

## CLAIMS

1. Use of a composition comprising a therapeutically effective number of T cells comprising a chimeric antigen receptor (CAR) in the manufacture of a medicament for the treatment of a subject, said chimeric antigen receptor (CAR) comprising:

(a) an extracellular antigen binding domain comprising:

(1) a first anti-BCMA binding moiety comprising a first complementarity determining region (CDR1) comprising the amino acid sequence of SEQ ID NO: 18, a second complementarity determining region (CDR2) comprising the amino acid sequence of SEQ ID NO: 19, and a third complementarity determining region (CDR3) comprising the amino acid sequence of SEQ ID NO: 20; and

(2) a second anti-BCMA binding moiety comprising a first complementarity determining region (CDR1) comprising the amino acid sequence of SEQ ID NO: 21, a second complementarity determining region (CDR2) comprising the amino acid sequence of SEQ ID NO: 22, and a third complementarity determining region (CDR3) comprising the amino acid sequence of SEQ ID NO: 23;

(b) a transmembrane domain; and

(c) an intracellular signaling domain,

to deliver to the subject a dose of CAR expressing T cells (CAR-T cells),

wherein said subject:

(i) has multiple myeloma;

(ii) has received prior treatment with one, two or three prior lines of therapy; and

(iii) is lenalidomide-refractory.

2. The use of the composition of claim 1, wherein the subject received prior treatment with at least one prior line of therapy comprising treatment with lenalidomide and at least one non-lenalidomide medicament, said at least one non-lenalidomide medicament comprising at least one of:

(a) a proteasomal inhibitor;

(b) an immunomodulatory drug; or

(c) an anti-CD38 antibody.

3. The use of the composition of claim 1 or claim 2, wherein the subject received prior treatment with at least two prior lines of therapy or with at least three prior lines of therapy.

4. The use of the composition of any one of claims 1 to 3, wherein:
- the subject received prior treatment with dexamethasone, an alkylating agent, or daratumumab,
  - the multiple myeloma is refractory to the last line of therapy,
  - the subject has relapsed after said one, two or three prior lines of therapy, or
  - the multiple myeloma is refractory to three classes of medicaments.
5. The use of the composition of any one of claims 1 to 4, wherein said use is effective in obtaining minimal residual disease (MRD) negative status in said subject assessed in the bone marrow after administration of said CAR-T cells.
6. The use of the composition of claim 5, wherein said minimal residual disease (MRD) negative status is obtained at a first follow-up time of between approximately 29 days and approximately 184 days after said administration of said CAR-T cells, and optionally,
- wherein said use is effective in maintaining said minimal residual disease (MRD) negative status in said subject assessed in the bone marrow at a second follow-up time of between approximately 57 days and approximately 191 days after said administration of said CAR-T cells, further wherein said first follow-up time is earlier than said second follow-up time.
7. The use of the composition of claim 5, wherein said use is effective in obtaining said minimal residual disease (MRD) negative status:
- at a rate of between approximately 24% and approximately 61% at a sensitivity threshold level of  $10^{-4}$ ,  $10^{-5}$  or  $10^{-6}$ ,
  - at a rate of approximately 41% at a sensitivity threshold level of  $10^{-4}$ ,  $10^{-5}$  or  $10^{-6}$ ,
  - at a rate of between approximately 64% and approximately 99% in subjects with evaluable samples at a sensitivity threshold level of  $10^{-5}$ , or
  - at a rate of approximately 92% in subjects with evaluable samples at a sensitivity threshold level of  $10^{-5}$ .
8. The use of the composition of any one of claims 1 to 4, wherein said use is effective in obtaining at least one response in the subject after administration of said CAR-T cells, wherein said at least one response comprises, in order from better to worse:
- (i) a stringent complete response;

- (ii) a complete response;
- (iii) a very good partial response;
- (iv) a partial response; or
- (v) a minimal response.

9. The use of the composition of claim 8, wherein said use is effective in obtaining:

a first response before a time of between approximately 21 days and approximately 99 days after said administration of said CAR-T cells,

a first response before a time of between approximately 21 days and approximately 55 days after said administration of said CAR-T cells,

a first response before approximately 36 days after said administration of said CAR-T cells, or

a first response before approximately 30 days after said administration of said CAR-T cells.

10. The use of the composition of claim 8, wherein said use is effective in obtaining:

a best response of any one of minimal response, partial response, very good partial response, complete response or stringent complete response,

a best response of any one of partial response, very good partial response, complete response or stringent complete response,

a best response of any one of very good partial response, complete response or stringent complete response,

a best response of complete response or stringent complete response, or

a best response of stringent complete response.

11. The use of the composition of claim 10, wherein said use is effective in obtaining:

said best response of any one of minimal response, partial response, very good partial response, complete response or stringent complete response at a rate of between approximately 52% and approximately 87%,

said best response of any one of minimal response, partial response, very good partial response, complete response or stringent complete response at a rate of approximately 72%,

said best response of any one of partial response, very good partial response, complete response or stringent complete response at a rate of between approximately 49% and approximately 84%,

said best response of any one of partial response, very good partial response, complete response or stringent complete response at a rate of approximately 69%,

said best response of any one of very good partial response, complete response or stringent complete response at a rate of between approximately 49% and approximately 84%,

said best response of any one of very good partial response, complete response or stringent complete response at a rate of approximately 69%,

said best response of complete response or stringent complete response at a rate of between approximately 39% and approximately 76%,

said best response of complete response or stringent complete response at a rate of approximately 58%,

said best response of stringent complete response at a rate of between approximately 33% and approximately 70%, or

said best response of stringent complete response at a rate of approximately 52%.

12. The use of the composition of any one of claims 1 to 4, wherein said use is effective in obtaining progression-free survival of the subject.

13. The use of the composition of claim 12, wherein said use is effective in obtaining:

said progression-free survival of the subject at a time between administration of said CAR-T cells and approximately 55 days after said administration of said CAR-T cells, or

said progression-free survival of the subject at a time between administration of said CAR-T cells and approximately 297 days after said administration of said CAR-T cells.

14. The use of the composition of claim 12, wherein said use is effective in obtaining:

said progression-free survival at a rate of between approximately 62% and approximately 95% at a follow-up time of approximately 6 months or approximately 9 months after administration of said CAR-T cells, or

said progression-free survival at a rate of approximately 86% at a follow-up time of approximately 6 months or approximately 9 months after administration of said CAR-T cells.

15. The use of the composition of any one of claims 1 to 4, wherein said use further comprises treating said subject for cytokine release syndrome more than approximately 3 days after administration of said CAR-T cells, and optionally,

wherein said use is effective in obtaining a rate of recovery from said cytokine release syndrome of between approximately 1% and approximately 90% at a time of approximately 7 days after first observance of said cytokine release syndrome.

16. The use of the composition of any one of claims 1 to 4, wherein said use is effective in obtaining a rate of immune-effector cell associated neurotoxicity of between approximately 20% and approximately 99%.

17. The use of the composition of claim 10 or claim 11, wherein said use is effective in obtaining:

said best response before a time of between approximately 27 days and approximately 237 days after administration of said CAR-T cells,

said best response before a time of between approximately 46 days and approximately 172 days after administration of said CAR-T cells,

said best response before approximately 109 days after administration of said CAR-T cells, or

said best response before approximately 87 days after administration of said CAR-T cells.

18. The use of the composition of claim 9, wherein said use is effective in maintaining a response in the subject at a follow-up time between the time of said first response and approximately 270 days after said administration of said CAR-T cells.

19. The use of the composition of any one of claims 8 to 11, wherein said use is effective in maintaining:

a response at a rate of between approximately 70% and approximately 99% at a follow-up time of approximately 6 months after said administration of said CAR-T cells,

a response at a rate of approximately 95% at a follow-up time of approximately 6 months after said administration of said CAR-T cells,

a response at a rate of between approximately 7% and approximately 92% at a follow-up time of approximately 9 months after said administration of said CAR-T cells, or

a response at a rate of approximately 63% at a follow-up time of approximately 9 months after said administration of said CAR-T cells.

20. The use of the composition of claim 10 or claim 11, further wherein said use is effective in obtaining minimal residual disease (MRD) negative status in said subject assessed in the bone marrow at a sensitivity threshold level of  $10^{-5}$  between the time of said administration of said CAR-T cells and approximately 3 months after said administration of said CAR-T cells, and optionally,

wherein said use is effective in obtaining either minimal residual disease (MRD) negative complete response or minimal residual disease (MRD) negative stringent complete response at a rate of between approximately 18% and approximately 54% at a follow-up time of approximately 291 days after said administration of said CAR-T cells, or

wherein said use is effective in obtaining either minimal residual disease (MRD) negative complete response or minimal residual disease (MRD) negative stringent complete response at a rate of approximately 35% at a follow-up time of approximately 291 days after said administration of said CAR-T cells.

21. The use of the composition of any one of claims 1 to 16, wherein the multiple myeloma is refractory to at least two medicaments, at least three medicaments, at least four medicaments, or at least five medicaments.

22. The use of the composition of any one of claims 1 to 16, wherein the subject has bone marrow plasma cells of between approximately 10% and approximately 30% before administration of said CAR-T cells.

23. The use of the composition of any one of claims 1 to 16, wherein the dose comprises:

$1.0 \times 10^5$  to  $5.0 \times 10^6$  of said CAR-T cells per kilogram of mass of the subject,  
 $5.0 \times 10^5$  to  $1.0 \times 10^6$  of said CAR-T cells per kilogram of mass of the subject,  
approximately  $0.75 \times 10^6$  of said CAR-T cells per kilogram of mass of the subject, or  
less than  $1.0 \times 10^8$  of said CAR-T cells per subject.

24. The use of the composition of any one of claims 1 to 16, wherein administration of said CAR-T cells is via a single intravenous infusion.

25. The use of the composition of claim 24, wherein said single intravenous infusion is to be administered:

using a single bag of said CAR-T cells, or

using two bags of said CAR-T cells.

26. The use of the composition of claim 25, wherein said administration of said single bag of said CAR-T cells is completed between the time at which said single bag of CAR-T cells is thawed and three hours after said single bag of CAR-T cells is thawed, or

wherein said administration of each of said two bags of said CAR-T cells is completed between the time at which a first bag of said two bags of CAR-T cells is thawed and three hours after said first bag of CAR-T cells is thawed.

27. The use of the composition of any one of claims 1 to 16, wherein a lymphodepleting regimen precedes administration of said CAR-T cells by approximately 5 days to approximately 7 days, and optionally,

wherein said lymphodepleting regimen is to be administered intravenously.

28. The use of the composition of claim 27, wherein said lymphodepleting regimen comprises:

- (a) administration of cyclophosphamide; or
- (b) administration of fludarabine.

29. The use of the composition of claim 28, wherein said cyclophosphamide is to be administered intravenously at 300 mg/m<sup>2</sup>, or

wherein said fludarabine is to be administered intravenously at 30 mg/m<sup>2</sup>.

30. The use of the composition of any one of claims 1 to 16, wherein a lymphodepleting regimen comprising cyclophosphamide is to be administered intravenously at 300 mg/m<sup>2</sup> and fludarabine is to be administered intravenously at 30 mg/m<sup>2</sup>, and wherein said lymphodepleting regimen precedes administration of said CAR-T cells by approximately 5 days to approximately 7 days.

31. The use of the composition of claim 27, wherein the subject further receives bridging therapy, wherein said bridging therapy comprises short-term treatment with at least one bridging medicament between apheresis and said lymphodepleting regimen, and wherein said at least one bridging medicament had previously obtained an outcome of stable disease,

minimal response, partial response, very good partial response, complete response or stringent complete response for the subject, and optionally,

wherein the subject had an increase in tumor burden despite said bridging therapy, and/or

wherein the subject had an increase in tumor burden of approximately 25% or greater despite said bridging therapy.

32. The use of the composition of claim 15, wherein said use further comprises treating said subject for cytokine release syndrome more than approximately 3 days following said administration of said CAR-T cells without significantly reducing expansion of said CAR-T cells *in vivo*.

33. The use of the composition of claim 15, wherein said treatment of cytokine release syndrome comprises an IL-6R inhibitor to be administered the subject, and optionally, wherein said IL-6R inhibitor is an antibody, wherein said IL-6R inhibitor prevents the binding of IL-6 to IL-6R, and/or wherein said IL-6R inhibitor is tocilizumab.

34. The use of the composition of claim 33, wherein said antibody inhibits IL-6R by binding its extracellular domain.

35. The use of the composition of any one of claims 1 to 16, wherein the subject is treated with pre-administration medication comprising an antipyretic and an antihistamine up to approximately 1 hour before administration of said CAR-T cells, and optionally, wherein said antipyretic comprises either paracetamol or acetaminophen, wherein said antipyretic is to be administered to the subject either orally or intravenously, wherein said antipyretic is to be administered to the subject at a dosage of between 650 mg and 1000 mg,

wherein said antihistamine comprises diphenhydramine, wherein said antihistamine is to be administered to the subject either orally or intravenously, wherein said antihistamine is to be administered at a dosage of between 25 mg and 50 mg, or its equivalent, or

wherein said antipyretic comprises either paracetamol or acetaminophen and said antipyretic is to be administered to the subject either orally or intravenously at a dosage of between 650 mg and 1000 mg, and wherein said antihistamine comprises diphenhydramine and said antihistamine is to be administered to the subject either orally or intravenously at a dosage of between 25 mg and 50 mg, or its equivalent.

36. The use of the composition of any one of claims 1 to 16, wherein the composition comprising CAR-T cells is to be administered to the subject further comprises an excipient selected from dimethylsulfoxide or dextran-40.

37. The use of the composition of any one of claims 1 to 16, wherein the first anti-BCMA binding moiety and/or the second anti-BCMA binding moiety is an anti-BCMA VHH, and, optionally,

wherein the first anti-BCMA binding moiety is a first anti-BCMA VHH and the second anti-BCMA binding moiety is a second anti-BCMA VHH,

wherein the first anti-BCMA binding moiety comprises the amino acid sequence of SEQ ID NO: 2,

wherein the first anti-BCMA binding moiety comprises a polypeptide encoded by the nucleic acid sequence of SEQ ID NO: 10,

wherein the second anti-BCMA binding moiety comprises the amino acid sequence of SEQ ID NO: 4, and/or

wherein the second anti-BCMA binding moiety comprises a polypeptide encoded by the nucleic acid sequence of SEQ ID NO: 12.

38. The use of the composition of any one of claims 1 to 16, wherein the first anti-BCMA binding moiety and the second anti-BCMA binding moiety are connected to each other via a peptide linker, and optionally,

wherein the peptide linker comprises the amino acid sequence of SEQ ID NO: 3, or

wherein the peptide linker comprises a polypeptide encoded by the nucleic acid sequence of SEQ ID NO: 11.

39. The use of the composition of any one of claims 1 to 16, wherein the CAR polypeptide further comprises a signal peptide located at the N-terminus of the polypeptide, and optionally,

wherein the signal peptide is derived from CD8-alpha,  
wherein the signal peptide comprises the amino acid sequence of SEQ ID NO: 1, or  
wherein the signal peptide comprises a polypeptide encoded by the nucleic acid  
sequence of SEQ ID NO: 9.

40. The use of the composition of any one of claims 1 to 16, wherein the transmembrane  
domain comprises:

the amino acid sequence of SEQ ID NO: 6, or  
a polypeptide encoded by the nucleic acid sequence of SEQ ID NO: 14.

41. The use of the composition of any one of claims 1 to 16, wherein the intracellular  
signaling domain comprises a primary intracellular signaling domain of an immune effector  
cell, and optionally,

wherein the intracellular signaling domain is derived from CD3ζ,  
wherein the intracellular signaling domain comprises at least one co-stimulatory  
signaling domain,  
wherein the intracellular signaling domain comprises the amino acid sequence of SEQ  
ID NO: 8,  
wherein the intracellular signaling domain comprises a polypeptide encoded by the  
nucleic acid sequence of SEQ ID NO: 16,  
wherein the intracellular signaling domain comprises the amino acid sequence of SEQ  
ID NO: 7, or  
wherein the intracellular signaling domain comprises a polypeptide encoded by the  
nucleic acid sequence of SEQ ID NO: 15.

42. The use of the composition of any one of claims 1 to 16, wherein the CAR polypeptide  
further comprises a hinge domain located between the C-terminus of the extracellular antigen  
binding domain and the N-terminus of the transmembrane domain, and optionally,

wherein the hinge domain comprises the amino acid sequence of SEQ ID NO: 5, or  
wherein the hinge domain comprises a polypeptide encoded by the nucleic acid  
sequence of SEQ ID NO: 13.

43. The use of the composition of any one of claims 1 to 16, wherein the CAR comprises the  
amino acid sequence of SEQ ID NO: 17.

44. The use of the composition of any one of claims 1 to 16, wherein the T cells are autologous T cells or the T cells are allogeneic T cells.
45. The use of the composition of any one of claims 1 to 16, wherein the subject is human.
46. The use of the composition of any one of claims 1 to 16, wherein the subject has had no prior exposure to a BCMA-targeting medicament.
47. The use of the composition of any one of claims 1 to 16, wherein the multiple myeloma is progressive.