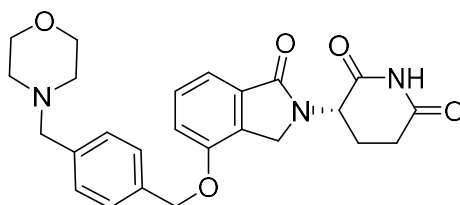


[0004] Various strategies are available for immunotherapy, for example administering engineered T cells for adoptive therapy. For example, strategies are available for engineering T cells expressing genetically engineered antigen receptors, such as CARs, and administering compositions containing such cells to subjects. Improved strategies are needed to improve efficacy of the cells, for example, improving the persistence, activity and/or proliferation of the cells upon administration to subjects. Provided are methods, compositions, kits, and systems that meet such needs.

Summary

[0005] Provided herein is a method of treating multiple myeloma, the method comprising: (a) administering a T cell therapy to a subject having a relapsed or refractory multiple myeloma (R/R MM), said T cell therapy comprising a dose of genetically engineered T cells expressing a chimeric antigen receptor (CAR) that specifically binds to BCMA; and (b) administering to the subject an immunomodulatory compound that is (S)-3-[4-(4-morpholin-4-ylmethyl-benzyloxy)-1-oxo-1,3-dihydro-isoindol-2-yl]-piperidine-2,6-dione having the following structure:

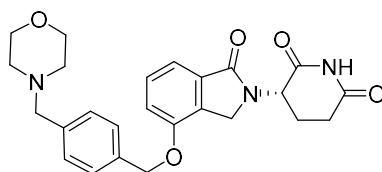


or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, wherein administration of the immunomodulatory compound is initiated after administration of the T cell therapy.

[0005a] In one aspect, the present disclosure refers to 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.

[0005b] In one aspect, the present disclosure refers to 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.

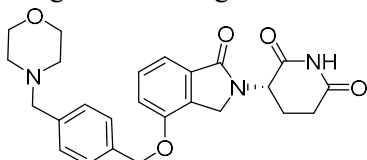
[0006] Also provided is a method of treating multiple myeloma, the method comprising administering, to a subject having a relapsed or refractory multiple myeloma (R/R MM) that has been administered a cell therapy comprising a dose of genetically engineered T cells expressing a chimeric antigen receptor (CAR) that specifically binds to BCMA, an immunomodulatory compound that is (S)-3-[4-(4-morpholin-4-ylmethyl-benzyloxy)-1-oxo-1,3-dihydro-isoindol-2-yl]-piperidine-2,6-dione having the following structure:



or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, wherein administration of the immunomodulatory compound is initiated after administration of the T cell therapy.

[0007] In some of any **embodimentexamples**, 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, said one or more prior therapies comprising an immunomodulatory agent.

[0008] Provided herein is a method of treating multiple myeloma, the method comprising: (a) administering a T cell therapy to a subject having a relapsed or refractory multiple myeloma (R/R MM), said T cell therapy comprising a dose of genetically engineered T cells expressing a chimeric antigen receptor (CAR) that specifically binds to BCMA; and (b) administering to the subject an immunomodulatory compound that is (S)-3-[4-(4-morpholin-4-ylmethyl-benzyloxy)-1-oxo-1,3-dihydro-isoindol-2-yl]-piperidine-2,6-dione having the following structure:



or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof; 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, said one or more prior therapies comprising an immunomodulatory agent.

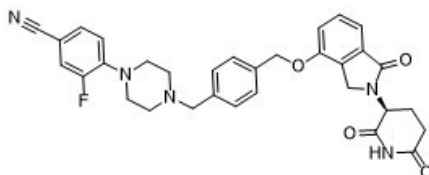
[0008a] In one aspect, the present disclosure refers to use of a T cell therapy in the manufacture of a medicament for treating a subject having a relapsed or refractory multiple myeloma (R/R MM), the T cell therapy comprising a dose of genetically engineered T cells expressing a chimeric antigen receptor (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.

[0008b] In one aspect, the present disclosure refers to 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.

[0009] In some of any **embodimentexamples**, the immunomodulatory compound is or comprises a pharmaceutically acceptable salt of (S)-3-[4-(4-morpholin-4-ylmethyl-benzyloxy)-1-oxo-1,3-dihydro-isoindol-2-yl]-piperidine-2,6-dione. In some of any **embodimentexamples**, the immunomodulatory compound is or comprises a hydrate of (S)-3-[4-(4-morpholin-4-ylmethyl-benzyloxy)-1-oxo-1,3-dihydro-isoindol-2-yl]-piperidine-2,6-dione. In some of any **embodimentexamples**, the immunomodulatory compound is or comprises a solvate of (S)-3-[4-(4-morpholin-4-ylmethyl-benzyloxy)-1-oxo-1,3-dihydro-isoindol-2-yl]-piperidine-2,6-dione. In

some of any [embodiment examples](#), the immunomodulatory compound is or comprises (S)-3-[4-(4-morpholin-4-ylmethyl-benzyloxy)-1-oxo-1,3-dihydro-isoindol-2-yl]-piperidine-2,6-dione.

[0010] Provided herein is a method of treating multiple myeloma, the method comprising: (a) administering a T cell therapy to a subject having a relapsed or refractory multiple myeloma (R/R MM), said T cell therapy comprising a dose of genetically engineered T cells expressing a chimeric antigen receptor (CAR) that specifically binds to BCMA; and (b) administering to the subject an immunomodulatory compound that is (S)-4-(4-(4-(((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)oxy)methyl)benzyl)piperazin-1-yl)-3-fluorobenzonitrile having the following structure:

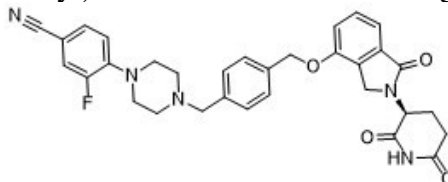


or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, wherein administration of the immunomodulatory compound is initiated after administration of the T cell therapy.

[0010a] In one aspect, the present disclosure refers to 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.

[0010b] In one aspect, the present disclosure refers to 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.

[0011] Also provided is a method of treating multiple myeloma, the method comprising administering, to a subject having a relapsed or refractory multiple myeloma (R/R MM) that has been administered a cell therapy comprising a dose of genetically engineered T cells expressing a chimeric antigen receptor (CAR) that specifically binds to BCMA, an immunomodulatory compound that is (S)-4-(4-(4-(((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)oxy)methyl)benzyl)piperazin-1-yl)-3-fluorobenzonitrile having the following structure:



or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, wherein administration of the immunomodulatory compound is initiated after administration of the T cell therapy.

[0012] In some of any [embodiment examples](#), 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, said one or more prior therapies comprising an immunomodulatory agent.

[0012a] In one aspect, the present disclosure refers to 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.

[0012b] In one aspect, the present disclosure refers to 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.

[0013] In some of any **embodimentexamples**, the immunomodulatory compound is or comprises a pharmaceutically acceptable salt of (S)-4-(4-(4-(((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)oxy)methyl)benzyl)piperazin-1-yl)-3-fluorobenzonitrile. In some of any **embodimentexamples**, the immunomodulatory compound is or comprises a hydrate of (S)-4-(4-(4-(((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)oxy)methyl)benzyl)piperazin-1-yl)-3-fluorobenzonitrile. In some of any **embodimentexamples**, the immunomodulatory compound is or comprises a solvate of (S)-4-(4-(4-(((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)oxy)methyl)benzyl)piperazin-1-yl)-3-fluorobenzonitrile. In some of any **embodimentexamples**, the immunomodulatory compound is or comprises (S)-4-(4-(4-(((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)oxy)methyl)benzyl)piperazin-1-yl)-3-fluorobenzonitrile.

[0014] In some of any **embodimentexamples**, the subject has relapsed or been refractory following at least 3 or at least 4 prior therapies for multiple myeloma. In some of any **embodimentexamples**, 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; a proteasome inhibitor; and an anti-CD38 antibody; unless the subject was not a candidate for or was contraindicated for one or more of the therapies. In some of any **embodimentexamples**, the immunomodulatory agent is selected from among thalidomide, lenalidomide and pomalidomide. In some of any **embodimentexamples**, the proteasome inhibitor is selected from among bortezomib, carfilzomib and ixazomib. In some of any **embodimentexamples**, the anti-CD38 antibody is or comprises daratumumab. In some of any **embodimentexamples**, at the time of administration, the subject has been refractory to or not responded to bortezomib, carfilzomib, lenalidomide, pomalidomide and/or an anti-CD38 monoclonal antibody. In some of any **embodimentexamples**, at the time of administration, the subject has IMWG high risk cytogenetics.

[0015] In some of any **embodimentexamples**, administration of the immunomodulatory compound is initiated at or prior to peak expansion of the T cell therapy in the subject. In some of any **embodimentexamples**, 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. In some of any **embodimentexamples**, administration of the immunomodulatory compound is initiated between at or about 1 day and at or about 15 days, inclusive, after administering the T cell therapy. In some of any **embodimentexamples**, administration of the immunomodulatory compound is initiated between at or about 1 day and at or about 11 days, inclusive, after administering the T cell therapy. In some of any **embodimentexamples**,

the administration of the immunomodulatory compound is initiated between at or about 8 days and at or about 15 days, inclusive, after administering the T cell therapy.

[0016] In some of any [embodimentexamples](#), administration of the immunomodulatory compound is initiated at or about 1 day after administering the T cell therapy. In some of any [embodimentexamples](#), administration of the immunomodulatory compound is initiated at or about 8 days after administering the T cell therapy. In some of any [embodimentexamples](#), the administration of the immunomodulatory compound is initiated at or about 15 days after administering the T cell therapy.

[0017] In some of any [embodimentexamples](#), the administration of the immunomodulatory compound is initiated about 14 to about 35 days after initiation of administration of the T cell therapy. In some of any [embodimentexamples](#), the administration of the immunomodulatory compound is initiated about 21 to about 35 days after initiation of administration of the T cell therapy. In some of any [embodimentexamples](#), the administration of the immunomodulatory compound is initiated about 21 to about 28 days after initiation of administration of the T cell therapy.

[0018] In some of any [embodimentexamples](#), the administration of the immunomodulatory compound is initiated 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. In some of any [embodimentexamples](#), the administration of the immunomodulatory compound is initiated at or about 28 days after the initiation of the administration of the T cell therapy.

[0019] In some of any [embodimentexamples](#), the immunomodulatory compound is 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. In some of any [embodimentexamples](#), the immunomodulatory compound is administered no more than about 96 hours, 72 hours, 48 hours, or 24 hours prior to initiation of the T cell therapy.

[0020] In some of any [embodimentexamples](#), the immunomodulatory compound is administered at least once daily in a cycle regimen. In some [embodimentexamples](#), the immunomodulatory compound is administered 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. In some [embodimentexamples](#), the plurality of consecutive days is up to 21 days.

[0021] In some of any [embodimentexamples](#), the cycle regimen is a four-week (28-day) cycle wherein the immunomodulatory compound is administered daily in the four-week cycle. In some of any [embodimentexamples](#), the cycle regimen is a four-week (28-day) cycle wherein the immunomodulatory compound is administered daily for three consecutive weeks in the four-week cycle and is not administered for the last week. In some of any [embodimentexamples](#), the cycle regimen is a four-week (28-day) cycle wherein the immunomodulatory compound is administered daily for days 1 through 21 of each four-week cycle.

[0022] In some of any [embodimentexamples](#), the cycling regimen is repeated a plurality of times. In some of any [embodimentexamples](#), the plurality of times is between two and 12 cycling regimens. In some of any [embodimentexamples](#), the cycling regimen is repeated 3 times. In some of any [embodimentexamples](#), the cycling regimen is repeated 4 times. In some of any [embodimentexamples](#), the cycling regimen is repeated 5 times. In some of any [embodimentexamples](#), the cycling regimen is repeated 6 times.

[0023] In some of any [embodimentexamples](#), the immunomodulatory compound is administered up to at or about three months after initiation of administration of the T cell therapy. In some of any [embodimentexamples](#), the immunomodulatory compound is administered up to at or about six months after initiation of administration of the T cell therapy.

[0024] In some of any [embodimentexamples](#), the immunomodulatory compound is administered in an amount that is at or about 0.1 mg to about 1.0 mg per day. In some of any [embodimentexamples](#), the immunomodulatory compound is administered in an amount that is at or about 0.3 mg to about 0.6 mg. In some of any [embodimentexamples](#), the immunomodulatory compound is administered in an amount that is at or about 0.3 mg. In some of any [embodimentexamples](#), the immunomodulatory compound is administered in an amount that is at or about 0.45 mg. In some of any [embodimentexamples](#), the immunomodulatory compound is administered in an amount that is at or about 0.6 mg.

[0025] In some of any [embodimentexamples](#), the immunomodulatory compound is administered orally.

[0026] In some of any [embodimentexamples](#), at the time of the initiation of the administration of the immunomodulatory compound, the subject does not exhibit a severe toxicity following the administration of the T cell therapy. In some of any [embodimentexamples](#), the severe toxicity is severe cytokine release syndrome (CRS), optionally grade 3 or higher, prolonged grade 3 or higher or grade 4 or 5 CRS; and/or the severe toxicity is severe neurotoxicity, optionally grade 3 or higher, prolonged grade 3 or higher or grade 4 or 5 neurotoxicity.

[0027] In some of any [embodimentexamples](#), the administration of the immunomodulatory compound is suspended and/or the cycling regimen is modified if the subject exhibits a toxicity following the administration of the immunomodulatory compound, optionally a hematologic toxicity. In some of any [embodimentexamples](#), the toxicity is selected from severe neutropenia, optionally febrile neutropenia, prolonged grade 3 or higher neutropenia.

[0028] In some of any [embodimentexamples](#), the administration of the immunomodulatory compound: reverses an exhaustion phenotype in CAR-expressing T cells in the subject; prevents, inhibits or delays the onset of an exhaustion phenotype in CAR-expressing T cells in the subject; or reduces the level or degree of an exhaustion phenotype in CAR-expressing T cells in the subject; or reduces the percentage, of the total number of CAR-expressing T cells in the subject, that have an exhaustion phenotype.

[0029] In some of any [embodimentexamples](#), following administration of the immunomodulatory compound or initiation thereof, the subject exhibits a restoration or rescue of an antigen- or tumor-specific activity or function of CAR-expressing T cells in said subject, optionally wherein said restoration, rescue, and/or initiation of administration of said compound, is at a point in time after CAR-expressing T cells in the subject or the in the blood of the subject have exhibited an exhausted phenotype.

[0030] In some of any [embodimentexamples](#), the administration of the immunomodulatory compound comprises 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 said 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 said administration of said compound; or (b) prevent, inhibit or delay the onset of an exhaustion phenotype, in naïve or non-exhausted T cells T cells in the subject, which optionally comprise T cells expressing said 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 said administration of said compound; or (c) reverse an exhaustion phenotype in exhausted T cells, optionally comprising T cells expressing said CAR, in the subject, as compared to the absence of said administration of said subject.

[0031] In some of any [embodimentexamples](#), at the time of the administration of the immunomodulatory compound an exhausted phenotype of one or more of the CAR-expressing T cells, or a marker or parameter indicative thereof, has been detected or measured in the subject

or in a biological sample from the subject. In some of any embodimentexamples, at least at or about 10%, at least at or about 20%, at least at or about 30%, at least at or about 40%, or at least at or about 50% of the total CAR-expressing T cells in a biological sample from the subject has an exhausted phenotype. In some of any embodimentexamples, greater than at or about 10%, greater than at or about 20%, greater than at or about 30%, greater than at or about 40%, or greater than at or about 50% of the CAR-expressing T cells in a biological sample from the subject has an exhausted phenotype compared to the percentage of the CAR-expressing T cells having the exhausted phenotype in a comparable biological sample at a prior time point.

[0032] In some of any embodimentexamples, the exhaustion phenotype, with reference to a T cell or population of T cells, comprises: an increase in the level or degree of surface expression on the T cell or T cells, or in the percentage of T said population of T cells exhibiting surface expression, of one or more exhaustion marker, optionally 2, 3, 4, 5 or 6 exhaustion markers, compared to a reference T cell population under the same conditions; or a decrease in the level or degree of an activity exhibited by said T cells or population of T cells upon exposure to BCMA or an agonist of the CAR, optionally wherein the agonist is an anti-idiotypic antibody, compared to a reference T cell population, under the same conditions. In some of any embodimentexamples, the increase in the level, degree or percentage is by greater than at or about 1.2-fold, at or about 1.5-fold, at or about 2.0-fold, at or about 3-fold, at or about 4-fold, at or about 5-fold, at or about 6-fold, at or about 7-fold, at or about 8-fold, at or about 9-fold, at or about 10-fold or more. In some of any embodimentexample, the decrease in the level, degree or percentage is by greater than at or about 1.2-fold, at or about 1.5-fold, at or about 2.0-fold, at or about 3-fold, at or about 4-fold, at or about 5-fold, at or about 6-fold, at or about 7-fold, at or about 8-fold, at or about 9-fold, at or about 10-fold or more.

[0033] In some of any embodimentexamples, the reference T cell population is a population of T cells known to have a non-exhausted phenotype, is a population of naïve T cells, is a population of central memory T cells, or is a population of stem central memory T cells, optionally from the same subject, or of the same species as the subject, from which the T cell or T cells having the exhausted phenotype are derived. In some of any embodimentexamples, the reference T cell population (a) is a subject-matched population comprising bulk T cells isolated from the blood of the subject from which the T cell or T cells having the exhausted phenotype is derived, optionally wherein the bulk T cells do not express the CAR and/or (b) is obtained from the subject from which the T cell or T cells having the exhausted phenotype is derived, prior to receiving administration of a dose of T cells expressing the CAR. In some of any embodimentexamples, the

reference T cell population is a composition comprising a sample of the T cell therapy, or pharmaceutical composition comprising T cells expressing the CAR, prior to its administration to the subject, optionally wherein the composition is a cryopreserved sample.

[0034] In some of any [embodimentexamples](#), one or more of the one or more exhaustion marker is an inhibitory receptor. In some of any [embodimentexamples](#), one or more of the one or more exhaustion marker is selected from among PD-1, CTLA-4, TIM-3, LAG-3, BTLA, 2B4, CD160, CD39, VISTA, and TIGIT. In some of any [embodimentexamples](#), the activity or is one or more of proliferation, cytotoxicity or production of one or a combination of inflammatory cytokines, optionally wherein the one or a combination of cytokines is selected from the group consisting of IL-2, IFN-gamma and TNF-alpha.

[0035] In some of any [embodimentexamples](#), the exposure to BCMA or an agonist of the CAR, optionally wherein the agonist is an anti-idiotypic antibody, comprises incubation with BCMA or the agonist of the CAR. In some of any [embodimentexamples](#), the antigen is comprised on the surface of antigen-expressing target cells, optionally multiple myeloma cells or cell line.

[0036] In some of any [embodimentexamples](#), the dose of T cells is between at or about 5×10^7 CAR+ T cells and at or about 1×10^9 CAR+ T cells. In some of any [embodimentexamples](#), the dose of T cells is between at or about 1×10^8 CAR+ T cells and at or about 1×10^9 CAR+ T cells. In some of any [embodimentexamples](#), the dose of T cells is at or about 1.5×10^8 cells or CAR+ T cells. In some of any [embodimentexamples](#), the dose of T cells is at or about 3×10^8 cells or CAR+ T cells. In some of any [embodimentexamples](#), the dose of T cells is at or about 4.5×10^8 cells or CAR+ T cells. In some of any [embodimentexamples](#), the dose of T cells is at or about 6×10^8 cells or CAR+ T cells.

[0037] In some of any [embodimentexamples](#), the dose comprises $CD3^+$ CAR-expressing T cells. In some of any [embodimentexamples](#), the dose comprises a combination of $CD4^+$ T cells and $CD8^+$ T cells and/or a combination of $CD4^+$ CAR-expressing T cells and $CD8^+$ CAR-expressing T cells. In some of any [embodimentexamples](#), the ratio of $CD4^+$ CAR-expressing T cells to $CD8^+$ CAR-expressing T cells and/or of $CD4^+$ T cells to $CD8^+$ T cells, is or is approximately 1:1 or is between at or approximately 1:3 and at or approximately 3:1.

[0038] In some of any [embodimentexamples](#), prior to the administration of the dose of 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. In some of any [embodimentexamples](#), 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.

[0039] In some of any [embodimentexamples](#), 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.

[0040] In some of any [embodimentexamples](#), the antigen binding domain is a single chain variable fragment (scFv).

[0041] In some of any [embodimentexamples](#), 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. In some of any [embodimentexamples](#), the antigen binding domain comprises a V_H region that has 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%, at least 99% to SEQ ID NO:36, and a V_L region has 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%, at least 99% to SEQ ID NO:37. In some of any [embodimentexamples](#), the antigen binding domain comprises the V_H region sequence of amino acids set forth in SEQ ID NO:36 and the V_L region sequence of amino acids set forth in SEQ ID NO:37. In some of any [embodimentexamples](#), the antigen-binding domain is an scFv that has 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%, at least 99% to SEQ ID NO:180. In some of any [embodimentexamples](#), the antigen-binding domain is an scFv that has the sequence of amino acids set forth in SEQ ID NO:180.

[0042] In some of any [embodimentexamples](#), the anti-BCMA CAR 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. In some of any [embodimentexamples](#), the antigen binding domain comprises a V_H region that has 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%, at least 99% to SEQ ID NO:30, and the V_L region

has 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%, at least 99% to SEQ ID NO:31. In some of any [embodimentexamples](#), the antigen binding domain comprises the V_H region that has the sequence of amino acids set forth in SEQ ID NO:30 and the V_L region has the sequence of amino acids set forth in SEQ ID NO:31. In some of any [embodimentexamples](#), the antigen binding domain is an scFv that has 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%, at least 99% to SEQ ID NO:68. In some of any [embodimentexamples](#), the antigen binding domain is an scFv set forth in SEQ ID NO:68.

[0043] In some of any [embodimentexamples](#), the intracellular signaling region further comprises a costimulatory signaling domain. In some of any [embodimentexamples](#), the costimulatory signaling region comprises an intracellular signaling domain of CD28, 4-1BB, or ICOS, or a signaling portion thereof. In some of any [embodimentexamples](#), the costimulatory signaling region comprises an intracellular signaling domain of 4-1BB, optionally human 4-1BB. In some of any [embodimentexamples](#), the costimulatory signaling region is between the transmembrane domain and the cytoplasmic signaling domain of a CD3-zeta (CD3ζ) chain.

[0044] In some of any [embodimentexamples](#), the transmembrane domain is or comprises a transmembrane domain from human CD28. In some of any [embodimentexamples](#), the transmembrane domain is or comprises a transmembrane domain from human CD8.

[0045] In some of any [embodimentexamples](#), the CAR further comprises an extracellular spacer between the antigen binding domain and the transmembrane domain. In some of any [embodimentexamples](#), the spacer is between at or about 50 amino acids and at or about 250 amino acids. In some of any [embodimentexamples](#), the spacer is between at or about 125 amino acids and at or about 250 amino acids, optionally wherein the spacer is at or about 228 amino acids. In some of any [embodimentexamples](#), the spacer is an immunoglobulin spacer comprising all or a portion of an immunoglobulin constant domain or a modified form thereof. In some of any [embodimentexamples](#), the spacer comprises an IgG4/2 chimeric hinge or a modified IgG4 hinge; an IgG2/4 chimeric C_H2 region; and an IgG4 C_H3 region. In some of any [embodimentexamples](#), the spacer is set forth in SEQ ID NO: 29 or is encoded by a sequence of nucleotides set forth in SEQ ID NO:179. In some of any [embodimentexamples](#), the spacer is a CD8 hinge.

[0046] In some of any [embodimentexamples](#), the anti-BCMA CAR has a sequence 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 any one of SEQ ID NOS: 126-177.

[0047] In some of any embodimentexamples, the anti-BCMA CAR has the sequence of amino acids set forth in SEQ ID NO:160 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 SEQ ID NO:160.

[0048] In some of any embodimentexamples, the CAR is encoded by the sequence of nucleotides set forth in SEQ ID NO:69.

[0049] In some of any embodimentexamples, the anti-BCMA CAR has the sequence of amino acids set forth in SEQ ID NO:161 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 SEQ ID NO:161.

[0050] In some of any embodimentexamples, the anti-BCMA CAR has the sequence of amino acids set forth in SEQ ID NO:152 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 SEQ ID NO:152.

[0051] In some of any embodimentexamples, the anti-BCMA CAR has the sequence of amino acids set forth in SEQ ID NO:168 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 SEQ ID NO:168.

[0052] In some of any embodimentexamples, the anti-BCMA CAR has the sequence of amino acids set forth in SEQ ID NO: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 SEQ ID NO:171.

[0053] In some of any embodimentexamples, the anti-BCMA CAR binds BCMA, optionally wherein the BCMA is human BCMA. In some of any embodimentexamples, the BCMA is membrane-bound BCMA expressed on the surface of a cell. In some of any embodimentexamples, the anti-BCMA CAR has a greater binding affinity for membrane-bound BCMA than soluble BCMA, optionally wherein the ratio of dissociation constant (K_D) for soluble BCMA and the K_D for membrane-bound BCMA is more than 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, 200, 500, 1000, 2000 or more.

[0054] Also provided are uses of an immunomodulatory compound and/or T cell therapy for treating a relapsed or refractory multiple myeloma (R/R MM) in accord with any of the provided

methods. Also provided an immunomodulatory compound and/or T cell therapy for formulation of a medicament of use in treating a relapsed or refractory multiple myeloma (R/R MM) in accord with any of the provided methods.

[0055] Exemplary features of any of the provided methods are described herein, including in the ~~exemplary embodiments~~examples.

Brief Description of the Drawings

[0056] **FIG. 1** shows intracellular Ikaros and Aiolos expression in CD4⁺ anti-BCMA CAR-expressing T cells and CD8⁺ anti-BCMA CAR-expressing T cells after incubation with varying concentrations of Compound A.

[0057] **FIG. 2** shows the amount of IFN γ , IL-2, and TNF- α observed in supernatants after incubation of RPMI-8226 target cells (**FIG. 2A**) and OPM-2 (**FIG. 2B**) anti-BCMA CAR T cells in the presence of increasing concentrations of Compound A.

[0058] **FIG. 3A** shows the cytolytic activity of anti-BCMA CAR⁺ T cells following re-challenge with RPMI target cells with concurrent treatment of Compound A or Compound B during chronic activation. **FIG. 3B** shows the cytokine production of anti-BCMA CAR⁺ T cells following re-challenge with RPMI target cells with concurrent treatment of Compound A or Compound B during chronic activation.

[0059] **FIG. 4A** shows the cytolytic activity of anti-BCMA CAR⁺ T cells following re-challenge with RPMI target cells with treatment of Compound A or Compound B during rechallenge. **FIG. 4B** shows the cytokine production of anti-BCMA CAR⁺ T cells following re-challenge with RPMI target cells with concurrent treatment of Compound A or Compound B during rechallenge.

[0060] **FIG. 5A** shows the analysis of population doublings of anti-BCMA CAR⁺ T cells in the presence of absence of Compound A for two donors. **FIG. 5B** shows the cytokine production in the cultures 24 hours after a first reset (day 5) or second reset (day 9) following replating with fresh target cells in the serial stimulation assay.

[0061] **FIG. 6A** shows the tumor volume and **FIG. 6B** shows the survival of iberdomide-sensitive mice (NOD.Cg-Prkdc^{scid}IL-2rg^{tm1Wjl}/SzJ mice (NSG; Jackson Labs)) that were administered Compound A in combination with anti-BCMA CAR T cells via concurrent or delayed dosing. **FIG. 6C** shows the numbers of CD3⁺ CAR⁺ T cells in the blood in mice having