

Claims

1. 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 subject having a disease or disorder associated with B-cell maturation antigen (BCMA) expression, 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 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.

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.

4. 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

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.

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

the cell therapy is to be administered to the subject for treating a subject having a disease or disorder associated with B-cell maturation antigen (BCMA) expression, 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.

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.

7. The use of any of claims 1-6, 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.

8. The use of any of claims 1-7, wherein the at least one dose of the IL-1Ra 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 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.

9. The use of 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 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 use of any of claims 1-10, 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 wherein the at least one dose of IL-1Ra to be administered 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.

12. 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.

13. The use of any of claims 1-12, 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 wherein the at least one additional dose of the IL-1Ra comprises 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.

14. The use of any of claims 11-13, 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 wherein the administration of the IL-1Ra each day is to be administered at or about the same time each day.

15. The use of any of claims 1-14, wherein the IL-1Ra is a recombinant IL-1Ra.

16. The use of any of claims 1-15, 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.

17. The use of any of claims 1-16, wherein the IL-1Ra is anakinra.

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

19. The use of any of claims 1-18, wherein the use reduces the severity of, attenuates, and/or prevents the onset of a toxicity associated with administration of the cell therapy.

20. The use of any of claims 3-19, wherein the toxicity is a neurotoxicity (NT) or is a macrophage activation syndrome (MAS) or a hemophagocytic lympho-histiocytosis (HLH).

21. The use of any of claims 1-20, 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).

22. 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).

23. The use of any of claims 21-22, wherein the subject has relapsed following or has been refractory to the one or more prior BCMA-directed therapy, optionally 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.

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

25. The use of claim 24, 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.

26. The use of claim 23 or claim 25, 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.

27. The use of any of claims 24-26, 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.

28. The use of any of claims 1-27, 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 (CD3 ζ) chain and a costimulatory signaling region comprising an intracellular signaling domain of a T cell costimulatory molecule or a signaling portion thereof.

29. The use of any of claims 24-28, 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.

30. The use of any of claims 1-23, 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.

31. The use of claim 30, 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.

32. The use of any of claims 30 or claim 31, 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.

33. The use of any of claims 1-23 and 30-33, 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.

34. The use of any of claims 24-33, 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.

35. The use of any of claims 24-34, wherein the costimulatory signaling region comprises an intracellular signaling domain of CD28, 4-1BB, or ICOS, or a signaling portion thereof.

36. The use of any of claims 24-35, 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.

37. The use of any of claims 1-29 and 34-36, wherein the first CAR comprises the sequence set forth in SEQ ID NO:19.

38. The use of any of claims 1-23 and 30-36, wherein the first CAR comprises the sequence set forth in SEQ ID NO:312.

39. The use of any of claims 20-38, wherein the first CAR and the second CAR bind to the same epitope of BCMA.

40. The use of any of claims 20-38, wherein the first CAR and the second CAR bind to different epitopes of BCMA.

41. The use of any of claims 20-40, wherein the first CAR and the second CAR are different.

42. The use of any of claims 20-39, wherein the first CAR and the second CAR are the same.

43. The use of any of claims 20-42, 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 wherein the dose of engineered T cells is obtained from the subject after the subject has been administered the prior dose of engineered T cells comprising the second CAR.

44. The use of any of claims 24-43, 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.

45. The use of any of claims 1-44, 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 1×10^9 CAR⁺ T cells.

46. The use of any of claims 1-45, 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.

47. The use of any of claims 1-46, 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.

48. The use of any of claims 1-47, wherein the disease or disorder associated with BCMA expression is an autoimmune disease or disorder.

49. The use of any of claims 1-48, wherein the disease or disorder associated with BCMA expression is a cancer, optionally a BCMA-expressing cancer.

50. The use of claim 49, wherein the cancer is multiple myeloma (MM), optionally a relapsed or refractory multiple myeloma (R/R MM).

51. The use of any of claims 1-50, 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.

52. The use of any of claims 1-51, wherein the subject has been administered between 3 and 15 or between 4 and 15 prior therapies, or about 10 prior therapies.

53. The use of claim 51 or 52, wherein the subject has relapsed following or has been refractory to one or more of the 3 or more prior therapies, and/or 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.

54. The use of any of claims 1-53, wherein the subject has had prior autologous stem cell transplant.

55. The use of any of claims 1-53, wherein the subject has not had prior autologous stem cell transplant.

56. The use of any of claims 1-55, wherein the subject does not have an active or a history of plasma cell leukemia (PCL), and/or wherein the subject has developed secondary plasma cell leukemia (PCL).

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