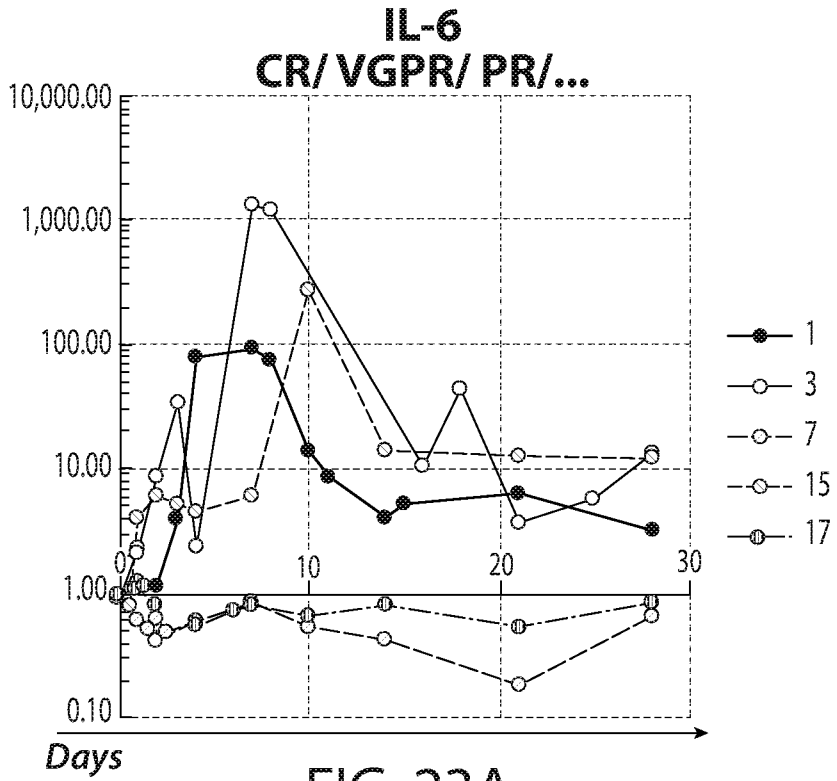
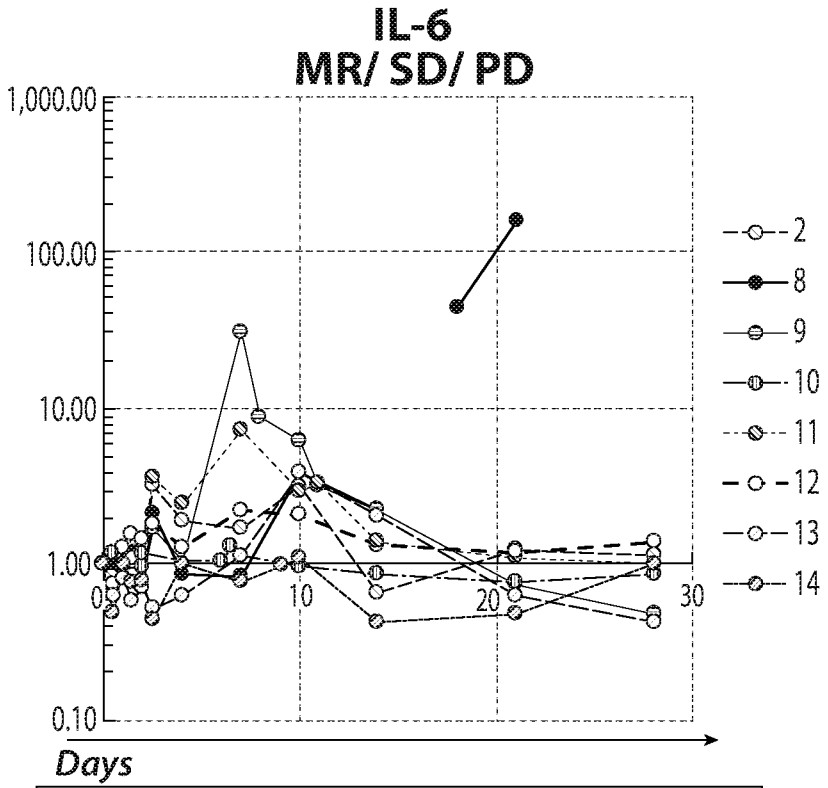


FIG. 23A



CR	VGPR	PR	MR	SD	PD
1	3, 15	7	2, 11, 13	9, 12, 14	8, 10
Unknown: 16, 17					

FIG. 23B

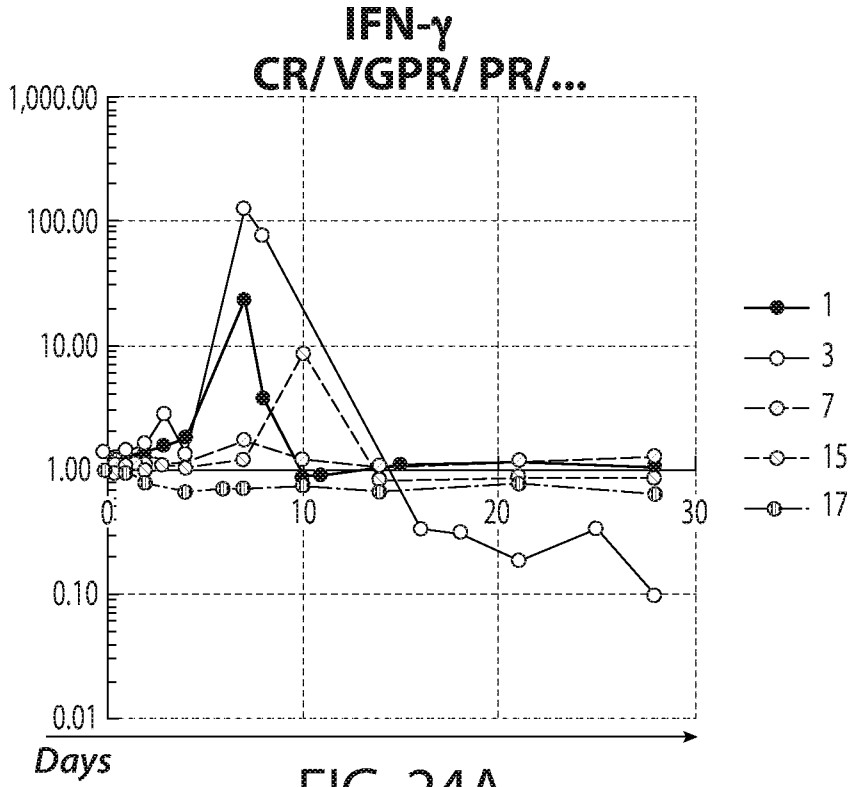
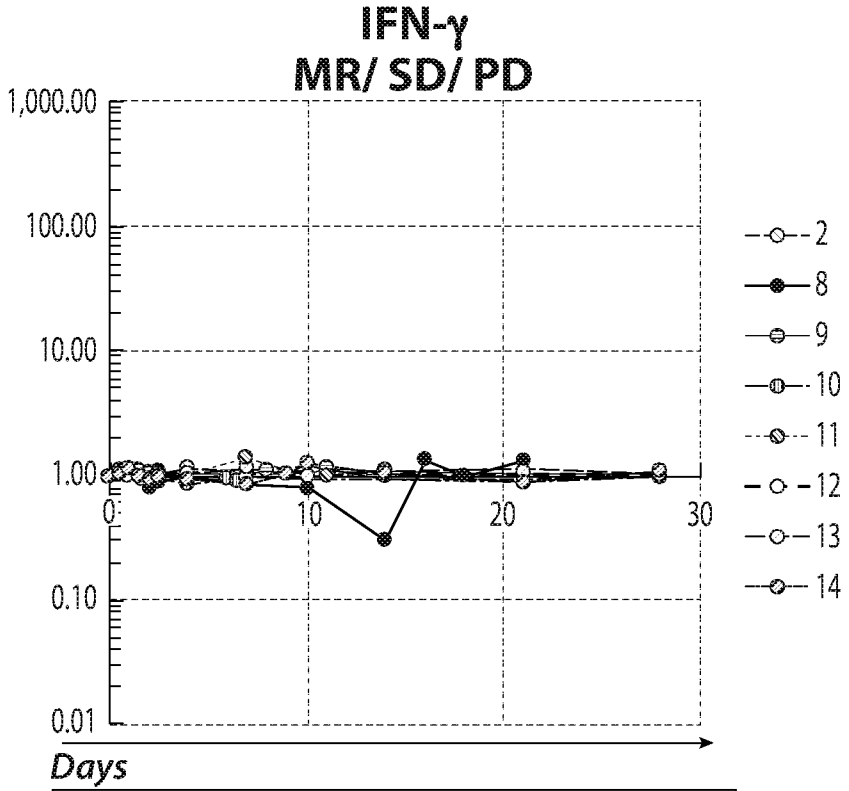


FIG. 24A



CR	VGPR	PR	MR	SD	PD
1	3, 15	7	2, 11, 13	9, 12, 14	8, 10

Unknown: 16, 17

FIG. 24B

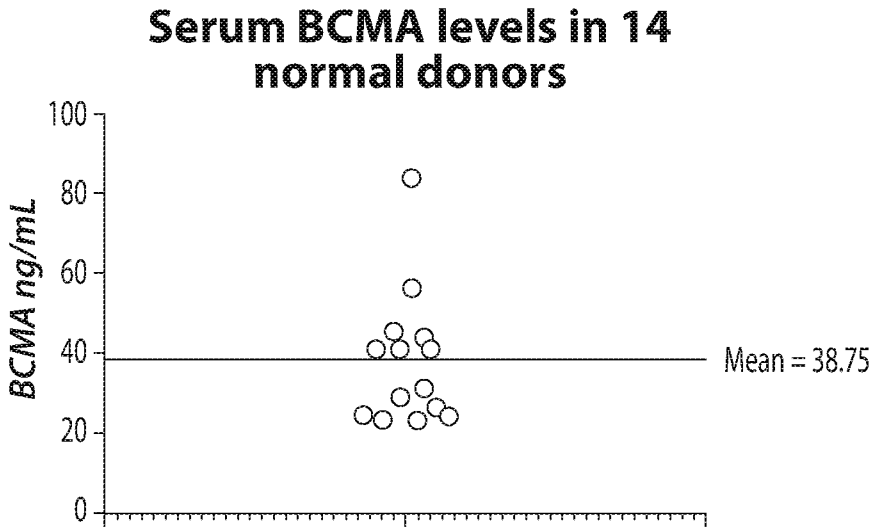


FIG. 25A

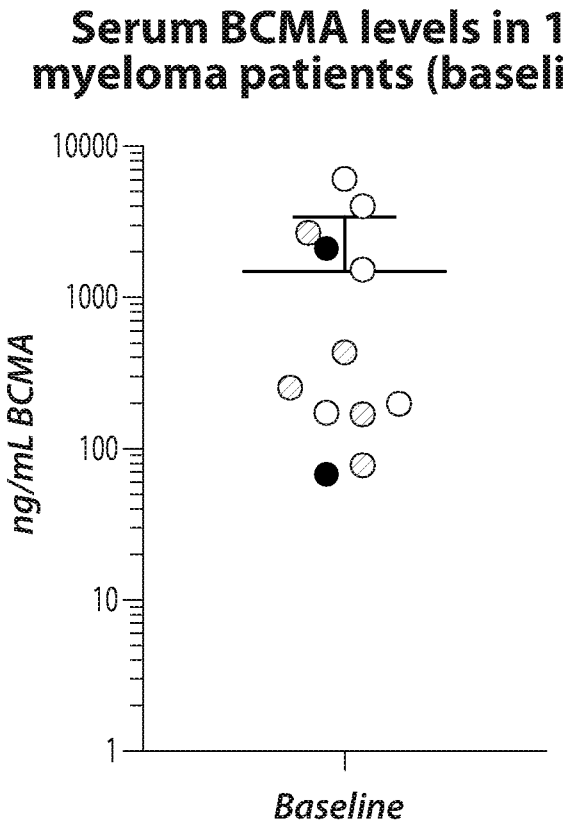


FIG. 25B

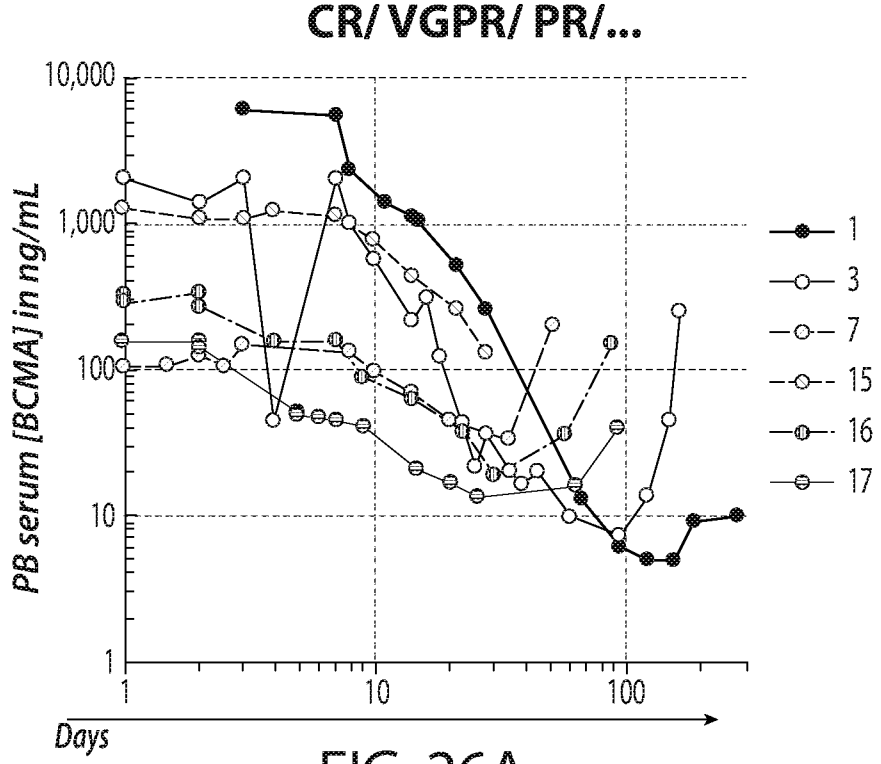
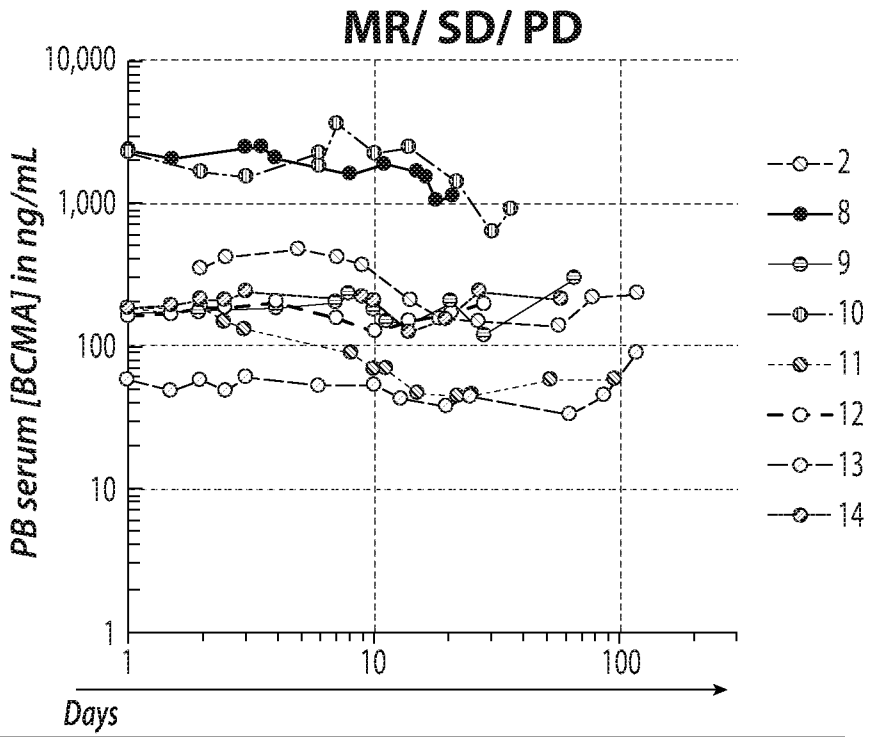


FIG. 26A



CR	VGPR	PR	MR	SD	PD
1	3, 15	7	2, 11, 13	9, 12, 14	8, 10
Unknown: 16, 17					

FIG. 26B

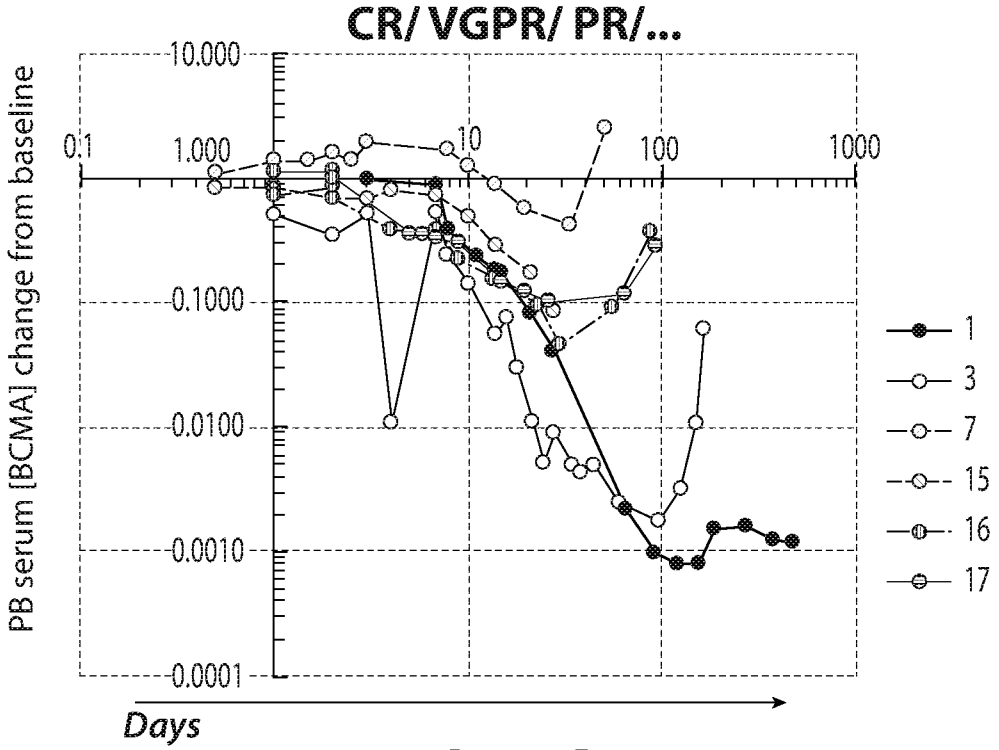
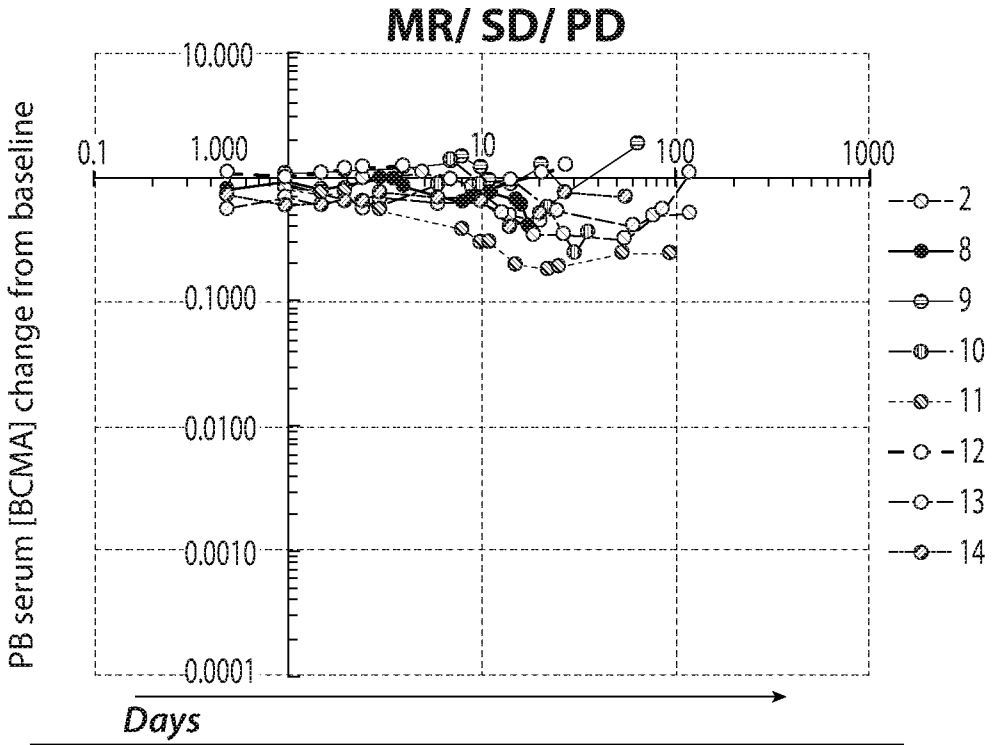


FIG. 26C



CR	VGPR	PR	MR	SD	PD
1	3, 15	7	2, 11, 13	9, 12, 14	8, 10

Unknown: 16, 17

FIG. 26D

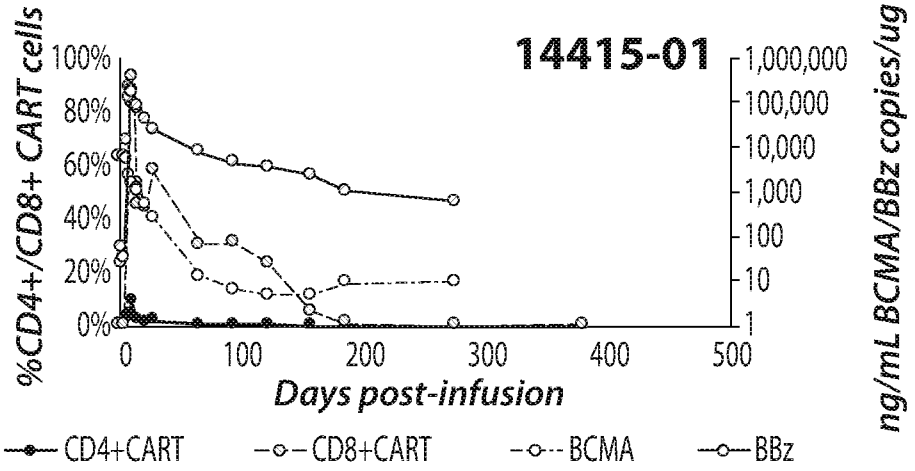


FIG. 27A

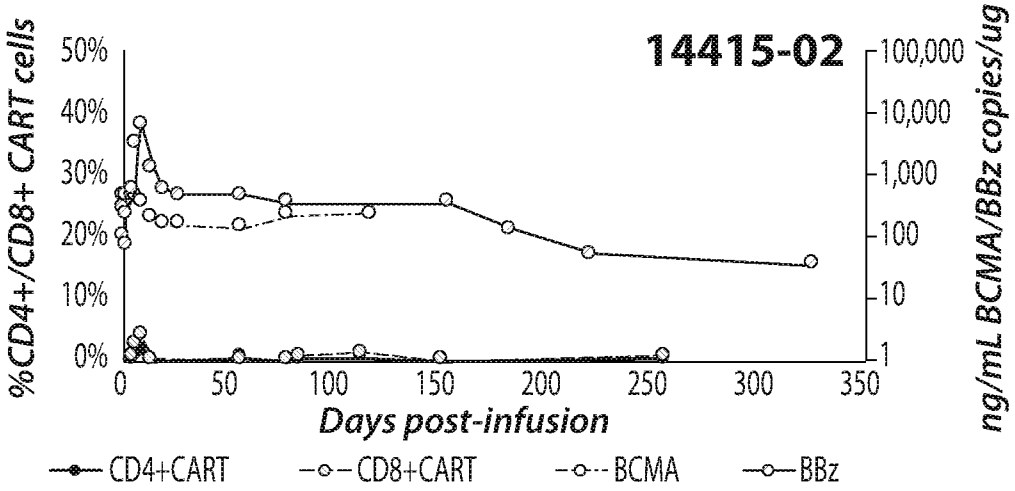


FIG. 27B

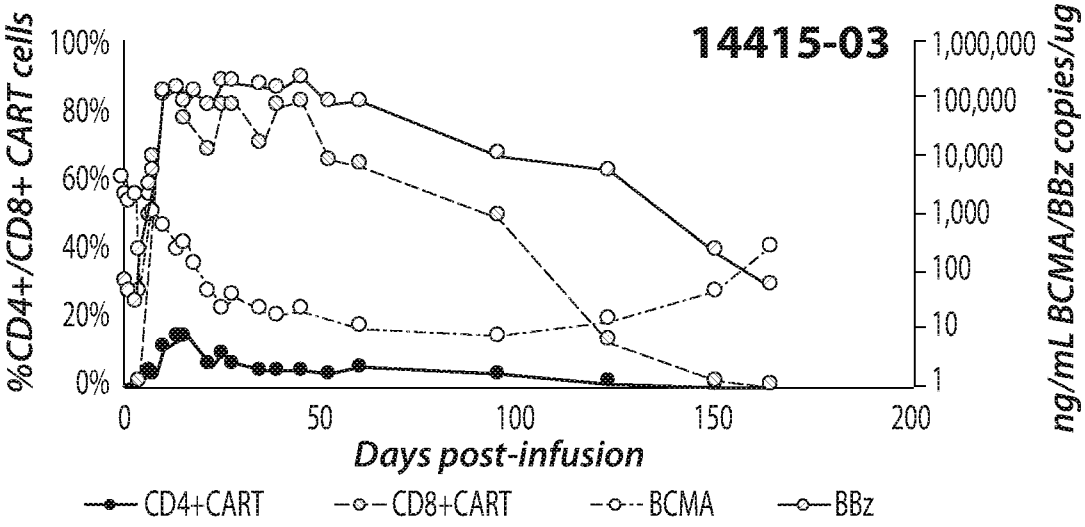


FIG. 27C

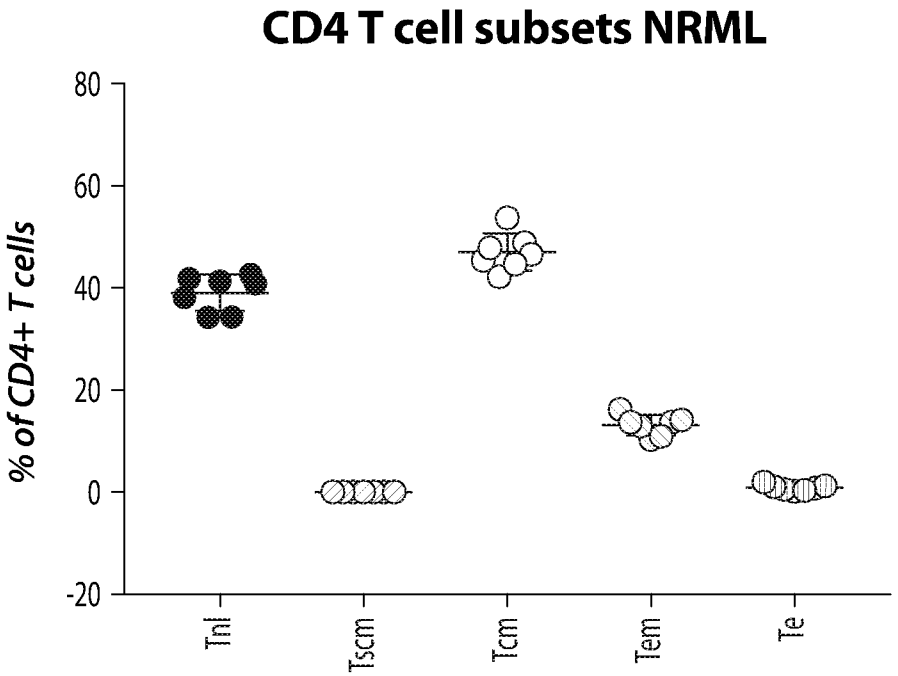


FIG. 28A

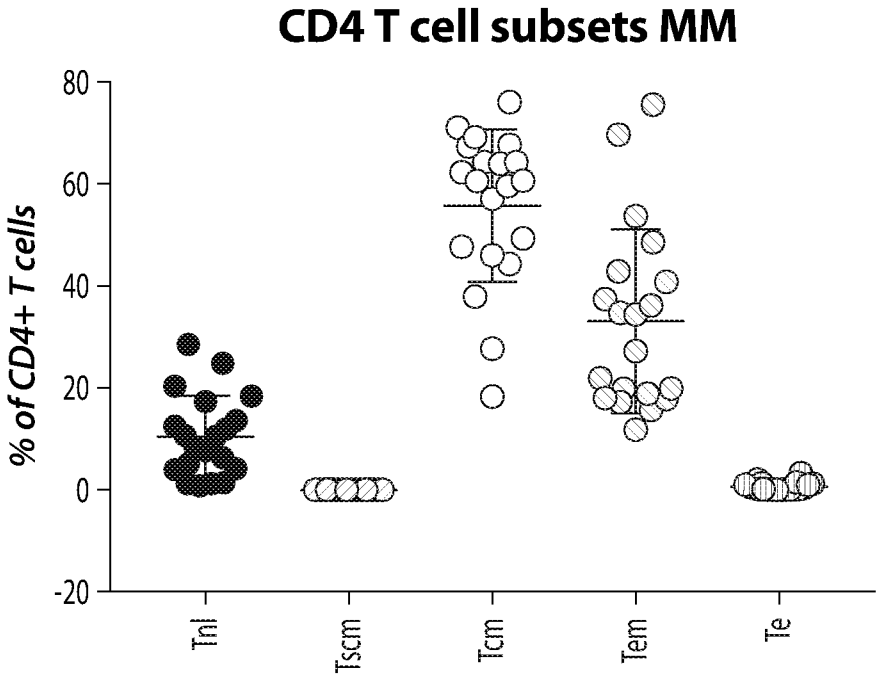


FIG. 28B

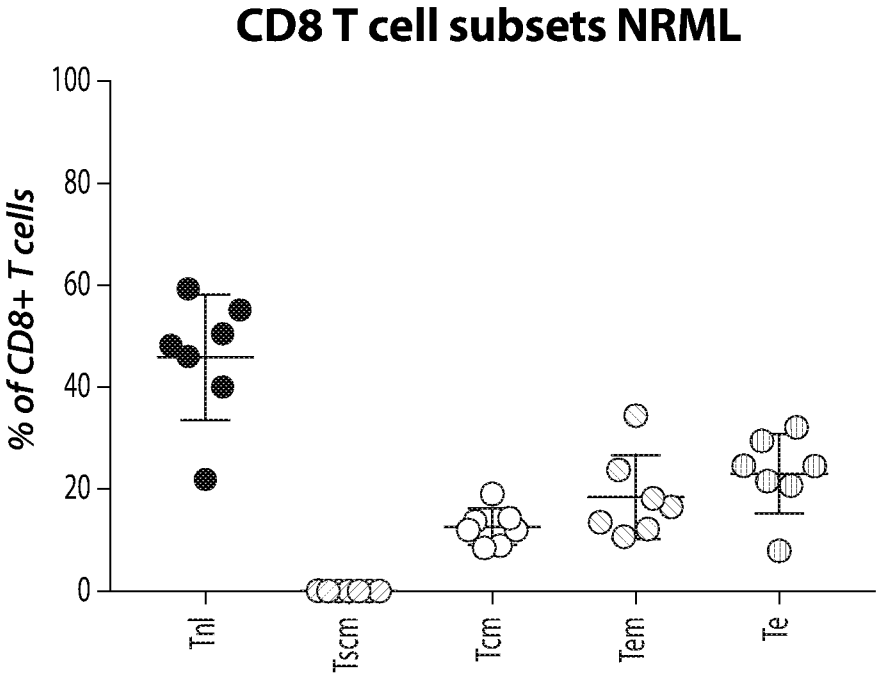


FIG. 28C

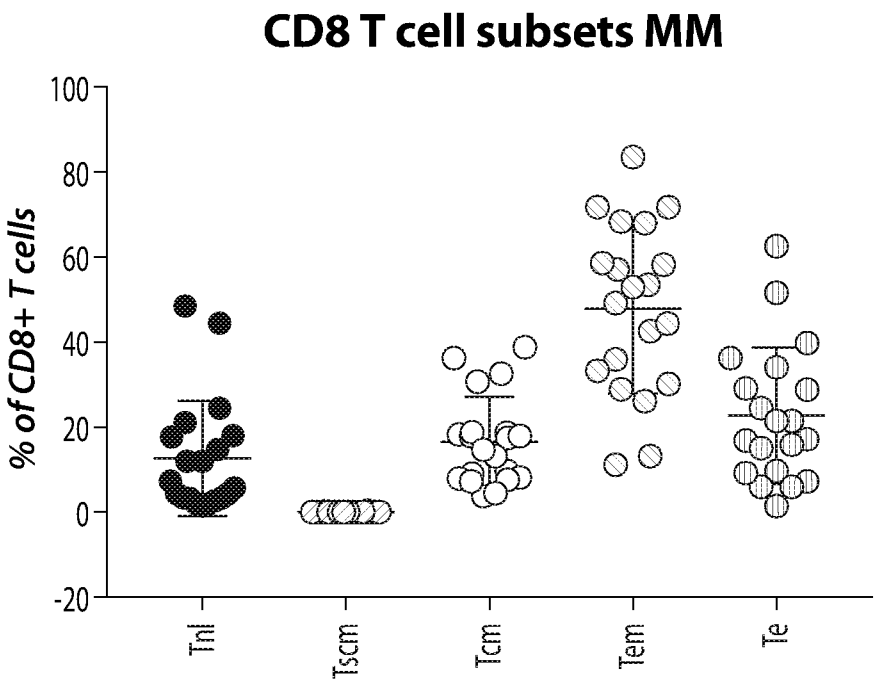


FIG. 28D

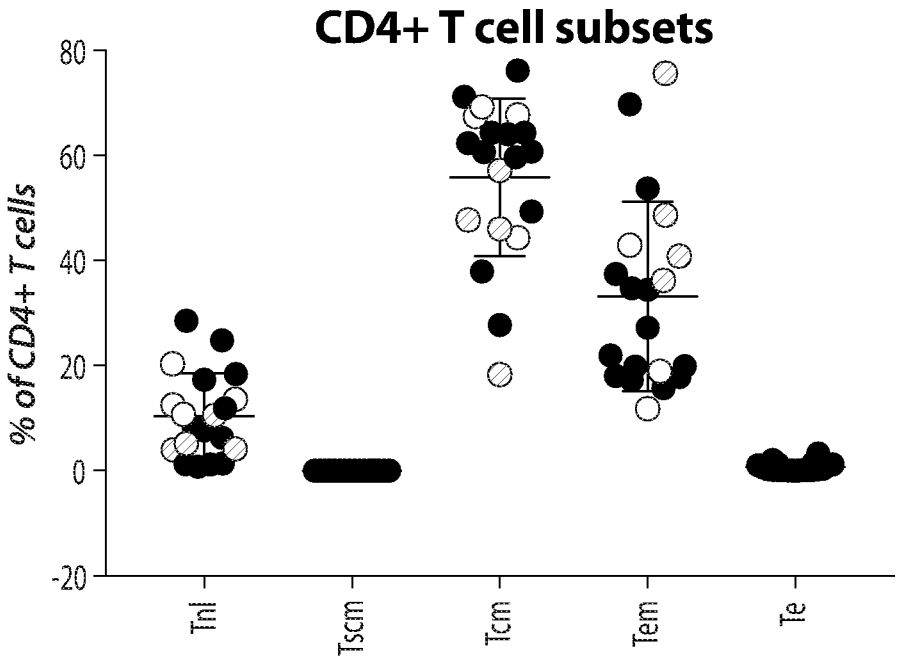


FIG. 28E

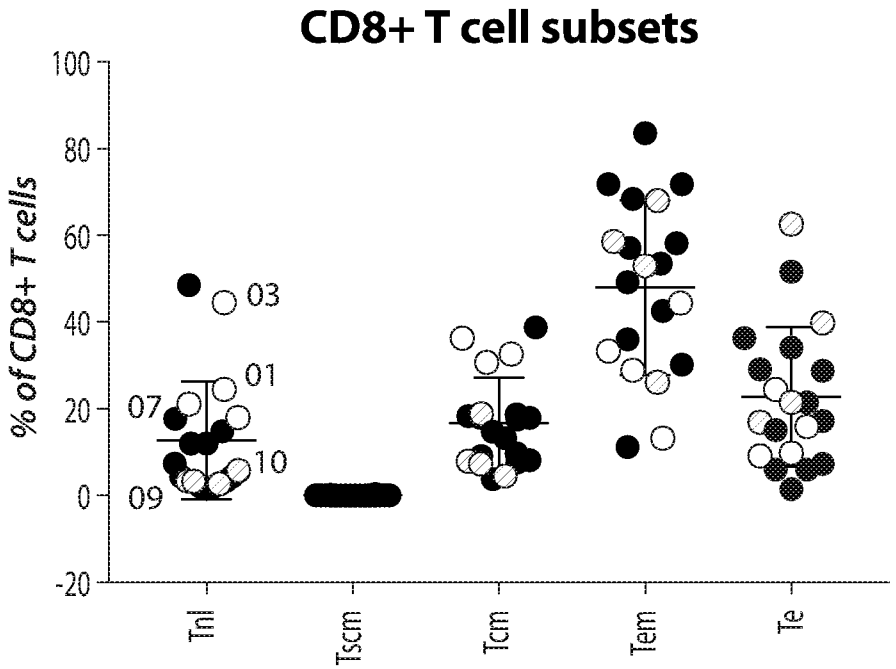


FIG. 28F

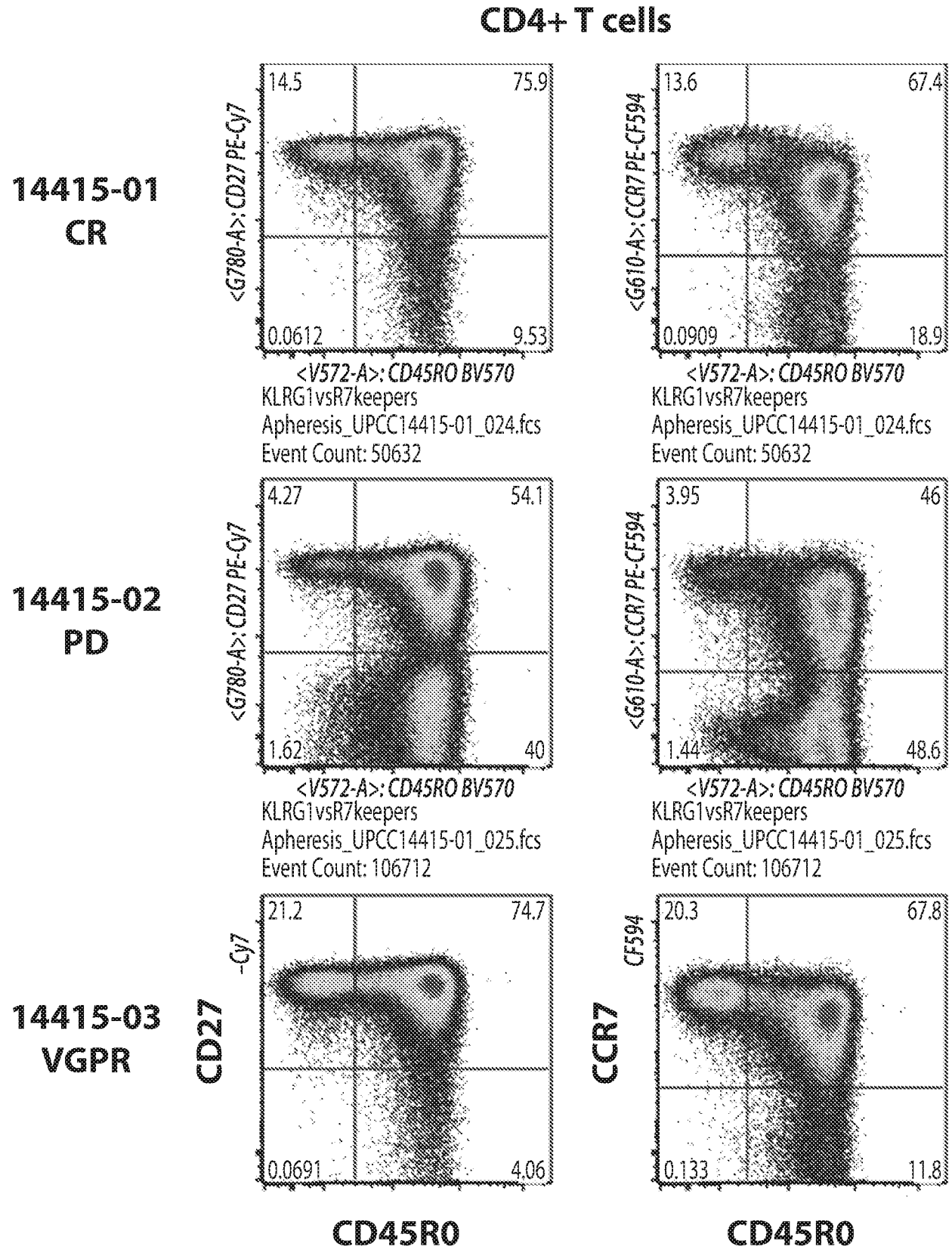

CD4+ T cells
14415-01
CR
14415-02
PD
14415-03
VGPR
<G780-A>: CD27 PE-Cy7
<G610-A>: CCR7 PE-CF594
14.5
75.9
0.0612
9.53
13.6
67.4
0.0909
18.9
<V572-A>: CD45RO BV570
KLRG1vsR7keepers
Apheresis_UPCC14415-01_024.fcs
Event Count: 50632
4.27
54.1
1.62
40
3.95
46
1.44
48.6
KLRG1vsR7keepers
Apheresis_UPCC14415-01_025.fcs
Event Count: 106712
CD27
-Cy7
CCR7
CF594
21.2
74.7
0.0691
4.06
20.3
67.8
0.133
11.8
CD45R0
CD45R0

FIG. 29-1

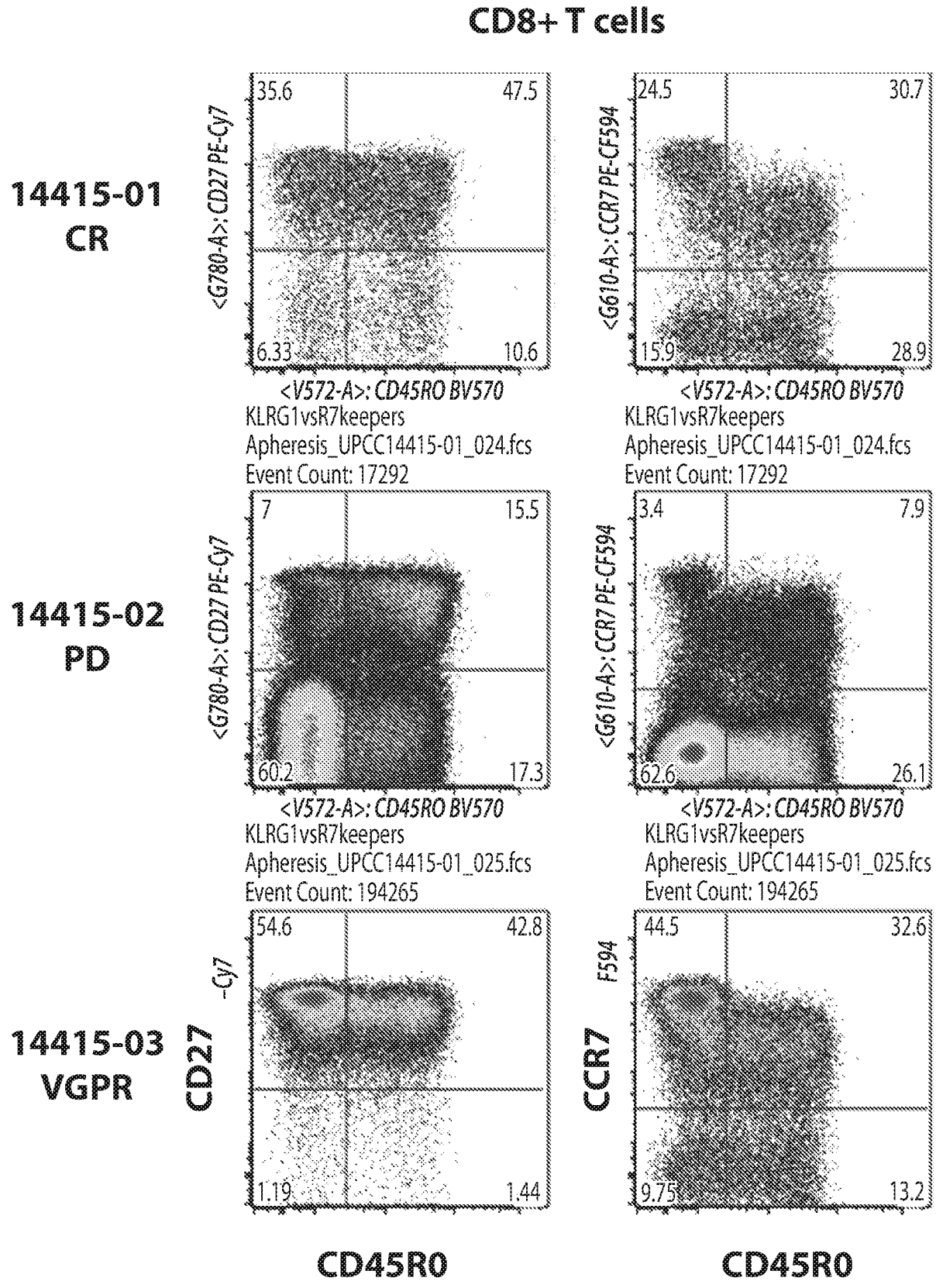

CD8+ T cells
14415-01
CR
14415-02
PD
14415-03
VGPR
<G780-A>: CD27 PE-Cy7
<G610-A>: CCR7 PE-CF594
<V572-A>: CD45RO BV570
35.6
47.5
6.33
10.6
24.5
30.7
15.9
28.9
KLRG1vsR7keepers
Apheresis_UPCC14415-01_024.fcs
Event Count: 17292
7
15.5
60.2
17.3
3.4
7.9
62.6
26.1
KLRG1vsR7keepers
Apheresis_UPCC14415-01_025.fcs
Event Count: 194265
CD27
-Cy7
CCR7
F594
54.6
42.8
1.19
1.44
44.5
32.6
9.75
13.2
CD45R0
CD45R0

FIG. 29-2

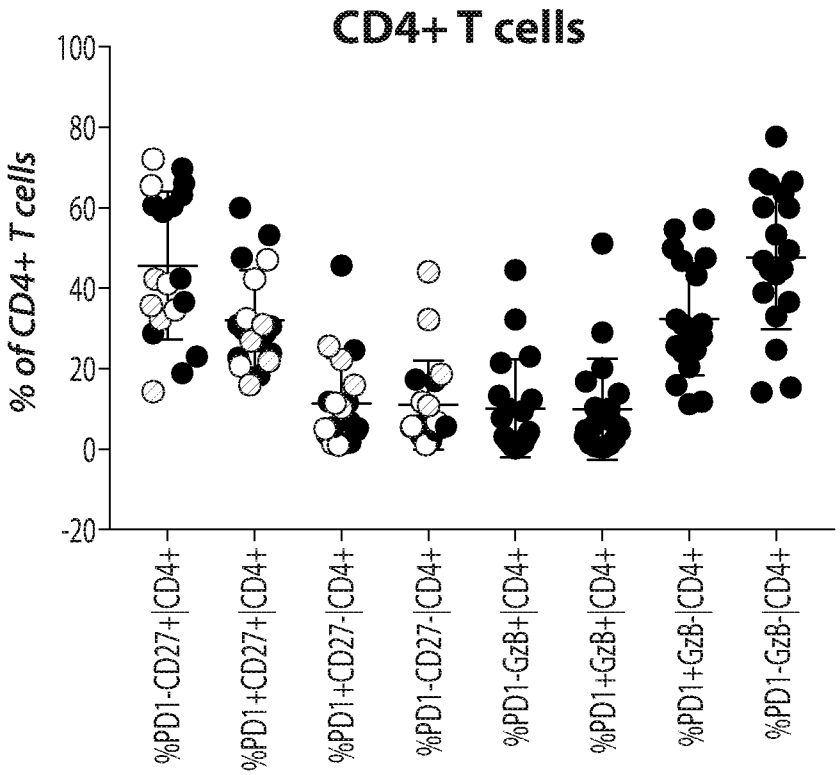


FIG. 30A

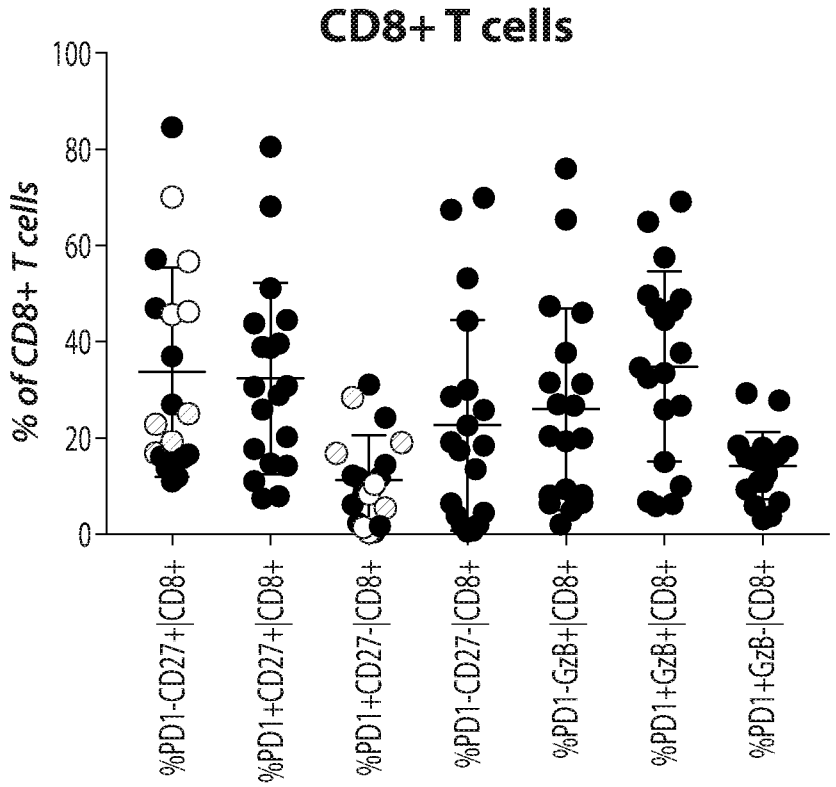
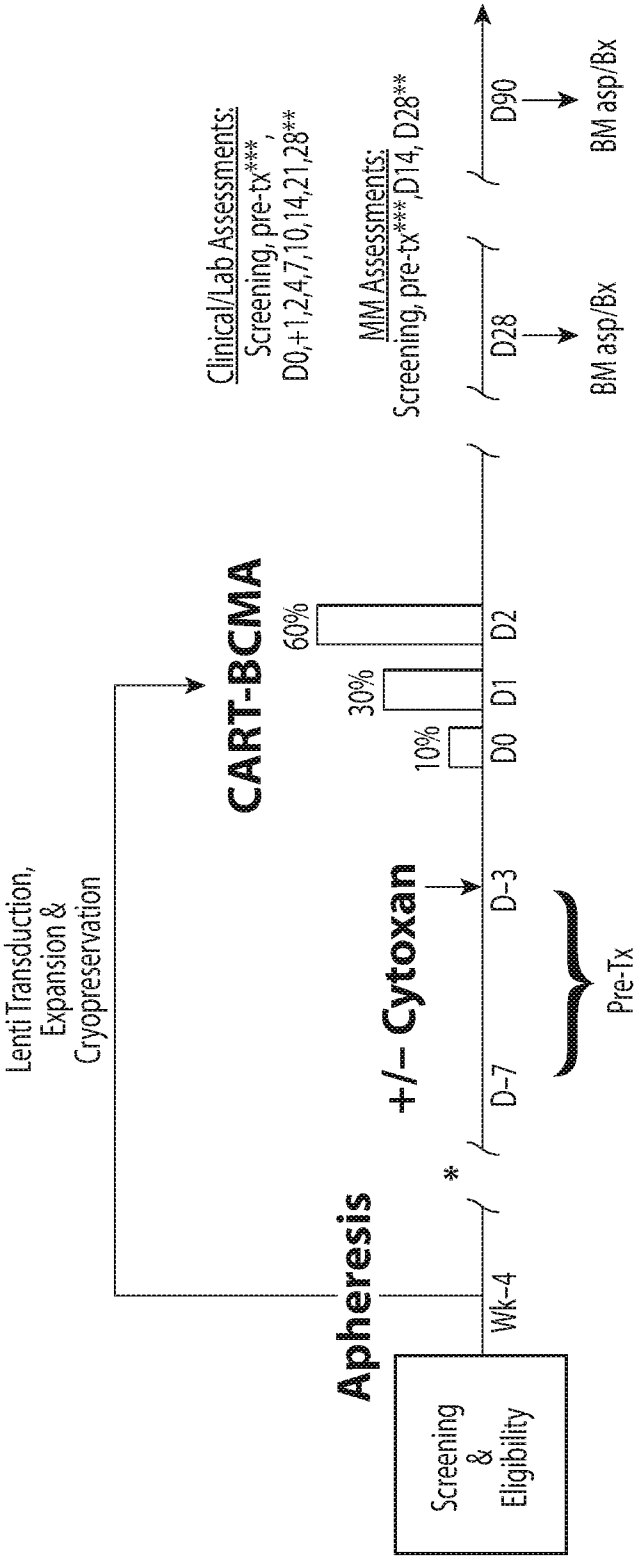


FIG. 30B



* Patients may receive therapy during manufacturing to maintain disease control
** After first 28 days, follow-up is q4 awks up to 6 mos., then q3 mos. up to 2 years
*** Pre-tx = pre-treatment, 3 to 7 days before CAR T cell infusion

FIG. 31

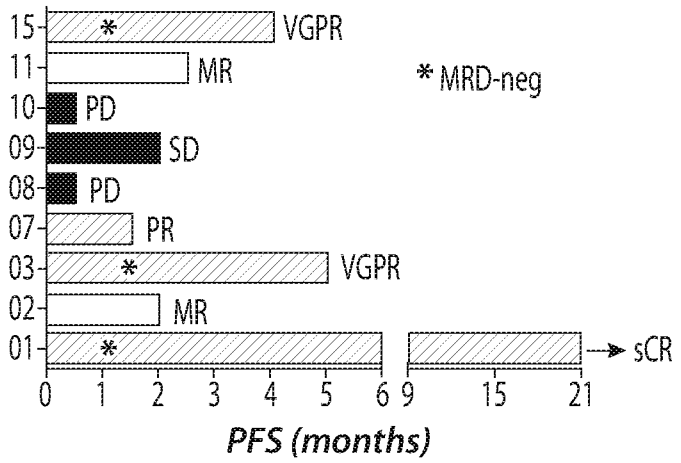


FIG. 32A

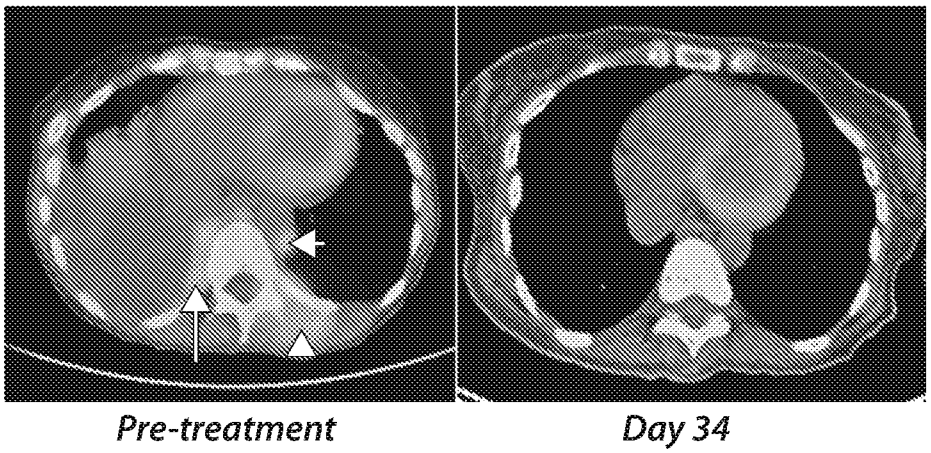


FIG. 32B

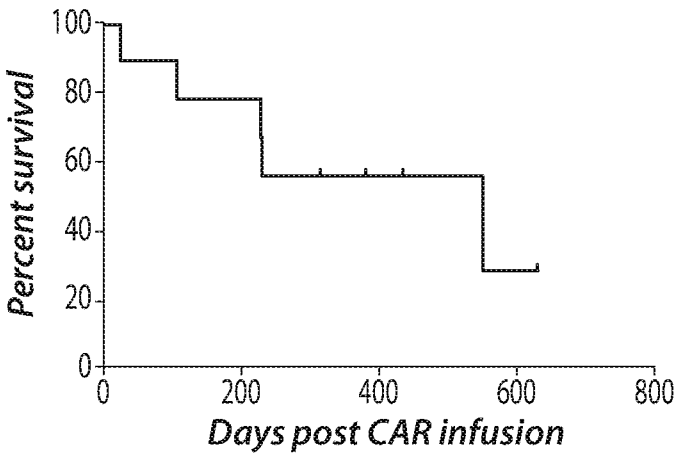


FIG. 32C

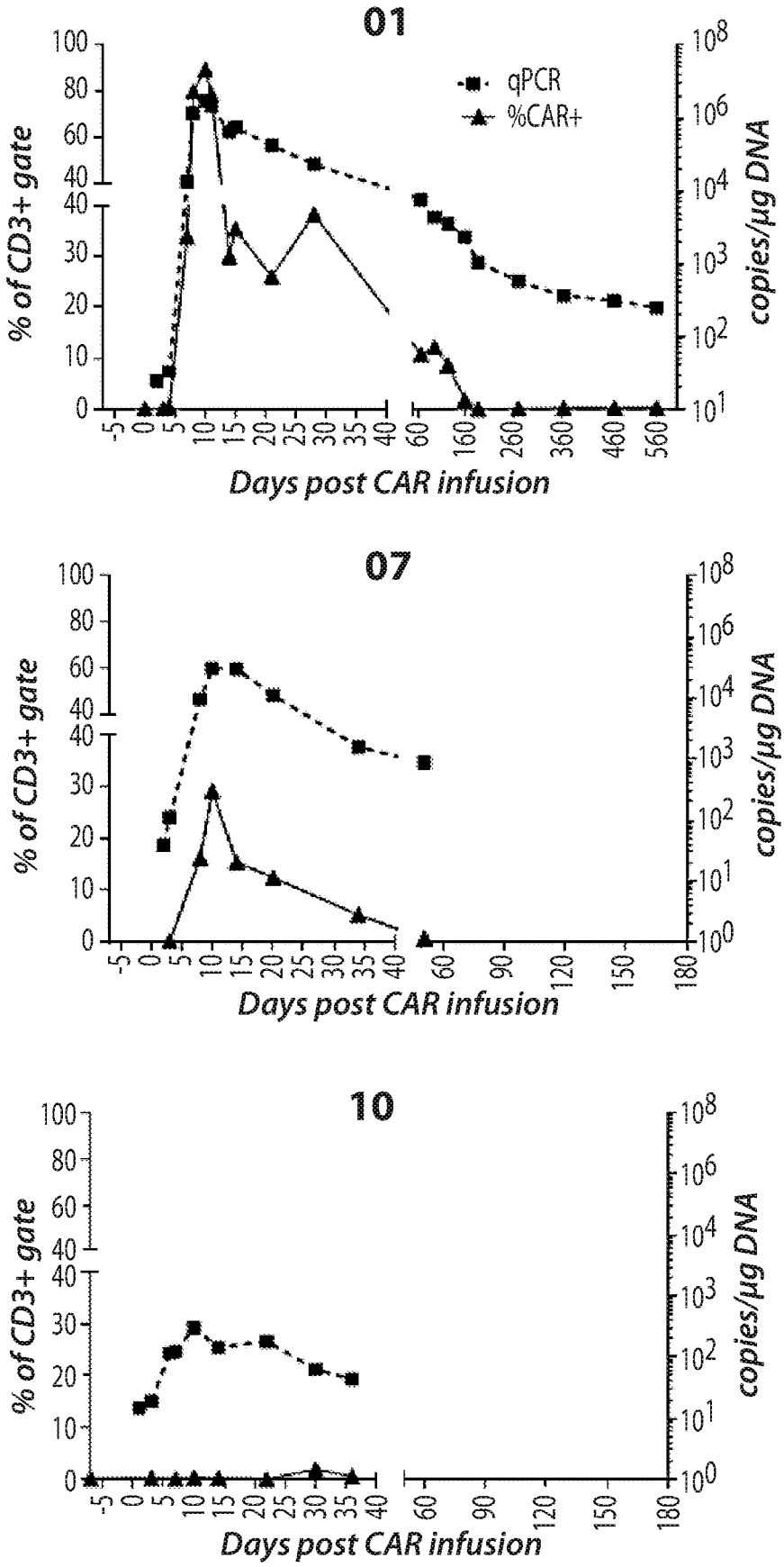

01
qPCR
%CAR+
% of CD3+ gate
copies/µg DNA
Days post CAR infusion
07
% of CD3+ gate
copies/µg DNA
Days post CAR infusion
10
% of CD3+ gate
copies/µg DNA
Days post CAR infusion

FIG. 33A-1

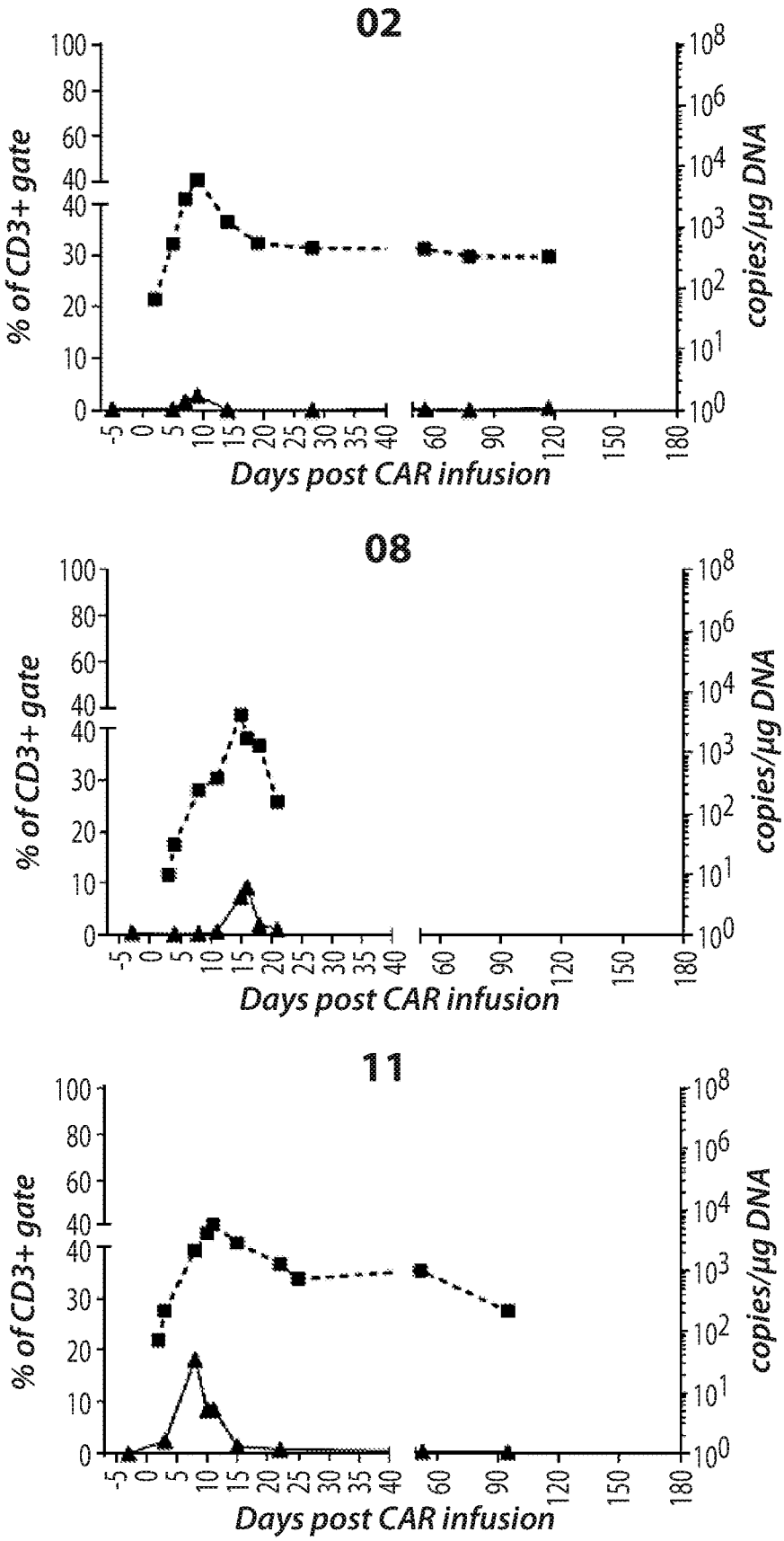

02
% of CD3+ gate
copies/µg DNA
Days post CAR infusion
08
% of CD3+ gate
copies/µg DNA
Days post CAR infusion
11
% of CD3+ gate
copies/µg DNA
Days post CAR infusion

FIG. 33A-2

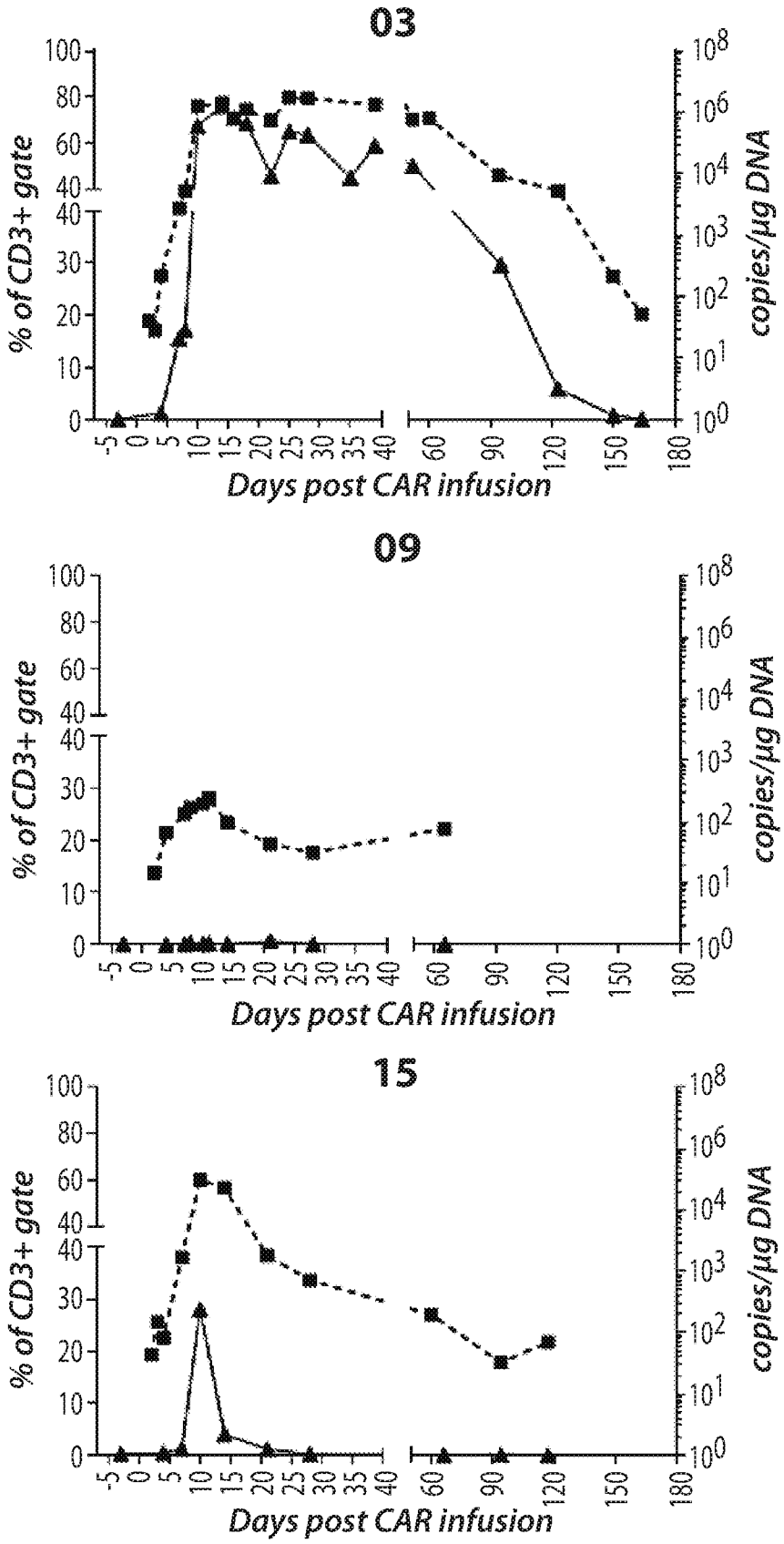


FIG. 33A-3

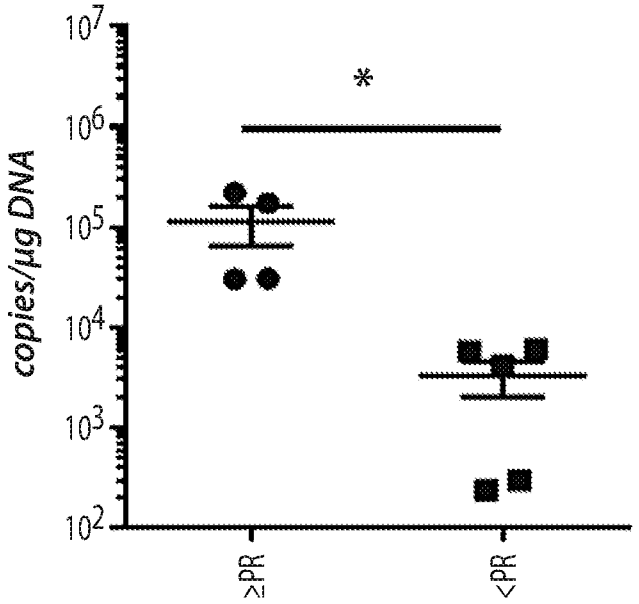


FIG. 33B

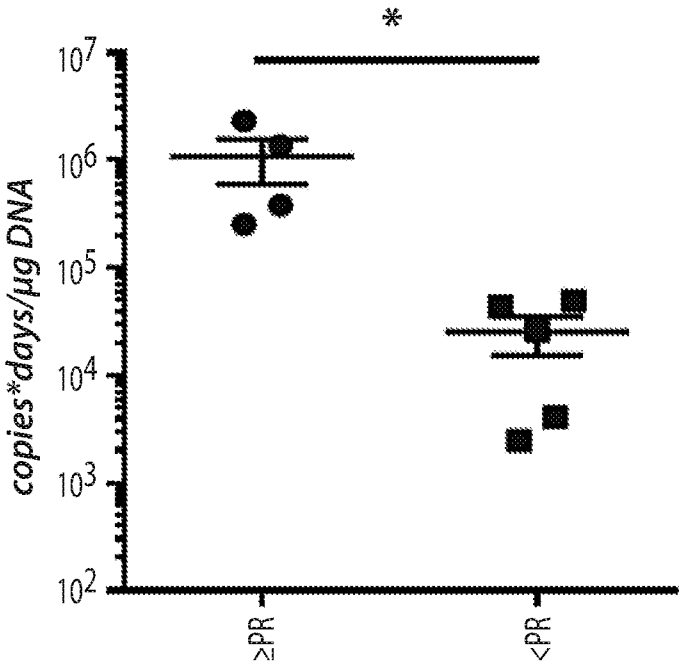
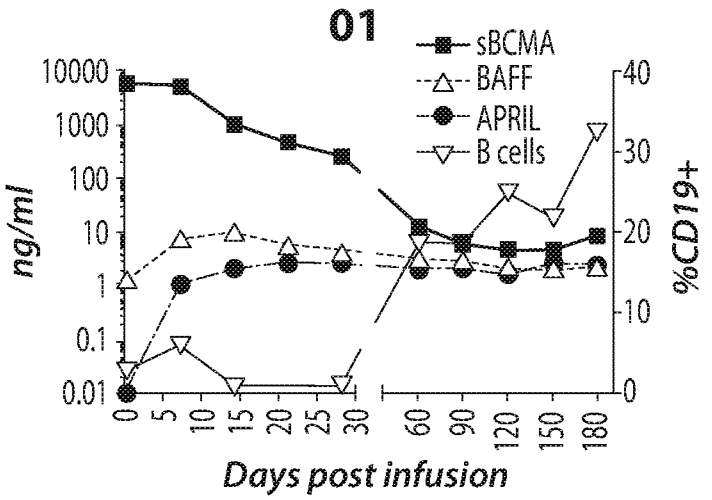
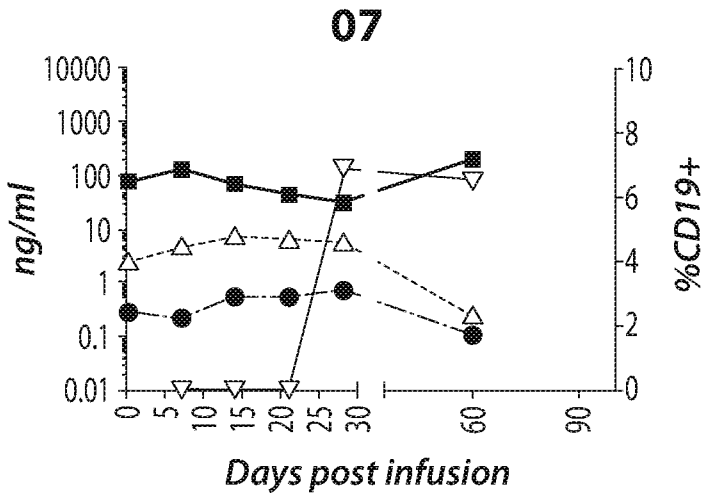


FIG. 33C


01
sBCMA
BAFF
APRIL
B cells
ng/ml
%CD19+
Days post infusion


07
ng/ml
%CD19+
Days post infusion

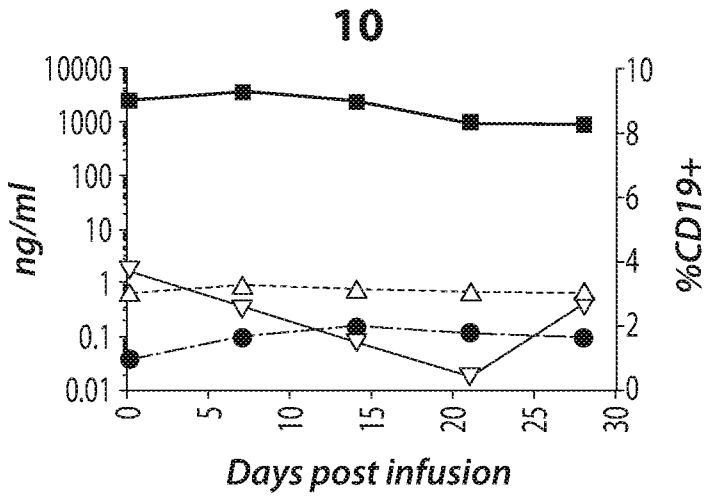
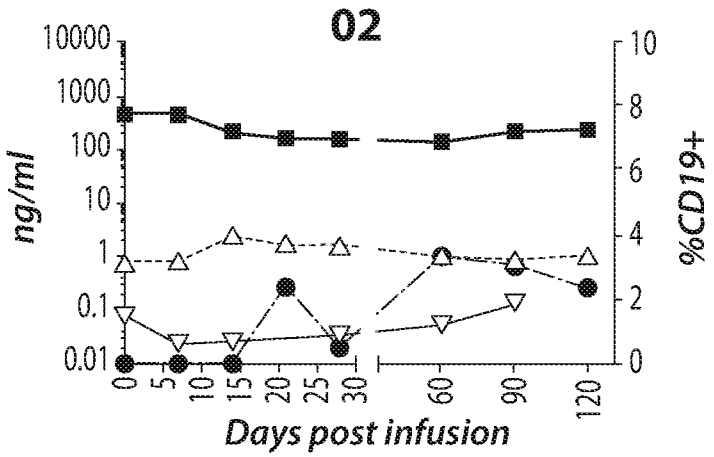
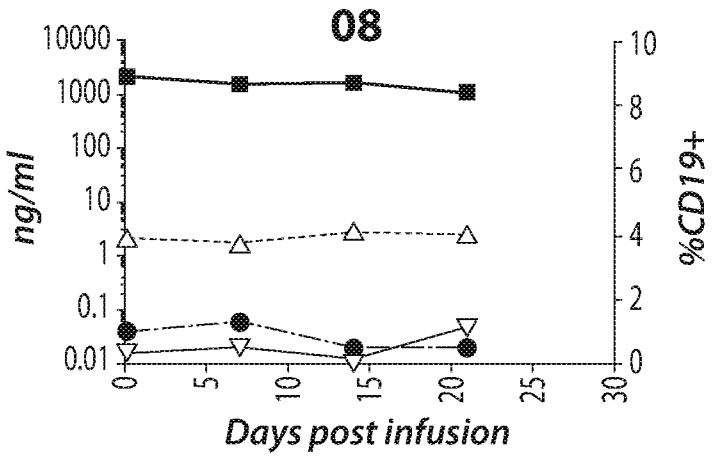

10
ng/ml
%CD19+
Days post infusion

FIG. 34-1


02
10000
1000
100
10
1
0.1
0.01
ng/ml
10
8
6
4
2
0
%CD19+
0 5 10 15 20 25 30 60 90 120
Days post infusion


08
10000
1000
100
10
1
0.1
0.01
ng/ml
10
8
6
4
2
0
%CD19+
0 5 10 15 20 25 30
Days post infusion

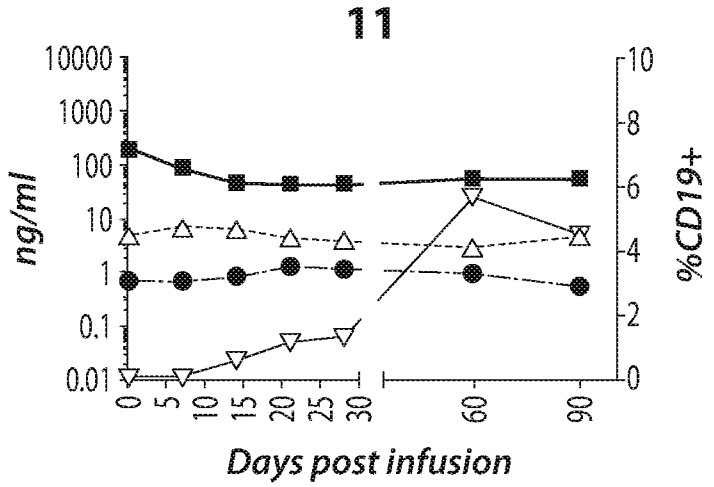
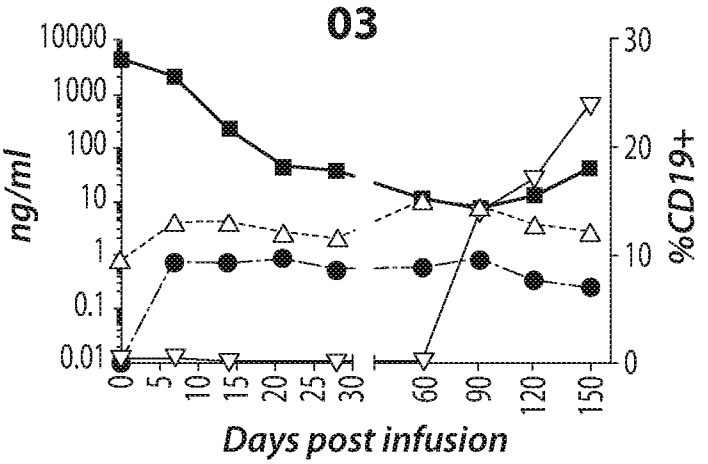
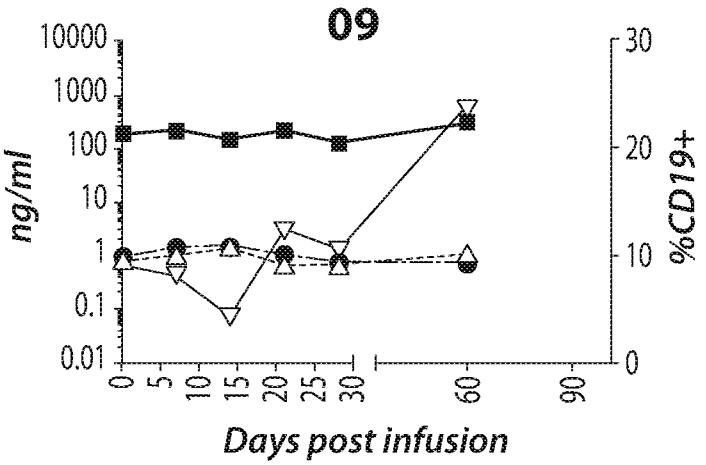

11
10000
1000
100
10
1
0.1
0.01
ng/ml
10
8
6
4
2
0
%CD19+
0 5 10 15 20 25 30 60 90
Days post infusion

FIG. 34-2


03
10000
1000
100
10
1
0.1
0.01
ng/ml
30
20
10
0
%CD19+
0 5 10 15 20 25 30 60 90 120 150
Days post infusion


09
10000
1000
100
10
1
0.1
0.01
ng/ml
30
20
10
0
%CD19+
0 5 10 15 20 25 30 60 90
Days post infusion

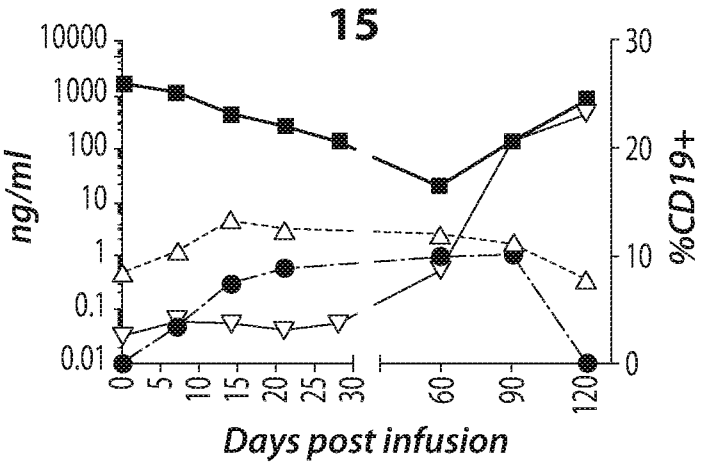

15
10000
1000
100
10
1
0.1
0.01
ng/ml
30
20
10
0
%CD19+
0 5 10 15 20 25 30 60 90 120
Days post infusion

FIG. 34-3

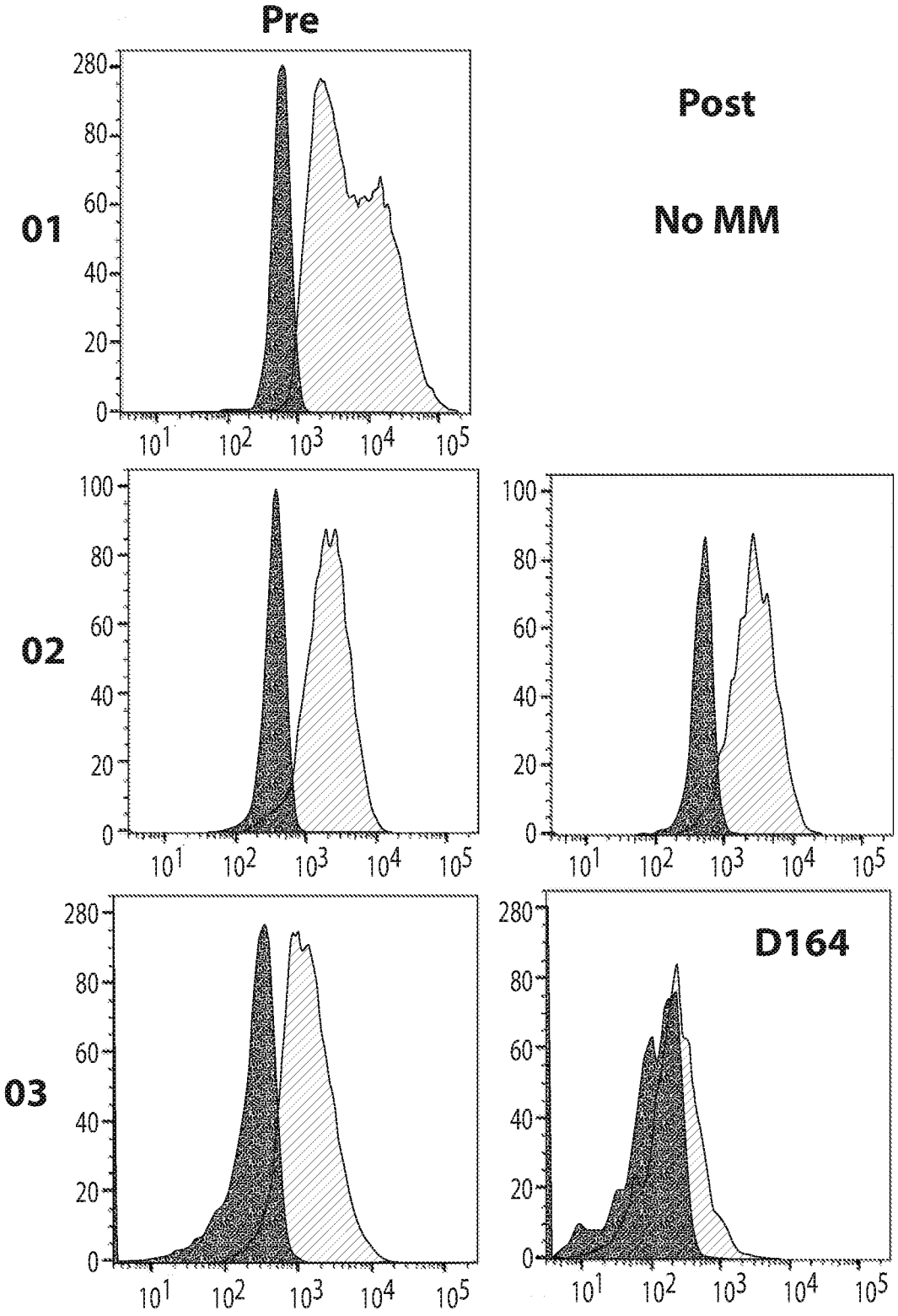

Pre
Post
No MM
01
02
03
D164
0
20
40
60
80
100
280
10^1
10^2
10^3
10^4
10^5

FIG. 35-1

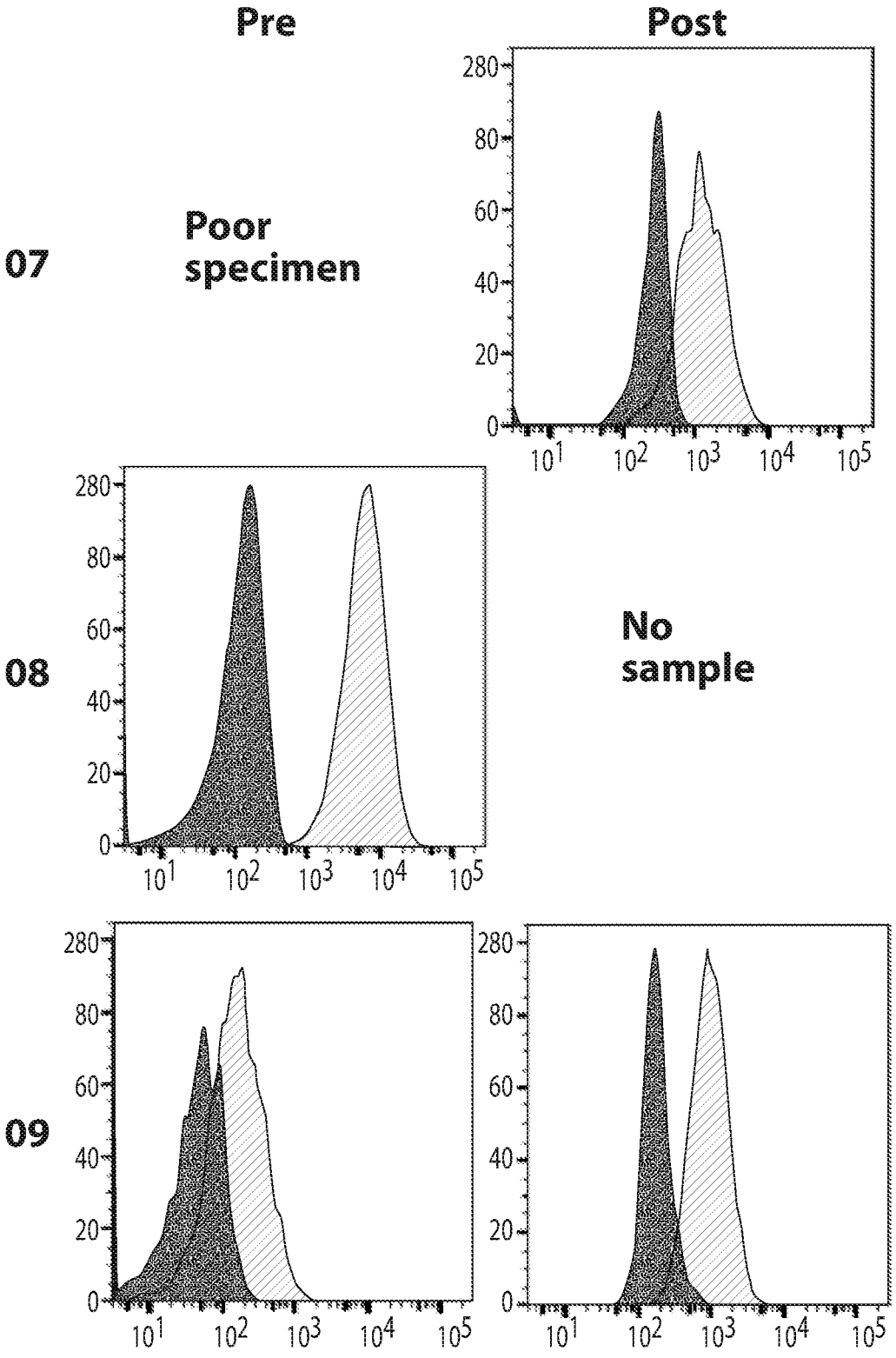

Pre
Post
07
Poor specimen
08
No sample
09
280
80
60
40
20
0
10^1
10^2
10^3
10^4
10^5

FIG. 35-2

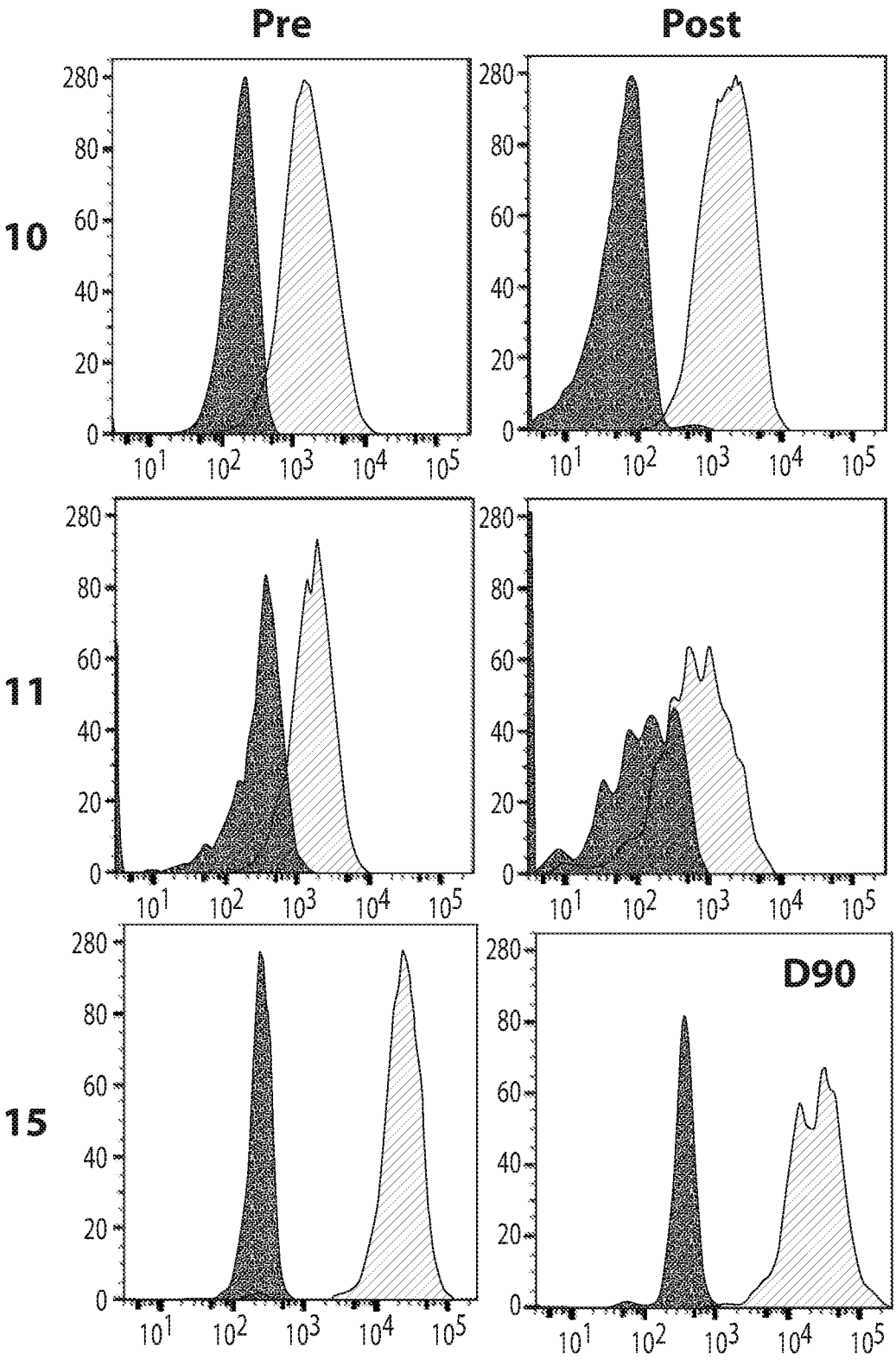


FIG. 35-3

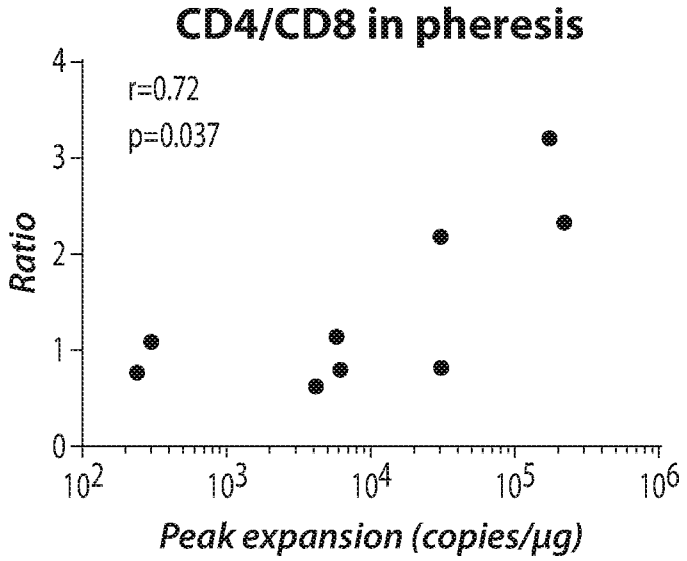


FIG. 36A

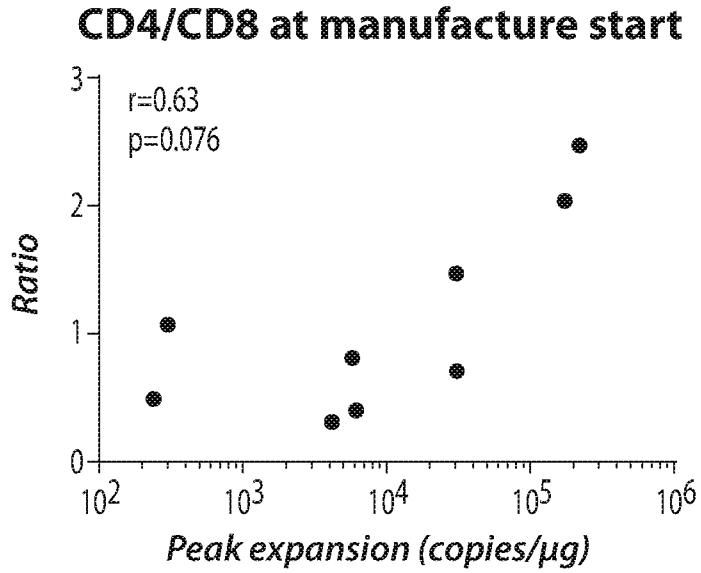


FIG. 36B

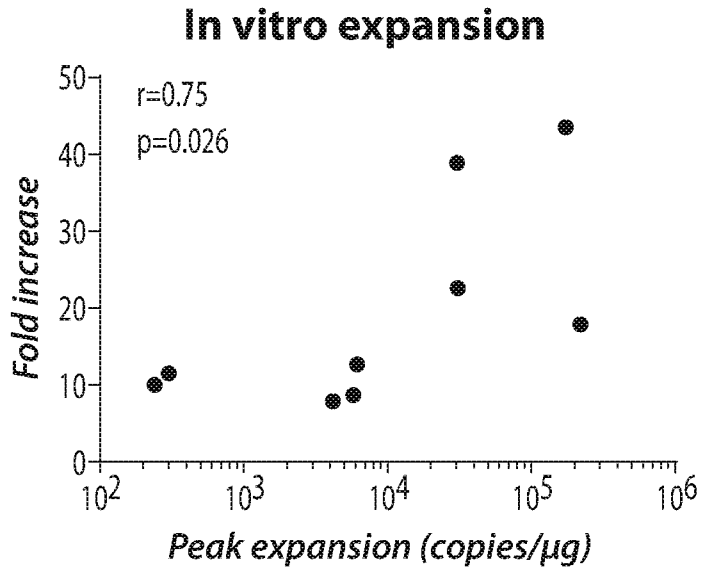


FIG. 36C

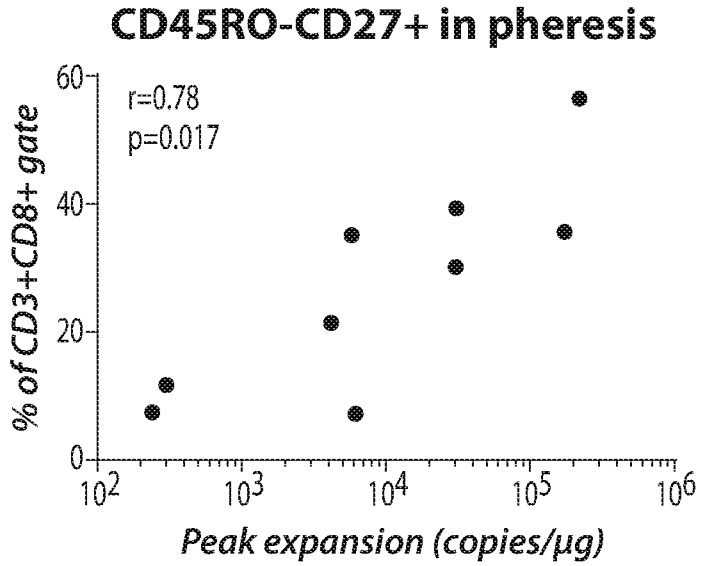


FIG. 36D

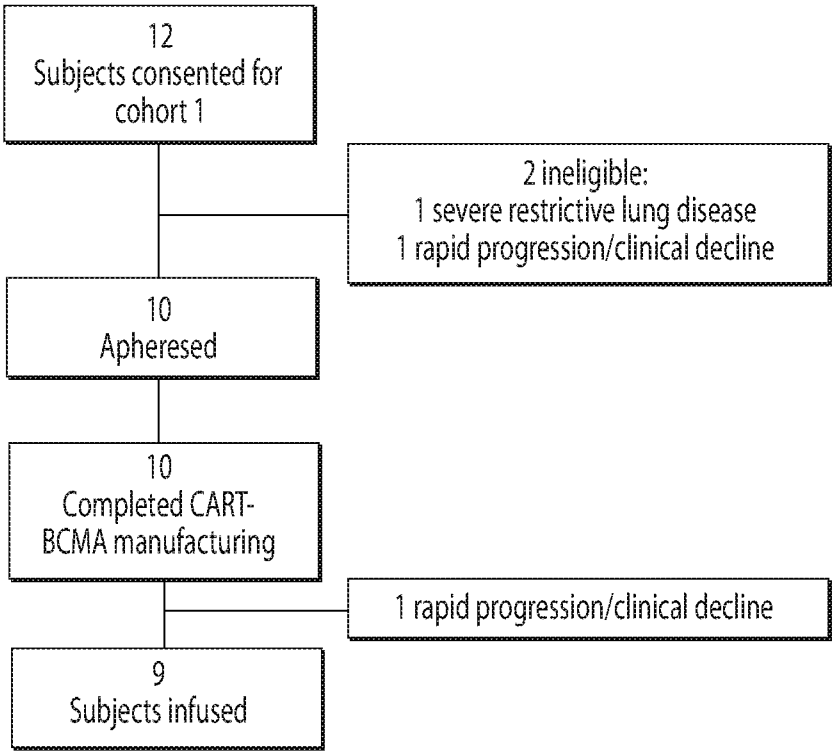

12
Subjects consented for cohort 1
2 ineligible:
1 severe restrictive lung disease
1 rapid progression/clinical decline
10
Apheresed
10
Completed CART-BCMA manufacturing
1 rapid progression/clinical decline
9
Subjects infused

FIG. 37

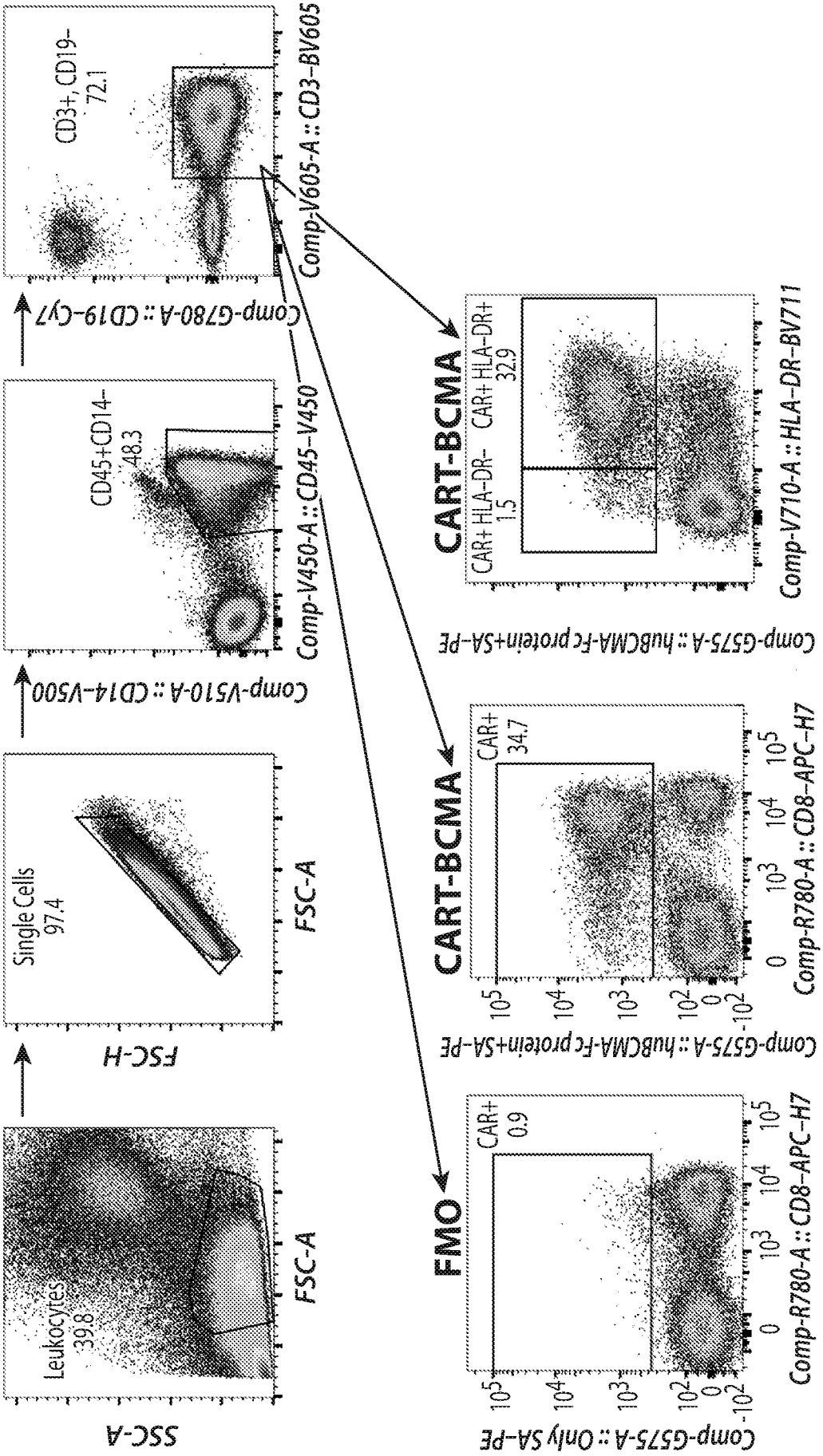
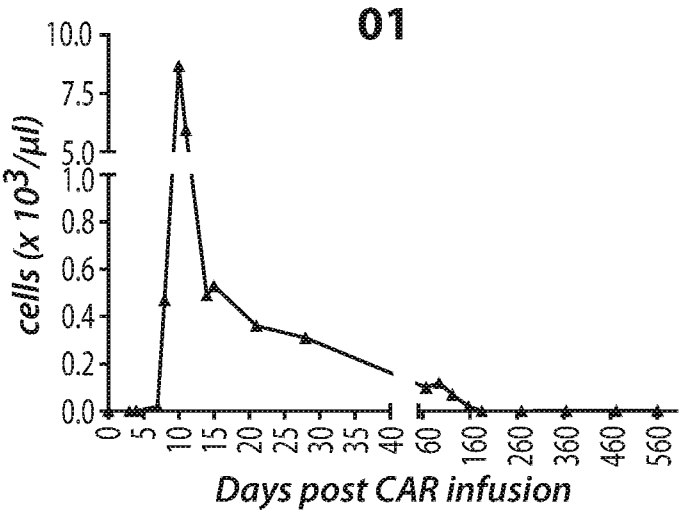
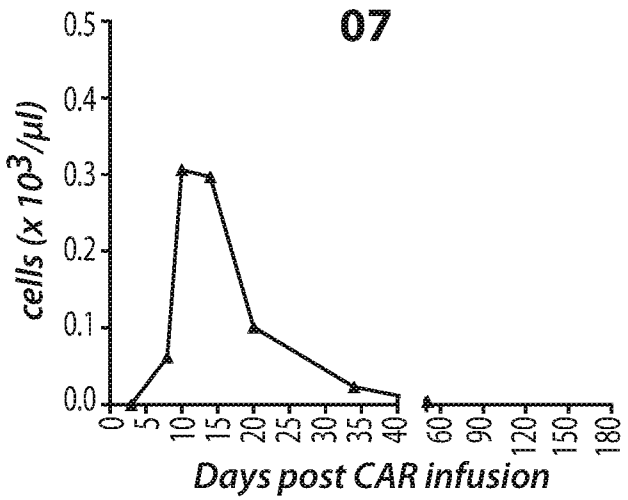

SSC-A
FSC-A
Leukocytes
39.8
FSC-H
FSC-A
Single Cells
97.4
Comp-V510-A :: CD14-V500
Comp-V450-A :: CD45-V450
CD45+CD14-
48.3
Comp-G780-A :: CD19-Cy7
Comp-V605-A :: CD3-BV605
CD3+, CD19-
72.1
FMO
Comp-G575-A :: Only SA-PE
CAR+
0.9
Comp-R780-A :: CD8-APC-H7
CART-BCMA
Comp-G575-A :: huBCMA-Fc protein+SA-PE
CAR+
34.7
Comp-R780-A :: CD8-APC-H7
CART-BCMA
Comp-G575-A :: huBCMA-Fc protein+SA-PE
CAR+ HLA-DR-
1.5
CAR+ HLA-DR+
32.9
Comp-V710-A :: HLA-DR-BV711

FIG. 38


01
cells (x 10^3/µl)
Days post CAR infusion


07
cells (x 10^3/µl)
Days post CAR infusion

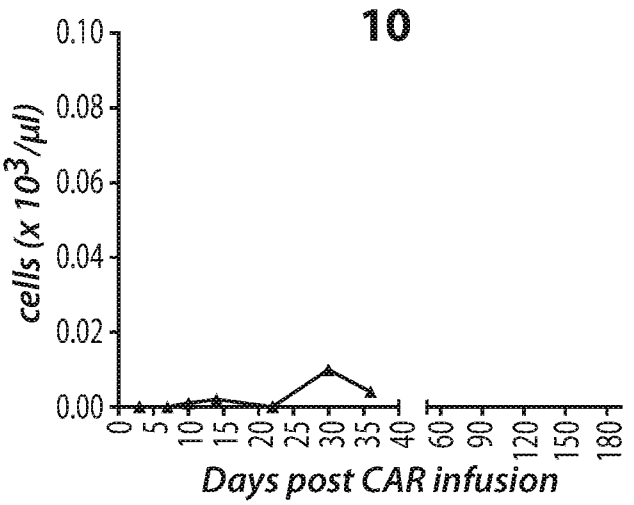

10
cells (x 10^3/µl)
Days post CAR infusion

FIG. 39-1

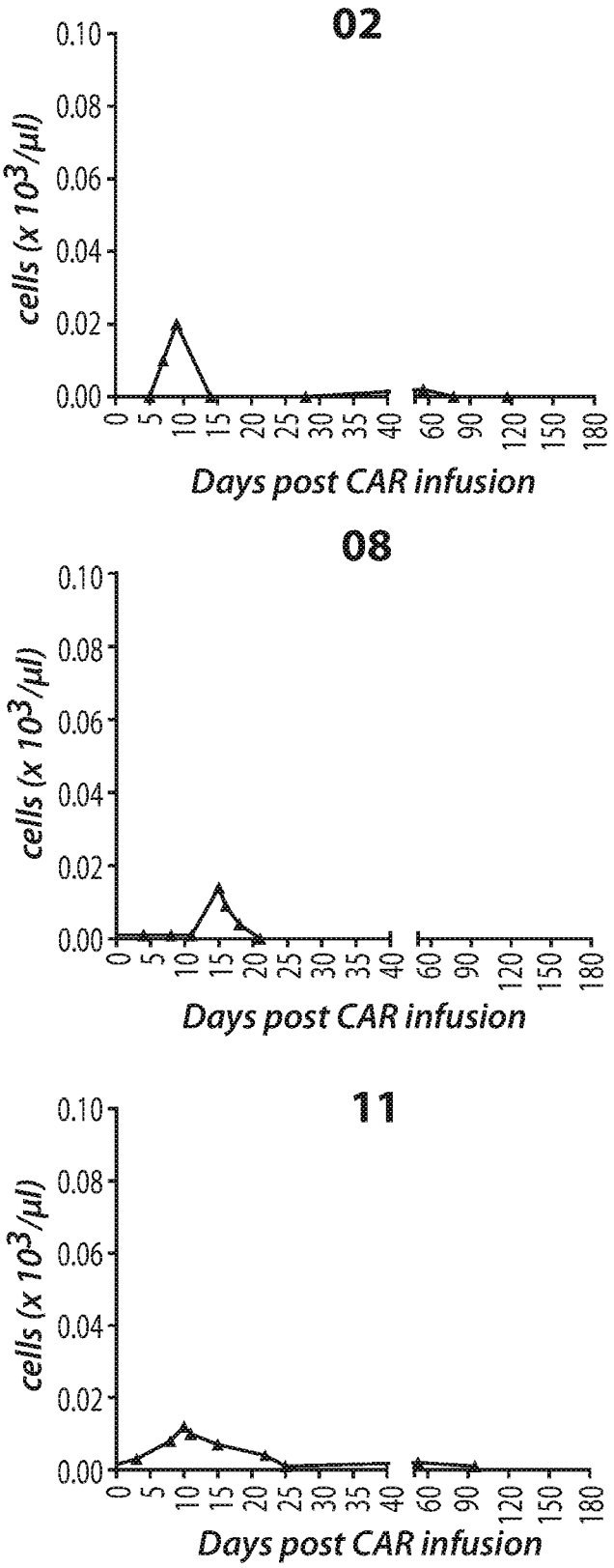

02
0.10
0.08
0.06
0.04
0.02
0.00
cells (x 10^3/µl)
0 5 10 15 20 25 30 35 40 60 90 120 150 180
Days post CAR infusion
08
0.10
0.08
0.06
0.04
0.02
0.00
cells (x 10^3/µl)
0 5 10 15 20 25 30 35 40 60 90 120 150 180
Days post CAR infusion
11
0.10
0.08
0.06
0.04
0.02
0.00
cells (x 10^3/µl)
0 5 10 15 20 25 30 35 40 60 90 120 150 180
Days post CAR infusion

FIG. 39-2

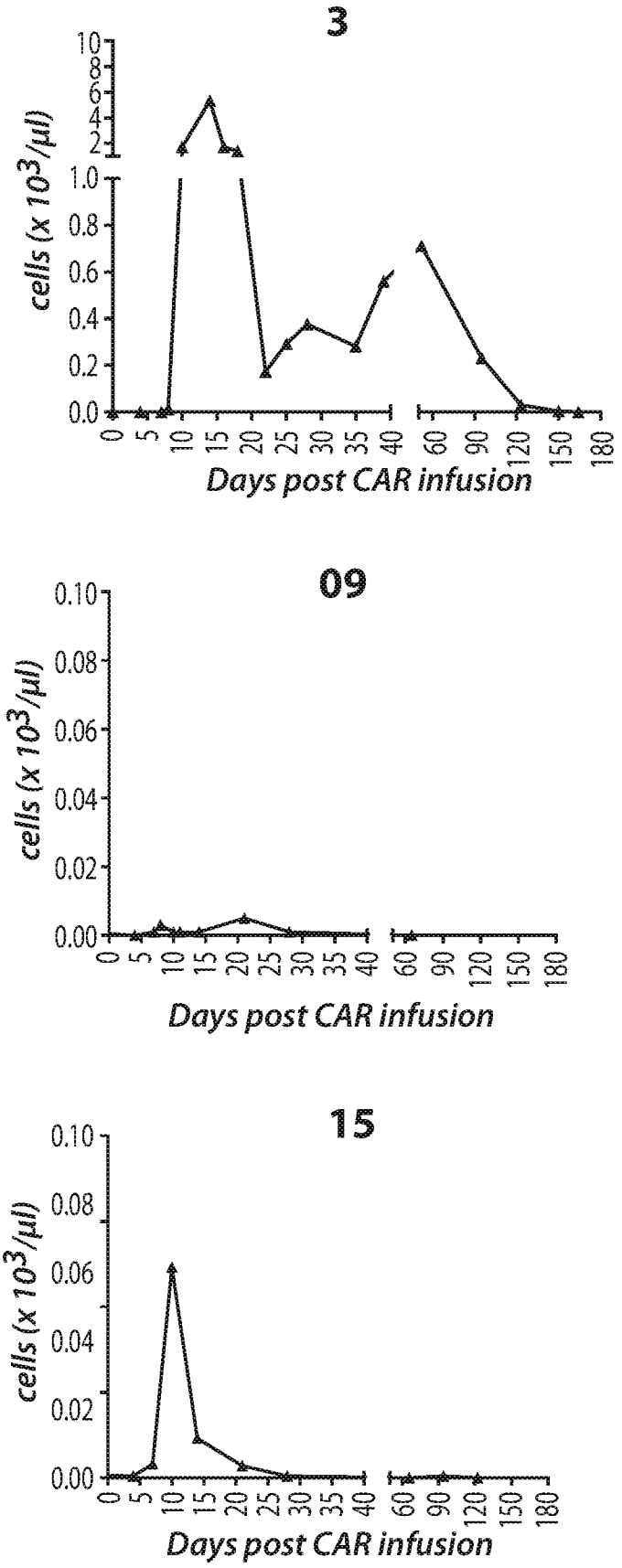

3
cells (x 10^3/µl)
Days post CAR infusion
09
cells (x 10^3/µl)
Days post CAR infusion
15
cells (x 10^3/µl)
Days post CAR infusion

FIG. 39-3

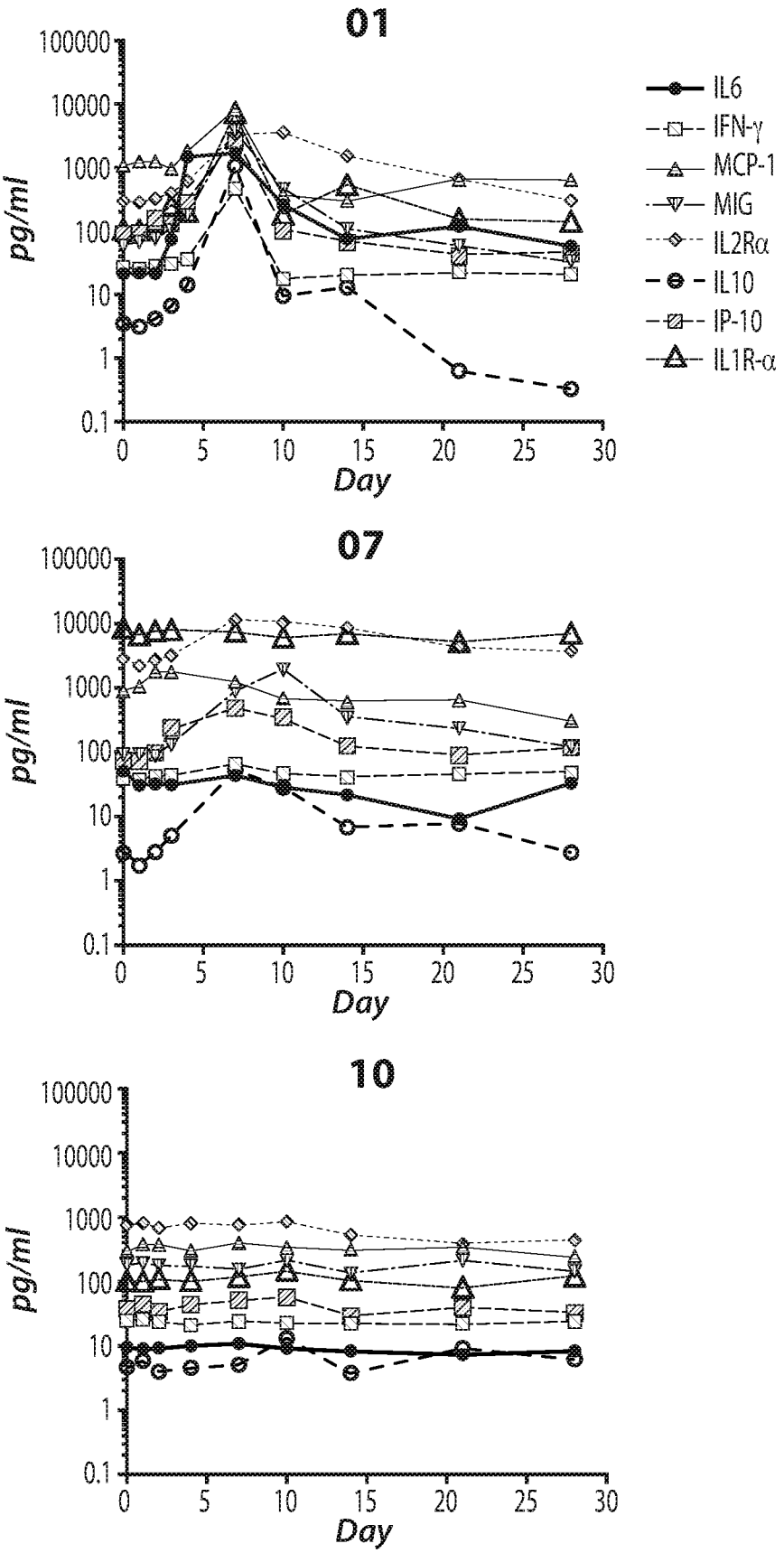

01
07
10
pg/ml
Day
100000
10000
1000
100
10
1
0.1
0
5
10
15
20
25
30
IL6
IFN-γ
MCP-1
MIG
IL2Rα
IL10
IP-10
IL1R-α

FIG. 40-1

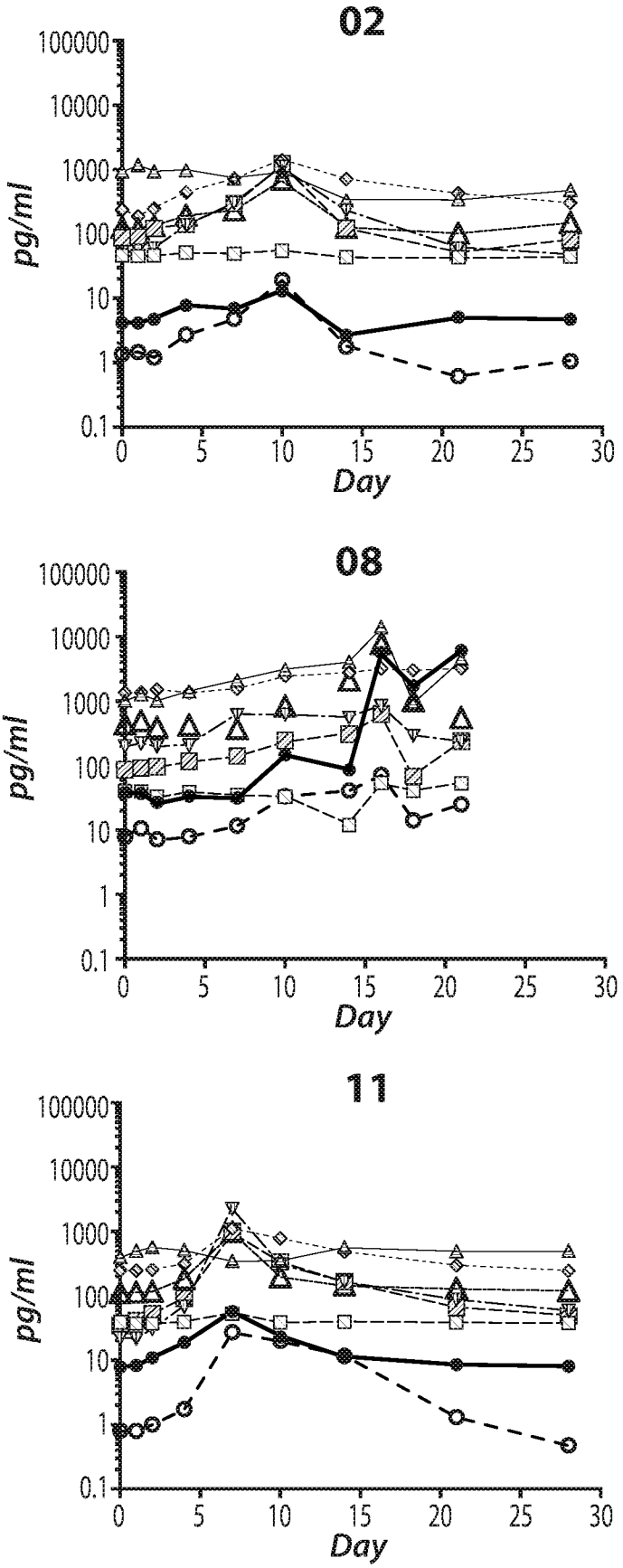


FIG. 40-2

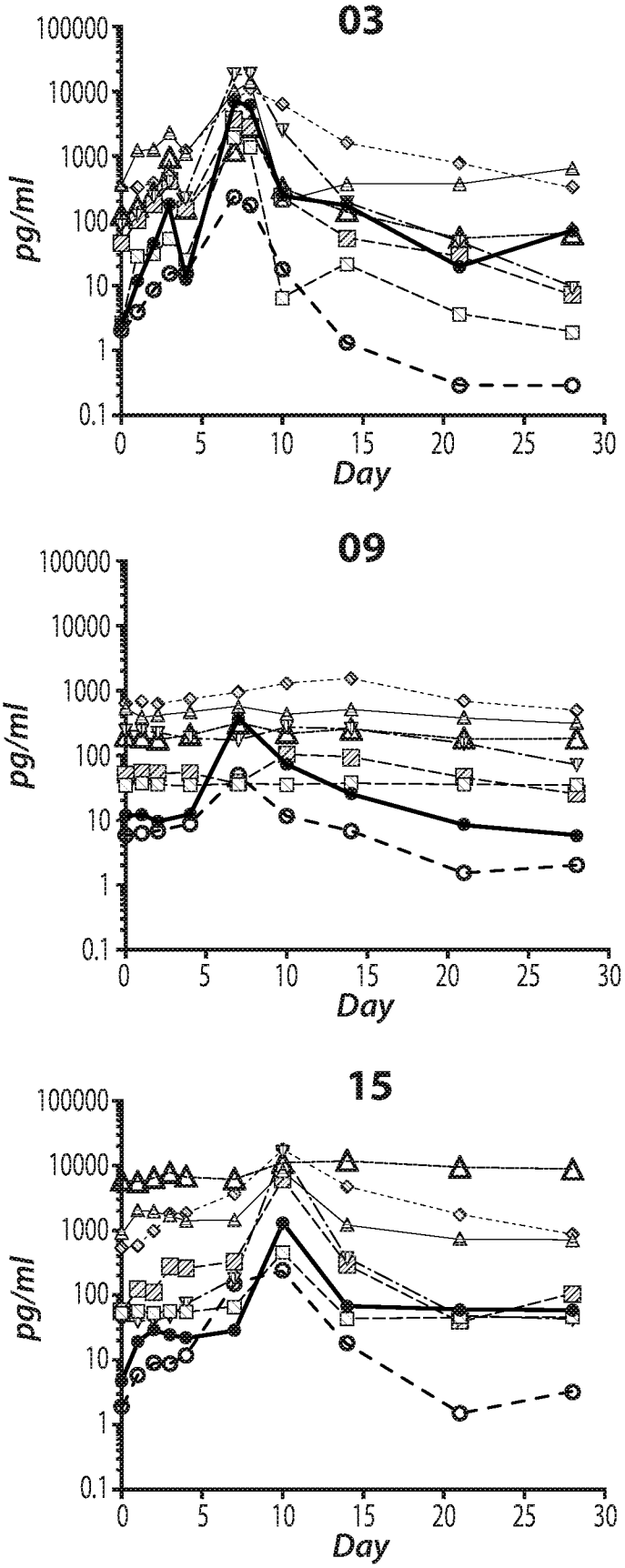


FIG. 40-3

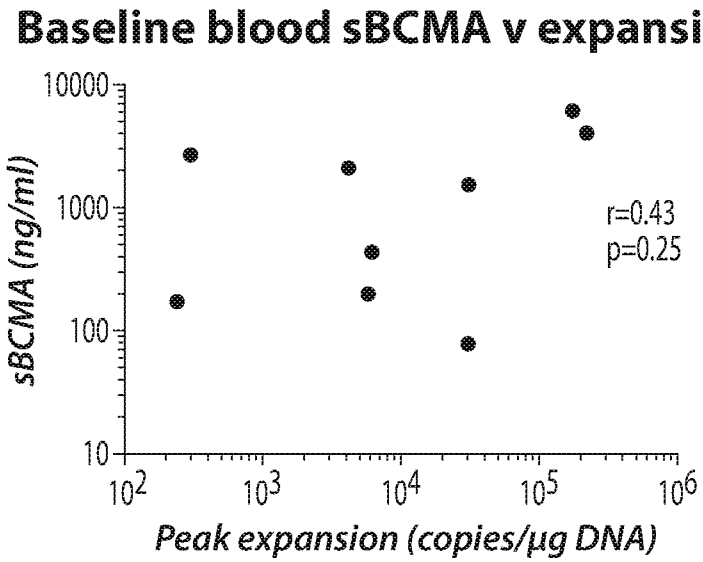


FIG. 41A

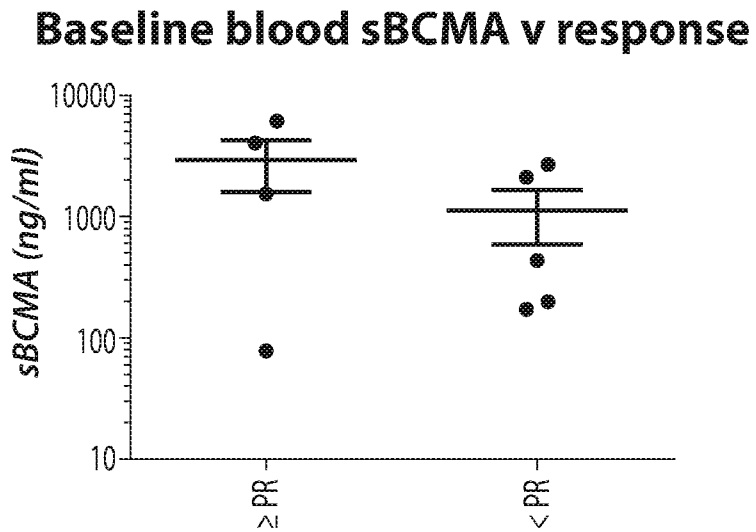


FIG. 41B

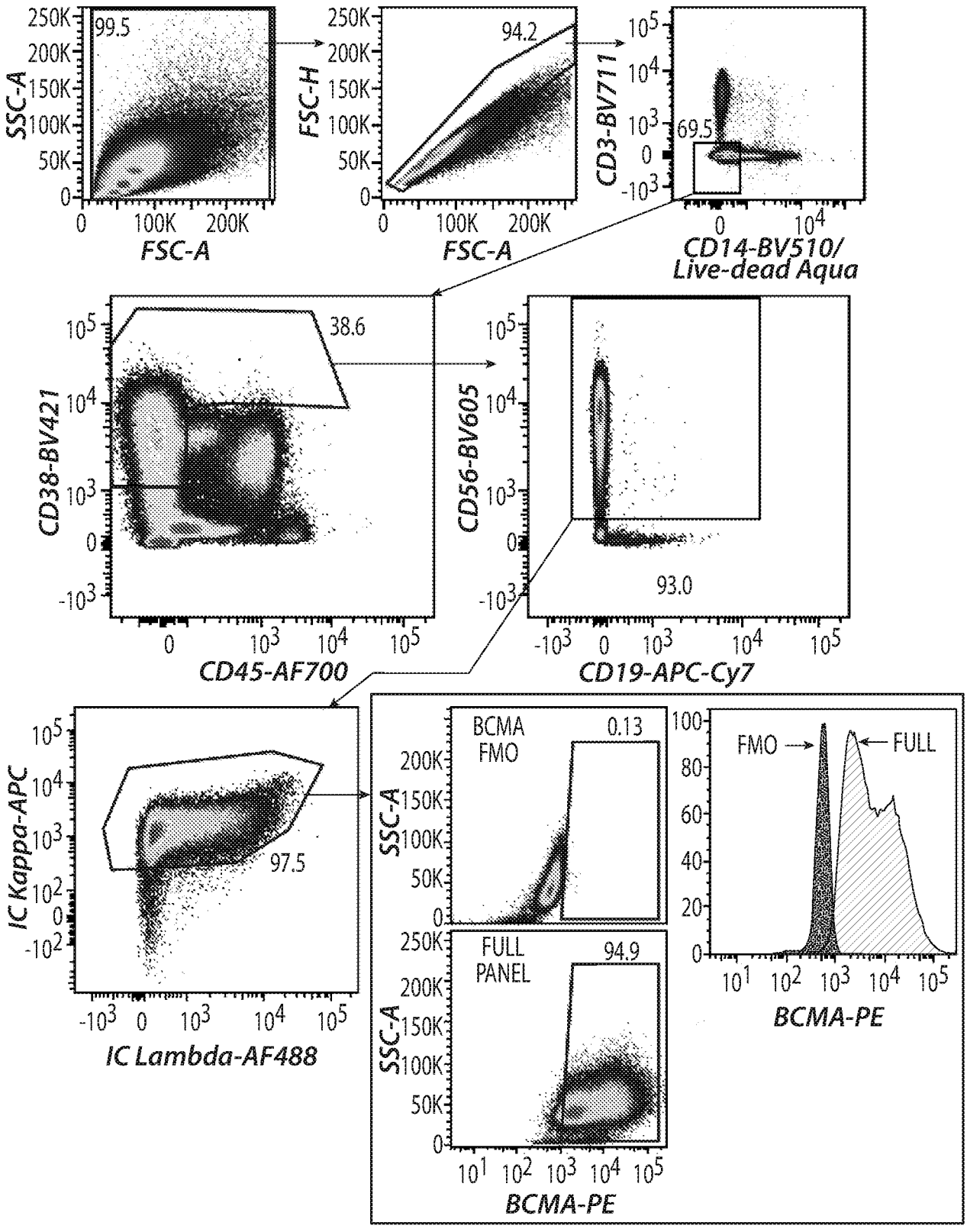

99.5
SSC-A
FSC-A
94.2
FSC-H
FSC-A
69.5
CD3-BV711
CD14-BV510/
Live-dead Aqua
38.6
CD38-BV421
CD45-AF700
CD56-BV605
93.0
CD19-APC-Cy7
IC Kappa-APC
97.5
IC Lambda-AF488
BCMA
FMO
0.13
FULL
PANEL
94.9
SSC-A
BCMA-PE
FMO
FULL
BCMA-PE

FIG. 42

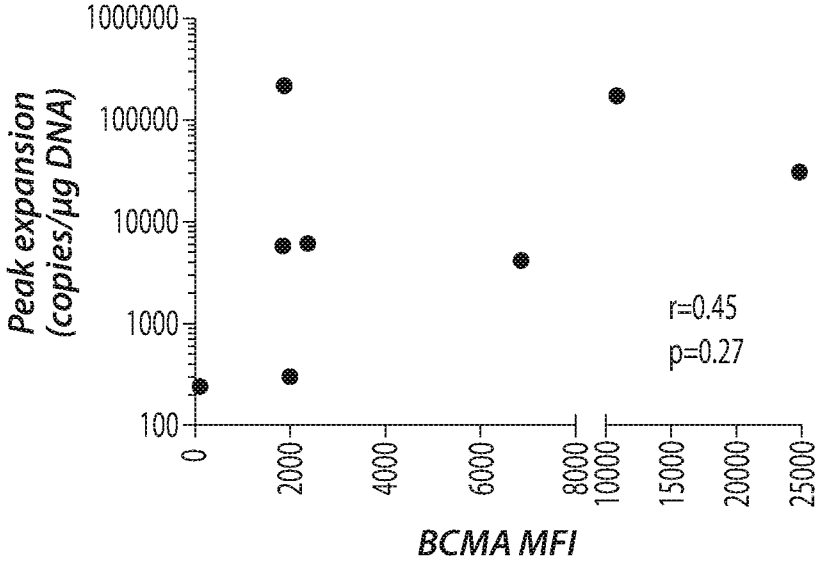


FIG. 43A

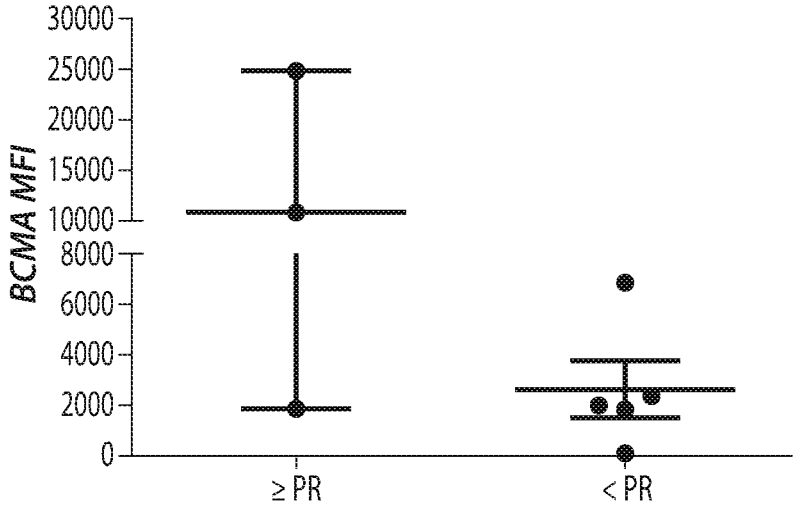


FIG. 43B

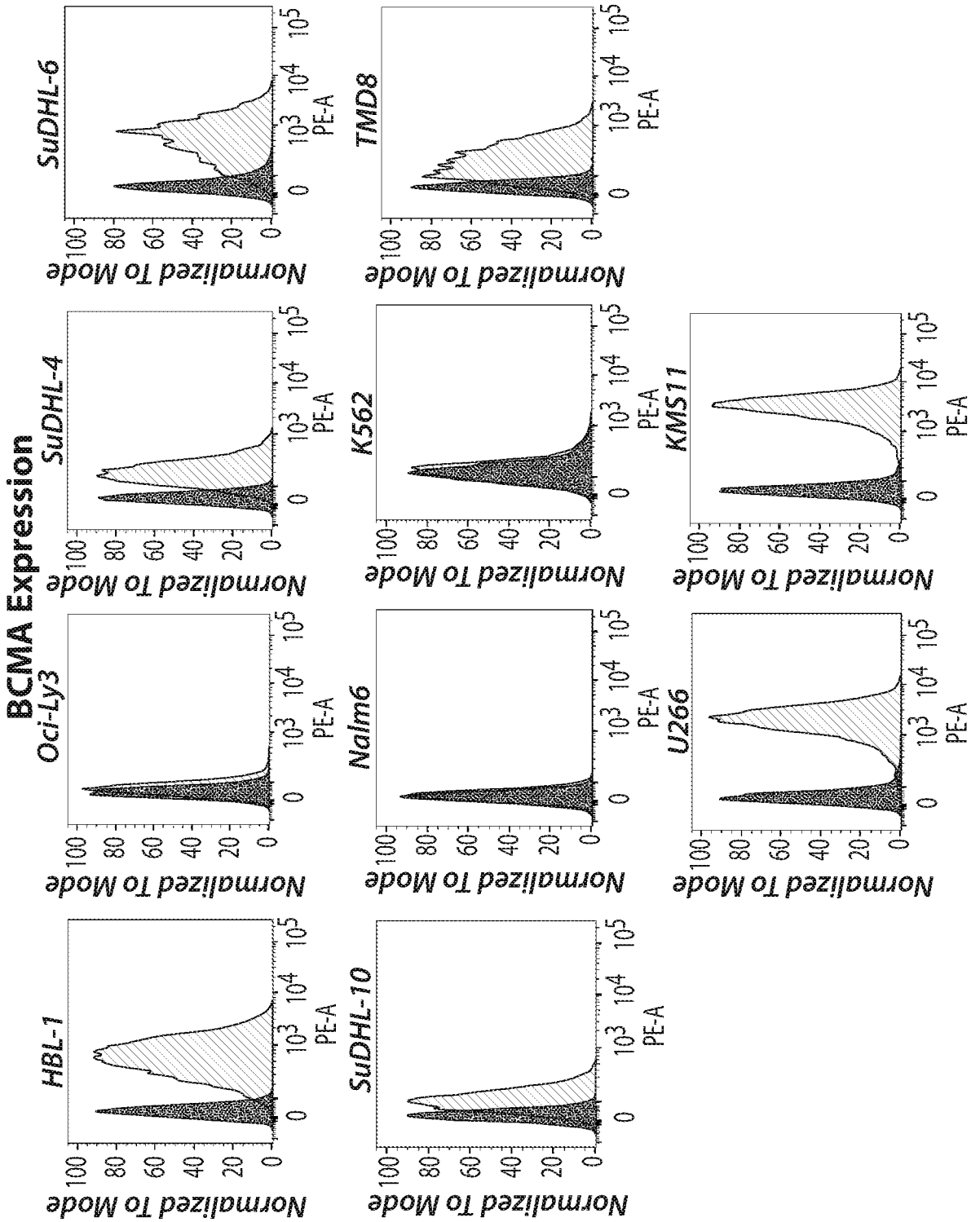

BCMA Expression
HBL-1
Oci-Ly3
SuDHL-4
SuDHL-6
SuDHL-10
Nalm6
K562
TMD8
KMS11
U266
Normalized To Mode
PE-A
0
20
40
60
80
100
10^3
10^4
10^5

FIG. 44A

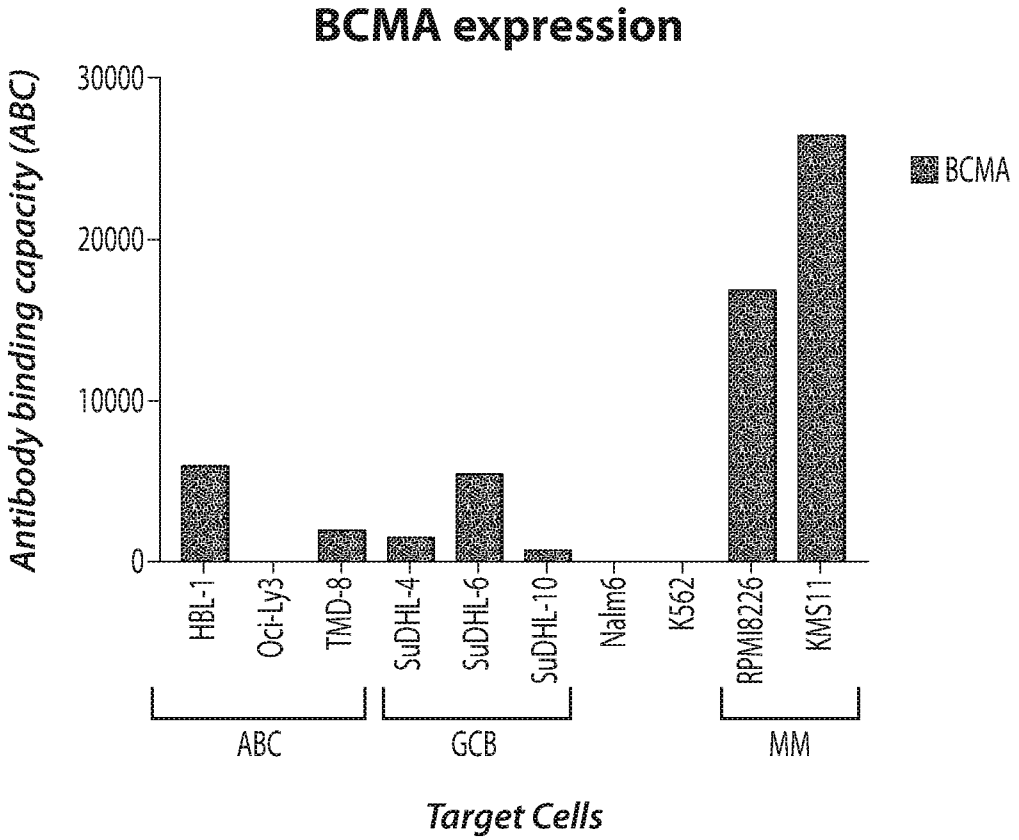

BCMA expression
Antibody binding capacity (ABC)
30000
20000
10000
0
BCMA
HBL-1
Oci-Ly3
TMD-8
SuDHL-4
SuDHL-6
SuDHL-10
Nalm6
K562
RPMI8226
KMS11
ABC
GCB
MM
Target Cells

FIG. 44B

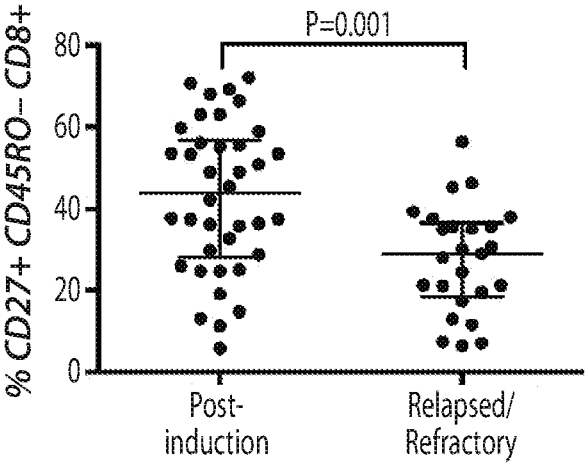


FIG. 45A

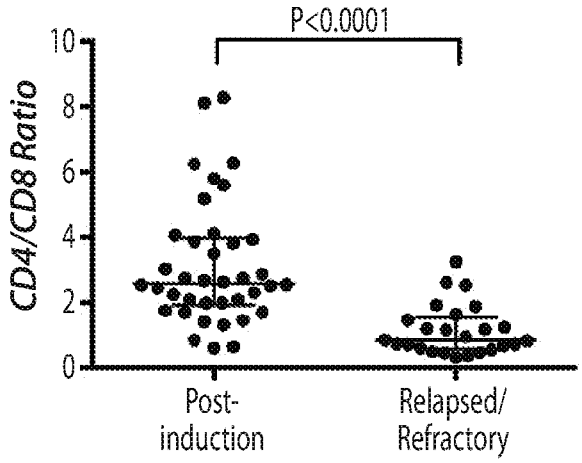


FIG. 45B

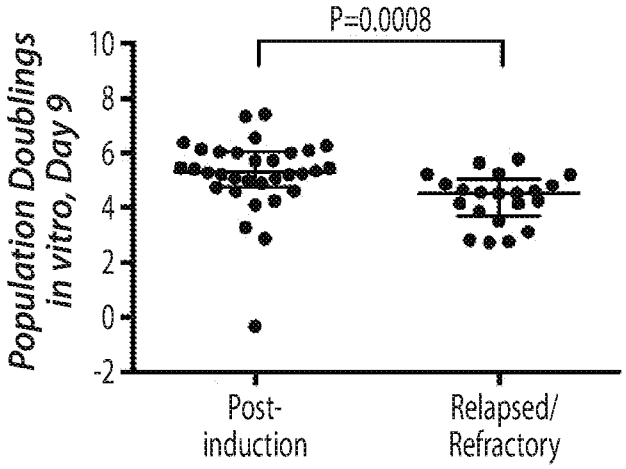
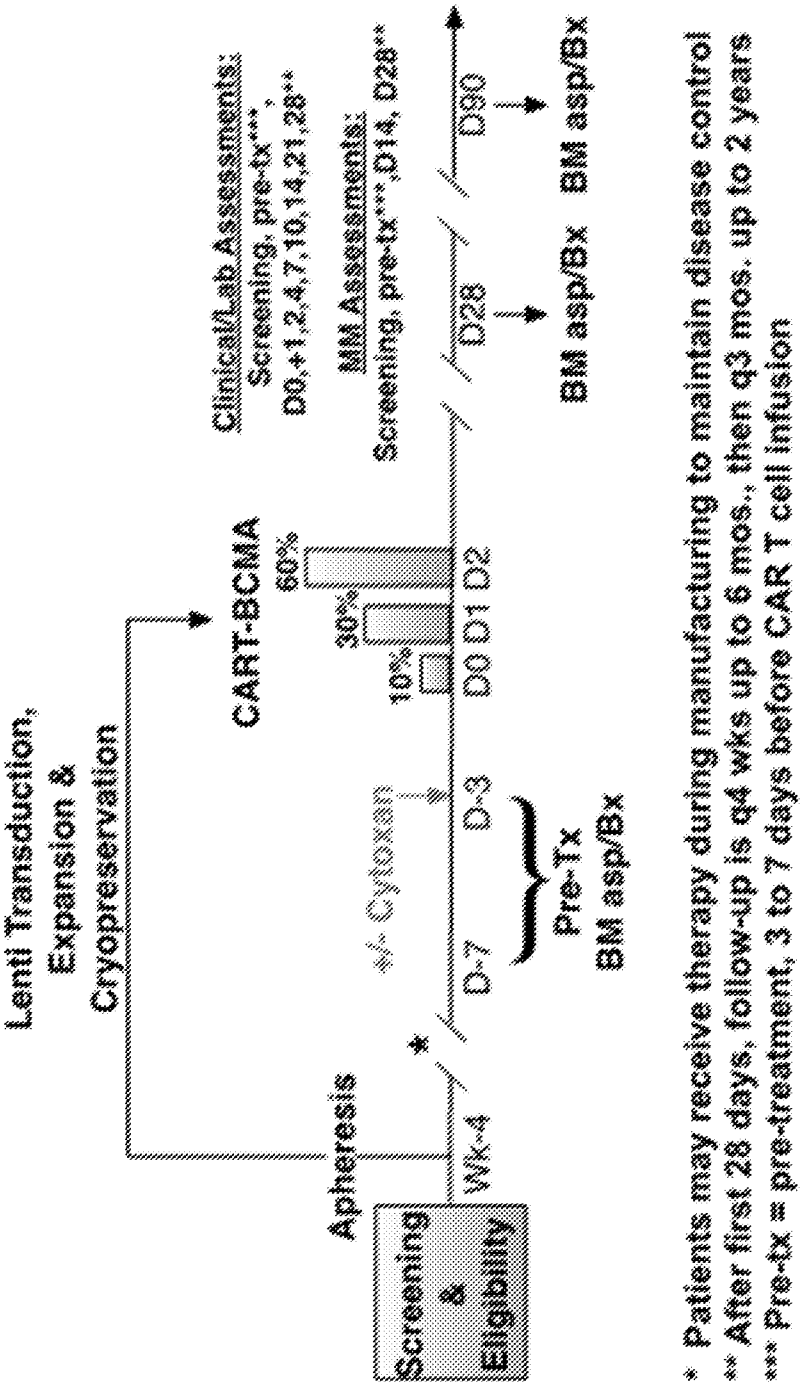


FIG. 45C

FIG. 46


Screening & Eligibility
Wk-4
Apheresis
*
Lenti Transduction, Expansion & Cryopreservation
CART-BCMA
+/- Cytoxan
D-7
D-3
Pre-Tx BM asp/Bx
10%
30%
60%
D0 D1 D2
Clinical/Lab Assessments: Screening, pre-tx***, D0,+1,2,4,7,10,14,21,28**
MM Assessments: Screening, pre-tx***,D14, D28**
D28
D90
BM asp/Bx
BM asp/Bx
* Patients may receive therapy during manufacturing to maintain disease control
** After first 28 days, follow-up is q4 wks up to 6 mos., then q3 mos. up to 2 years
*** Pre-tx = pre-treatment, 3 to 7 days before CAR T cell infusion

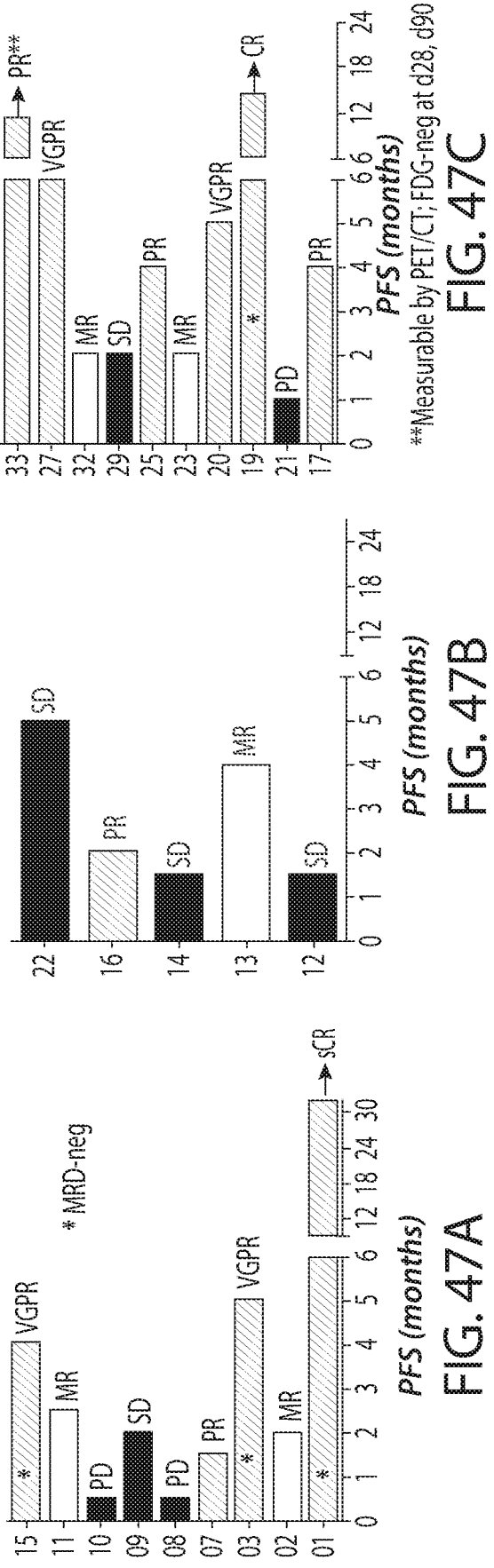


FIG. 47A

FIG. 47B

FIG. 47C

OS

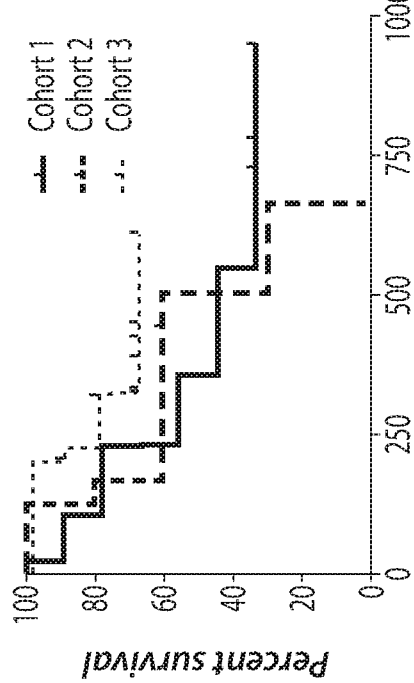


FIG. 47D

FIG. 48A

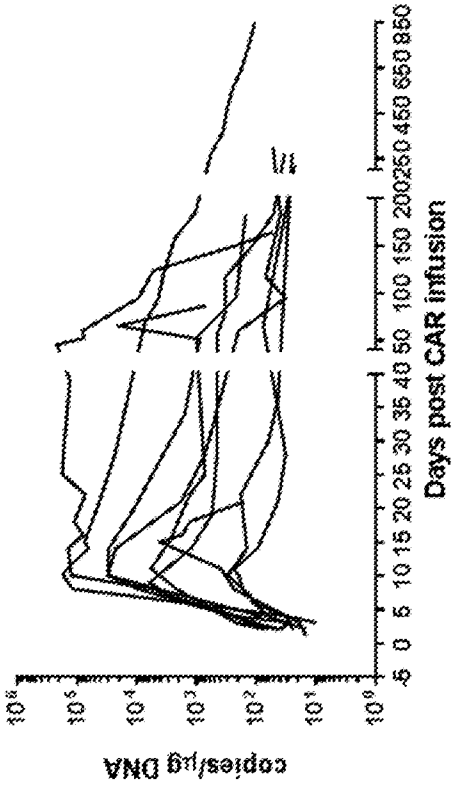


FIG. 48B

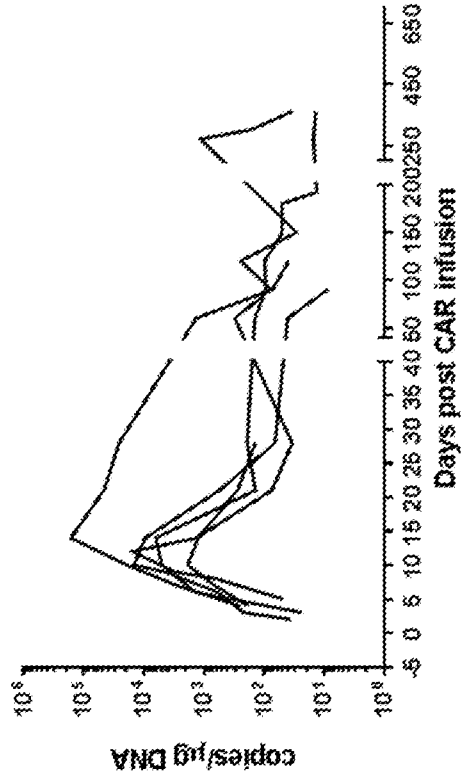


FIG. 48C

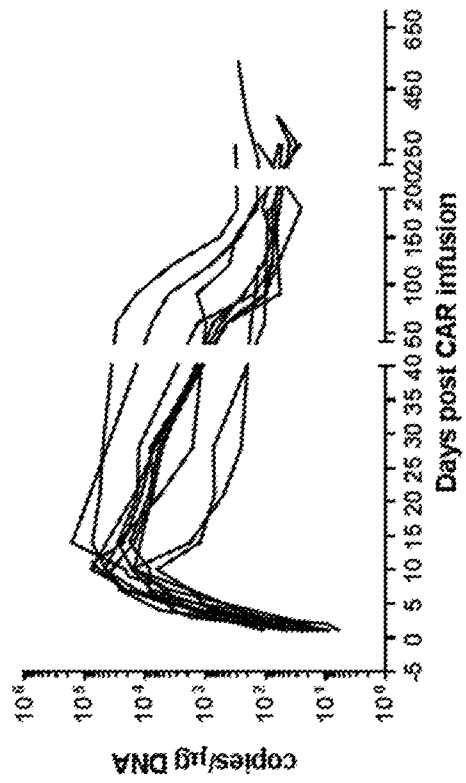


FIG. 48D

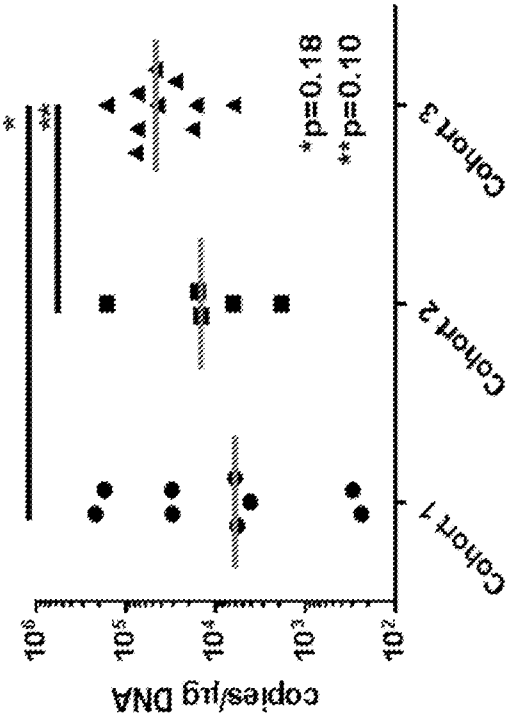


FIG. 49A

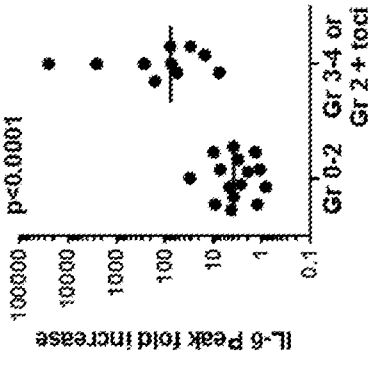


FIG. 49B

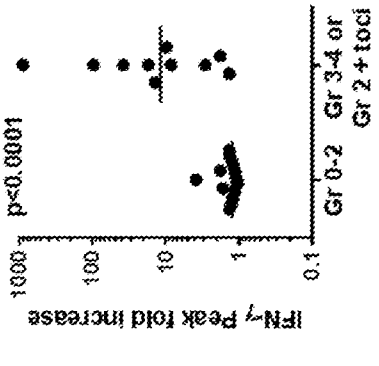


FIG. 49C

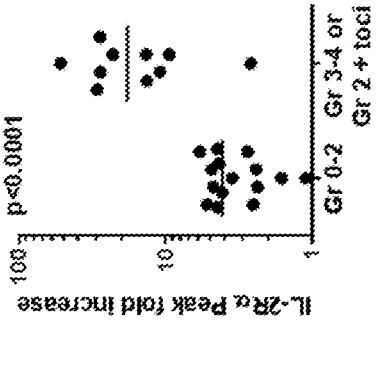


FIG. 49D

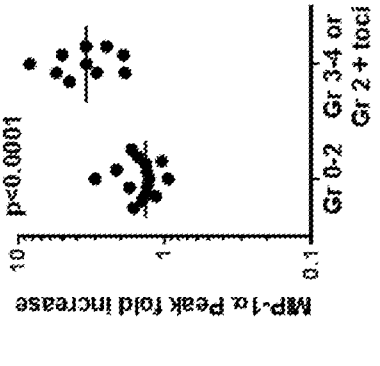


FIG. 49E

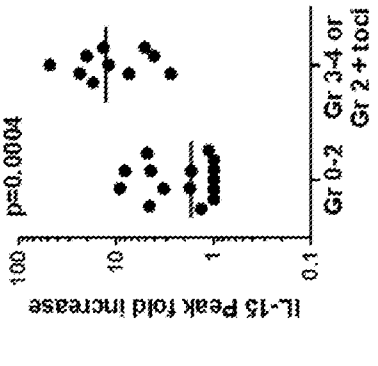


FIG. 49F

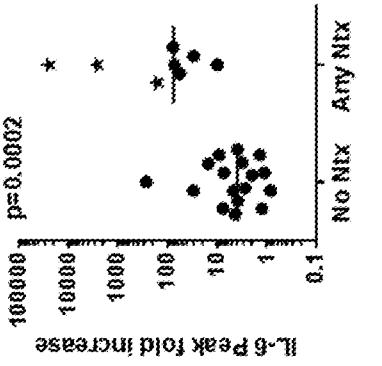


FIG. 49G

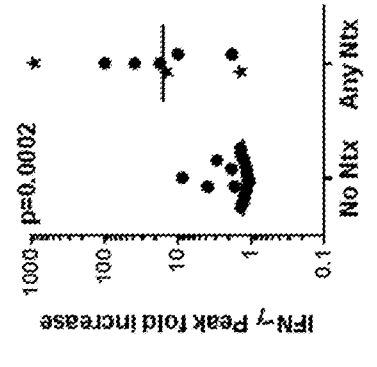


FIG. 49H

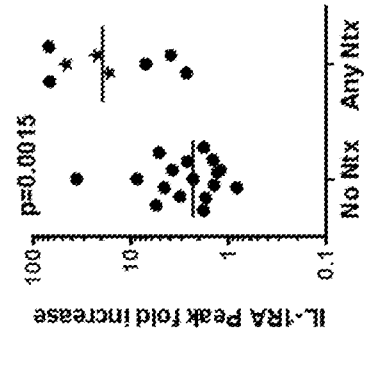
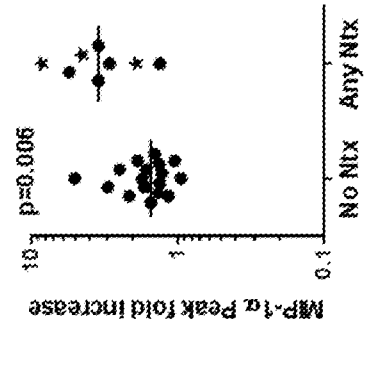


FIG. 49I



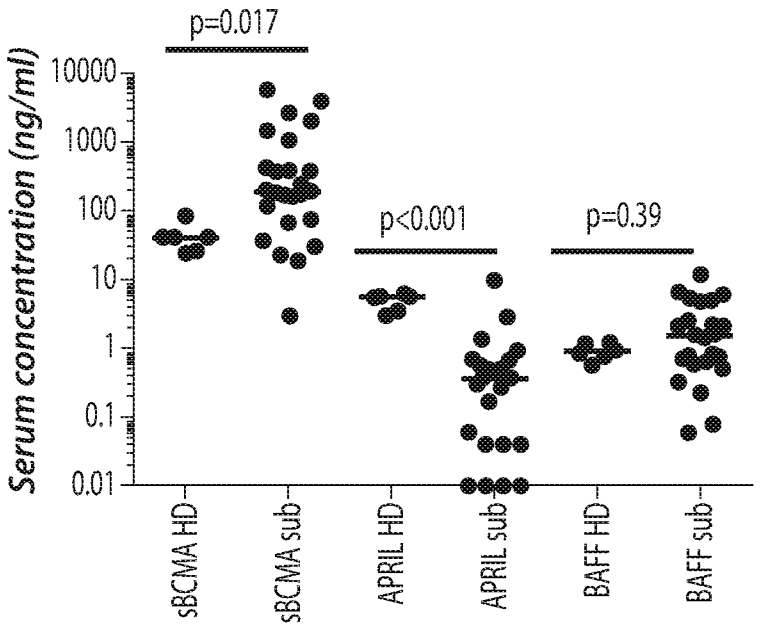


FIG. 50A

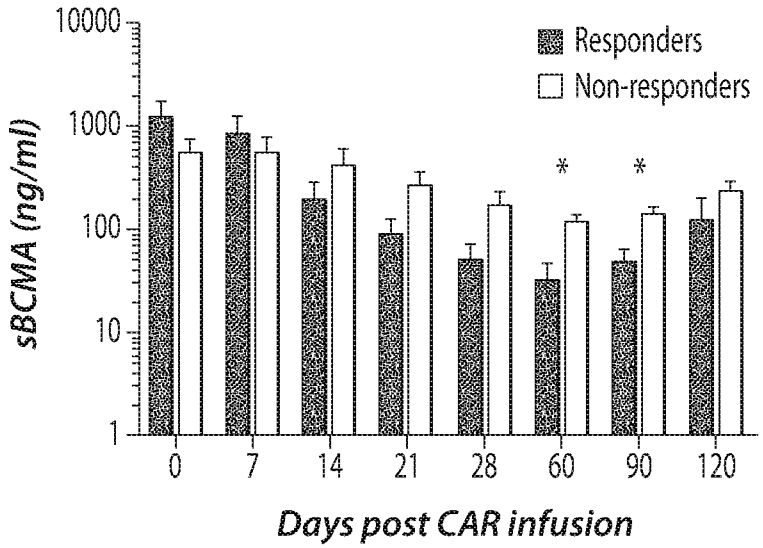


FIG. 50B

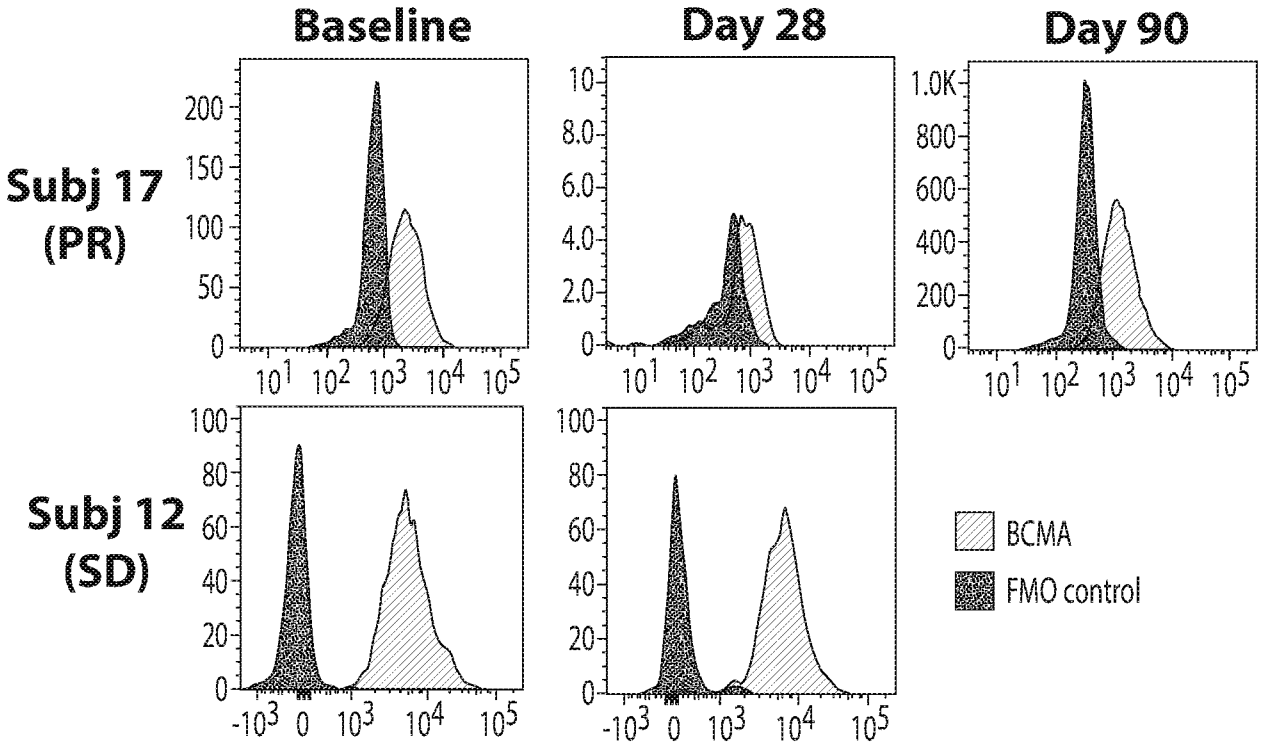


FIG. 50C

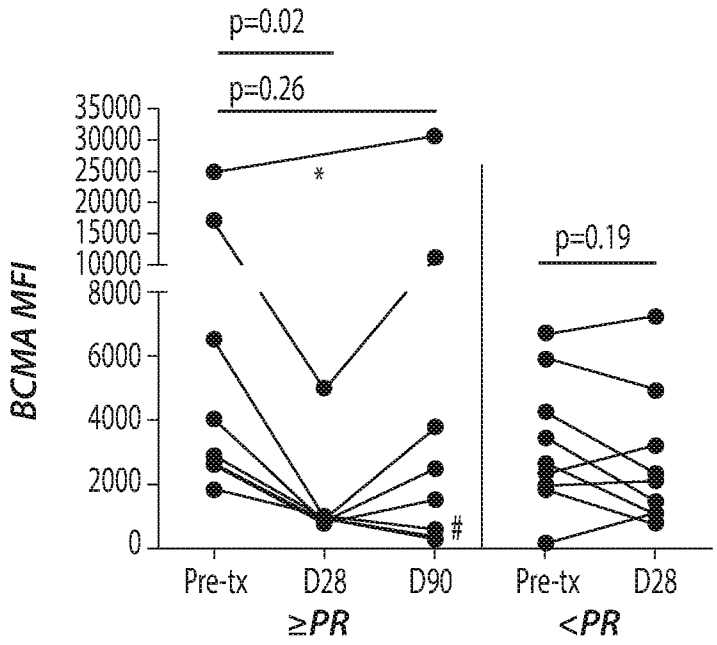


FIG. 50D

FIG. 51A

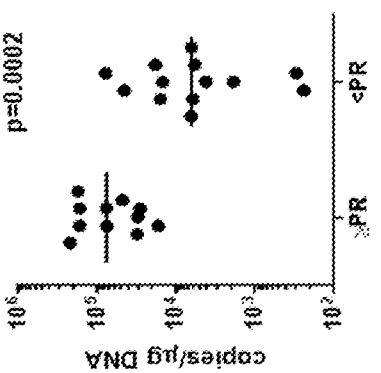


FIG. 51B

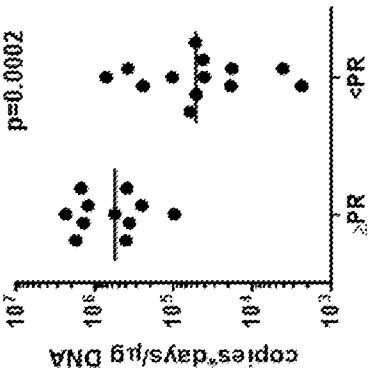


FIG. 51C

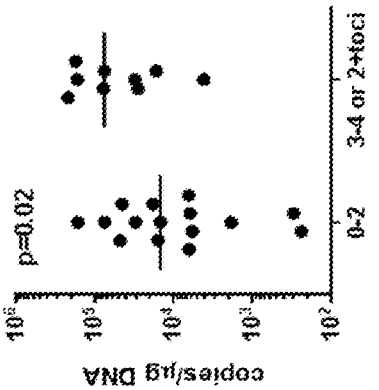


FIG. 51D

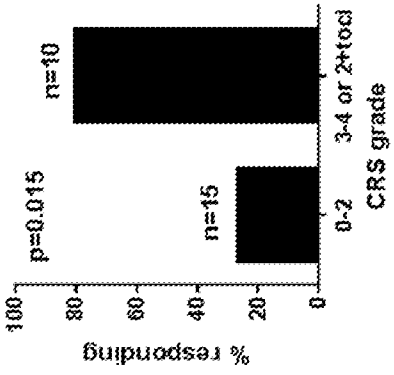


FIG. 51E

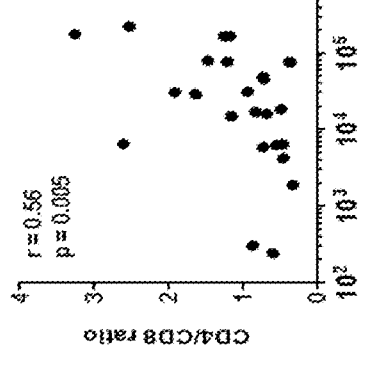


FIG. 51F

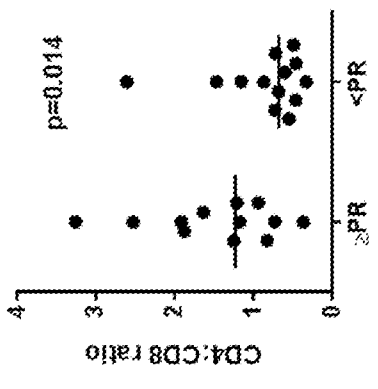


FIG. 51G

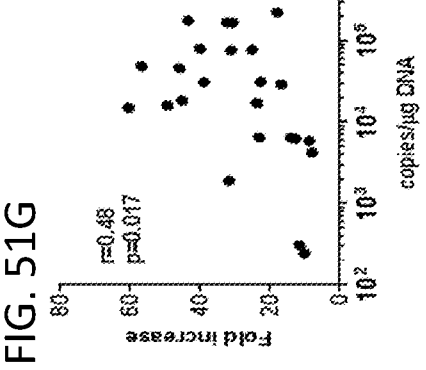


FIG. 51H

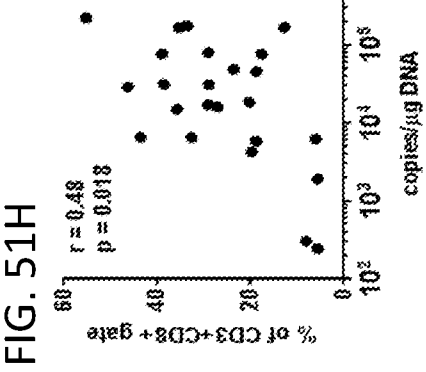


FIG. 51I

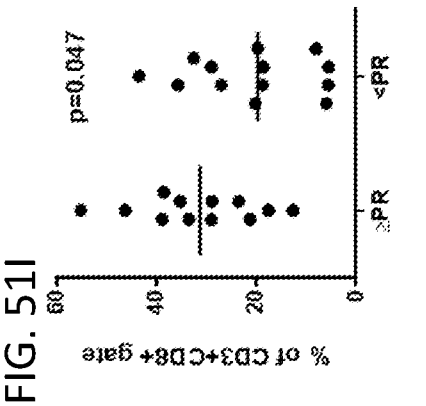


FIG. 52

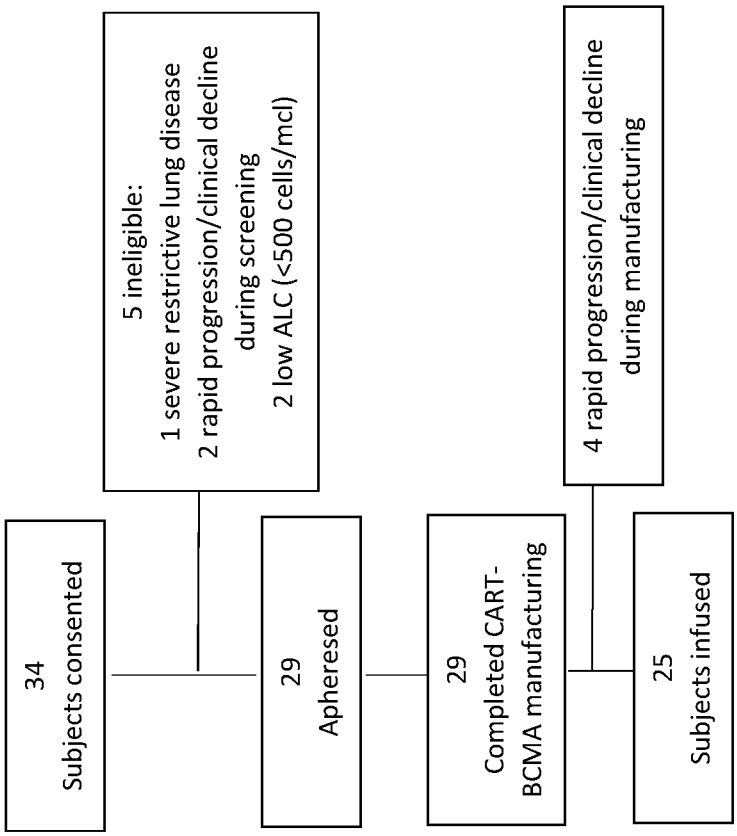

34
Subjects consented
5 ineligible:
1 severe restrictive lung disease
2 rapid progression/clinical decline during screening
2 low ALC (<500 cells/mcl)
29
Apheresed
29
Completed CART-BCMA manufacturing
4 rapid progression/clinical decline during manufacturing
25
Subjects infused

FIG. 53A

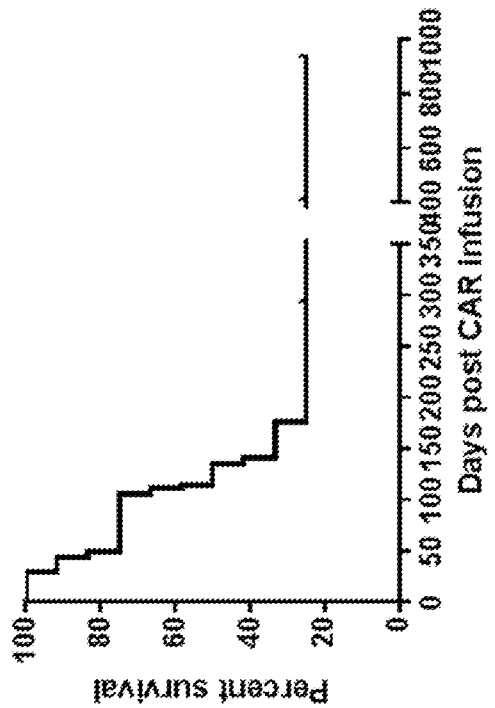


FIG. 53B

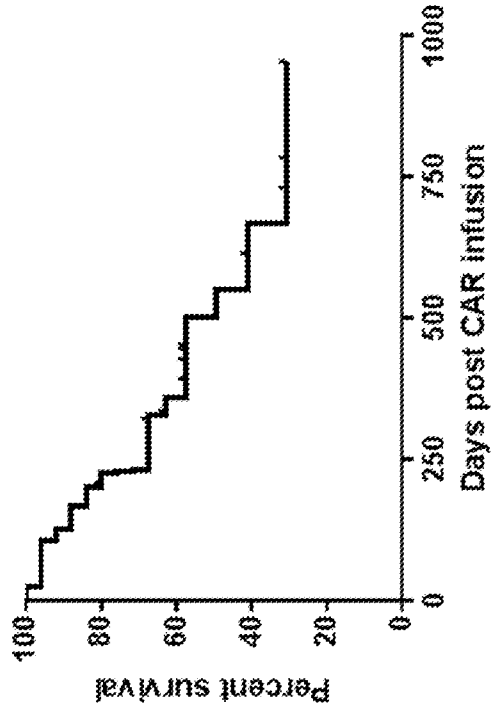


FIG. 53C

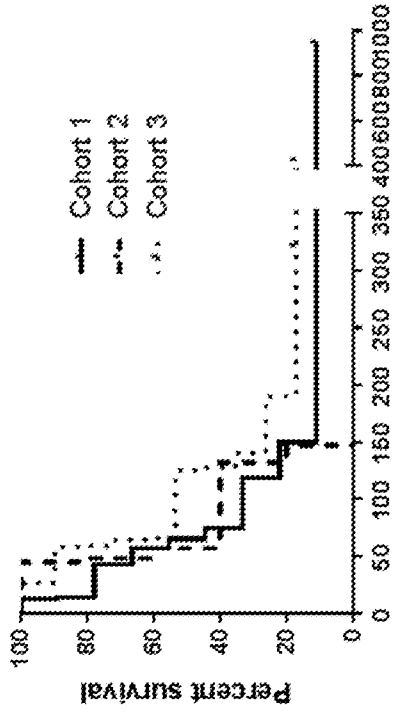


FIG. 53D

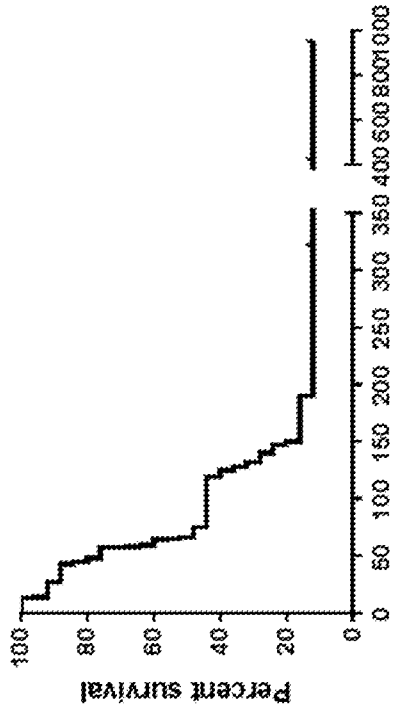


FIG. 54A

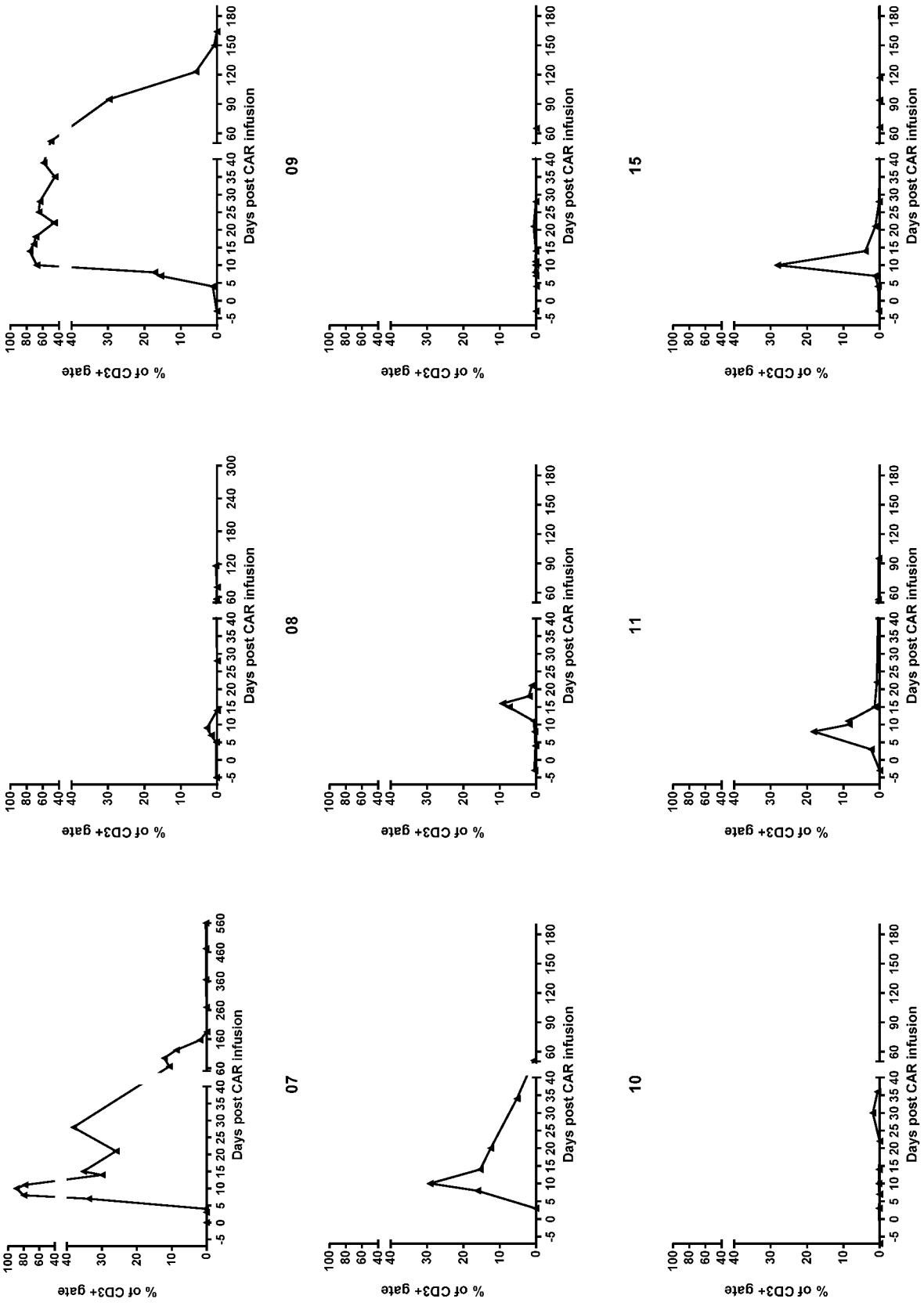
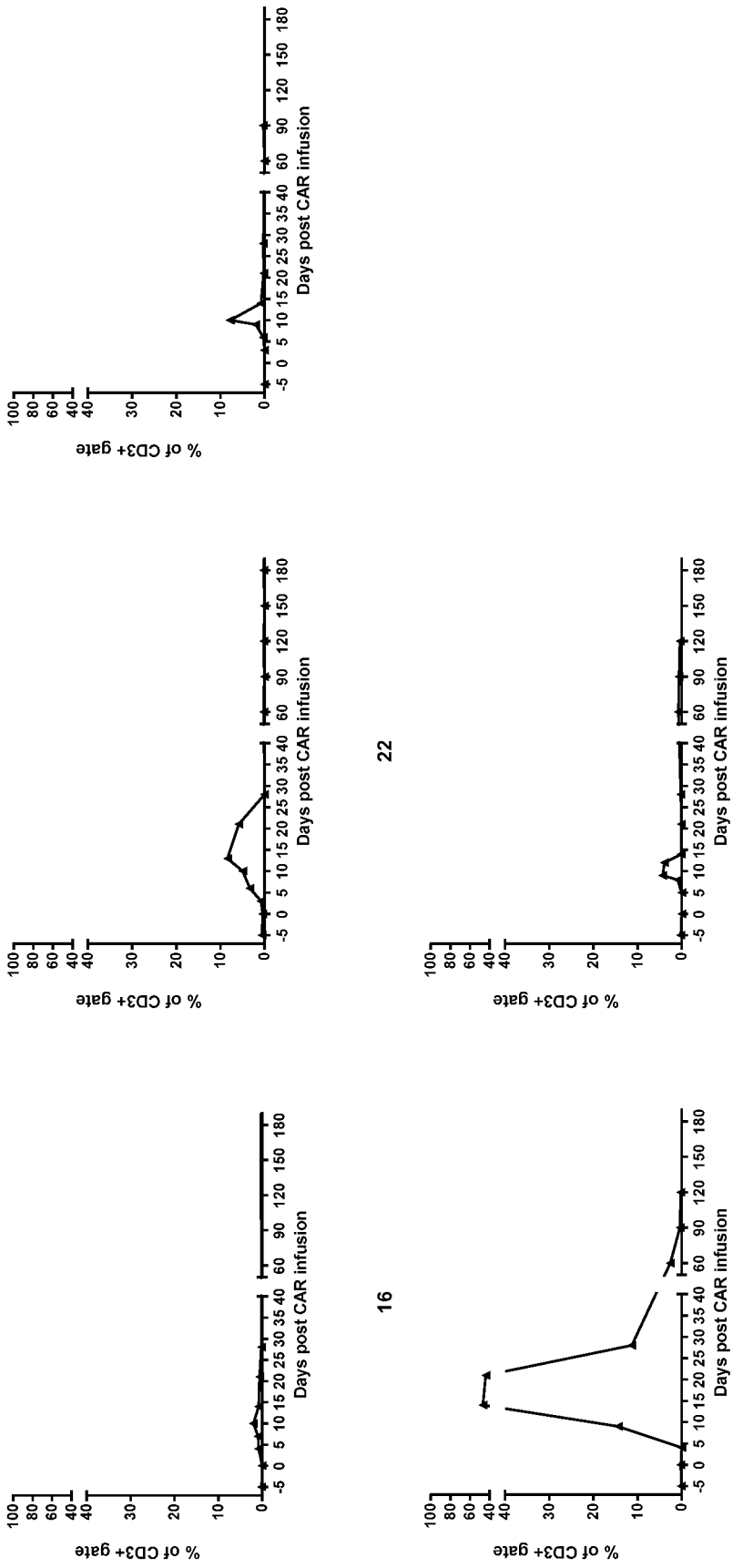


FIG. 54B



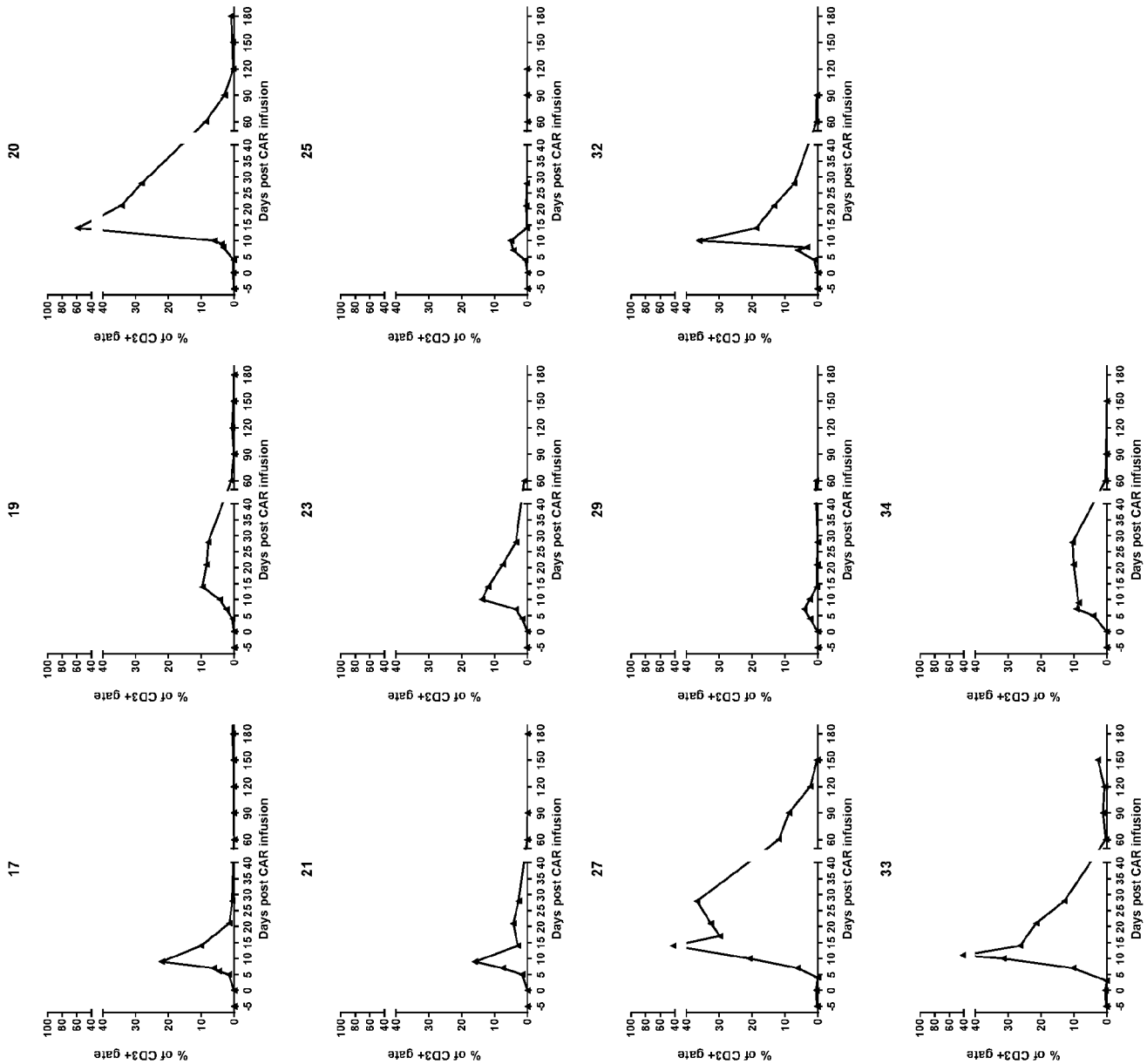

17
19
20
21
23
25
27
29
32
33
34
% of CD3+ gate
Days post CAR infusion

FIG. 54C

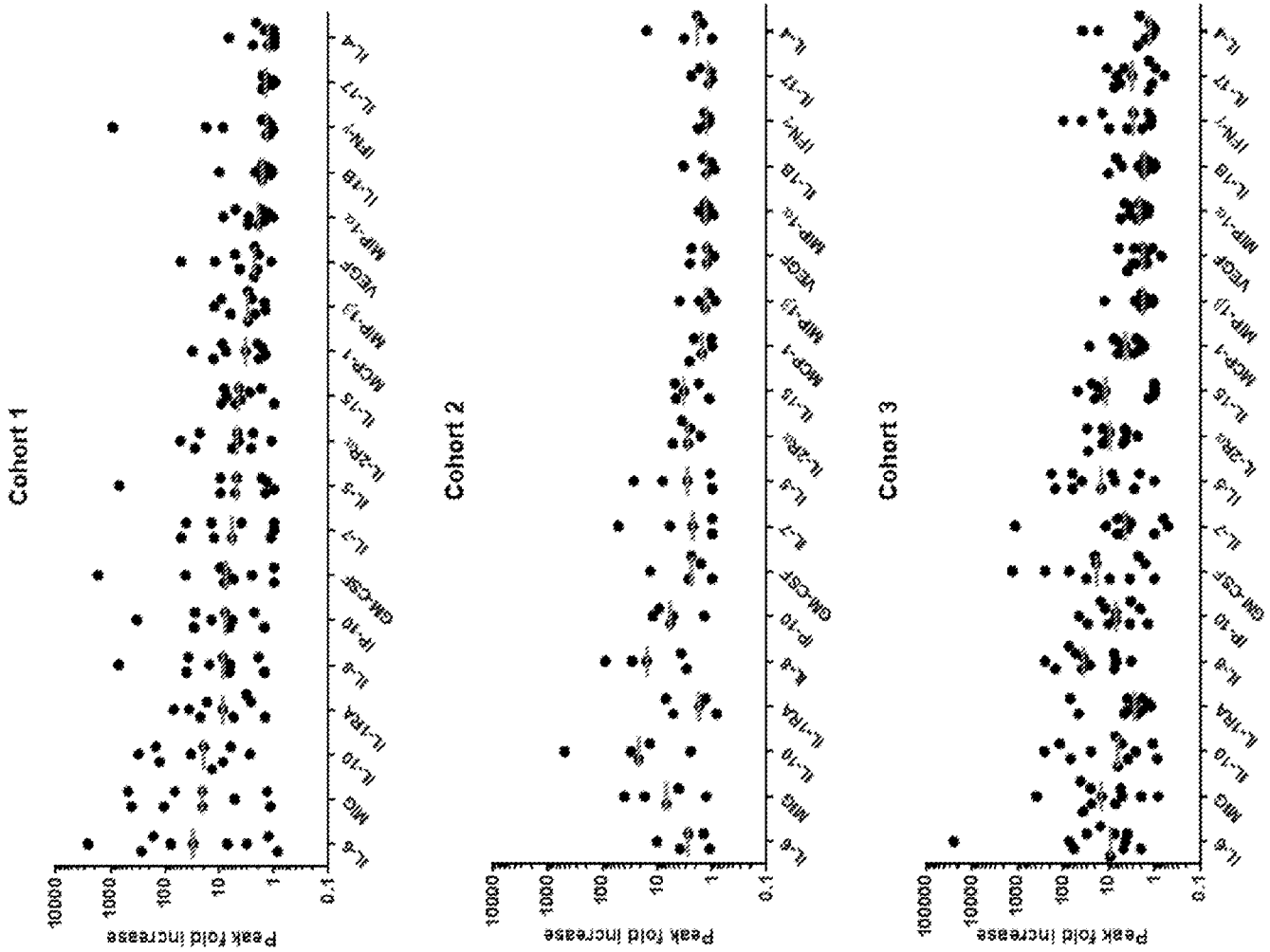

Cohort 1
Cohort 2
Cohort 3
Peak fold increase
10000
1000
100
10
1
0.1
IL-6
MIG
IL-10
IL-1RA
IL-8
IP-10
GM-CSF
IL-7
IL-5
IL-2Rα
IL-15
MCP-1
MIP-1β
VEGF
MIP-1α
IL-1β
IFNγ
IL-17
IL-4

FIG. 55

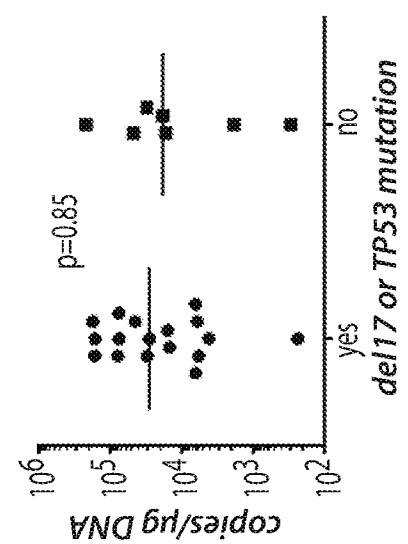


FIG. 56C

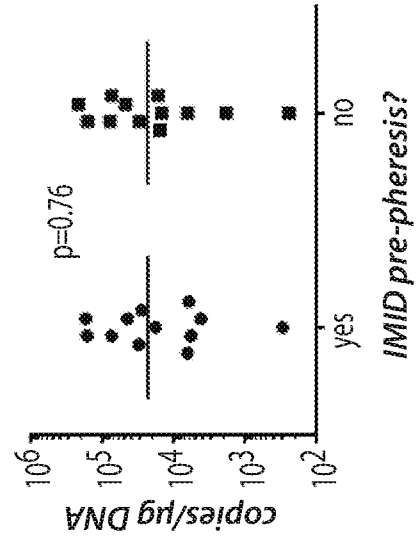


FIG. 56F

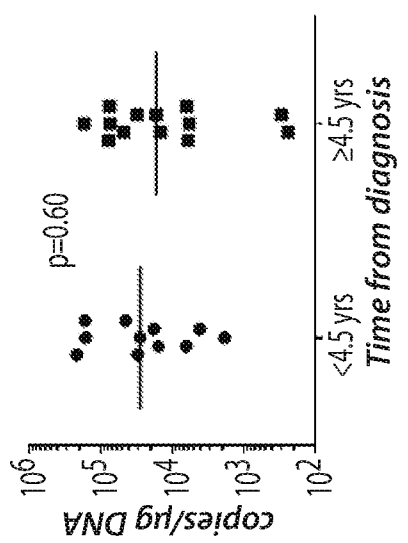


FIG. 56B

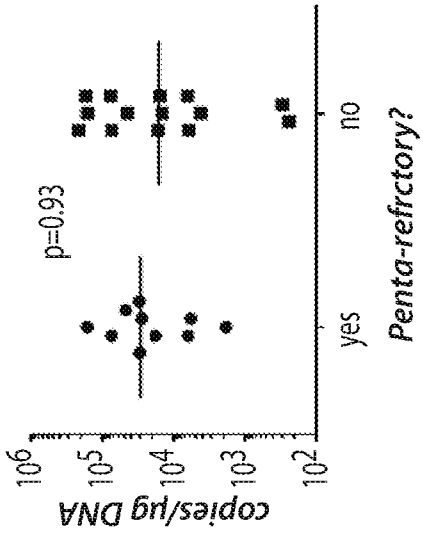


FIG. 56E

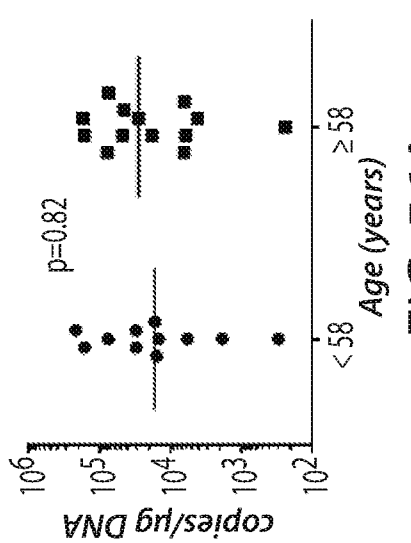


FIG. 56A

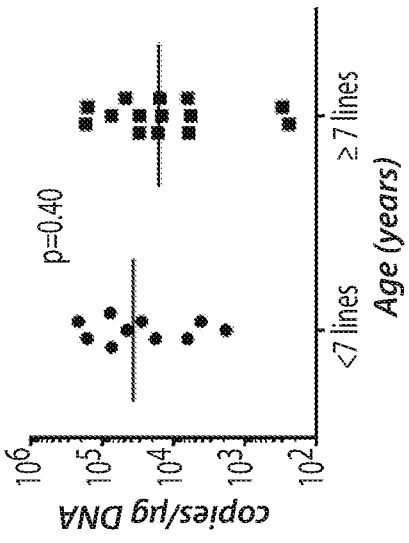


FIG. 56D

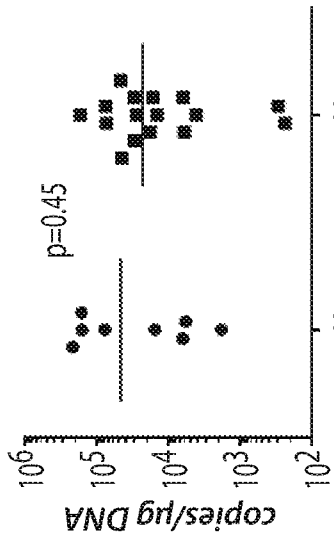


FIG. 56G

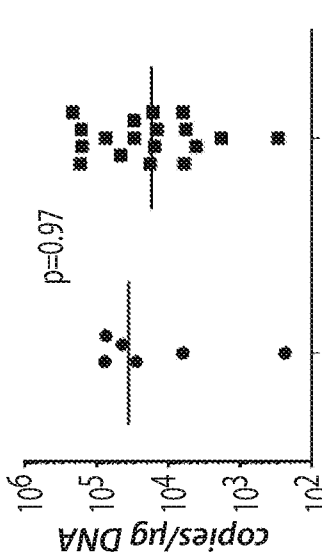


FIG. 56H

FIG. 56I



FIG. 56J

FIG. 56K

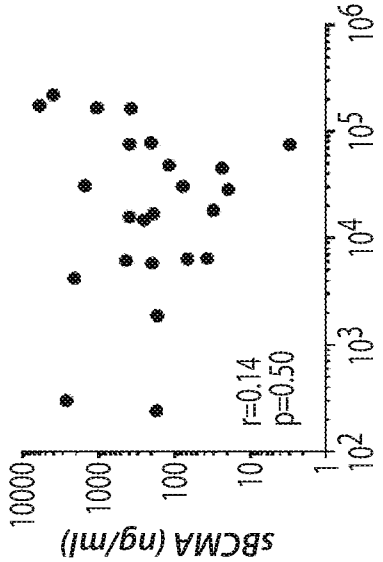


FIG. 56L

FIG. 57A

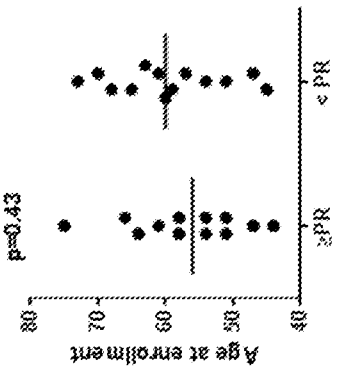


FIG. 57B

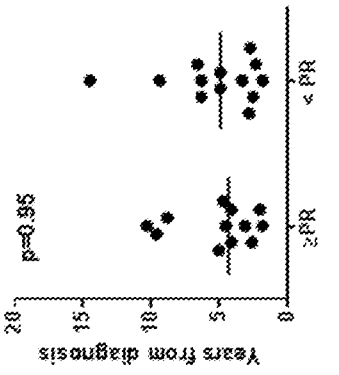


FIG. 57C

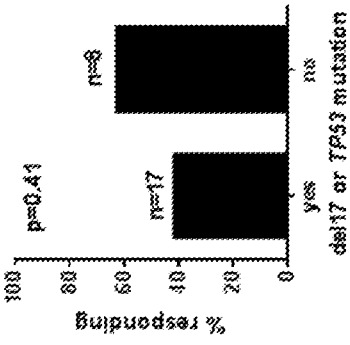


FIG. 57D

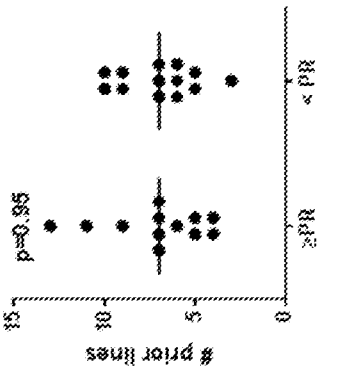


FIG. 57E

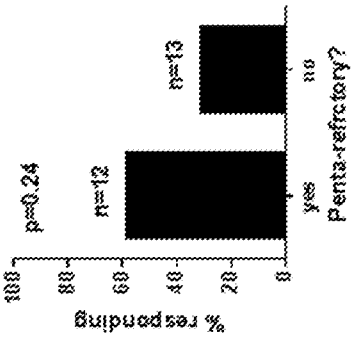


FIG. 57F

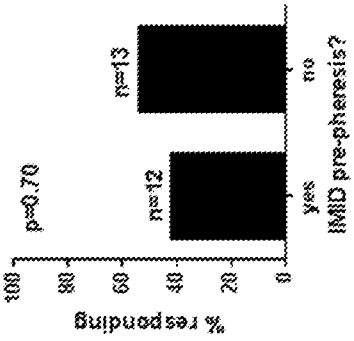


FIG. 57G

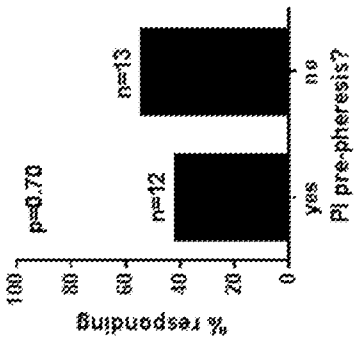


FIG. 57H

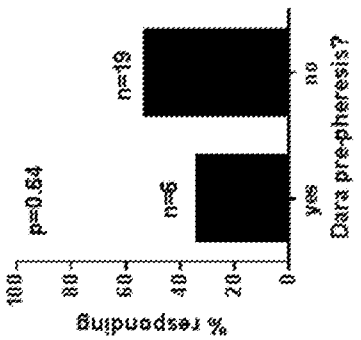


FIG. 57I

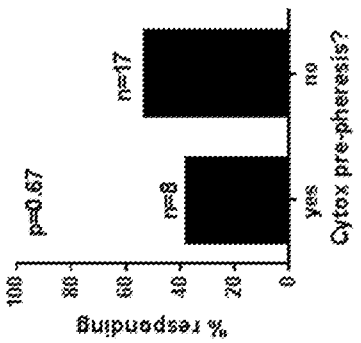


FIG. 57J

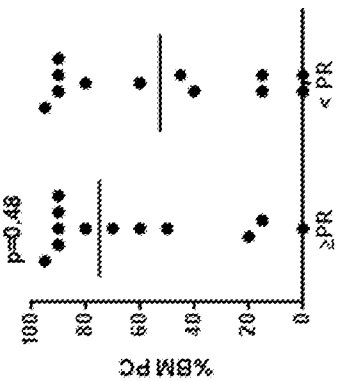


FIG. 57K

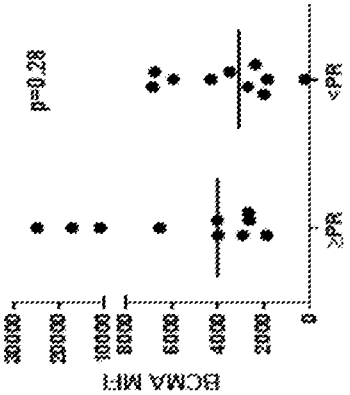
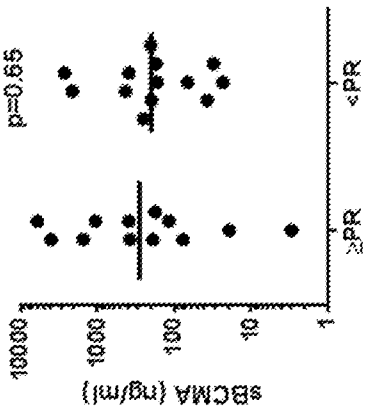


FIG. 57L



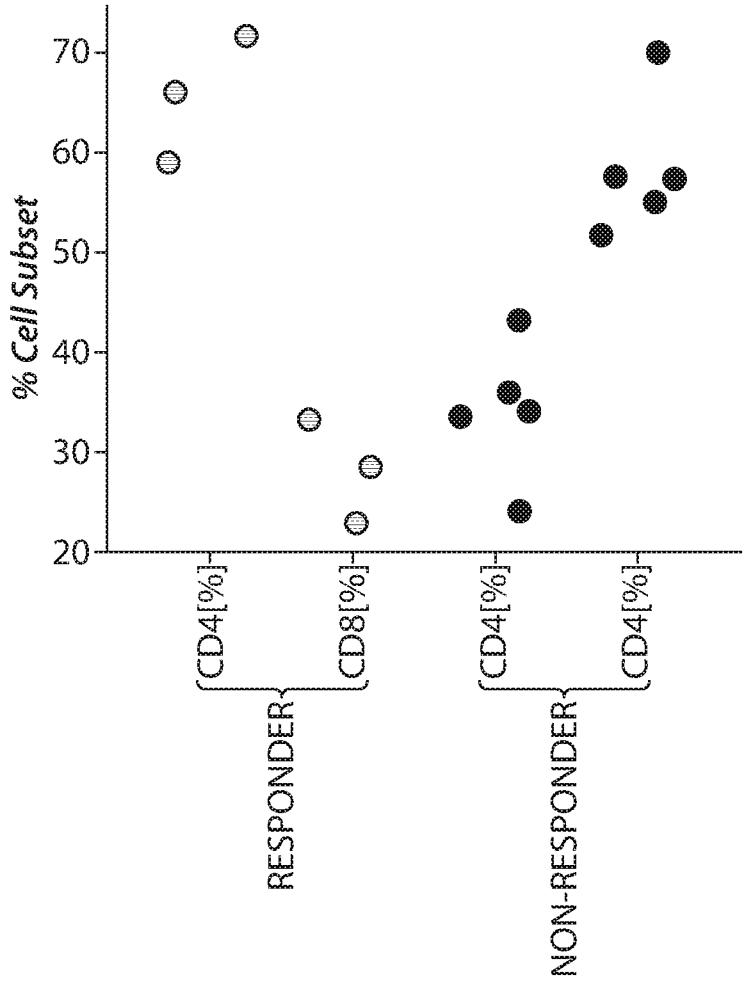

% Cell Subset
70
60
50
40
30
20
CD4[%]
CD8[%]
RESPONDER
CD4[%]
CD4[%]
NON-RESPONDER

FIG. 1A