

Claims

1. ~~A method of treating a subject having or suspected of having a disease or disorder associated with B-cell maturation antigen (BCMA) expression, the method comprising administering to the subject at least two doses~~Use of an interleukin-1 receptor antagonist (IL-1Ra) and a cell therapy in the manufacture of a medicament for the treatment of a subject having a disease or disorder associated with B-cell maturation antigen (BCMA) expression, wherein:
the cell therapy is to be administered to the subject, said cell therapy comprising a dose of engineered T cells comprising a first chimeric antigen receptor (CAR) specific for BCMA;
and
the interleukin-1 receptor antagonist (IL-1Ra) is to be administered to the subject,
wherein at least one dose of the IL-1Ra is to be administered within about or about 24 hours prior to the administration of the dose of engineered T cells; and at least one dose of the IL-1Ra is to be administered after the administration of the dose of engineered T cells.

2. Use of an interleukin-1 receptor antagonist (IL-1Ra) in the manufacture of a medicament for the treatment of~~A method of treating~~ a subject having ~~or suspected of having~~ a disease or disorder associated with B-cell maturation antigen (BCMA) expression, ~~the method comprising~~wherein the IL-1Ra is to be administered to the subject in combination with a cell therapy, wherein:
the cell therapy is to be administered to the subject, the~~administering a~~ cell therapy comprising a dose of engineered T cells comprising a first chimeric antigen receptor (CAR) specific for BCMA; and
at least one dose of the IL-1Ra is to be administered within about or about 24 hours prior to the administration of the dose of engineered T cells; and at least one dose of the IL-1Ra is to be administered after the administration of the dose of engineered T cells~~to a subject that has been administered at least one dose of an interleukin-1 receptor antagonist (IL-1Ra) within about or about 24 hours prior to the administration of the dose of engineered T cells; and~~
~~administering at least one dose of the IL-1Ra after the administration of the dose of engineered T cells.~~

3. Use of a cell therapy in the manufacture of a medicament for the treatment of a subject having a disease or disorder associated with B-cell maturation antigen (BCMA)

expression, wherein the cell therapy is to be administered to the subject in combination with an interleukin-1 receptor antagonist (IL-1Ra), wherein:

the cell therapy comprises a dose of engineered T cells comprising a first chimeric antigen receptor (CAR) specific for BCMA; and

at least one dose of the IL-1Ra is to be administered within about or about 24 hours prior to the administration of the dose of engineered T cells; and at least one dose of the IL-1Ra is to be administered after the administration of the dose of engineered T cells.

~~43. A method of reducing the severity of, attenuating, and/or preventing the onset of a toxicity in a subject having or suspected of having a disease or disorder associated with B-cell maturation antigen (BCMA) expression to be treated with a cell therapy, the method comprising administering to the subject at least two doses~~Use of an interleukin-1 receptor antagonist (IL-1Ra) and a cell therapy in the manufacture of a medicament for reducing the severity of, attenuating, and/or preventing the onset of a toxicity to a cell therapy for treating a subject having a disease or disorder associated with B-cell maturation antigen (BCMA) expression, wherein:

the cell therapy is to be administered to the subject, said cell therapy comprising a dose of engineered T cells comprising a first chimeric antigen receptor (CAR) specific for BCMA; and

~~wherein~~ at least one dose of the IL-1Ra is to be administered within about or about 24 hours prior to the administration of the dose of engineered T cells; and at least one dose of the IL-1Ra is to be administered after the administration of the dose of engineered T cells.

~~54. Use of an interleukin-1 receptor antagonist (IL-1Ra) in the manufacture of a medicament for A method of~~reducing the severity of, attenuating, and/or preventing the onset of a toxicity to a cell therapy, wherein:

~~in the cell therapy is to be administered to the subject for treating a subject having or suspected of having a disease or disorder associated with B-cell maturation antigen (BCMA) expression, to be treated with a cell therapy, the method comprising administering at the cell therapy comprising a dose of engineered T cells comprising a first chimeric antigen receptor (CAR) specific for BCMA; and~~

at least one dose of the IL-1Ra is to be administered within about or about 24 hours prior to the administration of the dose of engineered T cells; and at least one dose of the IL-1Ra is to be administered after the administration of the dose of engineered T cells to a subject that has

~~been administered at least one dose of an interleukin-1 receptor antagonist (IL-1Ra) within about or about 24 hour prior to the administration of the dose of engineered T cells; and administering at least one dose of the IL-1Ra is administered after the administration of the dose of engineered T cells.~~

6. Use of a cell therapy in the manufacture of a medicament for treating a subject having a disease or disorder associated with B-cell maturation antigen (BCMA) expression in combination with an interleukin-1 receptor antagonist (IL-1Ra) for reducing the severity of, attenuating, and/or preventing the onset of a toxicity to the cell therapy, wherein:

the cell therapy is to be administered to the subject, the cell therapy comprising a dose of engineered T cells comprising a first chimeric antigen receptor (CAR) specific for BCMA; and at least one dose of the IL-1Ra is to be administered within about or about 24 hours prior to the administration of the dose of engineered T cells; and at least one dose of the IL-1Ra is to be administered after the administration of the dose of engineered T cells.

75. The ~~method-use~~ of any of claims 1-~~64~~, wherein the at least one dose of IL-1Ra to be administered prior to the administration of the dose of engineered T cells is to be administered within about or about 21, 18, 15 or 12 hours prior to the administration of the dose of engineered T cells.

86. The ~~method-use~~ of any of claims 1-~~75~~, wherein the at least one dose of the IL-Ra to be administered prior to the administration of the dose of engineered T cells comprises at least two doses of the IL-1Ra to be administered prior to the administration of the dose of engineered T cells, optionally:-

7. ~~The method of claim 6,~~ wherein one dose of the at least two doses of IL-1Ra to be administered prior to the administration of the dose of engineered T cells is to be administered within at or about 6, 5, 4, 3 or 2 hours prior to the administration of the dose of engineered T cells.

8. ~~The method of claim 6 or 7, wherein one dose of the at least two doses of IL-1Ra administered prior to the administration of the dose of engineered T cells is administered within at or about 3 hours prior to the administration of the dose of engineered T cells.~~

9. The ~~method-use~~ of ~~any of claims 6-8~~claim 8, wherein one dose of the at least two doses of IL-1Ra is to be administered within about or about 24 hours prior to the administration of the dose of engineered T cells, and one dose of the at least two doses of IL-1Ra is to be administered within about or about 3 hours prior to the administration of the dose of engineered T cells.

10. The ~~method-use~~ of any of claims 1-9, wherein the at least one dose of the IL-1Ra to be administered after the administration of the dose of engineered T cells comprises at least 2, 3, 4, 5, 6, 7 or 8 doses of the IL-1Ra to be administered after the administration of the dose of engineered T cells.

~~11. The method of any of claims 1-10, wherein the at least one dose of the IL-1Ra administered after the administration of the dose of engineered T cells comprises 3, 4, 5, 6 or 7 doses of IL-1Ra administered after the administration of the dose of engineered T cells.~~

~~12. The method of any of claims 1-11, wherein the at least one dose of the IL-1Ra administered after the administration of the dose of engineered T cells comprises 4 doses of IL-1Ra administered after the administration of the dose of engineered T cells.~~

~~11~~13. The ~~method-use~~ of any of claims 1-~~10~~2, wherein the at least one dose of the IL-1Ra to be administered after the administration of the dose of engineered T cells is to be administered each day for consecutive days, optionally.

~~14. The method of any of claims 1-13, wherein the at least one dose of IL-1Ra to be administered after the administration of the dose of engineered T cells is 4 doses, wherein one of the four doses is to be administered each day for 4 consecutive days after the administration of the dose of engineered T cells.~~

~~15. The method of any of claims 1-14, wherein a dose of IL-1Ra is administered every 24 hours (q24h) on Days 2-5.~~

~~12~~16. A method of reducing the severity of, attenuating, and/or preventing the onset of a toxicity in a subject having or suspected of having a disease or disorder associated with B-cell maturation antigen (BCMA) expression to be treated with a cell therapy, the method comprising

~~administering to the subject at least 6 doses~~Use of an interleukin-1 receptor antagonist (IL-1Ra) and a cell therapy in the manufacture of a medicament for reducing the severity of, attenuating, and/or preventing the onset of a toxicity in a subject having a disease or disorder associated with B-cell maturation antigen (BCMA) expression to be treated with a cell therapy, wherein the cell therapy is to be administered to a subject having a disease or disorder associated with BCMA expression to be treated with a cell therapy, said cell therapy comprising a dose of engineered T cells comprising a first chimeric antigen receptor (CAR) specific for BCMA; and at least six doses of an interleukin-1 receptor antagonist (IL-1Ra) are to be administered to the subject, wherein the cell therapy is to be administered on Day 1 and:

(a) one dose of the IL-1Ra is to be administered within about or about 24 hours prior to the administration of the dose of engineered T cells, optionally the night before the administration of the dose of the engineered T cells;

(b) one dose of the IL-1Ra is to be administered within about or about 3 hours prior to the administration of the dose of engineered T cells on Day 1;

(c) four doses of the IL-1Ra are to be administered after the administration of the dose of engineered T cells, wherein one dose of the four doses is to be administered each day on Days 2, 3, 4, and 5.

~~1317.~~ The ~~method-use~~ of any of claims 1-126, ~~further comprising administering wherein the~~ at least one additional dose of the IL-1Ra is to be administered after the administration of the dose of engineered T cells if the subject exhibits symptoms or signs of a cytokine release syndrome (CRS), optionally;

~~18.—The method of claim 17,~~ wherein the at least one additional dose of the IL-1Ra comprises ~~administration of~~ at least one additional dose of the IL-1Ra to be administered each day for consecutive days, until the symptoms or signs of CRS resolve.

~~19.—The method of claim 18, wherein the at least one additional dose of the IL-1Ra is one additional dose, which is administered each day for consecutive days, until the symptoms or signs of CRS resolve.~~

~~1420.~~ The ~~method-use~~ of any of claims 113-139, wherein, if the subject exhibits symptoms or signs of a cytokine release syndrome (CRS), a dose of IL-1Ra is to be administered every 12 hours (q12h) until the symptoms or signs of CRS resolve, optionally;

~~21. The method of any of claims 13-20,~~ wherein the administration of the IL-1Ra each day is to be administered at or about the same time each day.

1522. The method-use of any of claims 1-~~1421~~, wherein the IL-1Ra is a recombinant IL-1Ra.

1623. The method-use of any of claims 1-1522, wherein the IL-1Ra comprises the sequence set forth in SEQ ID NO:256 or a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% or higher sequence identity to SEQ ID NO:256 that retains function as an IL-1Ra.

1724. The method-use of any of claims 1-1623, wherein the IL-1Ra is anakinra.

1825. The method-use of any of claims 1-1724, wherein each dose of the IL-1Ra is at or about 500 mg, at or about 400 mg, at or about 300 mg, at or about 200 mg, at or about 100 mg or at or about 50 mg, or a range defined by any of the foregoing, optionally wherein each dose of the recombinant IL-1Ra is from at or about 50 mg to at or about 200 mg.

~~26. The method of any of claims 1-25, wherein each dose of the IL-1Ra is at or about 100 mg.~~

~~27. The method of any of claims 1-26, wherein the IL-1Ra is administered subcutaneously.~~

1928. The method-use of any of claims 1-1827, wherein the method-use reduces the severity of, attenuates, and/or prevents the onset of a toxicity associated with administration of the cell therapy.

~~29. The method of any of claims 3-28, wherein the toxicity is a cytokine release syndrome (CRS).~~

~~30. The method of claim 29, wherein the CRS is a severe CRS or a grade 3 or higher CRS.~~

2034. The ~~method-use~~ of any of claims 3-1928, wherein the toxicity is a neurotoxicity (NT) or is a macrophage activation syndrome (MAS) or a hemophagocytic lympho-histiocytosis (HLH).

~~32.—The method of claim 31, wherein the NT is a severe NT or a grade 2 or higher NT or a grade 3 or higher NT.~~

~~33.—The method of any of claims 3-28, wherein the toxicity is a macrophage activation syndrome (MAS) or a hemophagocytic lympho-histiocytosis (HLH).~~

2134. The ~~method-use~~ of any of claims 1-2033, wherein at or prior to the administration of the dose of engineered T cells, the subject has been administered one or more prior BCMA-directed therapy selected from among:

- a prior dose of engineered T cells comprising a second CAR specific for BCMA;
- a prior administration of a BCMA-directed T cell engager (TCE); and
- a prior administration of a BCMA-directed antibody-drug conjugate (ADC).

~~2235. A method of treating a subject having or suspected of having a disease or disorder associated with B-cell maturation antigen (BCMA) expression, the method comprising administering to the subject~~Use of a cell therapy comprising a dose of engineered T cells comprising a first chimeric antigen receptor (CAR) specific for B-cell maturation antigen (BCMA) in the manufacture of a medicament to treat a subject having a disease or disorder associated with BCMA expression, wherein at or prior to the administration of the dose of engineered T cells, the subject has been administered one or more prior BCMA-directed therapy selected from among:

- a prior dose of engineered T cells comprising a second CAR specific for BCMA;
- a prior administration of a BCMA-directed T cell engager (TCE); and
- a prior administration of a BCMA-directed antibody-drug conjugate (ADC).

~~36.—A method of treating a subject having or suspected of having a disease or disorder associated with B-cell maturation antigen (BCMA) expression, the method comprising administering to the subject a cell therapy comprising a dose of engineered T cells comprising a first chimeric antigen receptor (CAR) specific for BCMA, to a subject that has previously~~

~~received one or more prior BCMA-directed therapy selected from among:~~

- ~~a prior dose of engineered T cells comprising a second CAR specific for BCMA;~~
- ~~a prior administration of a BCMA-directed T cell engager (TCE); and~~
- ~~a prior administration of a BCMA-directed antibody drug conjugate (ADC).~~

2337. The ~~method-use~~ of any of claims 2134-2236, wherein the subject has relapsed following or has been refractory to the one or more prior BCMA-directed therapy, optionally:

~~38.—The method of any of claims 34-37, wherein the subject has relapsed following or has been refractory to the one or more prior BCMA-directed therapy within about or about 1 year prior to the administration of the dose of engineered T cells comprising the first CAR.~~

~~39.—The method of any of claims 34-38, wherein the subject has relapsed following or has been refractory to the one or more prior BCMA-directed therapy within about or about 6 months prior to the administration of the dose of engineered T cells comprising the first CAR.~~

~~40.—The method of any of claims 34-39, wherein the subject has relapsed following or has been refractory to the one or more prior BCMA-directed therapy within about or about 3 months prior to the administration of the dose of engineered T cells comprising the first CAR.~~

~~41.—The method of any of claims 34-40, wherein the BCMA-directed TCE is or comprises a bispecific antibody or a bispecific T cell engager (BiTE).~~

~~42.—The method of any of claims 34-41, wherein the BCMA-directed TCE is selected from among one or more of AMG 420/BI 836909, AMG 701, CC 93269, JNJ 64007957, PF-06863135 and REGN5458.~~

~~43.—The method of any of claims 34-42, wherein the BCMA-directed ADC is selected from among one or more of Belantamab mafodotin (GSK2857916), MEDI2228, CC 99712 and AMG 224.~~

2444. The ~~method-use~~ of any of claims 1-2343, wherein the first CAR comprises an extracellular antigen-binding domain comprising:

- a variable heavy chain (V_H) comprising a heavy chain complementarity determining

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

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

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

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

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

2545. The ~~method-use~~ of claim 2444, wherein the V_H is or comprises the amino acid sequence of SEQ ID NO: 116; and the V_L is or comprises the amino acid sequence of SEQ ID NO: 119.

2646. The ~~method-use~~ of claim 2344 or claim 2545, wherein the extracellular antigen-binding domain comprises the amino acid sequence of SEQ ID NO: 114 or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO: 114.

2747. The ~~method-use~~ of any of claims 2444-2646, wherein a nucleic acid encoding the extracellular antigen-binding domain comprises (a) the sequence of nucleotides of SEQ ID NO:113; (b) a sequence of nucleotides that has at least 90% sequence identity thereto; (c) a degenerate sequence of (a) or (b); and/or (d) the sequence of nucleotides of SEQ ID NO:115.

2848. The ~~method-use~~ of any of claims 1-2747, wherein the first CAR comprises:

(a) a spacer comprising an IgG4/2 chimeric hinge or a modified IgG4 hinge; an IgG2/4 chimeric C_H2 region; and an IgG4 C_H3 region, which optionally is about 228 amino acids in length; or a spacer set forth in SEQ ID NO: 174;

(b) a transmembrane domain, optionally a transmembrane domain from a human CD28; and

(c) an intracellular signaling region comprising a cytoplasmic signaling domain of a CD3-zeta (CD3ζ) chain and a costimulatory signaling region comprising an intracellular signaling domain of a T cell costimulatory molecule or a signaling portion thereof.

~~49. The method of any of claims 44-48, wherein the transmembrane domain is or comprises a transmembrane domain from human CD28.~~

~~2950.~~ The ~~method-use~~ of any of claims ~~2444-2849~~, wherein the transmembrane domain is or comprises the sequence set forth in SEQ ID NO:138 or a sequence of amino acids that has at least 90% sequence identity to SEQ ID NO:138.

~~3051.~~ The ~~method-use~~ of any of claims 1-~~2343~~, wherein the first CAR comprises an extracellular antigen-binding domain comprising:

a variable heavy chain (V_H) comprising a heavy chain complementarity determining region 1 (CDR-H1), a heavy chain complementarity determining region 2 (CDR-H2) and a heavy chain complementarity determining region 3 (CDR-H3) contained within the sequence set forth in SEQ ID NO: 125 and a variable light chain (V_L) comprising a light chain complementarity determining region 1 (CDR-L1), a light chain complementarity determining region 2 (CDR-L2) and a light chain complementarity determining region 3 (CDR-L3) contained within the sequence set forth in SEQ ID NO: 127; and/or

a V_H comprising a CDR-H1, a CDR-H2 and a CDR-H3 sequences set forth in SEQ ID NOS: 260, 261, and 262, respectively, and a V_L comprising a CDR-L1, a CDR-L2 and a CDR-L3 sequences set forth in SEQ ID NOS: 257, 258, and 259, respectively.

~~3152.~~ The ~~method-use~~ of claim ~~3051~~, wherein the V_H is or comprises the amino acid sequence of SEQ ID NO: 125; and the V_L is or comprises the amino acid sequence of SEQ ID NO: 127.

~~3253.~~ The ~~method-use~~ of any of claims ~~3051~~ or claim ~~3152~~, wherein the extracellular

antigen-binding domain comprises the amino acid sequence of SEQ ID NO: 128 or an amino acid sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO: 128.

3354. The ~~method-use~~ of any of claims 1-2343 and 3051-3353, wherein the first CAR comprises

- (a) a spacer comprising a CD8 hinge region;
 - (b) a transmembrane domain, optionally a transmembrane domain from a human CD8;
- and
- (c) an intracellular signaling region comprising a cytoplasmic signaling domain of a CD3-zeta (CD3 ζ) chain and a costimulatory signaling region comprising an intracellular signaling domain of a T cell costimulatory molecule or a signaling portion thereof.

3455. The ~~method-use~~ of any of claims 2444-3354, wherein the cytoplasmic signaling domain is or comprises the sequence set forth in SEQ ID NO:143 or a sequence of amino acids that has at least 90% sequence identity to SEQ ID NO:143.

3556. The ~~method-use~~ of any of claims 2444-3459, wherein the costimulatory signaling region comprises an intracellular signaling domain of CD28, 4-1BB, or ICOS, or a signaling portion thereof.

~~57. The method of any of claims 44-56, wherein the costimulatory signaling region comprises an intracellular signaling domain of 4-1BB, optionally human 4-1BB.~~

3658. The ~~method-use~~ of any of claims 2444-3557, wherein the costimulatory signaling region is or comprises the sequence set forth in SEQ ID NO:4 or a sequence of amino acids that has at least 90% sequence identity to the sequence set forth in SEQ ID NO: 4.

~~59. The method of any of claims 44-58, wherein the costimulatory signaling region is between the transmembrane domain and the cytoplasmic signaling domain of a CD3-zeta (CD3 ζ) chain.~~

3760. The ~~method-use~~ of any of claims 1-2950 and 3455-3659, wherein the first CAR comprises the sequence set forth in SEQ ID NO:19.

3861. The ~~method-use~~ of any of claims 1-2343 and 3051-3659, wherein the first CAR comprises the sequence set forth in SEQ ID NO:312.

3962. The ~~method-use~~ of any of claims 2034-3861, wherein the first CAR and the second CAR bind to the same epitope of BCMA.

4063. The ~~method-use~~ of any of claims 2034-3861, wherein the first CAR and the second CAR bind to different epitopes of BCMA.

4164. The ~~method-use~~ of any of claims 2034-4063, wherein the first CAR and the second CAR are different.

4265. The ~~method-use~~ of any of claims 2034-3962, wherein the first CAR and the second CAR are the same.

4366. The ~~method-use~~ of any of claims 2034-4265, wherein the dose of engineered T cells comprising the first CAR is generated from a sample comprising T cells obtained from the same subject that has previously been administered the prior dose of engineered T cells comprising the second CAR, optionally:-

~~67. The method of any of claims 34-66, wherein the dose of engineered T cells comprising the first CAR is generated from a sample comprising T cells~~ obtained from the subject after the subject has been administered the prior dose of engineered T cells comprising the second CAR.

4468. The ~~method-use~~ of any of claims 2444-4367, wherein the binding of the extracellular antigen-binding domain and/or the first CAR, or a measure indicative of function or activity of the first CAR following exposure to cells expressing surface BCMA, is not reduced or blocked or is not substantially reduced or blocked in the presence of a soluble or shed form of BCMA.

4569. The ~~method-use~~ of any of claims 1-4468, wherein the dose of engineered T cells comprising the first CAR comprises between at or about 1×10^7 CAR+ T cells and at or about 1

x 10⁹ CAR+ T cells.

~~70. The method of any of claims 1-69, wherein the dose of engineered T cells comprising the first CAR comprises between at or about 1 x 10⁸ CAR+ T cells and at or about 8 x 10⁸ CAR+ T cells.~~

~~71. The method of any of claims 1-70, wherein the dose of engineered T cells comprising the first CAR comprises at or about 1.5 x 10⁸ cells or CAR+ T cells.~~

~~72. The method of any of claims 1-70, wherein the dose of engineered T cells comprising the first CAR comprises at or about 3 x 10⁸ cells or CAR+ T cells.~~

~~73. The method of any of claims 1-70, wherein the dose of engineered T cells comprising the first CAR comprises at or about 4.5 x 10⁸ cells or CAR+ T cells.~~

~~74. The method of any of claims 1-70, wherein the dose of engineered T cells comprising the first CAR comprises at or about 6 x 10⁸ cells or CAR+ T cells.~~

4675. The ~~method-use~~ of any of claims 1-~~4574~~, wherein the dose of engineered T cells comprising the first CAR comprises a combination of CD4⁺ T cells and CD8⁺ T cells, optionally CD4⁺ CAR+ T cells and CD8⁺ CAR+ T cells.

4776. The ~~method-use~~ of any of claims 1-~~4675~~, wherein prior to the administration of the dose of engineered T cells comprising the first CAR, the subject has been administered a lymphodepleting therapy comprising the administration of fludarabine at or about 20-40 mg/m² body surface area of the subject, optionally at or about 30 mg/m², daily, for 2-4 days, and/or cyclophosphamide at or about 200-400 mg/m² body surface area of the subject, optionally at or about 300 mg/m², daily, for 2-4 days.

~~77. The method of claim 76, wherein the lymphodepleting therapy comprises the administration of fludarabine at or about 30 mg/m² body surface area of the subject, and cyclophosphamide at or about 300 mg/m² body surface area of the subject, each daily for 3 days.~~

4878. The method-use of any of claims 1-4777, wherein the disease or disorder associated with BCMA expression is an autoimmune disease or disorder.

4979. The method-use of any of claims 1-4878, wherein the disease or disorder associated with BCMA expression is a cancer, optionally a BCMA-expressing cancer.

~~80.—The method of claim 79, wherein the cancer is a B-cell malignancy.~~

~~81.—The method of claim 79 or claim 80, wherein the cancer is a lymphoma, a leukemia, or a plasma cell malignancy.~~

~~82.—The method of any of claims 79-81, wherein the cancer is a lymphoma and the lymphoma is Burkitt lymphoma, non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma, Waldenstrom macroglobulinemia, follicular lymphoma, small non-cleaved cell lymphoma, mucosa-associated lymphatic tissue lymphoma (MALT), marginal zone lymphoma, splenic lymphoma, nodal monocytoid B-cell lymphoma, immunoblastic lymphoma, large cell lymphoma, diffuse mixed cell lymphoma, pulmonary B-cell angiocentric lymphoma, small lymphocytic lymphoma, primary mediastinal B-cell lymphoma, lymphoplasmacytic lymphoma (LPL), or mantle cell lymphoma (MCL).~~

~~83.—The method of any of claims 79-81, wherein the cancer is a leukemia and the leukemia is chronic lymphocytic leukemia (CLL), plasma cell leukemia, or acute lymphocytic leukemia (ALL).~~

~~84.—The method of any of claims 79-81, wherein the cancer is a plasma cell malignancy and the plasma cell malignancy is multiple myeloma (MM) or plasmacytoma.~~

5085. The method-use of ~~any of claims 79-81 and 84~~claim 49, wherein the cancer is multiple myeloma (MM), optionally a relapsed or refractory multiple myeloma (R/R MM).

5186. The method-use of any of claims 1-5085, wherein the subject has been administered three or more prior therapies for the disease or disorder, optionally four or more prior therapies, optionally selected from among:

autologous stem cell transplant (ASCT);

an immunomodulatory agent;
a proteasome inhibitor; and
an anti-CD38 antibody.

~~87. The method of claim 86, wherein the immunomodulatory agent is selected from among thalidomide, lenalidomide and pomalidomide.~~

~~88. The method of claim 86 or claim 87, wherein the proteasome inhibitor is selected from among bortezomib, carfilzomib and ixazomib.~~

~~89. The method of any of claims 86-88, wherein the anti-CD38 antibody is or comprises daratumumab.~~

5290. The ~~method-use~~ of any of claims 1-5189, wherein the subject has been administered between 3 and 15 or between 4 and 15 prior therapies, or about 10 prior therapies.

5391. The ~~method-use~~ of claim 51 or 52~~any of claims 86-90~~, wherein the subject has relapsed following or has been refractory to one or more of the 3 or more prior therapies, and/or:

~~92. The method of any of claims 86-91, wherein the subject has relapsed following or has been refractory to at least 3 or at least 4 of the 3 or more prior therapies.~~

~~93. The method of claim 91 or claim 92, wherein the subject has been refractory to or has not responded to bortezomib, carfilzomib, lenalidomide, pomalidomide and/or an anti-CD38 monoclonal antibody.~~

5494. The ~~method-use~~ of any of claims 1-5393, wherein the subject has had prior autologous stem cell transplant.

5595. The ~~method-use~~ of any of claims 1-5393, wherein the subject has not had prior autologous stem cell transplant.

5696. The ~~method-use~~ of any of claims 1-5595, wherein the subject does not have an active or a history of plasma cell leukemia (PCL), and/or:

~~97. The method of any of claims 1-96,~~ wherein the subject has developed secondary plasma cell leukemia (PCL).

57. The use of any of claims 1-56, wherein the subject is human.

~~98. The method of any of claims 1-97, wherein the subject is an adult subject or is 25 or 35 years of age or older.~~

~~99. The method of any of claims 1-98, wherein the subject has a time from diagnosis of the disease or disorder of approximately 4 years, or between 2 and 15 years or between 2 and 12 years.~~

~~100. The method of any of claims 1-99, wherein the subject has IMWG high risk cytogenetics.~~