

WHAT IS CLAIMED:

1. Use of a T cell therapy in the manufacture of a medicament for treating a subject having a relapsed or refractory multiple myeloma (R/R MM), the T cell therapy comprising a dose of genetically engineered T cells expressing a chimeric antigen receptor (CAR) that specifically binds to BCMA, wherein:

the T cell therapy is to be administered in combination with an immunomodulatory compound that comprises (S)-3-[4-(4-morpholin-4-ylmethyl-benzyloxy)-1-oxo-1,3-dihydro-isoindol-2-yl]-piperidine-2,6-dione; and

administration of the immunomodulatory compound is to be initiated after administration of the T cell therapy.

2. Use of an immunomodulatory compound that comprises (S)-3-[4-(4-morpholin-4-ylmethyl-benzyloxy)-1-oxo-1,3-dihydro-isoindol-2-yl]-piperidine-2,6-dione in the manufacture of a medicament for treating a subject having a relapsed or refractory multiple myeloma (R/R MM), wherein:

the immunomodulatory compound is to be administered in combination with a T cell therapy comprising a dose of genetically engineered T cells expressing a chimeric antigen receptor (CAR) that specifically binds to BCMA; and

administration of the immunomodulatory compound is to be initiated after administration of the T cell therapy.

3. The use of claim 1 or claim 2, wherein prior to initiation of the administration of the T cell therapy and the immunomodulatory compound, the subject has received one or more prior therapies for treating the R/R MM, the one or more prior therapies comprising an immunomodulatory agent.

4. Use of a T cell therapy in the manufacture of a medicament for treating a subject having a relapsed or refractory multiple myeloma (R/R MM), the T cell therapy comprising a dose of genetically engineered T cells expressing a chimeric antigen receptor (CAR) that specifically binds to BCMA, wherein:

the T cell therapy is to be administered in combination with an immunomodulatory compound that comprises (S)-3-[4-(4-morpholin-4-ylmethyl-benzyloxy)-1-oxo-1,3-dihydro-isoindol-2-yl]-piperidine-2,6-dione; and

prior to initiation of the administration of the T cell therapy and the immunomodulatory compound, the subject has received one or more prior therapies for treating the R/R MM, the one or more prior therapies comprising an immunomodulatory agent.

5. Use of an immunomodulatory compound that comprises (S)-3-[4-(4-morpholin-4-ylmethyl-benzyloxy)-1-oxo-1,3-dihydro-isoindol-2-yl]-piperidine-2,6-dione in the manufacture of a medicament for treating a subject having a relapsed or refractory multiple myeloma (R/R MM), wherein:

the immunomodulatory compound is to be administered in combination with a T cell therapy comprising a dose of genetically engineered T cells expressing a chimeric antigen receptor (CAR) that specifically binds to BCMA; and

prior to initiation of the administration of the T cell therapy and the immunomodulatory compound, the subject has received one or more prior therapies for treating the R/R MM, the one or more prior therapies comprising an immunomodulatory agent.

6. The use of any one of claims 1-5, wherein the immunomodulatory compound is (S)-3-[4-(4-morpholin-4-ylmethyl-benzyloxy)-1-oxo-1,3-dihydro-isoindol-2-yl]-piperidine-2,6-dione or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof.

7. Use of a T cell therapy in the manufacture of a medicament for treating a subject having a relapsed or refractory multiple myeloma (R/R MM), the T cell therapy comprising a dose of genetically engineered T cells expressing a chimeric antigen receptor (CAR) that specifically binds to BCMA, wherein:

the T cell therapy is to be administered in combination with an immunomodulatory compound that comprises (S)-4-(4-(4-(((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)oxy)methyl)benzyl)piperazin-1-yl)-3-fluorobenzonitrile; and

administration of the immunomodulatory compound is to be initiated after administration of the T cell therapy.

8. Use of an immunomodulatory compound that comprises (S)-4-(4-(4-(((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)oxy)methyl)benzyl)piperazin-1-yl)-3-fluorobenzonitrile in the manufacture of a medicament for treating a subject having a relapsed or refractory multiple myeloma (R/R MM), wherein:

the immunomodulatory compound is to be administered in combination with a T cell therapy comprising a dose of genetically engineered T cells expressing a chimeric antigen receptor (CAR) that specifically binds to BCMA; and

administration of the immunomodulatory compound is to be initiated after administration of the T cell therapy.

9. The use of claim 7 or claim 8, wherein prior to initiation of the administration of the T cell therapy and the immunomodulatory compound, the subject has received one or more prior therapies for treating the R/R MM, the one or more prior therapies comprising an immunomodulatory agent.

10. Use of a T cell therapy in the manufacture of a medicament for treating a subject having a relapsed or refractory multiple myeloma (R/R MM), the T cell therapy comprising a dose of genetically engineered T cells expressing a chimeric antigen receptor (CAR) that specifically binds to BCMA, wherein:

the T cell therapy is to be administered in combination with an immunomodulatory compound that comprises (S)-4-(4-(4-(((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)oxy)methyl)benzyl)piperazin-1-yl)-3-fluorobenzonitrile; and

prior to initiation of the administration of the T cell therapy and the immunomodulatory compound, the subject has received one or more prior therapies for treating the R/R MM, the one or more prior therapies comprising an immunomodulatory agent.

11. Use of an immunomodulatory compound that comprises (S)-4-(4-(4-(((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)oxy)methyl)benzyl)piperazin-1-yl)-3-fluorobenzonitrile in the manufacture of a medicament for treating a subject having a relapsed or refractory multiple myeloma (R/R MM), wherein:

the immunomodulatory compound is to be administered in combination with a T cell therapy comprising a dose of genetically engineered T cells expressing a chimeric antigen receptor (CAR) that specifically binds to BCMA; and

prior to initiation of the administration of the T cell therapy and the immunomodulatory compound, the subject has received one or more prior therapies for treating the R/R MM, the one or more prior therapies comprising an immunomodulatory agent.

12. The use of any one of claims 7-11, wherein the immunomodulatory compound is (S)-4-(4-(4-(((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)oxy)methyl)benzyl)piperazin-1-yl)-3-fluorobenzonitrile or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof.

13. The use of any one of claims 1-12, wherein the subject has relapsed or been refractory following at least 3 or at least 4 prior therapies for multiple myeloma.

14. The use of any one of claims 1-13, wherein the subject has received, and has relapsed or been refractory to, three or more therapies selected from among:

autologous stem cell transplant (ASCT);

an immunomodulatory agent, optionally thalidomide, lenalidomide, or pomalidomide;

a proteasome inhibitor, optionally bortezomib, carfilzomib, or ixazomib; and

an anti-CD38 antibody, optionally daratumumab;

unless the subject was not a candidate for or was contraindicated for one or more of the therapies.

15. The use of any one of claims 3-6 and 9-14, wherein the immunomodulatory agent is selected from among thalidomide, lenalidomide, and pomalidomide.

16. The use of any one of claims 1-15, wherein, at the time of administration, the subject has IMWG high risk cytogenetics.

17. The use of any one of claims 1-16, wherein administration of the immunomodulatory compound is to be initiated at or prior to peak expansion of the T cell

therapy in the subject, optionally wherein peak expansion of the T cell therapy is between at or about 11 days and at or about 15 days after administering the T cell therapy.

18. The use of any one of claims 1-17, wherein administration of the immunomodulatory compound is to be initiated between at or about 1 day and at or about 15 days, between at or about 1 day and at or about 11 days, or between at or about 8 days and at or about 15 days, each inclusive, after administering the T cell therapy, optionally at or about 1 day, at or about 8 days, or at or about 15 days after administering the T cell therapy.

19. The use of any one of claims 1-16, wherein the administration of the immunomodulatory compound is to be initiated about 14 to about 35 days, about 21 to about 35 days, or about 21 to about 28 days after initiation of administration of the T cell therapy, optionally at or about 21 days, at or about 22 days, at or about 23 days, at or about 24 days, at or about 25 days, at or about 26 days, at or about 27 days, or at or about 28 days after initiation of administration of the T cell therapy, further optionally at or about 28 days after the initiation of the administration of the T cell therapy.

20. The use of any one of claims 4-6 and 10-16, wherein the immunomodulatory compound is to be administered from or from about 0 to 30 days, 0 to 15 days, 0 to 6 days, 0 to 96 hours, 2 hours to 15 days, 2 hours to 6 days, 2 hours to 96 hours, 6 hours to 30 days, 6 hours to 15 days, 6 hours to 6 days, 6 hours to 96 hours, 12 hours to 30 days, 12 hours to 15 days, 12 hours to 6 days, or 12 hours to 96 hours prior to initiation of the T cell therapy.

21. The use of any one of claims 4-6, 10-16, and 20, wherein the immunomodulatory compound is to be administered no more than about 96 hours, 72 hours, 48 hours, or 24 hours prior to initiation of the T cell therapy.

22. The use of any one of claims 1-21, wherein the immunomodulatory compound is to be administered at least once daily in a cycle regimen comprising the administration of the immunomodulatory compound for a plurality of consecutive days followed by a rest period during which the immunomodulatory compound is not administered, optionally wherein the plurality of consecutive days is up to 21 days, further optionally wherein the cycle regimen is a

four-week (28-day) cycle wherein the immunomodulatory compound is to be administered daily for three consecutive weeks in the four-week cycle and is not administered for the last week.

23. The use of any one of claims 1-22, wherein the immunomodulatory compound is to be administered in an amount that is at or about 0.1 mg to at or about 1.0 mg per day or at or about 0.3 mg to at or about 0.6 mg per day, optionally at or about 0.3 mg, at or about 0.45 mg, or at or about 0.6 mg per day.

24. The use of any one of claims 1-23, wherein the administration of the immunomodulatory compound is to comprise administration at an amount, frequency, and/or duration effective to:

(a) effect an increase in antigen-specific or antigen receptor-driven activity of naïve or non-exhausted T cells in the subject, which optionally comprise T cells expressing the CAR, following exposure of the T cells to BCMA or to an agonist of the CAR, optionally wherein the agonist is an anti-idiotypic antibody, as compared to the absence of the administration of the immunomodulatory compound;

(b) prevent, inhibit, or delay the onset of an exhaustion phenotype in naïve or non-exhausted T cells in the subject, which optionally comprise T cells expressing the CAR, following exposure of the T cells to BCMA or to an agonist of the CAR, optionally wherein the agonist is an anti-idiotypic antibody, as compared to the absence of the administration of the immunomodulatory compound; or

(c) reverse an exhaustion phenotype in exhausted T cells, optionally comprising T cells expressing the CAR, in the subject, as compared to the absence of the administration of the subject.

25. The use of any one of claims 1-24, wherein the dose of genetically engineered T cells is between at or about 5×10^7 CAR⁺ T cells and at or about 1×10^9 CAR⁺ T cells or between at or about 1×10^8 CAR⁺ T cells and at or about 1×10^9 CAR⁺ T cells, optionally at or about 1.5×10^8 CAR⁺ T cells, at or about 3×10^8 CAR⁺ T cells, at or about 4.5×10^8 CAR⁺ T cells, or at or about 6×10^8 CAR⁺ T cells.

26. The use of any one of claims 1-25, wherein the dose of genetically engineered T

cells comprises a combination of CD4⁺ CAR-expressing T cells and CD8⁺ CAR-expressing T cells, optionally wherein the ratio of CD4⁺ CAR-expressing T cells to CD8⁺ CAR-expressing T cells is between at or approximately 1:3 and at or approximately 3:1, further optionally wherein the ratio of CD4⁺ CAR-expressing T cells to CD8⁺ CAR-expressing T cells is or is approximately 1:1.

27. The use of any one of claims 1-26, wherein prior to the administration of the dose of genetically engineered T cells, the subject has received 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;

optionally wherein the subject has received a lymphodepleting therapy comprising the administration of fludarabine at or about 30 mg/m² body surface area of the subject, daily, and cyclophosphamide at or about 300 mg/m² body surface area of the subject, daily, for 3 days.

28. The use of any one of claims 1-27, wherein the CAR comprises an antigen binding domain that binds to BCMA, a transmembrane domain, and an intracellular signaling region comprising a CD3-zeta (CD3ζ) chain.

29. The use of claim 28, wherein the antigen binding domain is a single chain variable fragment (scFv).

30. The use of claim 28 or claim 29, wherein the antigen binding domain comprises a V_H and a V_L region, wherein the V_H region comprises a CDR-H1 set forth in SEQ ID NO: 56, a CDR-H2 set forth in SEQ ID NO:57, and a CDR-H3 set forth in SEQ ID NO:58, and the V_L region comprises a CDR-L1 set forth in SEQ ID NO: 59, a CDR-L2 set forth in SEQ ID NO:60, and a CDR-H3 set forth in SEQ ID NO: 61; optionally wherein the antigen binding domain comprises a V_H region that comprises the sequence of amino acids set forth in SEQ ID NO:36 or a sequence of amino acids that exhibits at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% to the sequence of amino acids set forth in SEQ ID NO: 36, and a V_L region that comprises the sequence of

amino acids set forth in SEQ ID NO: 37 or a sequence of amino acids that exhibits at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% to the sequence of amino acids set forth in SEQ ID NO:37; further optionally wherein the antigen-binding domain is an scFv that comprises the sequence of amino acids set forth in SEQ ID NO:180 or a sequence of amino acids exhibits at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% to the sequence of amino acids set forth in SEQ ID NO: 180.

31. The use of claim 28 or claim 29, wherein the antigen binding domain comprises a V_H and a V_L region, wherein the V_H region comprises a CDR-H1 set forth in SEQ ID NO: 62, a CDR-H2 set forth in SEQ ID NO:63, and a CDR-H3 set forth in SEQ ID NO:64, and the V_L region comprises a CDR-L1 set forth in SEQ ID NO: 65, a CDR-L2 set forth in SEQ ID NO:66, and a CDR-H3 set forth in SEQ ID NO:67; optionally wherein the antigen binding domain comprises a V_H region that comprises the sequence of amino acids set forth in SEQ ID NO:30 or a sequence of amino acids that exhibits at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% to the sequence of amino acids set forth in SEQ ID NO:30, and a V_L region that comprises the sequence of amino acids set forth in SEQ ID NO: 31 or a sequence of amino acids that exhibits at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% to the sequence of amino acids set forth in SEQ ID NO:31; further optionally wherein the antigen binding domain is an scFv that comprises the sequence of amino acids set forth in SEQ ID NO:68 or a sequence of amino acids exhibits at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% to the sequence of amino acids set forth in SEQ ID NO: 68.

32. The use of any one of claims 28-31, wherein the intracellular signaling region further comprises a costimulatory signaling domain, optionally wherein the costimulatory signaling domain comprises an intracellular signaling domain of CD28, 4-1BB, or ICOS, or a signaling portion thereof, further optionally an intracellular signaling domain of 4-1BB.

33. The use of claim 32, wherein the costimulatory signaling domain is between the transmembrane domain and the intracellular signaling region of the CD3-zeta (CD3 ζ) chain.

34. The use of any one of claims 28-33, wherein the transmembrane domain is or comprises a transmembrane domain from human CD28 or human CD8.

35. The use of any one of claims 28-34, wherein the CAR further comprises an extracellular spacer between the antigen binding domain and the transmembrane domain, optionally wherein:

the spacer is an immunoglobulin spacer comprising all or a portion of an immunoglobulin constant domain or a modified form thereof, further optionally an IgG4/2 chimeric hinge or a modified IgG4 hinge; an IgG2/4 chimeric C_H2 region; and an IgG4 C_H3 region; or

the spacer is a CD8 hinge.

36. The use of any one of claims 1-35, wherein the anti-BCMA CAR comprises the sequence of amino acids set forth in any one of SEQ ID NOS: 126-177 or a sequence of amino acids that exhibits at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to the sequence of amino acids set forth in any one of SEQ ID NOS: 126-177; optionally wherein the anti-BCMA CAR comprises the sequence of amino acids set forth in any one of SEQ ID NOS:160, 161, 152, 168, and 171 or a sequence of amino acids that exhibits at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to the sequence of amino acids set forth in any one of SEQ ID NOS:160, 161, 152, 168, and 171.