THERAPY FOR THE TREATMENT OF MULTIPLE MYELOMA

FIELD

[0001] Provided herein are therapies for treating and/or managing multiple myeloma, which comprise administering to a patient a cereblon E3 ligase modulator and a BCMA×CD3 bispecific antibody.

BACKGROUND

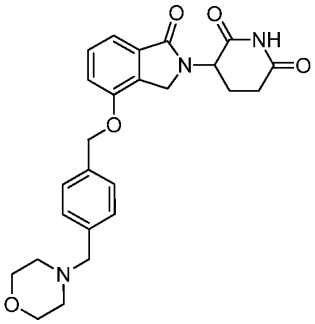
[0002] Multiple myeloma, especially relapsed refractory multiple myeloma (RRMM), remains challenging to treat although outcomes have improved with use of proteasome inhibitors, immunomodulatory compounds and cluster of differentiation 38-directed antibodies. Despite this, relapse rates remain high and relapsed multiple myeloma (MM) cells typically acquire a more aggressive phenotype that results in shorter durations of response and decreased survival rates. This highlights the need for new agents and combinations which may provide synergistic anti-myeloma activity, overcome resistance to prior therapies and represent well tolerated novel treatment options (Leow CC, Low MSY. Targeted Therapies for Multiple Myeloma. J Pers Med. 2021;11(5)).

[0003] Therapeutic strategies to optimize outcomes for MM patients may require a multifaceted approach to address the heterogeneous biological aspects of the disease, including immune dysfunction. Long-term disease control may be best achieved by combining therapies that have distinct mechanisms of action, especially those that target key components of the immune system and are able to restore its functionality. The combinations provided herein have the potential to provide additional enhanced clinical benefits to patients with RRMM.

SUMMARY

[0004] Provided herein are methods of treating or managing multiple myeloma. In one aspect, provided herein is a method of treating or managing multiple myeloma, comprising administering to a patient having multiple myeloma:

(a) a therapeutically effective amount of a compound, wherein the compound is Compound A



Compound A

or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof; in combination with

(b) a therapeutically effective amount of a bispecific antibody comprising a first binding part binding to B cell maturation antigen (BCMA) and a second binding part binding to cluster of differentiation 3 (CD3),

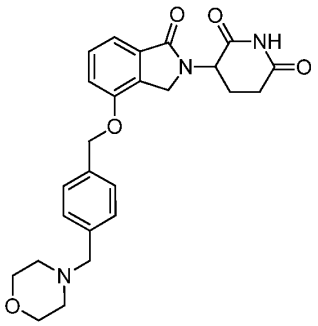
wherein the first binding part binding to BCMA comprises (i) a VH region comprising a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 9, 14, 16, and 17; a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 10, 15, 18, and 23; and a VH CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 11, and 19; and (ii) a VL region comprising a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 12, and 20; a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 7, 13, and 21; and a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8 and 22; and

wherein the second binding part binding to CD3 comprises (i) a VH region comprising a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 26, 32, 37, 39, and 40; a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 27, 33, 38, 41, and 46; and a VH CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 28, 34, and 42; and (ii) a VL region comprising a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 29, 35, and 43; a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 30, 36, and 44; and a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 31 and 45.

[0005] Also provided herein are compounds for use in a method of treating multiple

myeloma. In one aspect, provided herein is a compound for use in a method of treating multiple myeloma, wherein the method comprises administering to a patient having multiple myeloma:

(a) a therapeutically effective amount of the compound, wherein the compound is Compound A



Compound A

or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof; in combination with

(b) a therapeutically effective amount of a bispecific antibody comprising a first binding part binding to B cell maturation antigen (BCMA) and a second binding part binding to cluster of differentiation 3 (CD3),

wherein the first binding part binding to BCMA comprises (i) a VH region comprising a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 9, 14, 16, and 17; a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 10, 15, 18, and 23; and a VH CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 11, and 19; and (ii) a VL region comprising a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 12, and 20; a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 7, 13, and 21; and a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8 and 22; and

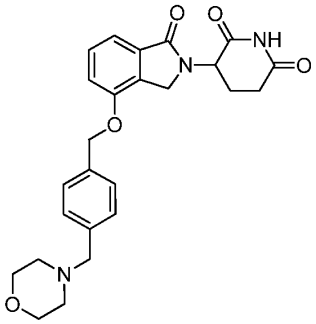
wherein the second binding part binding to CD3 comprises (i) a VH region comprising a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 26, 32, 37, 39, and 40; a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 27, 33, 38, 41, and 46; and a VH CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 28, 34, and 42; and (ii) a VL

region comprising a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 29, 35, and 43; a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 30, 36, and 44; and a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 31 and 45.

[0006] Also provided herein are bispecific antibodies for use in a method of treating multiple myeloma. In one aspect, provided herein is a bispecific antibody for use in a method of treating multiple myeloma, wherein the method comprises administering to a patient having multiple myeloma:

(a) a therapeutically effective amount of the bispecific antibody, where the bispecific antibody comprises a first binding part binding to B cell maturation antigen (BCMA) and a second binding part binding to cluster of differentiation 3 (CD3), wherein the first binding part binding to BCMA comprises (i) a VH region comprising a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 9, 14, 16, and 17; a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 10, 15, 18, and 23; and a VH CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 11, and 19; and (ii) a VL region comprising a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 12, and 20; a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 7, 13, and 21; and a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8 and 22; and wherein the second binding part binding to CD3 comprises (i) a VH region comprising a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 26, 32, 37, 39, and 40; a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 27, 33, 38, 41, and 46; and a VH CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 28, 34, and 42; and (ii) a VL region comprising a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 29, 35, and 43; a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 30, 36, and 44; and a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 31 and 45; in combination with

(b) a therapeutically effective amount of a compound, wherein the compound is Compound A

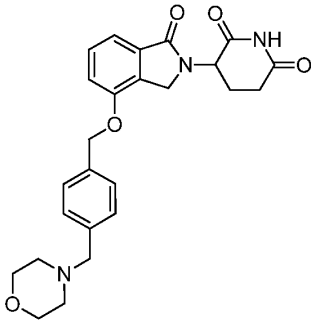


Compound A

or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof.

[0007] Also provided herein are compounds and bispecific antibodies for use in a method of treating multiple myeloma. In one aspect, provided herein are a compound and a bispecific antibody for use in a method of treating multiple myeloma, wherein the method comprises administering to a patient having multiple myeloma:

(a) a therapeutically effective amount of the compound, wherein the compound is Compound A



Compound A

or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof; in combination with

(b) a therapeutically effective amount of the bispecific antibody comprising a first binding part binding to B cell maturation antigen (BCMA) and a second binding part binding to cluster of differentiation 3 (CD3),

wherein the first binding part binding to BCMA comprises (i) a VH region comprising a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 3,

9, 14, 16, and 17; a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 10, 15, 18, and 23; and a VH CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 11, and 19; and (ii) a VL region comprising a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 12, and 20; a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 7, 13, and 21; and a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8 and 22; and wherein the second binding part binding to CD3 comprises (i) a VH region comprising a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 26, 32, 37, 39, and 40; a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 27, 33, 38, 41, and 46; and a VH CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 28, 34, and 42; and (ii) a VL region comprising a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 29, 35, and 43; a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 30, 36, and 44; and a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 31 and 45.

[0008] In certain embodiments, the first binding part binding to BCMA comprises:

(a) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:3, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:4, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:5; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:6, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:7, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:8;

(b) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:9, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:10, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:11; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:12, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:13, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:8;

(c) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:14, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:15, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:11; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:12, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:13, and a VL CDR3 comprising the amino acid

sequence of SEQ ID NO:8;

(d) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:16, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:10, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:11; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:12, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:13, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:8;

(e) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:17, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:18, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:19; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:20, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:21, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:22; or

(f) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:16, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:23, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:11; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:12, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:13, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:8.

[0009] In certain embodiments, the second binding part binding to CD3 comprises:

(a) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:26, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:27, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:28; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:29, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:30, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:31;

(b) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:32, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:33, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:34; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:35, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:36, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:31;

(c) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:37, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:38, a VH CDR3

comprising the amino acid sequence of SEQ ID NO:34; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:35, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:36, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:31;

(d) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:39, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:33, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:34; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:35, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:36, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:31;

(e) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:40, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:41, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:42; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:43, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:44, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:45; or

(f) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:39, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:46, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:34; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:35, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:36, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:31.

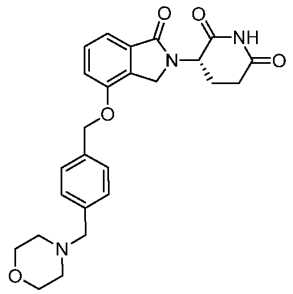
[0010] In certain embodiments, the first binding part binding to BCMA comprises a VH region comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:1 and a VL region comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:2, and the second binding part binding to CD3 comprises a VH region comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:24 and a VL region comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:25.

[0011] In certain embodiments, the first binding part binding to BCMA comprises a heavy chain and a light chain; and the second binding part binding to CD3 comprises a heavy chain and a light chain. In certain embodiments, the heavy chain of the first binding part binding to BCMA comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:47 and the light chain of the first binding part binding to BCMA comprises an

amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:48, and the heavy chain of the second binding part binding to CD3 comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:49 and the light chain of the second binding part binding to CD3 comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:50. In certain embodiments, the heavy chain of the first binding part binding to BCMA comprises the amino acid sequence of SEQ ID NO:47 and the light chain of the first binding part binding to BCMA comprises the amino acid sequence of SEQ ID NO:48, and the heavy chain of the second binding part binding to CD3 comprises the amino acid sequence of SEQ ID NO:49 and the light chain of the second binding part binding to CD3 comprises the amino acid sequence of SEQ ID NO:50.

[0012] In certain embodiments, the bispecific antibody is an IgG2 kappa antibody.

[0013] In certain embodiments, the compound is Compound A-S



Compound A-S

or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof. In certain embodiments, the compound is hydrochloride salt of Compound A-S.

[0014] In certain embodiments, the multiple myeloma is relapsed, refractory or resistant. In certain embodiments, the multiple myeloma is relapsed or refractory. In certain embodiments, the multiple myeloma is relapsed or refractory to at least two prior therapies, wherein the prior therapies are selected from lenalidomide, pomalidomide, and a proteasome inhibitor. In certain embodiments, the multiple myeloma is newly diagnosed multiple myeloma.

[0015] In certain embodiments, the compound is administered orally. In certain embodiments, the compound is administered in an amount of about 0.6 mg, 0.7 mg, 0.75 mg, 0.8 mg, 0.9 mg, 1.0 mg, 1.1 mg, 1.2 mg, 1.3 mg, 1.4 mg, 1.5 mg, or 1.6 mg per day. In certain embodiments, the compound is administered once daily for 21 days followed by 7 days of rest.

[0016] In certain embodiments, the bispecific antibody is administered subcutaneously. In certain embodiments, the bispecific antibody is administered in an amount of about 12 mg, about 32 mg, or about 76 mg. In certain embodiments, the bispecific antibody is administered once a week, once every two weeks, or once every four weeks. In certain embodiments, the bispecific antibody is administered on days 1, 4, and 8 in a 14-day priming dose cycle prior to administration of the compound, and then administered once a week, once every two weeks, or once every four weeks in a 28-day cycle while the compound is administered once a day on days 1 to 21 in the 28-day cycle. In certain embodiments, the bispecific antibody is administered on day 1 in an amount of 12 mg, on day 4 in an amount of 32 mg, and on day 8 in an amount of 76 mg in the 14-day priming dose cycle prior to administration of the compound. In certain embodiments, following the priming dose cycle, the bispecific antibody is administered in an amount of 76 mg once a week, once every two weeks, or once every four weeks in a 28-day cycle while the compound is administered in an amount of 1.0 mg, 1.3 mg or 1.6 mg once a day on days 1 to 21 in the 28-day cycle. In certain embodiments, following the priming dose cycle, the bispecific antibody is administered in an amount of 76 mg once a week, once every two weeks, or once every four weeks in a 28-day cycle while the compound is administered in an amount of 0.75 mg once a day on days 1 to 21 in the 28-day cycle. In certain embodiments, following the priming dose cycle and subsequent six 28-day cycles, the bispecific antibody is administered in an amount of 76 mg once every two weeks if the patient has received treatment for at least 6 months and a disease response shows at least a partial response or better with responses persisting for at least 2 months. In certain embodiments, following the priming dose cycle and subsequent twelve 28-day cycles, the bispecific antibody is administered in an amount of 76 mg once every four weeks if a disease response shows at least a partial response or better with responses persisting for at least 2 months. In certain embodiments, following the priming dose cycle and subsequent three 28-day cycles, the bispecific antibody is administered in an amount of 76 mg once every two weeks in a 28-day cycle. In certain embodiments, following three 28-day cycles in which the bispecific antibody is administered in an amount of 76 mg once every two weeks, the bispecific antibody is administered in an amount of 76 mg once every four weeks in a 28-day cycle. In certain embodiments, the compound is administered in an amount of 1.0 mg once a day on days 1 to 21 of each 28-day cycle. In certain embodiments, following the priming dose cycle and subsequent seven or more 28-day cycles, the bispecific antibody is administered in an amount of 76 mg once every two weeks for three 28-day cycles. In certain embodiments, following the priming dose cycle and subsequent ten

or more 28-day cycles, the bispecific antibody is administered in an amount of 76 mg once every four weeks.

[0017] In certain embodiments, following the priming dose cycle, the bispecific antibody is administered in an amount of 76 mg once every two weeks in a 28-day cycle. In certain embodiments, following the priming dose cycle and subsequent three 28-day cycles in which the bispecific antibody is administered in an amount of 76 mg once every two weeks, the bispecific antibody is administered in an amount of 76 mg once every four weeks in a 28-day cycle. In certain embodiments, the compound is administered in an amount of 0.75 mg, 1.0 mg, or 1.3 mg once a day on days 1 to 21 of each 28-day cycle.

BRIEF DESCRIPTION OF THE FIGURES

[0018] **FIG. 1** illustrates an exemplary format of the bispecific antibody for use in the present application.

[0019] **FIG. 2** illustrates the study design in Example 1 (C1. Overall Design 1). The exemplary elranatamab dosing regimen includes: Priming C0: 12/32/76 mg; 76 mg QW Cycle 1-6; 76mg Q2W Cycle 7-12; 76 mg Q4W Cycle 13+. "DL A" means Dose Level A for iberdomide; "DL B" means Dose Level B for iberdomide.

[0020] **FIG. 3** illustrates the exemplary dosing schedule for elranatamab and iberdomide under Overall Design 1.

[0021] **FIG. 4** illustrates the study design in Example 1 (C2. Overall Design 2). In Part 1, the exemplary elranatamab dosing regimen includes: Priming C0 (14 days): 12/32/76 mg; 76 mg QW Cycle 1-3; 76mg Q2W Cycle 4-6; 76 mg Q4W Cycle 7+. In dose escalation, the exemplary elranatamab dosing regimen includes: Priming C0 (14 days): 12/32/76 mg; 76 mg Q2W Cycle 1-3; 76mg Q4W Cycle 4+.

[0022] **FIG. 5** illustrates the exemplary dosing schedule for elranatamab and iberdomide for Dose Level 1 (DL1) under Overall Design 2.

[0023] **FIG. 6** illustrates the exemplary dosing schedule for elranatamab and iberdomide for Dose Level 2 (DL2), Dose Level -1 (DL -1), or Dose Level -2 (DL -2) under Overall Design 2.

DETAILED DESCRIPTION

DEFINITIONS

[0024] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications are incorporated by reference in

their entirety. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[0025] The use of the word "a" or "an" when used in conjunction with the term "comprising" in the claims and/or the description can mean "one", but it is also consistent with the meaning of "one or more", "at least one" and "one or more than one".

[0026] As used herein, the terms "comprising" and "including" can be used interchangeably. The terms "comprising" and "including" are to be interpreted as specifying the presence of the stated features or components as referred to, but does not preclude the presence or addition of one or more features, or components, or groups thereof. Additionally, the terms "comprising" and "including" are intended to include examples encompassed by the term "consisting of". Consequently, the term "consisting of" can be used in place of the terms "comprising" and "including" to provide for more specific embodiments of the invention.

[0027] The term "consisting of" means that a subject-matter has at least 90%, 95%, 97%, 98% or 99% of the stated features or components of which it consists. In another embodiment the term "consisting of" excludes from the scope of any succeeding recitation any other features or components, excepting those that are not essential to the technical effect to be achieved.

[0028] As used herein, the term "or" is to be interpreted as an inclusive "or" meaning any one or any combination. Therefore, "A, B or C" means any of the following: "A; B; C; A and B; A and C; B and C; A, B and C". An exception to this definition will occur only when a combination of elements, functions, steps or acts are in some way inherently mutually exclusive.

[0029] As used herein, and unless otherwise specified, the term "about" or "approximately" means an acceptable error for a particular value as determined by one of ordinary skill in the art, which depends in part on how the value is measured or determined. In certain embodiments, the term "about" or "approximately" means within 1, 2, 3, or 4 standard deviations. In certain embodiments, the term "about" or "approximately" that the numeric value or range of values may vary within 25%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1.5%, 1%, 0.5%, or 0.25% of the recited value or range of values. In one embodiment, the term "about" refers to a value that is no more than 10% above or below the value being modified by the term. For example, the term "about 10 mg/m^2" means a range of from 9 mg/m^2 to 11 mg/m^2.

[0030] The term "optional" or "optionally" means that the subsequently described circumstance may or may not occur, so that the description includes instances wherein the circumstance occurs, and the instances wherein the circumstance does not occur.

[0031] Unless specifically stated otherwise, where a compound may assume alternative tautomeric, regioisomeric and/or stereoisomeric forms, all alternative isomers are intended to be encompassed within the scope of the claimed subject matter. For example, where a compound can have one of two tautomeric forms, it is intended that both tautomers be encompassed herein.

[0032] Thus, the compounds provided herein may be enantiomerically pure, or be stereoisomeric or diastereomeric mixtures. As used herein and unless otherwise indicated, the term "stereomerically pure" means a composition that comprises one stereoisomer of a compound and is substantially free of other stereoisomers of that compound. For example, a stereomerically pure composition of a compound having one chiral center will be substantially free of the opposite enantiomer of the compound. A stereomerically pure composition of a compound having two chiral centers will be substantially free of other diastereomers of the compound. A typical stereomerically pure compound comprises greater than about 80% by weight of one stereoisomer of the compound and less than about 20% by weight of other stereoisomers of the compound, in one embodiment greater than about 90% by weight of one stereoisomer of the compound and less than about 10% by weight of the other stereoisomers of the compound, in one embodiment greater than about 95% by weight of one stereoisomer of the compound and less than about 5% by weight of the other stereoisomers of the compound, and in one embodiment greater than about 97% by weight of one stereoisomer of the compound and less than about 3% by weight of the other stereoisomers of the compound. A stereomerically pure compound A, A-S, or A-R used herein comprises greater than about 80% by weight of one stereoisomer of the compound, in one embodiment greater than about 90% by weight of one stereoisomer of the compound, in one embodiment greater than about 95% by weight of one stereoisomer of the compound, and in one embodiment greater than about 97% by weight of one stereoisomer of the compound. As used herein and unless otherwise indicated, the term "stereomerically enriched" means a composition that comprises greater than about 60% by weight of one stereoisomer of a compound, in one embodiment greater than about 70% by weight, and in one embodiment greater than about 80% by weight of one stereoisomer of a compound. As used herein and unless otherwise indicated, the term "enantiomerically pure" means a stereomerically pure composition of a compound having one chiral center. Similarly, the term "stereomerically

enriched" means a stereomerically enriched composition of a compound having one chiral center. As used herein, stereoisomeric or diastereomeric mixtures means a composition that comprises more than one stereoisomer of a compound. A typical stereoisomeric mixture of a compound comprises about 50% by weight of one stereoisomer of the compound and about 50% by weight of other stereoisomers of the compound, or comprises greater than about 50% by weight of one stereoisomer of the compound and less than about 50% by weight of other stereoisomers of the compound, or comprises greater than about 45% by weight of one stereoisomer of the compound and less than about 55% by weight of the other stereoisomers of the compound, or comprises greater than about 40% by weight of one stereoisomer of the compound and less than about 60% by weight of the other stereoisomers of the compound, or comprises greater than about 35% by weight of one stereoisomer of the compound and less than about 65% by weight of the other stereoisomers of the compound.

[0033] It is to be understood that the compounds provided herein may contain chiral centers. Such chiral centers may be of either the (*R*) or (*S*) configuration, or may be a mixture thereof. It is to be understood that the chiral centers of the compounds provided herein may undergo epimerization *in vivo*. As such, one of skill in the art will recognize that administration of a compound in its (*R*) form is equivalent, for compounds that undergo epimerization *in vivo*, to administration of the compound in its (S) form.

[0034] Optically active (+) and (-), (*R*)- and (*S*)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, such as chromatography on a chiral stationary phase.

[0035] As used herein, an "isotopolog" is an isotopically enriched compound. The term "isotopically enriched" refers to an atom having an isotopic composition other than the natural isotopic composition of that atom. "Isotopically enriched" may also refer to a compound containing at least one atom having an isotopic composition other than the natural isotopic composition of that atom. The term "isotopic composition" refers to the amount of each isotope present for a given atom. Radiolabeled and isotopically enriched compounds are useful as therapeutic agents, e.g., multiple myeloma therapeutic agents, research reagents, e.g., binding assay reagents, and diagnostic agents, e.g., in vivo imaging agents. All isotopic variations of the compounds as described herein, whether radioactive or not, are intended to be encompassed within the scope of the embodiments provided herein. In some embodiments, there are provided isotopologues of the compounds. In some embodiments, isotopologues provided herein are deuterium enriched compounds. In some embodiments,

isotopologues provided herein are deuterium enriched compounds, where the deuteration occurs on the chiral center.

[0036] In the description herein, if there is any discrepancy between a chemical name and chemical structure, the structure controls.

[0037] As used herein and unless otherwise indicated, the term "solvate" means a compound provided herein or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of solvent bound by non-covalent intermolecular forces. Where the solvent is water, the solvate is a hydrate.

[0038] As used herein and unless otherwise indicated, the term "stereomerically pure" means a composition that comprises one stereoisomer of a compound and is substantially free of other stereoisomers of that compound. For example, a stereomerically pure composition of a compound having one chiral center is substantially free of the opposite enantiomer of the compound. A stereomerically pure composition of a compound having two chiral centers is substantially free of other diastereomers of the compound. In certain embodiments, a stereomerically pure compound comprises greater than about 80% by weight of one stereoisomer of the compound and less than about 20% by weight of other stereoisomers of the compound, greater than about 90% by weight of one stereoisomer of the compound and less than about 10% by weight of the other stereoisomers of the compound, greater than about 95% by weight of one stereoisomer of the compound and less than about 5% by weight of the other stereoisomers of the compound, or greater than about 97% by weight of one stereoisomer of the compound and less than about 3% by weight of the other stereoisomers of the compound. As used herein and unless otherwise indicated, the term "stereomerically enriched" means a composition that comprises greater than about 60% by weight of one stereoisomer of a compound, greater than about 70% by weight, or greater than about 80% by weight of one stereoisomer of a compound. As used herein and unless otherwise indicated, the term "enantiomerically pure" means a stereomerically pure composition of a compound having one chiral center. Similarly, the term "stereomerically enriched" means a stereomerically enriched composition of a compound having one chiral center.

[0039] The term "human BCMA" as used herein relates to human B cell maturation antigen, TR17_HUMAN, TNFRSF17 (UniProt Q02223), which is a member of the tumor necrosis receptor superfamily that is preferentially expressed in differentiated plasma cells. The extracellular domain of BCMA consists according to UniProt of amino acids 1 – 54 (or 5-51). The term "antibody against BCMA" or "anti-BCMA antibody" as used herein relates to an antibody specifically binding to BCMA.

[0040] The term "antibody against CD3" or "anti-CD3 antibody" relates to an antibody specifically binding to CD3. In one embodiment, the antibody specifically binds to CD3ε. The term "CD3ε" as used herein relates to human CD3ε described under UniProt P07766 (CD3E_HUMAN).

[0041] The term "antibody" as used herein refers to a monoclonal antibody. An antibody consists of two pairs of a "light chain" (LC) and a "heavy chain" (HC) (such light chain (LC) /heavy chain pairs are abbreviated herein as LC/HC). The light chains and heavy chains of such antibodies are polypeptides consisting of several domains. Each heavy chain comprises a heavy chain variable region (abbreviated herein as HCVR or VH) and a heavy chain constant region. The heavy chain constant region comprises the heavy chain constant domains CH1, CH2 and CH3 (antibody classes IgA, IgD, and IgG) and optionally the heavy chain constant domain CH4 (antibody classes IgE and IgM). Each light chain comprises a light chain variable domain VL and a light chain constant domain CL. The variable domains VH and VL can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FRs, arranged from amino terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The "constant domains" of the heavy chain and of the light chain are not involved directly in binding of an antibody to a target, but exhibit various effector functions. An antibody (or antibody portion) can be in one embodiment a Fab fragment, if said antibody portion is comprised in a bispecific antibody according to the invention. The antibody according to the invention can also be a Fab', $F(ab')_2$, a scFv, a di-scFv, or a bi-specific T-cell engager (BiTE®).

[0042] The terms "antibody," "immunoglobulin," and "Ig" are used interchangeably herein, and are used in the broadest sense and specifically cover, for example polyclonal antibodies, monoclonal antibodies (including agonist, antagonist, neutralizing antibodies, full-length monoclonal antibodies), antibody compositions with polyepitopic or monoepitopic specificity, recombinantly produced antibodies, single domain (*e.g.*, VHH) antibodies, monospecific antibodies, multispecific antibodies (including bispecific antibodies), synthetic antibodies, chimeric antibodies, humanized antibodies, or human versions of antibodies having full-length heavy and/or light chains. VHH as used herein refers to a domain antibody derived from a variable region of a heavy chain only antibody. Exemplary single domain antibodies include, but are not limited to, antibodies naturally devoid of light chains such as

those from Camelidae species (*e.g.*, llama), single domain antibodies derived from conventional 4-chain antibodies, engineered antibodies and single domain scaffolds other than those derived from antibodies. Single domain antibodies may be derived from any species including, but not limited to mouse, human, camel, llama, goat, rabbit, and bovine. VHH can also be derived from other species besides Camelidae that may produce heavy chain antibodies naturally devoid of light chain. Antibodies also include antibody fragments (and/or polypeptides that comprise antibody fragments) that retain antigen binding characteristics. Non-limiting examples of antibody fragments include antigen-binding regions and/or effector regions of the antibody, *e.g.*, Fab, Fab', $F(ab')_2$, Fv, scFv, $(scFv)_2$, single chain antibody molecule, dual variable domain antibody, single variable domain, linear antibody, V region, a multispecific antibody formed from antibody fragments, $F(ab)_2$, Fd, Fc, diabody, di-diabody, disulfide-linked Fvs (dsFv), single-domain antibody (*e.g.*, nanobody) or other fragments (*e.g.*, fragments consisting of the variable regions of the heavy and light chains that are non-covalently coupled). In general terms, a variable (V) region domain may be any suitable arrangement of immunoglobulin heavy (VH) and/or light (VL) variable domains. For example, antibodies also include tetrameric antibodies comprising two heavy chain and two light chain molecules, an antibody light chain monomer, and an antibody heavy chain monomer. Thus, for example, the V region domain may be dimeric and contain VHH-VHH, VH-VH, VH-VL, or VL-VL dimers that bind to an antigen. If desired, the VH and VL may be covalently coupled either directly or through a linker to form a single chain Fv (scFv). For ease of reference, scFv proteins are referred to herein as included in the category "antibody fragments." Another form of an antibody fragment is a peptide comprising one or more complementarity determining regions (CDRs) of an antibody. CDRs (also termed "minimal recognition units" or "hypervariable regions") can be obtained by constructing polynucleotides that encode one or more CDRs of interest. Such polynucleotides are prepared, for example, by using the polymerase chain reaction to synthesize the variable region using mRNA of antibody-producing cells as a template (see, for example, Larrick *et al.*, Methods: A Companion to Methods in Enzymology, 2:106 (1991); Courtenay-Luck, "Genetic Manipulation of Monoclonal Antibodies," in Monoclonal Antibodies Production, Engineering and Clinical Application, Ritter *et al.* (eds.), page 166, Cambridge University Press (1995); and Ward *et al.*, "Genetic Manipulation and Expression of Antibodies," in Monoclonal Antibodies: Principles and Applications, Birch *et al.*, (eds.), page 137, Wiley-Liss, Inc. (1995)). Antibody fragments may be incorporated, for example, into single domain antibodies, maxibodies, minibodies, intrabodies, diabodies, triabodies,

tetrabodies, variable domains of new antigen receptors (v-NAR), and bis-single chain Fv regions (see, *e.g.*, Hollinger and Hudson, Nature Biotechnology, 23(9):1126-1136, 2005). In some embodiments, antibodies comprising a VH and/or VL further contain a light chain and/or a heavy chain constant region, such as one or more constant regions, including one or more IgG1, IgG2, IgG3 and/or IgG4 constant regions. In some embodiments, antibodies can include epitope-binding fragments of any of the above. The antibodies described herein can be of any class (*e.g.*, IgG, IgE, IgM, IgD, and IgA) or any subclass (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2) or any subclass (*e.g.*, IgG2a or IgG2b) of immunoglobulin molecule. In some embodiments, antibodies described herein are IgG antibodies (*e.g.*, human IgG), or a class (*e.g.*, human IgG1, IgG2, IgG3 or IgG4) or a subclass thereof.

[0043] Bispecific antibody formats are well known in the state of the art and e.g. also described in Kontermann RE, mAbs 4:2 1-16 (2012); Holliger P., Hudson PJ, Nature Biotech.23 (2005) 1126- 1136 and Chan AC, Carter PJ Nature Reviews Immunology 10, 301-316 (2010) and Cuesta AM et al., Trends Biotech 28 (2011) 355-362. The term "bispecific antibody" as used herein refers in one embodiment to an antibody in which one of the two pairs of heavy chain and light chain (HC/LC) is specifically binding to CD3 and the other one is specifically binding to BCMA. The term also refers to other formats of bispecific antibodies according to the state of the art. In one embodiment, the term "bispecific antibody" includes bispecific single-chain antibodies, such as antibodies in the BiTE® format, DART antibodies, diabodies, tandem scFvs and antibody mimetics such as DARPins.

[0044] The terms "identical" or percent "identity" in the context of two or more nucleic acids or polypeptides, refer to two or more sequences or subsequences that are the same or have a specified percentage of nucleotides or amino acid residues that are the same, when compared and aligned (introducing gaps, if necessary) for maximum correspondence, not considering any conservative amino acid substitutions as part of the sequence identity. The percent identity can be measured using sequence comparison software or algorithms or by visual inspection. Various algorithms and software that can be used to obtain alignments of amino acid or nucleotide sequences are well-known in the art. These include, but are not limited to, BLAST, ALIGN, Megalign, BestFit, GCG Wisconsin Package, and variants thereof. In some embodiments, two nucleic acids or polypeptides are substantially identical, meaning they have at least 70%, at least 75%, at least 80%, at least 85%, or at least 90%, and in some embodiments at least 95%, 96%, 97%, 98%, or 99% nucleotide or amino acid residue identity, when compared and aligned for maximum correspondence, as measured

using a sequence comparison algorithm or by visual inspection. In some embodiments, identity exists over a region of the amino acid sequences that is at least about 10 residues, at least about 20 residues, at least about 40-60 residues, at least about 60-80 residues in length or any integral value there between. In some embodiments, identity exists over a longer region than 60-80 residues, such as at least about 80-100 residues, and in some embodiments the sequences are substantially identical over the full length of the sequences being compared, such as the coding region of a target protein or an antibody. In some embodiments, identity exists over a region of the nucleotide sequences that is at least about 10 bases, at least about 20 bases, at least about 40-60 bases, at least about 60-80 bases in length or any integral value there between. In some embodiments, identity exists over a longer region than 60-80 bases, such as at least about 80-1000 bases or more, and in some embodiments the sequences are substantially identical over the full-length of the sequences being compared, such as a nucleotide sequence encoding a protein of interest. As used herein, an "antigen" is a moiety or molecule that contains an epitope to which a binding agent (*e.g.*, an antibody) can bind. As such, an antigen can be bound by an antibody. In some embodiments, the antigen, to which a binding agent (*e.g.*, an antibody) described herein binds, is BCMA (*e.g.*, human BCMA), or a fragment thereof, including a fragment that comprises one or more domains of BCMA. In some embodiments, the antigen, to which a binding agent (*e.g.*, an antibody) described herein binds, is CD3 (*e.g.*, human CD3), or a fragment thereof, including a fragment that comprises one or more domains of CD3.

[0045] As used herein, the terms "specifically binds," "specifically recognizes," "immunospecifically binds," "selectively binds," "immunospecifically recognizes" and "immunospecific" are analogous terms in the context of antibodies and refer to molecules that bind to an antigen (*e.g.*, epitope) as such binding is understood by one skilled in the art. In some embodiments, "specifically binds" means, for instance that a polypeptide or molecule interacts more frequently, more rapidly, with greater duration, with greater affinity, or with some combination of the above to the epitope, protein, or target molecule than with alternative substances, including related and unrelated proteins. For example, a molecule that specifically binds to an antigen may bind to other peptides or polypeptides, generally with lower affinity as determined by, *e.g.*, immunoassays, BIACORE™, KinExA 3000 instrument (Sapidyne Instruments, Boise, ID), the OctetQK384 system (ForteBio, Menlo Park, CA), or other assays known in the art. In some embodiments, an antibody or antigen-binding domain binds to or specifically binds to an antigen when it binds to the antigen with higher affinity than to any cross-reactive antigen as determined using experimental techniques, such as

radioimmunoassays (RIAs) and enzyme linked immunosorbent assays (ELISAs). Typically a specific or selective reaction will be at least twice background signal or noise and may be more than 10 times background. See, *e.g.*, Fundamental Immunology 332-36 (Paul ed., 2d ed. 1989) for a discussion regarding binding specificity. In some embodiments, the extent of binding of an antibody or antigen-binding domain to a "non-target" protein is less than about 10% of the binding of the antibody or antigen-binding domain to its particular target antigen, for example, as determined by fluorescence activated cell sorting (FACS) analysis or RIAs. In some embodiments, molecules that specifically bind to an antigen bind to the antigen with a Ka that is at least 2 logs, 2.5 logs, 3 logs, 4 logs or greater than the Ka when the molecules bind to another antigen. In some embodiments, molecules that specifically bind to an antigen do not cross react with other proteins. In another specific embodiment, molecules that specifically bind to an antigen do not cross react with other proteins. In some embodiments "specifically binds" means, for instance, that a polypeptide or molecule binds a protein or target with a K_D of about 0.1mM or less, but more usually less than about 1μM. In some embodiments, "specifically binds" means that a polypeptide or molecule binds a target with a K_D of at least about 0.1μM or less, at least about 0.01μM or less, or at least about 1nM or less. Because of the sequence identity between homologous proteins in different species, specific binding can include a polypeptide or molecule that recognizes a protein or target in more than one species. Likewise, because of homology within certain regions of polypeptide sequences of different proteins, specific binding can include a polypeptide or molecule that recognizes more than one protein or target. It is understood that, in some embodiments, a polypeptide or molecule that specifically binds a first target may or may not specifically bind a second target. As such, "specific binding" does not necessarily require (although it can include) exclusive binding, *e.g.*, binding to a single target. Thus, a polypeptide or molecule can, in some embodiments, specifically bind more than one target. In some embodiments, multiple targets can be bound by the same antigen-binding site on the polypeptide or molecule. For example, an antibody can, in certain instances, comprise two identical antigen-binding sites, each of which specifically binds the same epitope on two or more proteins. In certain alternative embodiments, an antibody can be bispecific and comprise at least two antigen-binding sites with differing specificities. Generally, but not necessarily, reference to "binding" means "specific binding".

[0046] "Binding affinity" generally refers to the strength of the sum total of noncovalent interactions between a single binding site of a molecule (e.g., a binding agent such as an antibody) and its binding partner (e.g., an antigen such as NKG2A). Unless indicated

otherwise, as used herein, "binding affinity" refers to intrinsic binding affinity which reflects a 1:1 interaction between members of a binding pair (e.g., antibody and antigen). The affinity of a binding molecule X for its binding partner Y can generally be represented by the dissociation constant (K_D). Affinity can be measured by common methods known in the art, including those described herein. Low-affinity antibodies generally bind antigen slowly and tend to dissociate readily, whereas high-affinity antibodies generally bind antigen faster and tend to remain bound longer. A variety of methods of measuring binding affinity are known in the art, any of which can be used for purposes of the present disclosure. In one embodiment, the "K_D" or "K_D value" may be measured by biolayer interferometry (BLI) using, for example, the OctetQK384 system (ForteBio, Menlo Park, CA). Alternatively, the K_D may also be measured in a radiolabeled antigen-binding assay (RIA), for example, performed with the Fab version of an antibody of interest and its antigen (Chen, et al., (1999) J. Mol Biol 293:865-881) or using surface plasmon resonance (SPR) assays by BIACORE™, using, for example, a BIACORE™-2000 or a BIACORE™-3000 (BIACORE™, Inc., Piscataway, NJ). An "on-rate" or "rate of association" or "association rate" or "k_{on}," as well as an "off-rate" or "rate of dissociation" or "dissociation rate" or "k_{off}," can also be determined with the same SPR or BLI techniques described above using, for example, the OctetQK384 system (ForteBio, Menlo Park, CA) or a BIACORE™-2000 or a BIACORE™-3000 (BIACORE™, Inc., Piscataway, NJ), respectively.

[0047] The term "Fc region" herein is used to define a C-terminal region of an immunoglobulin heavy chain, including, for example, native sequence Fc regions, recombinant Fc regions, and variant Fc regions. Although the boundaries of the Fc region of an immunoglobulin heavy chain might vary, the human IgG heavy chain Fc region is often defined to stretch from an amino acid residue at position Cys226 (according to the EU numbering system), or from Pro230 (according to the EU numbering system), to the carboxyl-terminus thereof. The C-terminal lysine (residue 447 according to the EU numbering system) of the Fc region may be removed, for example, during production or purification of the antibody, or by recombinantly engineering the nucleic acid encoding a heavy chain of the antibody.

[0048] As used herein, the term "heavy chain" when used in reference to an antibody refers to a polypeptide chain of about 50-70 kDa, wherein the amino-terminal portion includes a variable region of about 120 to 130 or more amino acids, and a carboxy-terminal portion includes one or more constant regions. The "heavy chain" can refer to any distinct types, *e.g.*, for example, alpha (α), delta (δ), epsilon (ε), gamma (γ) and mu (μ), based on the amino

acid sequence of the constant domain, which give rise to IgA, IgD, IgE, IgG and IgM classes of antibodies, respectively, including subclasses of IgG, *e.g.*, IgG1, IgG2, IgG3 and IgG4.

[0049] As used herein, the term "light chain" when used in reference to an antibody can refer to a polypeptide chain of about 25 kDa, wherein the amino-terminal portion includes a variable region of about 100 to about 110 or more amino acids, and a carboxy-terminal portion includes a constant region. The approximate length of a light chain is 211 to 217 amino acids. There are two distinct types, *e.g.*, kappa (κ) or lambda (λ) based on the amino acid sequence of the constant domains. Light chain amino acid sequences are well known in the art.

[0050] The terms "antigen-binding fragment," "antigen-binding domain," "antigen-binding region," "antigen-binding part," and similar terms refer to that portion of an antibody, which comprises the amino acid residues that interact with an antigen and confer on the binding fragment, domain, region, or part its specificity and affinity for the antigen (*e.g.*, the CDRs). "Antigen-binding fragment" as used herein includes "antibody fragment," which comprises a portion of an antibody including one or more CDRs, such as the antigen-binding or variable region of the antibody.

[0051] A universal numbering system has been developed and widely adopted, ImMunoGeneTics (IMGT®) Information System (Lefranc *et al.*, Dev. Comp. Immunol. 27(1):55-77 (2003)). IMGT is an integrated information system specializing in immunoglobulins (IG), T cell receptors (TR) and major histocompatibility complex (MHC) of human and other vertebrates. Herein, the CDRs are referred to in terms of both the amino acid sequence and the location within the light or heavy chain. As the "location" of the CDRs within the structure of the immunoglobulin variable domain is conserved between species and present in structures called loops, by using numbering systems that align variable domain sequences according to structural features, CDR and framework residues and are readily identified. This information can be used in grafting and replacement of CDR residues from immunoglobulins of one species into an acceptor framework from, typically, a human antibody. An additional numbering system (AHon) has been developed by Honegger and Plückthun, *J. Mol. Biol.* 309: 657-670 (2001). Correspondence between the numbering system, including, for example, the Kabat numbering and the IMGT unique numbering system, is well known to one skilled in the art (see, *e.g.,* Kabat, *supra*; Chothia and Lesk, *supra*; Martin, *supra*; Lefranc *et al.*, *supra*) and is also illustrated below. Various systems known in the art or described herein represent different ways of delineating CDRs, and when they are used to define the same antibody, they are often considered equivalent. An

Exemplary system, shown herein, combines Kabat and Chothia. The residues from each of these hypervariable regions or CDRs are exemplified in Table 1 below.

Table 1: Exemplary CDRs according to various numbering systems

	Exemplary	IMGT	Kabat	AbM	Chothia	Contact
V_H CDR1	26-35	27-38	31-35	26-35	26-32	30-35
V_H CDR2	50-65	56-65	50-65	50-58	53-55	47-58
V_H CDR3	95-102	105-117	95-102	95-102	96-101	93-101
V_L CDR1	24-34	27-38	24-34	24-34	26-32	30-36
V_L CDR2	50-56	56-65	50-56	50-56	50-52	46-55
V_L CDR3	89-97	105-117	89-97	89-97	91-96	89-96

[0052] Hypervariable regions may comprise "extended hypervariable regions" as follows: 24-36 or 24-34 (L1), 46-56 or 50-56 (L2) and 89-97 or 89-96 (L3) in the VL and 26-35 or 26-35A (H1), 50-65 or 49-65 (H2) and 93-102, 94-102, or 95-102 (H3) in the VH. As used herein, the terms "hypervariable region," "HVR," "HV," "complementarity determining region," or "CDR" are used interchangeably.

[0053] As used herein "multiple myeloma" refers to hematological conditions characterized by malignant plasma cells and includes the following disorders: monoclonal gammopathy of undetermined significance (MGUS); relapsed, refractory or resistant multiple myeloma; low risk, intermediate risk, and high risk multiple myeloma; newly diagnosed multiple myeloma (including low risk, intermediate risk, and high risk newly diagnosed multiple myeloma); transplant eligible and transplant ineligible multiple myeloma; smoldering (indolent) multiple myeloma (including low risk, intermediate risk, and high risk smouldering multiple myeloma); active multiple myeloma; solitary plasmacytoma; extramedullary plasmacytoma; plasma cell leukemia; central nervous system multiple myeloma; light chain myeloma; non-secretory myeloma; Immunoglobulin D myeloma; and Immunoglobulin E myeloma; and multiple myeloma characterized by genetic abnormalities, such as Cyclin D translocations (for example, t(11;14)(q13;q32); t(6;14)(p21;32); t(12;14)(p13;q32); or t(6;20);); MMSET translocations (for example, t(4;14)(p16;q32)); MAF translocations (for example, t(14;16)(q32;q32); t(20;22); t(16; 22)(q11;q13); or t(14;20)(q32;q11)); or other chromosome factors (for example, deletion of 17p13, or chromosome 13; del(17/17p), nonhyperdiploidy, and gain(1q)).

[0054] As used herein, and unless otherwise specified, the term "subject" or "patient" refers to an animal, including, but not limited to, a mammal, including a primate (*e.g.*, human), cow, sheep, goat, horse, dog, cat, rabbit, rat, or mouse. The terms "subject" and

"patient" are used interchangeably herein in reference, for example, to a mammalian subject, such as a human subject.

[0055] As used herein, and unless otherwise specified, the terms "treat," "treating" and "treatment" refer to the eradication or amelioration of a disease or disorder, or of one or more symptoms associated with the disease or disorder. In certain embodiments, the terms refer to minimizing the spread or worsening of the disease or disorder resulting from the administration of one or more prophylactic or therapeutic agents to a patient with such a disease or disorder. In some embodiments, the terms refer to the administration of the compounds provided herein, with or without other additional active agent, after the onset of symptoms of the particular disease.

[0056] As used herein, and unless otherwise specified, the terms "prevent," "preventing" and "prevention" refer to the prevention of the onset, recurrence or spread of a disease or disorder, or of one or more symptoms thereof. In certain embodiments, the terms refer to the treatment with or administration of the compounds provided herein, with or without other additional active compound, prior to the onset of symptoms, particularly to patients at risk of diseases or disorders provided herein. The terms encompass the inhibition or reduction of a symptom of the particular disease. Patients with familial history of a disease in particular are candidates for preventive regimens in certain embodiments. In addition, patients who have a history of recurring symptoms are also potential candidates for the prevention. In this regard, the term "prevention" may be interchangeably used with the term "prophylactic treatment."

[0057] As used herein, and unless otherwise specified, the terms "manage," "managing" and "management" refer to preventing or slowing the progression, spread or worsening of a disease or disorder, or of one or more symptoms thereof. Often, the beneficial effects that a patient derives from a prophylactic and/or therapeutic agent do not result in a cure of the disease or disorder. In this regard, the term "managing" encompasses treating a patient who had suffered from the particular disease in an attempt to prevent or minimize the recurrence of the disease, or lengthening the time during which the disease remains in remission.

[0058] As used herein, and unless otherwise specified, a "therapeutically effective amount" of a compound or an antibody is an amount sufficient to provide a therapeutic benefit in the treatment or management of a disease or disorder, or to delay or minimize one or more symptoms associated with the disease or disorder. A therapeutically effective amount of a compound or an antibody means an amount of therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment or management of the disease or disorder. The term "therapeutically effective amount" can encompass an

amount that improves overall therapy, reduces or avoids symptoms or causes of disease or disorder, or enhances the therapeutic efficacy of another therapeutic agent.

[0059] Combination therapy or "in combination with" refer to the use of more than one therapeutic agent to treat a particular disorder or condition. By "in combination with," it is not intended to imply that the therapeutic agents must be administered at the same time and/or formulated for delivery together, although these methods of delivery are within the scope of this disclosure. A therapeutic agent can be administered concurrently with, prior to (*e.g.*, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, 12 weeks, or 16 weeks before), or subsequent to (*e.g.*, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, 12 weeks, or 16 weeks after), one or more other additional agents. The therapeutic agents in a combination therapy can also be administered on an alternating dosing schedule, with or without a resting period (*e.g.*, no therapeutic agent is administered on certain days of the schedule). The administration of a therapeutic agent "in combination with" another therapeutic agent includes, but is not limited to, sequential administration and concomitant administration of the two agents. In general, each therapeutic agent is administered at a dose and/or on a time schedule determined for that particular agent.

[0060] As used herein, and unless otherwise specified, a "prophylactically effective amount" of a compound or an antibody is an amount sufficient to prevent a disease or disorder, or prevent its recurrence. A prophylactically effective amount of a compound or an antibody means an amount of therapeutic agent, alone or in combination with other agents, which provides a prophylactic benefit in the prevention of the disease. The term "prophylactically effective amount" can encompass an amount that improves overall prophylaxis or enhances the prophylactic efficacy of another prophylactic agent.

[0061] As used herein, and unless otherwise specified, the term "pharmaceutically acceptable carrier," "pharmaceutically acceptable excipient," "physiologically acceptable carrier," or "physiologically acceptable excipient" refers to a pharmaceutically-acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, excipient, solvent, or encapsulating material. In one embodiment, each component is "pharmaceutically acceptable" in the sense of being compatible with the other ingredients of a pharmaceutical formulation, and suitable for use in contact with the tissue or organ of humans and animals without excessive toxicity, irritation, allergic response, immunogenicity, or other problems or

complications, commensurate with a reasonable benefit/risk ratio. S*ee, Remington: The Science and Practice of Pharmacy*, 21st Edition; Lippincott Williams & Wilkins: Philadelphia, PA, 2005; *Handbook of Pharmaceutical Excipients*, 5th Edition; Rowe *et al.*, Eds., The Pharmaceutical Press and the American Pharmaceutical Association: 2005; and *Handbook of Pharmaceutical Additives*, 3rd Edition; Ash and Ash Eds., Gower Publishing Company: 2007; *Pharmaceutical Preformulation and Formulation*, Gibson Ed., CRC Press LLC: Boca Raton, FL, 2004).

[0062] As used herein, and unless otherwise specified, the term "relapsed" refers to the return of a disease after a period of improvement. In certain embodiments, the term "relapsed" refers to a situation where a subject or a mammal, which has had a remission of cancer after therapy has a return of cancer cells. As used herein, and unless otherwise specified, the term "refractory" or "resistant" refers to a disease or condition that does not respond to treatment. In certain embodiments, the term "refractory" or "resistant" refers to a circumstance where a subject or a mammal, even after intensive treatment, has residual cancer cells in his body.

[0063] As used herein, "induction therapy" refers to the first treatment given for a disease, or the first treatment given with the intent of inducing complete remission in a disease, such as cancer. When used by itself, induction therapy is the one accepted as the best available treatment. If residual cancer is detected, patients are treated with another therapy, termed reinduction. If the patient is in complete remission after induction therapy, then additional consolidation and/or maintenance therapy is given to prolong remission or to potentially cure the patient.

[0064] As used herein, "consolidation therapy" refers to the treatment given for a disease after remission is first achieved. For example, consolidation therapy for cancer is the treatment given after the cancer has disappeared after initial therapy. Consolidation therapy may include radiation therapy, stem cell transplant, or treatment with cancer drug therapy. Consolidation therapy is also referred to as intensification therapy and post-remission therapy.

[0065] As used herein, "maintenance therapy" refers to the treatment given for a disease after remission or best response is achieved, in order to prevent or delay relapse. Maintenance therapy can include chemotherapy, hormone therapy or targeted therapy.

[0066] As used herein, and unless otherwise specified, an "effective patient tumor response" refers to any increase in the therapeutic benefit to the patient. An "effective patient

tumor response" can be, for example, a 5%, 10%, 25%, 50%, or 100% decrease in the rate of progress of the tumor. An "effective patient tumor response" can be, for example, a 5%, 10%, 25%, 50%, or 100% decrease in the physical symptoms of a cancer. An "effective patient tumor response" can also be, for example, a 5%, 10%, 25%, 50%, 100%, 200%, or more increase in the response of the patient, as measured by any suitable means, such as gene expression, cell counts, assay results, etc.

[0067] As used herein, and unless otherwise specified, the term "likelihood" generally refers to an increase in the probability of an event. The term "likelihood" when used in reference to the effectiveness of a patient tumor response generally contemplates an increased probability that the rate of tumor progress or tumor cell growth will decrease. The term "likelihood" when used in reference to the effectiveness of a patient tumor response can also generally mean the increase of indicators, such as mRNA or protein expression, that may evidence an increase in the progress in treating the tumor.

[0068] As used herein, and unless otherwise specified, the term "predict" generally means to determine or tell in advance. When used to "predict" the effectiveness of a cancer treatment, for example, the term "predict" can mean that the likelihood of the outcome of the cancer treatment can be determined at the outset, before the treatment has begun, or before the treatment period has progressed substantially.

[0069] As used herein, and unless otherwise specified, the term "monitor," as used herein, generally refers to the overseeing, supervision, regulation, watching, tracking, or surveillance of an activity. For example, the term "monitoring the effectiveness of a compound" refers to tracking the effectiveness in treating a cancer in a patient or in a tumor cell culture. Similarly, the "monitoring," when used in connection with patient compliance, either individually, or in a clinical trial, refers to the tracking or confirming that the patient is actually taking the immunomodulatory compound being tested as prescribed. The monitoring can be performed, for example, by following the expression of mRNA or protein biomarkers.

[0070] An improvement in the cancer or cancer-related disease can be characterized as a complete or partial response. "Complete response" refers to an absence of clinically detectable disease with normalization of any previously abnormal radiographic studies, bone marrow, and cerebrospinal fluid (CSF) or abnormal monoclonal protein measurements. "Partial response" refers to at least about a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% decrease in all measurable tumor burden (*i.e.*, the number of malignant cells present in the subject, or the measured bulk of tumor masses or the quantity of abnormal monoclonal protein) in the absence of new lesions. The term "treatment" contemplates both a complete

and a partial response.

[0071] As used herein, and unless otherwise specified, the term "drug resistance" refers to the condition when a disease does not respond to the treatment of a drug or drugs. Drug resistance can be either intrinsic, which means the disease has never been responsive to the drug or drugs, or it can be acquired, which means the disease ceases responding to a drug or drugs that the disease had previously responded to. In certain embodiments, drug resistance is intrinsic. In certain embodiments, the drug resistance is acquired.

[0072] As used herein, and unless otherwise specified, the term "sensitivity" and "sensitive" when made in reference to treatment with compound is a relative term which refers to the degree of effectiveness of the compound in lessening or decreasing the progress of a tumor or the disease being treated. For example, the term "increased sensitivity" when used in reference to treatment of a cell or tumor in connection with a compound refers to an increase of, at least a 5%, or more, in the effectiveness of the tumor treatment.

[0073] As used herein, and unless otherwise specified, the terms "determining", "measuring", "evaluating", "assessing" and "assaying" as used herein generally refer to any form of measurement, and include determining if an element is present or not. These terms include both quantitative and/or qualitative determinations. Assessing may be relative or absolute. "Assessing the presence of" can include determining the amount of something present, as well as determining whether it is present or absent.

[0074] As used herein and unless otherwise specified, the term "pharmaceutically acceptable salt" encompasses non-toxic acid and base addition salts of the compound to which the term refers. Acceptable non-toxic acid addition salts include those derived from organic and inorganic acids or bases know in the art, which include, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulphonic acid, acetic acid, tartaric acid, lactic acid, succinic acid, citric acid, malic acid, maleic acid, sorbic acid, aconitic acid, salicylic acid, phthalic acid, embolic acid, enanthic acid, and the like.

[0075] Compounds that are acidic in nature are capable of forming salts with various pharmaceutically acceptable bases. The bases that can be used to prepare pharmaceutically acceptable base addition salts of such acidic compounds are those that form non-toxic base addition salts, *i.e.*, salts containing pharmacologically acceptable cations such as, but not limited to, alkali metal or alkaline earth metal salts and the calcium, magnesium, sodium or potassium salts in particular. Suitable organic bases include, but are not limited to, N,N-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), lysine, and procaine.

CLINICAL STUDY ENDPOINTS

[0076] In the context of a cancer, inhibition may be assessed by inhibition of disease progression, inhibition of tumor growth, reduction of primary tumor, relief of tumor-related symptoms, inhibition of tumor secreted factors, delayed appearance of primary or secondary tumors, slowed development of primary or secondary tumors, decreased occurrence of primary or secondary tumors, slowed or decreased severity of secondary effects of disease, arrested tumor growth and regression of tumors, increased Time To Progression (TTP), increased Progression Free Survival (PFS), increased Overall Survival (OS), among others. OS as used herein means the time from treatment onset until death from any cause. TTP as used herein means the time from treatment onset until tumor progression; TTP does not include deaths. In one embodiment, PFS means the time from treatment onset until tumor progression or death. In one embodiment, PFS means the time from the first dose of compound to the first occurrence of disease progression or death from any cause. In one embodiment, PFS rates will be computed using the Kaplan-Meier estimates. Event-free survival (EFS) means the time from treatment onset until any treatment failure, including disease progression, treatment discontinuation for any reason, or death. In one embodiment, overall response rate (ORR) means the percentage of patients who achieve a response. In one embodiment, ORR means the sum of the percentage of patients who achieve complete and partial responses. In one embodiment, ORR means the percentage of patients whose best response ≥ partial response (PR), according to the IMWG Uniform Response Criteria. In one embodiment, duration of response (DoR) is the time from achieving a response until relapse or disease progression. In one embodiment, DoR is the time from achieving a response ≥ partial response (PR) until relapse or disease progression. In one embodiment, DoR is the time from the first documentation of a response until to the first documentation of progressive disease or death. In one embodiment, DoR is the time from the first documentation of a response ≥ partial response (PR) until to the first documentation of progressive disease or death. In one embodiment, time to response (TTR) means the time from the first dose of compound to the first documentation of a response. In one embodiment, TTR means the time from the first dose of compound to the first documentation of a response ≥ partial response (PR). In the extreme, complete inhibition, is referred to herein as prevention or chemoprevention. In this context, the term "prevention" includes either preventing the onset of clinically evident cancer altogether or preventing the onset of a preclinically evident stage of a cancer. Also intended to be encompassed by this definition is the prevention of transformation into malignant cells or to arrest or reverse the progression of premalignant

cells to malignant cells. This includes prophylactic treatment of those at risk of developing a cancer.

[0077] In the context of multiple myeloma, response may be assessed using the International Myeloma Working Group (IMWG) consensus criteria for response and minimal residual disease assessment (Rajkumar *et al.*, *Blood*, 2011, 117(18):4691-5; Kumar *et al.*, *Lancet Oncol.*, 2016,17(8):e328-e346). The criteria can be summarized as follows (with further details available in *Lancet Oncol.*, 2016,17(8):e328-e346).

	Response Criteria
MWG MRD criteria (requires a complete response as defined below)	
Sustained MRD-negative	MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years)
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Imaging plus MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue
Standard IMWG response criteria	
Stringent complete response	Complete response as defined below plus normal FLC ratio and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio $\leq$4:1 or $\geq$1:2 for κ and λ patients, respectively, after counting $\geq$100 plasma cells)
Complete response	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates
Very good partial response	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or $\geq$90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 h

	Response Criteria
Partial response	≥50% reduction of serum M-protein plus reduction in 24 h urinary M-protein by ≥90% or to <200 mg per 24 h; If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria; If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the size (SPD) of soft tissue plasmacytomas is also required
Minimal response	≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50–89%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size (SPD) of soft tissue plasmacytomas is also required
Stable disease	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease
Progressive disease	Any one or more of the following criteria: Increase of 25% from lowest confirmed response value in one or more of the following criteria: Serum M-protein (absolute increase must be ≥0·5 g/dL); Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL; Urine M-protein (absolute increase must be ≥200 mg/24 h); In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL); In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%); Appearance of a new lesion(s), ≥50% increase from nadir in SPD of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis; ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease

	Response Criteria
Clinical relapse	Clinical relapse requires one or more of the following criteria: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice; Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression); Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥1 cm) increase as measured serially by the SPD of the measurable lesion; Hypercalcaemia (>11 mg/dL); Decrease in haemoglobin of ≥2 g/dL not related to therapy or other non-myeloma-related conditions; Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma; Hyperviscosity related to serum paraprotein
Relapse from complete response (to be used only if the end point is disease-free survival)	Any one or more of the following criteria: Reappearance of serum or urine M-protein by immunofixation or electrophoresis; Development of ≥5% plasma cells in the bone marrow; Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcaemia see above)
Relapse from MRD negative (to be used only if the end point is disease-free survival)	Any one or more of the following criteria: Loss of MRD negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma); Reappearance of serum or urine M-protein by immunofixation or electrophoresis; Development of ≥5% clonal plasma cells in the bone marrow; Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcaemia)

RD= minimal residual disease. NGF= next-generation flow. NGS= next-generation sequencing. FLC= free light chain. M-protein= myeloma protein. SPD= sum of the products of the maximal perpendicular diameters of measured lesions. CRAB features= calcium elevation, renal failure, anaemia, lytic bone lesions. FCM= flow cytometry. SUVmax= maximum standardised uptake value. ^{18}F-FDG PET= ^{18}F-fluorodeoxyglucose PET.

[0078] In certain embodiments, the treatment of multiple myeloma may also be assessed by the International Uniform Response Criteria for Multiple Myeloma (IURC) (*see* Durie BGM, Harousseau J-L, Miguel JS, *et al.* International uniform response criteria for multiple

myeloma. *Leukemia*, 2006; (10) 10: 1-7), using the response and endpoint definitions shown below:

Response Subcategory	**Response Criteria**[a]
sCR	CR as defined below plus Normal FLC ratio and Absence of clonal cells in bone marrow[b] by immunohistochemistry or immunofluorescence[c]
CR	Negative immunofixation on the serum and urine and Disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow[b]
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level <100mg per 24 h
PR	≥50% reduction of serum M-protein and reduction in 24-h urinary M-protein by≥90% or to <200mg per 24 h If the serum and urine M-protein are unmeasurable,[d] a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30% In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required
SD (not recommended for use as an indicator of response; stability of disease is best described by providing the time to progression estimates)	Not meeting criteria for CR, VGPR, PR or progressive disease

Abbreviations: CR, complete response; FLC, free light chain; PR, partial response; SD, stable disease; sCR, stringent complete response; VGPR, very good partial response.

[a] All response categories require two consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.

[b] Confirmation with repeat bone marrow biopsy not needed.

[c] Presence/absence of clonal cells is based upon the κ/λ ratio. An abnormal κ/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of >4:1 or <1:2.

[d] Measurable disease defined by at least one of the following measurements: Bone marrow plasma cells ≥30%; Serum M-protein ≥1 g/dl (≥10 gm/l)[10 g/l]; Urine M-protein ≥200 mg/24 h; Serum FLC assay: Involved FLC level ≥10 mg/dl (≥100 mg/l); provided serum FLC ratio is abnormal.

[0079] As used herein, ECOG status refers to Eastern Cooperative Oncology Group (ECOG) Performance Status (Oken M, *et al* Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5(6):649-655), as shown below:

Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

[0080] In certain embodiments, the primary endpoint is the dose-limiting-toxicities (DLTs). In certain embodiments, adverse events (AEs) is characterized by type, frequency, severity as graded by NCI CTCAE v5.0, timing, seriousness, and relationship to the agents used. In certain embodiments, laboratory abnormalities are characterized by type, frequency, severity (as graded by NCI CTCAE v5.0), and timing. In certain embodiments, AEs (except CRS and ICANS) can be graded by the investigator according to NCI CTCAE v5.0 and coded using MedDRA. In certain embodiments, CRS and ICANS can be assessed according to the ASTCT criteria (Appendix 13) and coded using MedDRA. In certain embodiments, AEs can be presented with and without regard to causality based on the investigator's judgment. In certain embodiments, the frequency of overall toxicity, categorized by toxicity Grades 1 through 5, is described. In certain embodiments, clinical laboratory data is classified by grade according to NCI CTCAE v5.0 and will be analyzed using summary statistics. The worst on-treatment grades during the treatment period is summarized with number and percentage.

[0081] In certain embodiments, Best Overall Response (BOR) is assessed based on reported overall responses (per IMWG response criteria) recorded at evaluation time points from the date of first dose until the first documentation of confirmed PD, death or start of

new anti-cancer therapy, whichever occurs first. Objective response is defined as having a BOR of confirmed sCR, CR, VGPR, or PR.

[0082] In certain embodiments, Objective Response Rate (ORR) is defined as the proportion of participants with an objective response per IMWG response criteria as determined by investigator. Point estimate of ORR will be calculated along with the 2-sided exact 95% CIs using the Clopper-Pearson method.

[0083] In certain embodiments, Complete Response Rate (CRR) is defined as the proportion of participants with a CR/sCR per IMWG response criteria as determined by investigator. Point estimates of CRR is calculated along with the 2-sided exact 95% CIs using the Clopper-Pearson method.

[0084] In certain embodiments, Time to Response (TTR) is defined, for participants with an objective response per IMWG criteria, as the time from the date of first dose to the first documentation of objective response that is subsequently confirmed. TTR is summarized using mean, standard deviation, minimum, median, and maximum.

[0085] In certain embodiments, Duration of Response (DOR) is defined, for participants with an objective response per IMWG criteria, as the time from the first documentation of objective response that is subsequently confirmed, until the first documentation of confirmed PD per IMWG criteria, or death due to any cause, whichever occurs first. DOR can be censored for participants who do not have an event (confirmed PD or death due to any cause), on the date of the last adequate disease assessment before the new anti-cancer therapy for participants who start a new anti-cancer therapy prior to an event, or on the date of the last adequate disease assessment before the 2 or more missing disease assessments for participants with an event after 2 or more missing disease assessments DOR is summarized using Kaplan Meier method and displayed graphically.

[0086] In certain embodiments, Duration of Complete Response (DOCR) is defined, for participants with a CR/sCR per IMWG criteria, as the time from the first documentation of CR/sCR that is subsequently confirmed, until the first documentation of confirmed PD per IMWG criteria, or death due to any cause, whichever occurs first. DOCR is censored for participants who do not have an event (confirmed PD or death due to any cause), on the date of the last adequate disease assessment before the new anti-cancer therapy for participants who start a new anti-cancer therapy prior to an event, or on the date of the last adequate disease assessment before the 2 or more missing disease assessments for participants with an event after 2 or more missing disease assessments. DOCR is summarized using Kaplan Meier method and displayed graphically.

[0087] In certain embodiments, Progression-free Survival (PFS) is defined as the time from the date of first dose until the first documentation of confirmed PD per IMWG criteria or death due to any cause, whichever occurs first. In certain embodiments, PFS is censored as follows: (1) for participants who do not have an event (confirmed PD per IMWG criteria or death due to any cause), censoring occurs on the date of the last adequate disease assessment; (2) for participants who start a new anticancer therapy prior to an event, censoring occurs on the date of the last adequate disease assessment before the new anticancer therapy; (3) for participants with an event after a gap of 2 or more missing disease assessments, censoring occurs on the date of the last adequate disease assessment before the gap; (4) participants who do not have an adequate post-baseline disease assessment are censored on the date of first dose of study intervention unless death occurs on or before the time of the second planned disease assessment (ie, ≤70 days after the date of first dose) in which case the death is considered an event. PFS can be summarized using Kaplan Meier method and displayed graphically.

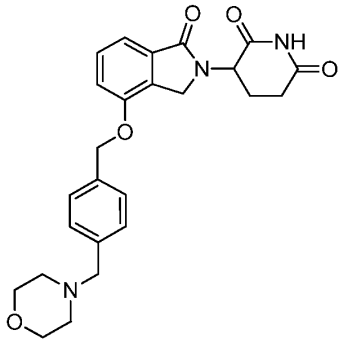
[0088] In certain embodiments, Overall Survival (OS) is defined as the time from the date of first dose until death due to any cause. Survival status is expected to be collected irrespective of study intervention discontinuation or participant's request to discontinue study procedures. All participants who have not withdrawn consent for further participation in the study are followed for survival until the end of this study. OS for participants not known to have died are censored on the date they are last known alive. OS is summarized using Kaplan Meier method and displayed graphically.

[0089] In certain embodiments, MRD Negative Rate is the proportion of participants in the Safety Analysis Set with negative MRD per IMWG sequencing criteria from the date of first dose until the first documentation of confirmed PD, death or start of new anticancer therapy. Point estimates of MRD negativity rate are calculated along with the exact 2-sided 95% CIs using the Clopper-Pearson method.

[0090] In certain embodiments, the methods provided herein are useful for achieving one or more of these clinical trial endpoints in a patient. In certain embodiments, the methods provided herein are useful for improving one or more of these clinical trial endpoints in a patient.

COMPOUND

[0091] In certain embodiments, the compound for use in the compositions and methods provided herein is 3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (Compound A), having the following structure:

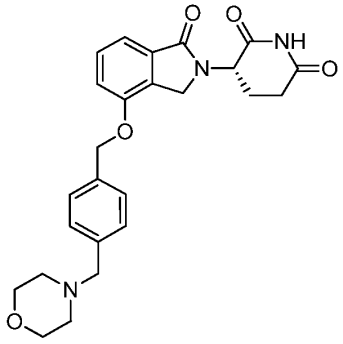


Compound A

or an enantiomer or a mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof.

[0092] In one embodiment, the compound is 3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione. In one embodiment, the compound is a pharmaceutically acceptable salt of Compound A. In one embodiment, the compound is 3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione hydrochloride.

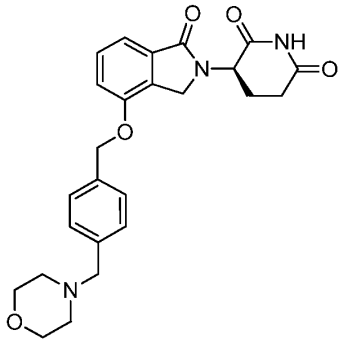
[0093] In one embodiment, the compound is (*S*)-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (Compound A-S), having the following structure:



Compound A-S

[0094] In one embodiment, the compound is a pharmaceutically acceptable salt of Compound A-S. In one embodiment, the compound is a hydrochloride salt of Compound A-S. In one embodiment, the compound is iberdomide (CC-220).

[0095] In one embodiment, the compound is (*R*)-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (Compound A-R), having the following structure:



Compound A-R

[0096] In one embodiment, the compound is a pharmaceutically acceptable salt of Compound A-R. In one embodiment, the compound is (*R*)-3-(4-((4-(morpholinomethyl)benzyl)oxy)-1-oxoisoindolin-2-yl)piperidine-2,6-dione hydrochloride.

[0097] Compound A, A-S, or A-R can be prepared according to the methods described in U.S. Application Publication Nos. US2011-0196150 and US2014-0045843, the entirety of each of which is incorporated herein by reference. The compound can be also synthesized according to other methods apparent to those of skill in the art based upon the teaching of these publications.

[0098] Compounds provided herein markedly inhibit TNF-α, IL-1β, and other inflammatory cytokines in LPS-stimulated hPBMC and human whole blood. TNF-α is an inflammatory cytokine produced by macrophages and monocytes during acute inflammation. TNF-α is responsible for a diverse range of signaling events within cells. TNF-α may play a pathological role in cancer. Without being limited by theory, one of the biological effects exerted by the immunomodulatory compounds provided herein is the reduction of synthesis of TNF-α. The immunomodulatory compounds provided herein enhance the degradation of TNF-α mRNA. The compounds provided herein also potently inhibit IL-1β and stimulate IL-10 under these conditions.

[0099] Further, without being limited by any particular theory, the compounds provided herein are potent co-stimulators of T cells and increase cell proliferation in a dose dependent manner under appropriate conditions.

[00100] In certain embodiments, without being limited by theory, the biological effects exerted by the immunomodulatory compounds provided herein include, but not limited to, anti-angiogenic and immune modulating effects.

[00101] Compound A provided herein contains one chiral center, and can exist as a mixture of enantiomers, *e.g.*, a racemic mixture. This disclosure encompasses the use of

stereomerically pure forms of such a compound, as well as the use of mixtures of those forms. For example, mixtures comprising equal or unequal amounts of the enantiomers of Compound A provided herein may be used in methods and compositions disclosed herein. These isomers may be asymmetrically synthesized or resolved using standard techniques such as chiral columns or chiral resolving agents. *See, e.g.*, Jacques, J., *et al., Enantiomers, Racemates and Resolutions* (Wiley-Interscience, New York, 1981); Wilen, S. H., *et al., Tetrahedron* 33:2725 (1977); Eliel, E. L., *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, S. H., *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN, 1972).

BISPECIFIC ANTIBODY

[00102] In certain embodiments, provided herein for use in the compositions and methods is a bispecific antibody.

Overview

[00103] In certain embodiments, the bispecific antibody is a heterodimeric antibody. In certain embodiments, the bispecific antibody is a chimeric, human or humanized antibody. In certain embodiments, the bispecific antibody is a full length antibody. In certain embodiments, the bispecific antibody is an immunoglobulin (IgG) antibody. In certain embodiments, the bispecific antibody is an immunoglobulin 2 (IgG2) kappa antibody, e.g., immunoglobulin 2-alanine (IgG2Δa) kappa antibody. In certain embodiments, the bispecific antibody comprises an antibody fragment that binds to BCMA and an antibody fragment that binds to CD3. In certain embodiments, the antibody fragment that binds to BCMA or CD3 is selected from Fab, Fab', $F(ab')_2$, Fv, scFv, $(scFv)_2$, single chain antibody molecule, dual variable domain antibody, single variable domain, linear antibody, V region, $F(ab)_2$, Fd, Fc, diabody, di-diabody, disulfide-linked Fvs (dsFv), and single-domain antibody. In certain embodiments, the bispecific antibody is selected from BiTEs®, DART antibodies, diabodies, tandem scFvs and antibody mimetics such as DARPins. In certain embodiments, the bispecific antibody is derived from two monoclonal antibodies (mAbs), an anti-BCMA mAb and an anti-CD3 mAb. In certain embodiments, the anti-BCMA mAb contributes to the first binding part binding to B cell maturation antigen (BCMA) in the bispecific antibody. In certain embodiments, the anti-CD3 mAb contributes to the second binding part binding to CD3 in the bispecific antibody. In certain embodiments, each of these mAbs contributes one distinct heavy (H) chain and one distinct light (L) chain to the bispecific antibody, resulting in four chains in the bispecific antibody. In certain embodiments, the four chains in the

bispecific antibody are covalently linked via five inter-chain disulfide bonds. In certain embodiments, the bispecific antibody leads to targeted T-cell-mediated cytotoxicity follows the binding of an epitope on CD3-expressing T-cells and a second epitope on BCMA-expressing MM cells. In certain embodiments, the bispecific antibody is elranatamab (PF-06863135).

[00104] In certain embodiments, the bispecific antibody comprising a first binding part binding to B cell maturation antigen (BCMA) and a second binding part binding to cluster of differentiation 3 (CD3). In certain embodiments, the bispecific antibody comprising a first binding part binding to human B cell maturation antigen (BCMA) and a second binding part binding to human cluster of differentiation 3 (CD3). In certain embodiments, the bispecific antibody comprises a structure as illustrated in **FIG. 1**. Tables 2 and 3 list the exemplary amino acid sequences of the first binding part binding to B cell maturation antigen (BCMA) and the second binding part binding to cluster of differentiation 3 (CD3).

Table 2: Amino acid sequences of the first binding part binding to BCMA

Method	IMGT	Kabat	Chothia	Extended [Kabat + Chothia]	Contact	AbM
VH CDR1	GFTFSSYP (SEQ ID NO:3)	SYPMS (SEQ ID NO:9)	GFTFSSY (SEQ ID NO:14)	GFTFSSYPMS (SEQ ID NO:16)	SSYPMS (SEQ ID NO:17)	GFTFSSYPMS (SEQ ID NO:16)
VH CDR2	IGGSGGSL (SEQ ID NO:4)	AIGGSGGSLPYADIVKG (SEQ ID NO:10)	GGSGGS (SEQ ID NO:15)	-	WVSAIGGSGGSLP (SEQ ID NO:18)	AIGGSGGSLP (SEQ ID NO:23)
VH CDR3	ARYWPMDI (SEQ ID NO:5)	YWPMDI (SEQ ID NO:11)	YWPMDI (SEQ ID NO:11)	-	ARYWPMD (SEQ ID NO:19)	YWPMDI (SEQ ID NO:11)
VL CDR1	QSVSSSY (SEQ ID NO:6)	RASQSVSSSYLA (SEQ ID NO:12)	RASQSVSSSYLA (SEQ ID NO:12)	-	SSSYLAWY (SEQ ID NO:20)	RASQSVSSSYLA (SEQ ID NO:12)
VL CDR2	DAS (SEQ ID NO:7)	DASIRAT (SEQ ID NO:13)	DASIRAT (SEQ ID NO:13)	-	LLMYDASIRA (SEQ ID NO:21)	DASIRAT (SEQ ID NO:13)
VL CDR3	QQYQSWPLT (SEQ ID NO:8)	QQYQSWPLT (SEQ ID NO:8)	QQYQSWPLT (SEQ ID NO:8)	-	QQYQSWPL (SEQ ID NO:22)	QQYQSWPLT (SEQ ID NO:8)
VH Sequence: EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYPMSWVRQAPGKGLEWVSAIGGSGGSLPYADIVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARYWPMDIWGQGTLVTVSS (SEQ ID NO:1)					

VL Sequence: EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLMYDASIRATGIPDRFSGSGSGTD FTLTISRLEPEDFAVYYCQQYQSWPLTFGQGTKVEIK (SEQ ID NO:2)

Table 3: Amino acid sequences of the first binding part binding to CD3

Method	**IMGT**	**Kabat**	**Chothia**	**Extended [Kabat + Chothia]**	**Contact**	**AbM**
VH CDR1	GFTFSDYY (SEQ ID NO:26)	DYYMT (SEQ ID NO:32)	GFTFSDY (SEQ ID NO:37)	GFTFSDYYMT (SEQ ID NO:39)	SDYYMT (SEQ ID NO:40)	GFTFSD YYMT (SEQ ID NO:39)
VH CDR2	IRNRARGY TS (SEQ ID NO:27)	FIRNRARGYT SDHNPSVKG (SEQ ID NO:33)	RNRARGYT (SEQ ID NO:38)	-	WVAFIRNR ARGYTSD (SEQ ID NO:41)	FIRNRA RGYTSD (SEQ ID NO:46)
VH CDR3	ARDRPSYY VLDY (SEQ ID NO:28)	DRPSYYVLD Y (SEQ ID NO:34)	DRPSYYVLD Y (SEQ ID NO:34)	-	ARDRPSYY VLD (SEQ ID NO:42)	DRPSYY VLDY (SEQ ID NO:34)
VL CDR1	QSLFNVRS RKNY (SEQ ID NO:29)	KSSQSLFNVR SRKNYLA (SEQ ID NO:35)	KSSQSLFNVR SRKNYLA (SEQ ID NO:35)	-	FNVRSRKN YLAWY (SEQ ID NO:43)	KSSQSLF NVRSRK NYLA (SEQ ID NO:35)
VL CDR2	WAS (SEQ ID NO:30)	WASTRES (SEQ ID NO:36)	WASTRES (SEQ ID NO:36)	-	LLISWASTR E (SEQ ID NO:44)	WASTRE S (SEQ ID NO:36)
VL CDR3	KQSYDLFT (SEQ ID NO:31)	KQSYDLFT (SEQ ID NO:31)	KQSYDLFT (SEQ ID NO:31)	-	KQSYDLF (SEQ ID NO:45)	KQSYDL FT (SEQ ID NO:31)
VH Sequence: EVQLVESGGGLVQPGGSLRLSCAASGFTFSDYYMTWVRQAPGKGLEWVAFIRNRARGYTSDHNPSVKG RFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDRPSYYVLDYWGQGTTVTVSS (SEQ ID NO:24)						
VL Sequence: DIVMTQSPDSLAVSLGERATINCKSSQSLFNVRSRKNYLAWYQQKPGQPPKLLISWASTRESGVPDRFSG SGSGTDFTLTISSLQAEDVAVYYCKQSYDLFTFGSGTKLEIK (SEQ ID NO:25)						

First binding part binding to B cell maturation antigen (BCMA)

[00105] In certain embodiments, the first binding part binding to BCMA comprises (i) a VH region comprising a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 9, 14, 16, and 17; a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 10, 15, 18, and 23; and a VH CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 11, and

19; and (ii) a VL region comprising a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 12, and 20; a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 7, 13, and 21; and a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8 and 22. In certain embodiments, the first binding part binding to BCMA comprises a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:3, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:4, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:5; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:6, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:7, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:8. In certain embodiments, the first binding part binding to BCMA comprises a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:9, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:10, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:11; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:12, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:13, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:8. In certain embodiments, the first binding part binding to BCMA comprises a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:14, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:15, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:11; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:12, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:13, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:8. In certain embodiments, the first binding part binding to BCMA comprises a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:16, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:10, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:11; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:12, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:13, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:8. In certain embodiments, the first binding part binding to BCMA comprises a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:17, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:18, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:19; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:20, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:21, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:22. In

certain embodiments, the first binding part binding to BCMA comprises a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:16, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:23, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:11; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:12, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:13, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:8.

[00106] In certain embodiments, the first binding part binding to BCMA comprises a VH region comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:1. In certain embodiments, the first binding part binding to BCMA comprises a VH region comprising an amino acid sequence at least 96% identical to the amino acid sequence of SEQ ID NO:1. In certain embodiments, the first binding part binding to BCMA comprises a VH region comprising an amino acid sequence at least 97% identical to the amino acid sequence of SEQ ID NO:1. In certain embodiments, the first binding part binding to BCMA comprises a VH region comprising an amino acid sequence at least 98% identical to the amino acid sequence of SEQ ID NO:1. In certain embodiments, the first binding part binding to BCMA comprises a VH region comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO:1. In certain embodiments, the first binding part binding to BCMA comprises a VH region comprising the amino acid sequence of SEQ ID NO:1. In certain embodiments, the first binding part binding to BCMA comprises a VL region comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:2. In certain embodiments, the first binding part binding to BCMA comprises a VL region comprising an amino acid sequence at least 96% identical to the amino acid sequence of SEQ ID NO:2. In certain embodiments, the first binding part binding to BCMA comprises a VL region comprising an amino acid sequence at least 97% identical to the amino acid sequence of SEQ ID NO:2. In certain embodiments, the first binding part binding to BCMA comprises a VL region comprising an amino acid sequence at least 98% identical to the amino acid sequence of SEQ ID NO:2. In certain embodiments, the first binding part binding to BCMA comprises a VL region comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO:2. In certain embodiments, the first binding part binding to BCMA comprises a VL region comprising the amino acid sequence of SEQ ID NO:2.

[00107] In certain embodiments, the first binding part binding to BCMA comprises a heavy chain and a light chain (**FIG. 1**). In certain embodiments, the heavy chain of the first binding part binding to BCMA, from N terminus to C terminus, comprises a VH region, a CH1

region, and an Fc region (**FIG. 1**). In certain embodiments, the Fc region comprises a CH2 region and CH3 region (**FIG. 1**). In certain embodiments, the heavy chain of the first binding part binding to BCMA comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:47. In certain embodiments, the heavy chain of the first binding part binding to BCMA comprises an amino acid sequence at least 96% identical to the amino acid sequence of SEQ ID NO:47. In certain embodiments, the heavy chain of the first binding part binding to BCMA comprises an amino acid sequence at least 97% identical to the amino acid sequence of SEQ ID NO:47. In certain embodiments, the heavy chain of the first binding part binding to BCMA comprises an amino acid sequence at least 98% identical to the amino acid sequence of SEQ ID NO:47. In certain embodiments, the heavy chain of the first binding part binding to BCMA comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO:47. In certain embodiments, the heavy chain of the first binding part binding to BCMA comprises the amino acid sequence of SEQ ID NO:47.

Heavy chain of the first binding part binding to BCMA

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYPMSWVRQAPGKGLEWVSAIGGSGG
SLPYADIVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARYWPMDIWGQGTLVT
VSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA
VLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCEVECPECPAP
PVAGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSHEDPEVQFNWYVDGVEVHNAKT
KPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPSSIEKTISKTKGQPREP
QVYTLPPSREEMTKNQVSLTCEVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGS
FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:47)

[00108] In certain embodiments, the light chain of the first binding part binding to BCMA, from N terminus to C terminus, comprises a VL region and a CL region (**FIG. 1**). In certain embodiments, the light chain of the first binding part binding to BCMA comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:48. In certain embodiments, the light chain of the first binding part binding to BCMA comprising an amino acid sequence at least 96% identical to the amino acid sequence of SEQ ID NO:48. In certain embodiments, the light chain of the first binding part binding to BCMA comprising an amino acid sequence at least 97% identical to the amino acid sequence of SEQ ID NO:48. In certain embodiments, the light chain of the first binding part binding to BCMA comprising an amino acid sequence at least 98% identical to the amino acid sequence of SEQ ID NO:48. In certain

embodiments, the light chain of the first binding part binding to BCMA comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO:48. In certain embodiments, the light chain of the first binding part binding to BCMA comprising the amino acid sequence of SEQ ID NO:48.

Light chain of the first binding part binding to BCMA

[00109] EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLMYDA SIRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYQSWPLTFGQGTKVEIKRTV AAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD SKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:48)

Second binding part binding to cluster of differentiation 3 (CD3)

[00110] In certain embodiments, the second binding part binding to CD3 comprises (i) a VH region comprising a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 26, 32, 37, 39, and 40; a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 27, 33, 38, 41, and 46; and a VH CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 28, 34, and 42; and (ii) a VL region comprising a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 29, 35, and 43; a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 30, 36, and 44; and a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 31 and 45. In certain embodiments, the second binding part binding to CD3 comprises a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:26, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:27, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:28; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:29, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:30, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:31. In certain embodiments, the second binding part binding to CD3 comprises a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:32, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:33, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:34; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:35, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:36, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:31. In certain embodiments, the second binding part binding to CD3 comprises a VH region comprising a VH CDR1 comprising the amino acid sequence of

SEQ ID NO:37, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:38, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:34; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:35, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:36, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:31. In certain embodiments, the second binding part binding to CD3 comprises a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:39, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:33, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:34; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:35, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:36, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:31. In certain embodiments, the second binding part binding to CD3 comprises a region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:40, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:41, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:42; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:43, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:44, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:45. In certain embodiments, the second binding part binding to CD3 comprises a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:39, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:46, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:34; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:35, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:36, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:31.

[00111] In certain embodiments, the second binding part binding to CD3 comprises a VH region comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:24. In certain embodiments, the second binding part binding to CD3 comprises a VH region comprising an amino acid sequence at least 96% identical to the amino acid sequence of SEQ ID NO:24. In certain embodiments, the second binding part binding to CD3 comprises a VH region comprising an amino acid sequence at least 97% identical to the amino acid sequence of SEQ ID NO:24. In certain embodiments, the second binding part binding to CD3 comprises a VH region comprising an amino acid sequence at least 98% identical to the amino acid sequence of SEQ ID NO:24. In certain embodiments, the second binding part binding to CD3 comprises a VH region comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO:24. In certain

embodiments, the second binding part binding to CD3 comprises a VH region comprising the amino acid sequence of SEQ ID NO:24. In certain embodiments, the second binding part binding to CD3 comprises a VL region comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:25. In certain embodiments, the second binding part binding to CD3 comprises a VL region comprising an amino acid sequence at least 96% identical to the amino acid sequence of SEQ ID NO:25. In certain embodiments, the second binding part binding to CD3 comprises a VL region comprising an amino acid sequence at least 97% identical to the amino acid sequence of SEQ ID NO:25. In certain embodiments, the second binding part binding to CD3 comprises a VL region comprising an amino acid sequence at least 98% identical to the amino acid sequence of SEQ ID NO:25. In certain embodiments, the second binding part binding to CD3 comprises a VL region comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO:25. In certain embodiments, the second binding part binding to CD3 comprises a VL region comprising the amino acid sequence of SEQ ID NO:25.

[00112] In certain embodiments, the second binding part binding to CD3 comprises a heavy chain and a light chain (**FIG. 1**). In certain embodiments, the heavy chain of the second binding part binding to CD3, from N terminus to C terminus, comprises a VH region, a CH1 region, and an Fc region (**FIG. 1**). In certain embodiments, the Fc region comprises a CH2 region and CH3 region (**FIG. 1**). In certain embodiments, the heavy chain of the second binding part binding to CD3 comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:49. In certain embodiments, the heavy chain of the second binding part binding to CD3 comprises an amino acid sequence at least 96% identical to the amino acid sequence of SEQ ID NO:49. In certain embodiments, the heavy chain of the second binding part binding to CD3 comprises an amino acid sequence at least 97% identical to the amino acid sequence of SEQ ID NO:49. In certain embodiments, the heavy chain of the second binding part binding to CD3 comprises an amino acid sequence at least 98% identical to the amino acid sequence of SEQ ID NO:49. In certain embodiments, the heavy chain of the second binding part binding to CD3 comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO:49. In certain embodiments, the heavy chain of the second binding part binding to CD3 comprises amino acid sequence of SEQ ID NO:49.

Heavy chain of the second binding part binding to CD3

EVQLVESGGGLVQPGGSLRLSCAASGFTFSDYYMTWVRQAPGKGLEWVAFIRNRAR
GYTSDHNPSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDRPSYYVLDYW

GQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS
GVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCRVR
CPRCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSHEDPEVQFNWYVDGVE
VHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPSSIEKTISKTK
GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPM
LDSDGSFFLYSRLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:49).

[00113] In certain embodiments, the light chain of the second binding part binding to CD3, from N terminus to C terminus, comprises a VL region and a CL region (**FIG. 1**). In certain embodiments, the light chain of the second binding part binding to CD3 comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:50. In certain embodiments, the light chain of the second binding part binding to CD3 comprising an amino acid sequence at least 96% identical to the amino acid sequence of SEQ ID NO:50. In certain embodiments, the light chain of the second binding part binding to CD3 comprising an amino acid sequence at least 97% identical to the amino acid sequence of SEQ ID NO:50. In certain embodiments, the light chain of the second binding part binding to CD3 comprising an amino acid sequence at least 98% identical to the amino acid sequence of SEQ ID NO:50. In certain embodiments, the light chain of the second binding part binding to CD3 comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO:50. In certain embodiments, the light chain of the second binding part binding to CD3 comprising the amino acid sequence of SEQ ID NO:50.

Light chain of the second binding part binding to CD3

DIVMTQSPDSLAVSLGERATINCKSSQSLFNVRSRKNYLAWYQQKPGQPPKLLISWA
STRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCKQSYDLFTFGSGTKLEIKRTV
AAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD
SKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC(SEQ ID NO:50)

[00114] In some embodiments, the heavy chain of the first binding part binding to BCMA may lack the C-terminal lysine residue that is present in SEQ ID NO:47. In some embodiments, the heavy chain of the second binding part binding to CD3 may lack the C-terminal lysine residue that is present in SEQ ID NO:49. In some embodiments, the heavy chain of the first binding part binding to BCMA may lack the C-terminal lysine residue that is present in SEQ ID NO:47 and the heavy chain of the first binding part binding to CD3 may lack the C-terminal lysine residue that is present in SEQ ID NO:49.

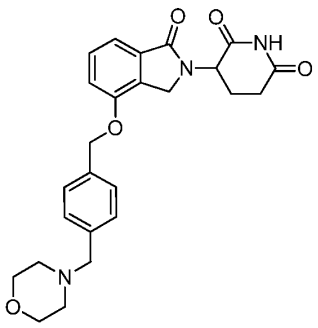
METHODS OF TREATMENT AND COMPOSITION FOR USE IN SUCH METHODS

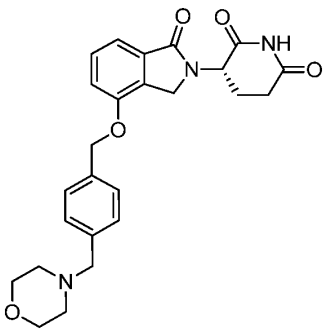
[00115] The compounds provided herein in combination with the bispecific antibody binding to BCMA and to CD3 provided herein can be used in all methods of treatment as provided herein.

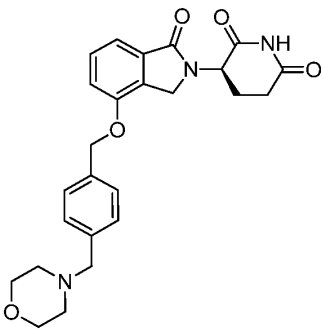
[00116] In certain embodiments, provided herein is a method of treating or managing multiple myeloma, comprising administering to a patient having multiple myeloma (a) a therapeutically effective amount of a compound provided herein in combination with (b) a therapeutically effective amount of a bispecific antibody comprising a first binding part binding to BCMA and a second binding part binding to CD3 provided herein.

Method of treatment

[00117] In certain embodiments, provided herein is a method of treating or managing multiple myeloma, comprising administering to a patient having multiple myeloma:
(a) a therapeutically effective amount of a compound, wherein the compound is Compound A, A-S, or A-R


Compound A


Compound A-S


Compound A-R

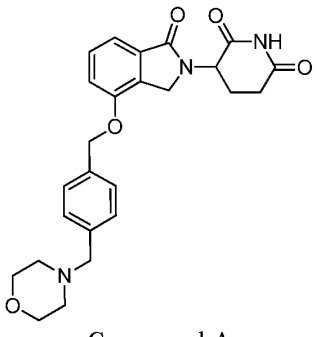
or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof; in combination with (b) a therapeutically effective amount of a bispecific antibody comprising a first binding part binding to BCMA and a second binding part binding to CD3 provided herein.

[00118] In certain embodiments, provided herein is a method of treating or managing multiple myeloma, comprising administering to a patient having multiple myeloma (a) a therapeutically effective amount of a compound provided herein in combination with (b) a therapeutically effective amount of a bispecific antibody comprising a first binding part

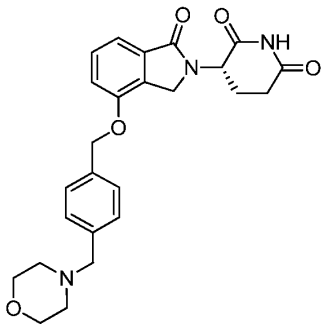
binding to BCMA and a second binding part binding to CD3, wherein the first binding part binding to BCMA comprises (i) a VH region comprising a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 9, 14, 16, and 17; a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 10, 15, 18, and 23; and a VH CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 11, and 19; and (ii) a VL region comprising a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 12, and 20; a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 7, 13, and 21; and a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8 and 22; and wherein the second binding part binding to CD3 comprises (i) a VH region comprising a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 26, 32, 37, 39, and 40; a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 27, 33, 38, 41, and 46; and a VH CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 28, 34, and 42; and (ii) a VL region comprising a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 29, 35, and 43; a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 30, 36, and 44; and a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 31 and 45.

[00119] In certain embodiments, provided herein is a method of treating or managing multiple myeloma, comprising administering to a patient having multiple myeloma:

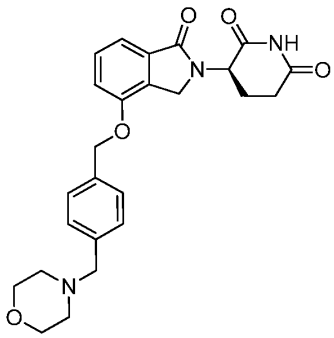
(a) a therapeutically effective amount of a compound, wherein the compound is Compound A, A-S, or A-R



Compound A



Compound A-S



Compound A-R

or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically

acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof; in combination with

(b) a therapeutically effective amount of a bispecific antibody comprising a first binding part binding to B cell maturation antigen (BCMA) and a second binding part binding to cluster of differentiation 3 (CD3),

wherein the first binding part binding to BCMA comprises (i) a VH region comprising a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 9, 14, 16, and 17; a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 10, 15, 18, and 23; and a VH CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 11, and 19; and (ii) a VL region comprising a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 12, and 20; a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 7, 13, and 21; and a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8 and 22; and

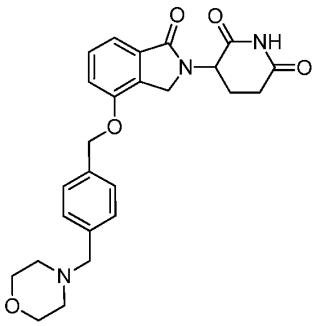
wherein the second binding part binding to CD3 comprises (i) a VH region comprising a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 26, 32, 37, 39, and 40; a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 27, 33, 38, 41, and 46; and a VH CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 28, 34, and 42; and (ii) a VL region comprising a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 29, 35, and 43; a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 30, 36, and 44; and a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 31 and 45.

Compound for use

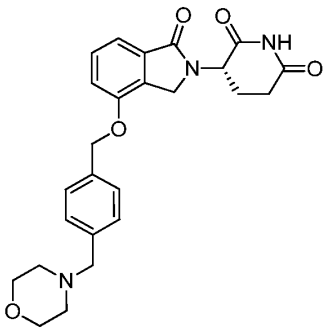
[00120] In certain embodiments, provided herein is a compound for use in a method of treating multiple myeloma, wherein the compound is a compound provided herein, and wherein the method comprises administering to a patient having multiple myeloma (a) a therapeutically effective amount of the compound provided herein in combination with (b) a therapeutically effective amount of a bispecific antibody comprising a first binding part binding to BCMA and a second binding part binding to CD3 provided herein.

[00121] In certain embodiments, provided herein is a compound for use in a method of treating multiple myeloma, wherein the method comprises administering to a patient having multiple myeloma (a) a therapeutically effective amount of the compound, wherein the

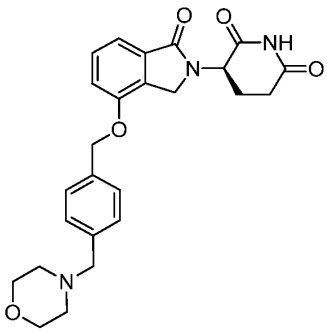
compound is Compound A, A-S, or A-R



Compound A



Compound A-S



Compound A-R

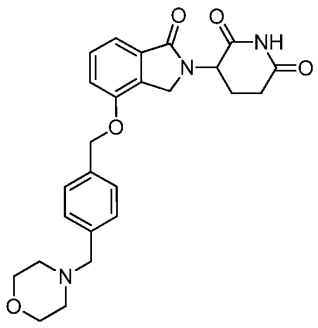
or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof; in combination with (b) a therapeutically effective amount of a bispecific antibody comprising a first binding part binding to BCMA and a second binding part binding to CD3 provided herein.

[00122] In certain embodiments, provided herein is a compound for use in a method of treating multiple myeloma, wherein the compound is a compound provided herein, and wherein the method comprises administering to a patient having multiple myeloma (a) a therapeutically effective amount of the compound provided herein in combination with (b) a therapeutically effective amount of a bispecific antibody comprising a first binding part binding to BCMA and a second binding part binding to CD3, wherein the first binding part binding to BCMA comprises (i) a VH region comprising a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 9, 14, 16, and 17; a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 10, 15, 18, and 23; and a VH CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 11, and 19; and (ii) a VL region comprising a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 12, and 20; a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 7, 13, and 21; and a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8 and 22; and wherein the second binding part binding to CD3 comprises (i) a VH region comprising a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 26, 32, 37, 39, and 40; a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 27, 33, 38, 41, and 46; and a VH CDR3 having an amino acid sequence selected from the group

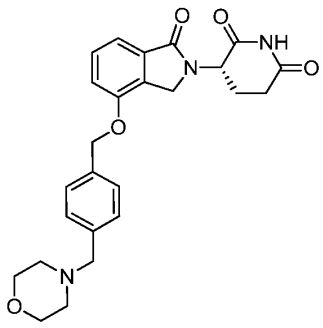
consisting of SEQ ID NOs: 28, 34, and 42; and (ii) a VL region comprising a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 29, 35, and 43; a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 30, 36, and 44; and a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 31 and 45.

[00123] In certain embodiments, provided herein is a compound for use in a method of treating multiple myeloma, wherein the method comprises administering to a patient having multiple myeloma:

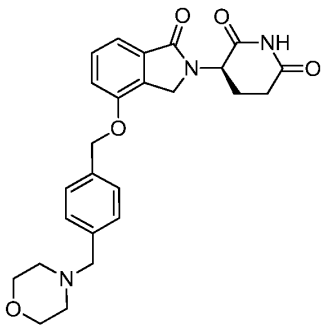
(a) a therapeutically effective amount of the compound, wherein the compound is Compound A, A-S, or A-R



Compound A



Compound A-S



Compound A-R

or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof; in combination with

(b) a therapeutically effective amount of a bispecific antibody comprising a first binding part binding to B cell maturation antigen (BCMA) and a second binding part binding to cluster of differentiation 3 (CD3),

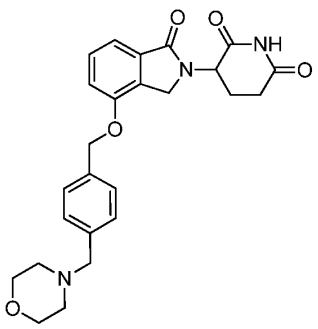
wherein the first binding part binding to BCMA comprises (i) a VH region comprising a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 9, 14, 16, and 17; a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 10, 15, 18, and 23; and a VH CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 11, and 19; and (ii) a VL region comprising a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 12, and 20; a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 7, 13, and 21; and a VL CDR3 having an

amino acid sequence selected from the group consisting of SEQ ID NOs: 8 and 22; and wherein the second binding part binding to CD3 comprises (i) a VH region comprising a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 26, 32, 37, 39, and 40; a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 27, 33, 38, 41, and 46; and a VH CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 28, 34, and 42; and (ii) a VL region comprising a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 29, 35, and 43; a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 30, 36, and 44; and a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 31 and 45.

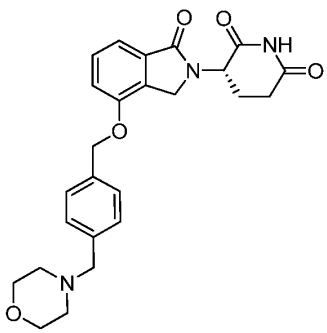
Bispecific antibody for use

[00124] In certain embodiments, provided herein is a bispecific antibody for use in a method of treating multiple myeloma, wherein the method comprises administering to a patient having multiple myeloma (a) a therapeutically effective amount of the bispecific antibody, wherein the bispecific antibody comprises a first binding part binding to BCMA and a second binding part binding to CD3 provided herein; in combination with (b) a therapeutically effective amount of a compound provided herein.

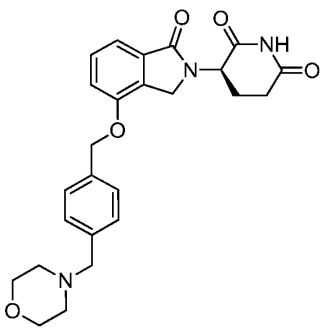
[00125] In certain embodiments, provided herein is a bispecific antibody for use in a method of treating multiple myeloma, wherein the method comprises administering to a patient having multiple myeloma (a) a therapeutic effective amount of the bispecific antibody, wherein the bispecific antibody comprises a first binding part binding to BCMA and a second binding part binding to CD3 provided herein; in combination with (b) a therapeutically effective amount of a compound, wherein the compound is Compound A, A-S, or A-R



Compound A



Compound A-S



Compound A-R

or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically

acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof.

[00126] In certain embodiments, provided herein is a bispecific antibody for use in a method of treating multiple myeloma, wherein the method comprises administering to a patient having multiple myeloma (a) a therapeutically effective amount of the bispecific antibody that comprises a first binding part binding to BCMA and a second binding part binding to CD3, wherein the first binding part binding to BCMA comprises (i) a VH region comprising a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 9, 14, 16, and 17; a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 10, 15, 18, and 23; and a VH CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 11, and 19; and (ii) a VL region comprising a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 12, and 20; a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 7, 13, and 21; and a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8 and 22; and wherein the second binding part binding to CD3 comprises (i) a VH region comprising a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 26, 32, 37, 39, and 40; a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 27, 33, 38, 41, and 46; and a VH CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 28, 34, and 42; and (ii) a VL region comprising a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 29, 35, and 43; a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 30, 36, and 44; and a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 31 and 45; in combination with (b) a therapeutically effective amount of a compound provided herein.

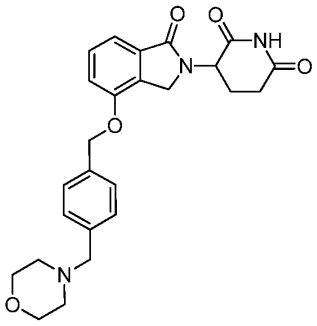
[00127] In certain embodiments, provided herein is a bispecific antibody for use in a method of treating multiple myeloma, wherein the method comprises administering to a patient having multiple myeloma:

(a) a therapeutically effective amount of the bispecific antibody, where the bispecific antibody comprises a first binding part binding to B cell maturation antigen (BCMA) and a second binding part binding to cluster of differentiation 3 (CD3); wherein the first binding part binding to BCMA comprises (i) a VH region comprising a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 9, 14, 16, and 17; a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 10, 15, 18, and 23; and a VH CDR3 having an amino acid sequence selected from the group

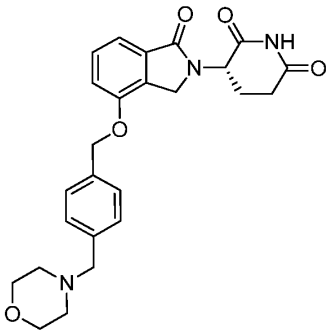
consisting of SEQ ID NOs: 5, 11, and 19; and (ii) a VL region comprising a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 12, and 20; a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 7, 13, and 21; and a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8 and 22; and

wherein the second binding part binding to CD3 comprises (i) a VH region comprising a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 26, 32, 37, 39, and 40; a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 27, 33, 38, 41, and 46; and a VH CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 28, 34, and 42; and (ii) a VL region comprising a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 29, 35, and 43; a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 30, 36, and 44; and a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 31 and 45;

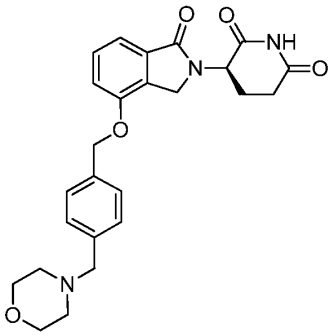
in combination with (b) a therapeutically effective amount of a compound, wherein the compound is Compound A, A-S, or A-R



Compound A



Compound A-S



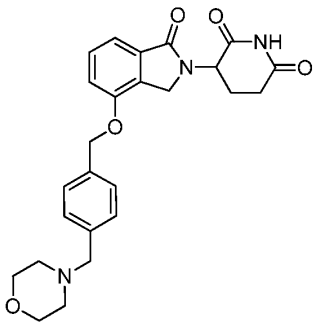
Compound A-R

or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof.

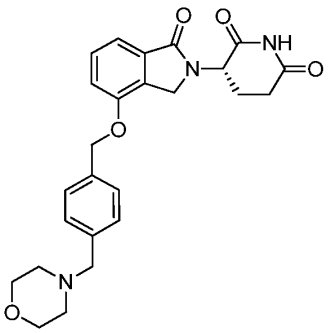
Compound and bispecific antibody for use

[00128] In certain embodiments, provided herein is a compound and a bispecific antibody for use in a method of treating multiple myeloma, wherein the method comprises administering to a patient having multiple myeloma (a) a therapeutically effective amount of the compound (e.g., a compound provided herein) in combination with (b) a therapeutically effective amount of the bispecific antibody (e.g., a bispecific antibody provided herein).

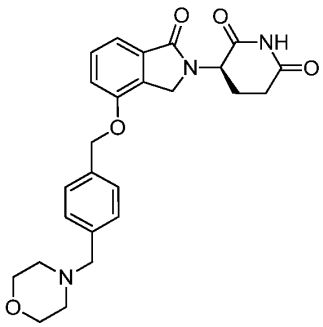
[00129] In certain embodiments, provided herein is a compound and a bispecific antibody for use in a method of treating multiple myeloma, wherein the method comprises administering to a patient having multiple myeloma (a) a therapeutically effective amount of the compound, wherein the compound is Compound A, A-S, or A-R



Compound A



Compound A-S



Compound A-R

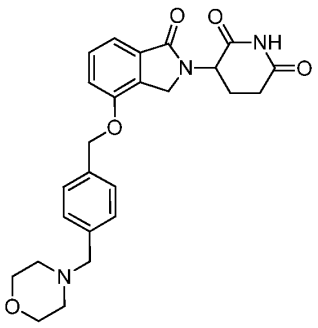
or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof; in combination with (b) a therapeutically effective amount of the bispecific antibody, wherein the bispecific antibody comprises a first binding part binding to BCMA and a second binding part binding to CD3 provided herein.

[00130] In certain embodiments, provided herein is a compound and a bispecific antibody for use in a method of treating multiple myeloma, wherein the method comprises administering to a patient having multiple myeloma (a) a therapeutically effective amount of the compound in combination with (b) a therapeutically effective amount of the bispecific antibody that comprises a first binding part binding to BCMA and a second binding part binding to CD3, wherein the first binding part binding to BCMA comprises (i) a VH region comprising a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 9, 14, 16, and 17; a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 10, 15, 18, and 23; and a VH CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 11, and 19; and (ii) a VL region comprising a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 12, and 20; a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 7, 13, and 21; and a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8 and 22; and wherein the second binding part binding to CD3 comprises (i) a VH region comprising a VH

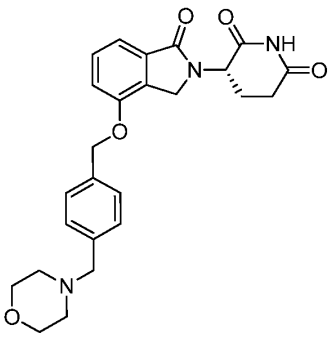
CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 26, 32, 37, 39, and 40; a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 27, 33, 38, 41, and 46; and a VH CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 28, 34, and 42; and (ii) a VL region comprising a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 29, 35, and 43; a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 30, 36, and 44; and a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 31 and 45.

[00131] In certain embodiments, provided herein is a compound and a bispecific antibody for use in a method of treating multiple myeloma, wherein the method comprises administering to a patient having multiple myeloma:

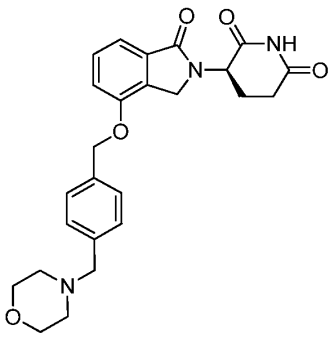
(a) a therapeutically effective amount of the compound, wherein the compound is Compound A, A-S, or A-R



Compound A



Compound A-S



Compound A-R

or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof; in combination with

(b) a therapeutically effective amount of the bispecific antibody comprising a first binding part binding to B cell maturation antigen (BCMA) and a second binding part binding to cluster of differentiation 3 (CD3),

wherein the first binding part binding to BCMA comprises (i) a VH region comprising a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 9, 14, 16, and 17; a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 10, 15, 18, and 23; and a VH CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 11, and 19; and (ii) a VL

region comprising a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 12, and 20; a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 7, 13, and 21; and a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8 and 22; and wherein the second binding part binding to CD3 comprises (i) a VH region comprising a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 26, 32, 37, 39, and 40; a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 27, 33, 38, 41, and 46; and a VH CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 28, 34, and 42; and (ii) a VL region comprising a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 29, 35, and 43; a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 30, 36, and 44; and a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 31 and 45.

Multiple myeloma

[00132] In certain embodiments, the multiple myeloma is smoldering myeloma, indolent myeloma, active multiple myeloma, extramedullary plasmacytoma, solitary plasmacytoma of the bone, light chain myeloma, or non-secretory myeloma. In some embodiments, provided herein are methods for the treatment or management of smoldering myeloma, indolent myeloma, active multiple myeloma, extramedullary plasmacytoma, solitary plasmacytoma of the bone, light chain myeloma, or non-secretory myeloma.

[00133] In certain embodiments, the multiple myeloma is relapsed, refractory or resistant multiple myeloma. In certain embodiments, the multiple myeloma is relapsed and refractory multiple myeloma. In certain embodiments, the multiple myeloma is relapsed or refractory multiple myeloma. In certain embodiments, the multiple myeloma is relapsed or refractory to at least two prior therapies, wherein the prior therapies are selected from lenalidomide, pomalidomide, and a proteasome inhibitor. In certain embodiments, the proteasome inhibitor is selected from caflizomib, bortezomib, and ixazomib.

[00134] In some embodiments, provided herein are methods for the treatment or management of relapsed, refractory or resistant multiple myeloma. In some embodiments, provided herein are methods for the treatment or management of relapsed and refractory multiple myeloma. In some embodiments, provided herein are methods for the treatment or management of relapsed or refractory multiple myeloma. In some embodiments, provided herein are methods for the treatment or management of relapsed or refractory multiple

myeloma, and the multiple myeloma is relapsed or refractory to at least two prior therapies, wherein the prior therapies are selected from lenalidomide, pomalidomide, and a proteasome inhibitor. In certain embodiments, the proteasome inhibitor is selected from caflizomib, bortezomib, and ixazomib.

[00135] In some embodiments, the methods for treating and/or managing multiple myeloma provided herein may be used in a patient who has not responded to standard treatment. In some embodiments, the prior multiple myeloma therapy comprises at least one drug selected from the group consisting of a proteasome inhibitor, an immunomodulatory drug and an anti-CD38 antibody. In some embodiments, the methods for treating and/or managing multiple myeloma provided herein may be used in a patient who has received at least two prior therapies. In some embodiments, the methods for treating and/or managing multiple myeloma provided herein may be used in a patient who has received at least two prior therapies including lenalidomide and a proteasome inhibitor. In certain embodiments, the proteasome inhibitor is selected from caflizomib, bortezomib, and ixazomib.

[00136] In certain embodiments, the cancer is triple class refractory multiple myeloma. In certain embodiments, the multiple myeloma of the subject is refractory to all three types of the following multiple myeloma therapies (1) a prior multiple myeloma therapy that comprises a proteasome inhibitor, (2) a prior multiple myeloma therapy that comprises an immunomodulatory agent, and (3) a prior multiple myeloma therapy that comprises an anti-CD38 antibody.

[00137] In certain embodiments, the multiple myeloma is newly diagnosed multiple myeloma. In some embodiments, provided herein are methods for the treatment or management of newly diagnosed multiple myeloma. In some embodiments, the methods for treating and/or managing multiple myeloma provided herein is used in treatment naive patients, i.e., patients that have not yet received treatment.

[00138] In some embodiments, provided herein are methods of treating patients who have been previously treated for multiple myeloma but are non-responsive to standard therapies, as well as those who have not previously been treated. The invention also encompasses methods of treating patients regardless of patient's age, although some diseases or disorders are more common in certain age groups. The invention further encompasses methods of treating patients who have undergone surgery in an attempt to treat the disease or condition at issue, as well as those who have not. Because patients with multiple myeloma have heterogeneous clinical manifestations and varying clinical outcomes, the treatment given to a patient may vary, depending on his/her prognosis. The skilled clinician is able to readily

determine without undue experimentation specific secondary agents, types of surgery, and types of non-drug based standard therapy that can be effectively used to treat an individual patient with cancer.

Administration of the combination therapy

[00139] Compound A, A-S, or A-R, or an enantiomer or a mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, in combination with the bispecific antibody, may be administered by oral, parenteral (*e.g.*, intramuscular, intraperitoneal, intravenous, CIV, intracistemal injection or infusion, subcutaneous administration, or implant), inhalation, nasal, vaginal, rectal, sublingual, or topical (*e.g.*, transdermal or local) routes of administration. Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, may be formulated alone or together, in suitable dosage unit with pharmaceutically acceptable excipients, carriers, adjuvants and vehicles, appropriate for each route of administration. In one embodiment, Compound A, A-S, or A-R, or an enantiomer or a mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, in combination with the bispecific antibody, is administered orally.

[00140] The bispecific antibody, in combination with a compound provided herein, may be administered by oral, parenteral (*e.g.*, intramuscular, intraperitoneal, intravenous, CIV, intracistemal injection or infusion, subcutaneous administration, or implant), inhalation, nasal, vaginal, rectal, sublingual, or topical (*e.g.*, transdermal or local) routes of administration. The bispecific antibody may be formulated alone or together, in suitable dosage unit with pharmaceutically acceptable excipients, carriers, adjuvants and vehicles, appropriate for each route of administration. In one embodiment, the bispecific antibody, in combination with a compound provided herein, is administered subcutaneously.

Amount of the compound

[00141] Provided herein is Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof for use in methods of treating and/or managing multiple myeloma in patients.

[00142] In certain embodiments, a therapeutically or prophylactically effective amount of

Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is from about 0.01 mg to about 50 mg per day, from about 0.1 mg to about 50 mg per day, from about 0.5 mg to about 50 mg per day, from about 1 mg to about 50 mg per day, from about 0.02 mg to about 25 mg per day, from about 0.05 mg to about 10 mg per day, or from about 0.1 mg to about 5 mg per day. In some embodiments, a therapeutically or prophylactically effective amount of Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is from about 0.01 mg to about 50 mg per day. In some embodiments, a therapeutically or prophylactically effective amount of Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is from about 0.1 mg to about 50 mg per day. In some embodiments, a therapeutically or prophylactically effective amount of Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is from about 0.5 mg to about 50 mg per day. In some embodiments, a therapeutically or prophylactically effective amount of Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is from about 1 mg to about 50 mg per day. In some embodiments, a therapeutically or prophylactically effective amount of Compound A, A-S, or A-R is from about 0.02 mg to about 25 mg per day. In some embodiments, a therapeutically or prophylactically effective amount of Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is from about 0.05 mg to about 10 mg per day. In some embodiments, a therapeutically or prophylactically effective amount of Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is from about 0.1 mg to about 5 mg per day. In some embodiments, a therapeutically or prophylactically effective amount of Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is from about 0.1 mg to about 1.3 mg per day. In some embodiments, a therapeutically or prophylactically effective amount of Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers,

a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is from about 0.6 mg to about 1.3 mg per day.

[00143] In certain embodiments, the therapeutically or prophylactically effective amount of Compound A, A-S, or A-R, is about 0.1 mg, about 0.15 mg, about 0.2 mg, about 0.25 mg, about 0.3 mg, about 0.35 mg, about 0.4 mg, about 0.45 mg, about 0.5 mg, about 0.55 mg, about 0.6 mg, about 0.65 mg, about 0.7 mg, about 0.75 mg, about 0.8 mg, about 0.85 mg, about 0.9 mg, about 0.95 mg, about 1 mg, about 1.05 mg, about 1.1 mg, about 1.15 mg, about 1.2 mg, about 1.25 mg, about 1.3 mg, about 1.35 mg, about 1.4 mg, about 1.45 mg, about 1.5 mg, about 1.55 mg, about 1.6 mg, about 1.65 mg, about 1.7 mg, about 1.75 mg, about 1.8 mg, about 1.85 mg, about 1.9 mg, about 1.95 mg, about 2 mg, about 2.05 mg, about 2.1 mg, about 2.15 mg, about 2.2 mg, about 2.25 mg, about 2.3 mg, about 2.35 mg, about 2.4 mg, about 2.45 mg, about 2.5 mg, about 2.55 mg, about 2.6 mg, about 2.65 mg, about 2.7 mg, about 2.75 mg, about 2.8 mg, about 2.85 mg, about 2.9 mg, about 2.95 mg, about 3 mg, about 3.05 mg, about 3.1 mg, about 3.15 mg, about 3.2 mg, about 3.25 mg, about 3.3 mg, about 3.35 mg, about 3.4 mg, about 3.45 mg, about 3.5 mg, about 3.55 mg, about 3.6 mg, about 3.65 mg, about 3.7 mg, about 3.75 mg, about 3.8 mg, about 3.85 mg, about 3.9 mg, about 3.95 mg, about 4 mg, about 4.05 mg, about 4.1 mg, about 4.15 mg, about 4.2 mg, about 4.25 mg, about 4.3 mg, about 4.35 mg, about 4.4 mg, about 4.45 mg, about 4.5 mg, about 4.55 mg, about 4.6 mg, about 4.65 mg, about 4.7 mg, about 4.75 mg, about 4.8 mg, about 4.85 mg, about 4.9 mg, about 4.95, or about 5 mg per day. In certain embodiments, the therapeutically or prophylactically effective amount of Compound A, A-S, or A-R, is about 0.6 mg, about 0.65 mg, about 0.7 mg, about 0.75 mg, about 0.8 mg, about 0.85 mg, about 0.9 mg, about 0.95 mg, about 1 mg, about 1.05 mg, about 1.1 mg, about 1.15 mg, about 1.2 mg, about 1.25 mg, or about 1.3 mg. In some embodiments, the therapeutically or prophylactically effective amount of Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is about 0.6 mg per day. In some embodiments, the therapeutically or prophylactically effective amount of Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is about 0.65 mg per day. In some embodiments, the therapeutically or prophylactically effective amount of Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is about 0.7 mg per day. In some embodiments, the therapeutically or prophylactically

effective amount of Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is about 0.75 mg per day. In some embodiments, the therapeutically or prophylactically effective amount of Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is about 0.8 mg per day. In some embodiments, the therapeutically or prophylactically effective amount of Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is about 0.85 mg per day. In some embodiments, the therapeutically or prophylactically effective amount of Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is about 0.9 mg per day. In some embodiments, the therapeutically or prophylactically effective amount of Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is about 0.95 mg per day. In some embodiments, the therapeutically or prophylactically effective amount of Compound A, A-S, or A-R is or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof about 1 mg per day. In some embodiments, the therapeutically or prophylactically effective amount of Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is about 1.2 mg per day. In some embodiments, the therapeutically or prophylactically effective amount of Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is about 1.25 mg per day. In some embodiments, the therapeutically or prophylactically effective amount of Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, A is about 1.3 mg per day. In some embodiments, the therapeutically or prophylactically effective amount of Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is about 1.35 mg per day. In some embodiments, the therapeutically or prophylactically

effective amount of Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is about 1.4 mg per day. In some embodiments, the therapeutically or prophylactically effective amount of Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is about 1.45 mg per day. In some embodiments, the therapeutically or prophylactically effective amount of Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is about 1.5 mg per day. In some embodiments, the therapeutically or prophylactically effective amount of Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is about 1.55 mg per day. In some embodiments, the therapeutically or prophylactically effective amount of Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is about 1.6 mg per day. In some embodiments, the therapeutically or prophylactically effective amount of Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is about 1.65 mg per day. In some embodiments, the therapeutically or prophylactically effective amount of Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is about 1.7 mg per day. In some embodiments, the therapeutically or prophylactically effective amount of Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is about 1.75 mg per day. In some embodiments, the therapeutically or prophylactically effective amount of Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is about 1.8 mg per day. In some embodiments, the therapeutically or prophylactically effective amount of Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is about 1.85 mg per day. In some embodiments, the therapeutically or prophylactically

effective amount of Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is about 1.9 mg per day. In some embodiments, the therapeutically or prophylactically effective amount of Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is about 1.95 mg per day. In some embodiments, the therapeutically or prophylactically effective amount of Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is about 2 mg per day.

[00144] In one embodiment, the recommended daily dose range of Compound A, A-S, or A-R, or an enantiomer or a mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, for the conditions described herein lie within the range of from about 0.1 mg to about 5 mg per day, preferably given as a single once-a-day dose, or in divided doses throughout a day. In some embodiments, the dosage ranges from about 1 mg to about 50 mg per day. In other embodiments, the dosage ranges from about 0.5 to about 5 mg per day. In other embodiments, the dosage ranges from about 0.6 to about 1.3 mg per day. Specific doses per day include 0.1 mg, 0.15 mg, 0.2 mg, 0.25 mg, 0.3 mg, 0.35 mg, 0.4 mg, 0.45 mg, 0.5 mg, 0.55 mg, 0.6 mg, 0.65 mg, 0.7 mg, 0.75 mg, 0.8 mg, 0.85 mg, 0.9 mg, 0.95 mg, 1 mg, 1.05 mg, 1.1 mg, 1.15 mg, 1.2 mg, 1.25 mg, 1.3 mg, 1.35 mg, 1.4 mg, 1.45 mg, 1.5 mg, 1.55 mg, 1.6 mg, 1.65 mg, 1.7 mg, 1.75 mg, 1.8 mg, 1.85 mg, 1.9 mg, 1.95 mg, 2 mg, 2.05 mg, 2.1 mg, 2.15 mg, 2.2 mg, 2.25 mg, 2.3 mg, 2.35 mg, 2.4 mg, 2.45 mg, 2.5 mg, 2.55 mg, 2.6 mg, 2.65 mg, 2.7 mg, 2.75 mg, 2.8 mg, 2.85 mg, 2.9 mg, 2.95 mg, 3 mg, 3.05 mg, 3.1 mg, 3.15 mg, 3.2 mg, 3.25 mg, 3.3 mg, 3.35 mg, 3.4 mg, 3.45 mg, 3.5 mg, 3.55 mg, 3.6 mg, 3.65 mg, 3.7 mg, 3.75 mg, 3.8 mg, 3.85 mg, 3.9 mg, 3.95 mg, 4 mg, 4.05 mg, 4.1 mg, 4.15 mg, 4.2 mg, 4.25 mg, 4.3 mg, 4.35 mg, 4.4 mg, 4.45 mg, 4.5 mg, 4.55 mg, 4.6 mg, 4.65 mg, 4.7 mg, 4.75 mg, 4.8 mg, 4.85 mg, 4.9 mg, 4.95 mg, or 5 mg per day. In certain embodiments, the compound is administered in an amount of about 0.6 mg, 0.7 mg, 0.75 mg, 0.8 mg, 0.9 mg, 1.0 mg, 1.1 mg, 1.2 mg, 1.3 mg, 1.4 mg, 1.5 mg, or 1.6 mg per day. In certain embodiments, the compound is administered in an amount of about 0.75 mg, about 1.0 mg, or about 1.3 mg per day.

[00145] In certain embodiments, Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate,

co-crystal, clathrate, or polymorph thereof is administered according to the locally approved label or Pharmacy manual for preparation, administration, and storage information.

Amount of the bispecific antibody

[00146] Provided herein is a bispecific antibody for use in methods of treating and/or managing multiple myeloma in patients.

[00147] In certain embodiments, the bispecific antibody is administered in a therapeutically effective amount. In certain embodiments, the bispecific antibody is administered according to the locally approved label or Pharmacy manual for preparation, administration, and storage information.

[00148] In certain embodiments, a therapeutically or prophylactically effective amount of the bispecific antibody is from about 1 mg to about 250 mg, from about 5 mg to about 250 mg, from about 7.5 mg to about 250 mg, from about 10 mg to about 250 mg, from about 1 mg to about 100 mg, from about 1 mg to about 80 mg, from about 10 mg to about 80 mg, or from about 12 mg to about 76 mg. In some embodiments, a therapeutically or prophylactically effective amount of the bispecific antibody is from about 1 mg to about 250 mg. In some embodiments, a therapeutically or prophylactically effective amount of the bispecific antibody is from about 5 mg to about 250 mg . In some embodiments, a therapeutically or prophylactically effective amount of the bispecific antibody is from about 7.5 mg to about 250 mg. In some embodiments, a therapeutically or prophylactically effective amount of the bispecific antibody is from about 10 mg to about 250 mg. In some embodiments, a therapeutically or prophylactically effective amount of the bispecific antibody is from about 1 mg to about 100 mg. In some embodiments, a therapeutically or prophylactically effective amount of the bispecific antibody is from about 1 mg to about 80 mg. In some embodiments, a therapeutically or prophylactically effective amount of the bispecific antibody is from about 10 mg to about 80 mg . In some embodiments, a therapeutically or prophylactically effective amount of the bispecific antibody is from about 12 mg to about 76 mg. In some embodiments, a therapeutically or prophylactically effective amount of the bispecific antibody is from about 40 mg to about 160 mg.

[00149] In certain embodiments, the therapeutically or prophylactically effective amount of the bispecific antibody is about 1 mg, about 2 mg, about 5 mg, about 10 mg, about 12 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 32 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 76 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg,

about 105 mg, about 110 mg, about 115 mg, about 116 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 152 mg, about 155 mg, or about 160 mg. In some embodiments, the therapeutically or prophylactically effective amount of the bispecific antibody is about 12 mg. In some embodiments, the therapeutically or prophylactically effective amount of the bispecific antibody is about 32 mg. In some embodiments, the therapeutically or prophylactically effective amount of the bispecific antibody is about 76 mg.

[00150] In one embodiment, the recommended dose range of the bispecific antibody for the conditions described herein lie within the range of from about 0.5 mg to about 100 mg. In some embodiments, the dosage ranges from about 1 mg to about 100 mg. In other embodiments, the dosage ranges from about 12 mg to about 76 mg. Specific doses include 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg, 20 mg, 21 mg, 22 mg, 23 mg, 24 mg, 25 mg, 26 mg, 27 mg, 28 mg, 29 mg, 30 mg, 31 mg, 32 mg, 33 mg, 34 mg, 35 mg, 36 mg, 37 mg, 38 mg, 39 mg, 40 mg, 41 mg, 42 mg, 43 mg, 44 mg, 45 mg, 46 mg, 47 mg, 48 mg, 49 mg, 50 mg, 60 mg, 76 mg, 80 mg, 90 mg, or 100 mg. In one embodiment, the bispecific antibody is administered in an amount of about 12 mg. In one embodiment, the bispecific antibody is administered in an amount of about 32 mg. In one embodiment, the bispecific antibody is administered in an amount of about 76 mg.

[00151] Compound A, A-S, or A-R, or an enantiomer or a mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, in combination with the bispecific antibody provided herein, can be delivered as a single dose such as, *e.g.*, a single bolus injection, or oral tablets or pills; or over time, such as, *e.g.*, continuous infusion over time or divided bolus doses over time. Compound A, A-S, or A-R, or an enantiomer or a mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, in combination with the bispecific antibody provided herein, can be administered repeatedly if necessary, for example, until the patient experiences stable disease or regression, or until the patient experiences disease progression or unacceptable toxicity. The bispecific antibody, in combination with a compound provided herein, can be delivered as a single dose such as, *e.g.*, a single bolus injection, or oral tablets or pills; or over time, such as, *e.g.*, continuous infusion over time or divided bolus doses over time. The bispecific antibody, in combination with a compound provided herein, can be administered repeatedly if necessary, for example, until the patient experiences stable disease or regression, or until the

patient experiences disease progression or unacceptable toxicity.

[00152] Compound A, A-S, or A-R, or an enantiomer or a mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, in combination with the bispecific antibody provided herein, can be administered once daily (QD), or divided into multiple daily doses such as twice daily (BID), three times daily (TID), and four times daily (QID). The bispecific antibody, in combination with a compound provided herein, can be administered once daily (QD), weekly (Q1W or QW), twice weekly (Q2W) or four weekly (Q4W). In addition, the administration can be continuous (*i.e.*, daily for consecutive days or every day), intermittent, *e.g.*, in cycles (*i.e.*, including days, weeks, or months of rest without drug).

[00153] As used herein, the term "daily" is intended to mean that a therapeutic compound, such as Compound A, A-S, or A-R, is administered once or more than once each day, for example, for a period of time. The term "continuous" is intended to mean that a therapeutic compound, such as Compound A, A-S, or A-R, is administered daily for an uninterrupted period of at least 10 days to 52 weeks. The term "intermittent" or "intermittently" as used herein is intended to mean stopping and starting at either regular or irregular intervals. For example, intermittent administration of Compound A, A-S, or A-R is administration for one to six days per week, administration in cycles (*e.g.*, daily administration for two to eight consecutive weeks, then a rest period with no administration for up to one week), or administration on alternate days. The term "cycling" as used herein is intended to mean that a therapeutic compound, such as Compound A, A-S, or A-R, is administered daily or continuously but with a rest period.

[00154] In some embodiments, the frequency of administration of Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is in the range of about a daily dose to about a monthly dose. In certain embodiments, administration of Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof is once a day, twice a day, three times a day, four times a day, once every other day, twice a week, once every week, once every two weeks, once every three weeks, or once every four weeks.

[00155] In certain embodiments, Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered once per day from one day to six

months, from one week to three months, from one week to four weeks, from one week to three weeks, or from one week to two weeks. In certain embodiments, Compound A, A-S, or A-R, or a pharmaceutically acceptable salt or solvate thereof, is administered once per day for one week, two weeks, three weeks, or four weeks. In one embodiment, Compound A, A-S, or A-R or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered once per day for one week. In another embodiment, Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered once per day for two weeks. In yet another embodiment, Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered once per day for three weeks. In still another embodiment, Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered once per day for four weeks.

[00156] In certain embodiments, Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered once per day for 21 days in a 28-day cycle, namely administered once daily for 21 days followed by 7 days of rest. In certain embodiments, Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered is administered once daily for 21 days followed by 7 days of rest. In certain embodiments, Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered once per day on days 1 to 21 in a 28-day cycle. In certain embodiments, Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered for one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen or more cycles. In certain embodiments, Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered for one cycle. In certain embodiments, Compound A, A-S, or A-R, or an enantiomer or

mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered for two cycles. In certain embodiments, Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered for three cycles. In certain embodiments, Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered for four cycles. In certain embodiments, Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered for seven cycles. In certain embodiments, Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered for eight cycles. In certain embodiments, Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered for nine cycles. In certain embodiments, Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered for ten cycles. In certain embodiments, Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered for eleven cycles. In certain embodiments, Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered for twelve cycles. In certain embodiments, Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered for thirteen or more cycles.

[00157] In certain embodiments, the bispecific antibody is administered once per day from one day to six months, from one week to three months, from one week to four weeks, from one week to three weeks, or from one week to two weeks. In certain embodiments, the bispecific antibody is administered once per day for one week, two weeks, three weeks, or four weeks. In one embodiment, the bispecific antibody is administered once per day for one week. In another embodiment, the bispecific antibody is administered once per day for two

weeks. In yet another embodiment, the bispecific antibody is administered once per day for three weeks. In still another embodiment, the bispecific antibody is administered once per day for four weeks. In some embodiments, the frequency of administration of the bispecific antibody is in the range of about a daily dose to about a monthly dose.

[00158] In certain embodiments, administration of the bispecific antibody is once a day, twice a day, three times a day, four times a day, once every other day, twice a week, once every week, once every two weeks, once every three weeks, or once every four weeks.

[00159] In certain embodiments, the bispecific antibody is administered on days 1 and 4 of a week. In certain embodiments, the bispecific antibody is administered on day 1 of a week. In certain embodiments, the bispecific antibody is administered on days 1, 4, and 8 in a period of 14 days.

[00160] In certain embodiments, the bispecific antibody is administered once a week, once every two weeks, or once every four weeks.

[00161] In certain embodiments, the patient to be treated with one of the methods provided herein has not been treated with the bispecific antibody provided herein prior to the administration of Compound A, A-S, or A-R, or an enantiomer or a mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof. In certain embodiments, the patient to be treated with one of the methods provided herein has been treated with the bispecific antibody provided herein subsequent to the administration of Compound A, A-S, or A-R, or an enantiomer or a mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof. In certain embodiments, the patient to be treated with one of the methods provided herein has been treated with the bispecific antibody provided herein concurrently with the administration of Compound A, A-S, or A-R, or an enantiomer or a mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof. In certain embodiments, Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered concurrently with, prior to (*e.g.*, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, 12 weeks, or 16 weeks before), or subsequent to (*e.g.*, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, 12 weeks, or 16 weeks after),

the bispecific antibody provided herein. In certain embodiments, Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, in combination with the bispecific antibody, can be administered on an alternating dosing schedule, with or without a resting period (*e.g.*, no therapeutic agent is administered on certain days of the schedule). In certain embodiments, the administration of Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, in combination with the bispecific antibody includes, but is not limited to, sequential administration and concomitant administration.

[00162] In certain embodiments, the bispecific antibody is administered one, two, three, or more times prior to the administration of the compound. In certain embodiments, the bispecific antibody is administered in a priming dose cycle prior to administration of the compound. In certain embodiments, the priming dosing cycle is a 1-day cycle, a 3-day cycle, a 7-day cycle, a 14-day cycle, a 21-day cycle, or a 28-day cycle. In certain embodiments, the bispecific antibody is administered in a 14-day priming dose cycle prior to administration of the compound. In certain embodiments, the bispecific antibody administered on day 1 in a 7-day or 14-day priming dose cycle prior to administration of the compound. In certain embodiments, the bispecific antibody administered on days 1 and 4 in a 7-day or 14-day priming dose cycle prior to administration of the compound. In certain embodiments, the bispecific antibody is administered on days 1, 4, and 8 in a 14-day priming dose cycle prior to administration of the compound. In certain embodiments, a minimum of 2 days is maintained between the first dose and the second dose in the priming dose cycle. In certain embodiments, a minimum of 3 days is maintained between the second dose and the third dose in the priming dose cycle. In certain embodiments, a minimum of 6 days is maintained between the third dose in the priming dose cycle and the bispecific antibody dose thereafter. In certain embodiments, a minimum of 6 days is maintained between the third dose in the priming dose cycle and the beginning of the administration of Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof.

[00163] In certain embodiments, the bispecific antibody is administered once a week, once every two weeks, or every four weeks in a 28-day cycle. In certain embodiments, Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof,

is administered for 21 days in the 28-day cycle, namely administered for 21 days followed by 7 days of rest. In certain embodiments, Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered on days 1 to 21 in the 28-day cycle.

[00164] In certain embodiments, the bispecific antibody is administered once a week, namely on days 1, 8, 15, and 22 in a 28-day cycle, whereas Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered for 21 days in the 28-day cycle. In certain embodiments, the bispecific antibody is administered once every two weeks, namely on days 1, and 15 in a 28-day cycle, whereas Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered for 21 days in the 28-day cycle. In certain embodiments, the bispecific antibody is administered once every four weeks, namely on day 1 in a 28-day cycle, whereas Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered for 21 days in the 28-day cycle.

[00165] In certain embodiments, the combination therapy is administered as illustrated in **FIG. 3**. In certain embodiments, the combination therapy is administered in multiple 28-day cycles. In certain embodiments, the bispecific antibody is administered on days 1, 4, and 8 in a 14-day priming dose cycle prior to administration of the compound (C0). In certain embodiments, in the first 28-day cycle (C1), the bispecific antibody is administered once a week, namely on days 1, 8, 15, and 22 in a 28-day cycle, whereas Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered on days 1 to 21 in the 28-day cycle. In certain embodiments, in the second to the sixth 28-day cycles (C2-C6), the bispecific antibody is administered once a week, namely on days 1, 8, 15, and 22 in a 28-day cycle, whereas Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered on days 1 to 21 in the 28-day cycle. In certain embodiments, in the seventh to the twelfth 28-day cycles (C7-C12), if the patient has received treatment for at least 6 months and a disease response shows at least a partial response (PR) or better with responses persisting for at least 2 months, the

bispecific antibody is administered once every two weeks, namely on days 1, and 15 in a 28-day cycle, whereas Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered on days 1 to 21 in the 28-day cycle. In certain embodiments, in the thirteenth to the rest of the 28-day cycles (C13+), if a disease response shows at least a partial response (PR) or better with responses persisting for at least 2 months, the bispecific antibody is administered once every four weeks, namely on day 1 in a 28-day cycle, whereas Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered on days 1 to 21 in the 28-day cycle.

[00166] In certain embodiments, the bispecific antibody is administered on day 1 in an amount of 12 mg, on day 4 in an amount of 32 mg, and on day 8 in an amount of 76 mg in a 14-day priming dose cycle prior to administration of the compound (C0). In certain embodiments, in the first to the sixth 28-day cycles (C1-C6), the bispecific antibody is administered once every week in an amount of 76 mg, namely on days 1, 8, 15, and 22 in a 28-day cycle, whereas Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered in an amount of 1.0 mg, 1.3 mg or 1.6 mg per day on days 1 to 21 in the 28-day cycle. In certain embodiments, in the seventh to the twelfth 28-day cycles (C7-C12), if the patient has received treatment for at least 6 month and a disease response shows at least a partial response (PR) or better with responses persisting for at least 2 months, the bispecific antibody is administered once every two weeks in an amount of 76 mg, namely on days 1 and 15 in a 28-day cycle, whereas Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered in an amount of 1.0 mg, 1.3 mg or 1.6 mg per day on days 1 to 21 in the 28-day cycle. In certain embodiments, in the thirteenth to the rest of the 28-day cycles (C13+), if a disease response shows at least a partial response (PR) or better with responses persisting for at least 2 months, the bispecific antibody is administered once every four weeks in an amount of 76 mg, namely on day 1 in a 28-day cycle, whereas Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered in an amount of 1.0 mg, 1.3 mg or 1.6 mg per day on days 1 to 21 in the 28-day cycle. In

certain embodiments, following the priming dose cycle and subsequent six 28-day cycles, the bispecific antibody is administered in an amount of 76 mg once every two weeks if the patient has received treatment for at least 6 month and a disease response shows at least a partial response (PR) or better with responses persisting for at least 2 months. In certain embodiments, following the priming dose cycle and subsequent twelve 28-day cycles, the bispecific antibody is administered in an amount of 76 mg once every four weeks if a disease response shows at least a partial response (PR) or better with responses persisting for at least 2 months.

[00167] In certain embodiments, the combination therapy is administered as illustrated in **FIG. 5**. In certain embodiments, the bispecific antibody is administered on day 1 in an amount of 12 mg, on day 4 in an amount of 32 mg, and on day 8 in an amount of 76 mg in a 14-day priming dose cycle prior to administration of the compound (C0). In certain embodiments, in the first to the third 28-day cycles (C1-C3), the bispecific antibody is administered once every week in an amount of 76 mg, namely on days 1, 8, 15, and 22 in a 28-day cycle, whereas Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered in an amount of 1.0 mg, 1.3 mg or 1.6 mg per day on days 1 to 21 in the 28-day cycle. In certain embodiments, in the fourth to the sixth 28-day cycles (C4-C6), the bispecific antibody is administered once every two weeks in an amount of 76 mg, namely on days 1 and 15 in a 28-day cycle, whereas Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered in an amount of 1.0 mg, 1.3 mg or 1.6 mg per day on days 1 to 21 in the 28-day cycle. In certain embodiments, in the seventh to the rest of the 28-day cycles (C7+), the bispecific antibody is administered once every four weeks in an amount of 76 mg, namely on day 1 in a 28-day cycle, whereas Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered in an amount of 1.0 mg, 1.3 mg or 1.6 mg per day on days 1 to 21 in the 28-day cycle.

[00168] In certain embodiments, the bispecific antibody is further administered in one or more dose escalation cycles as illustrated in FIG. 4. In certain embodiments, following the priming dose cycle and subsequent seven or more 28-day cycles, the bispecific antibody is administered in an amount of 76 mg once every two weeks for three 28-day cycles, where as Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an

isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered in an amount of 1.3 mg, 1 mg, or 0.75 mg. In certain embodiments, following the priming dose cycle and subsequent ten or more 28-day cycles, the bispecific antibody is administered in an amount of 76 mg once every four weeks, where as Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered in an amount of 1.3 mg, 1 mg, or 0.75 mg.

[00169] In certain embodiments, the combination therapy is administered as illustrated in **FIG. 6**. In certain embodiments, the bispecific antibody is administered on day 1 in an amount of 12 mg, on day 4 in an amount of 32 mg, and on day 8 in an amount of 76 mg in a 14-day priming dose cycle prior to administration of the compound (C0). In certain embodiments, in the first to the third 28-day cycles (C1-C3), the bispecific antibody is administered once every two weeks in an amount of 76 mg, namely on days 1 and 15 in a 28-day cycle, whereas Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered in an amount of 0.75 mg, 1.0 mg, or 1.3 mg or 1.6 mg per day on days 1 to 21 in the 28-day cycle. In certain embodiments, in the fourth to the rest of the 28-day cycles (C4+), the bispecific antibody is administered once every four weeks in an amount of 76 mg, namely on day 1 in a 28-day cycle, whereas Compound A, A-S, or A-R, or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, is administered in an amount of 0.75 mg, 1.0 mg, or 1.3 mg or 1.6 mg per day on days 1 to 21 in the 28-day cycle.

[00170] In certain embodiments, the bispecific antibody is administered subcutaneously. In certain embodiments, the bispecific antibody is administered as a shot under the skin.

[00171] In certain embodiments, premedication for cytokine release syndrome (CRS) prophylaxis before bispecific antibody dosing is administered. In certain embodiments, the premedication for CRS prophylaxis is administered about 30 minutes, about 45 minutes, about 60 minutes, about 75 minutes, or about 90 minutes prior to the first, second and third doses of the bispecific antibody in the priming dose cycle prior to administration of the compound (C0). In certain embodiments, the premedication for CRS prophylaxis includes acetaminophen, diphenhydramine, and dexamethasone. In certain embodiments, the premedication for CRS prophylaxis includes acetaminophen in an amount of 650 mg (or paracetamol in an amount of 500 mg), diphenhydramine in an amount of 25 mg (or

equivalent; in an different but comparable amount due to local strength variations per local prescribing information) via oral or intravenous administration, and dexamethasone in an amount of 20 mg (or equivalent; in an different but comparable amount due to local strength variations per local prescribing information) via oral or intravenous administration.

PHARMACEUTICAL COMPOSITIONS AND DOSAGE FORMS

[00172] In one embodiment, provided herein are pharmaceutical compositions and dosage forms, which comprise Compound A, A-S, or A-R, or an enantiomer or a mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, that can be administered in combination with the bispecific antibody provided herein. In another embodiment, provided herein are pharmaceutical compositions and dosage forms, which comprise a bispecific antibody provided herein, that can be administered in combination with Compound A, A-S, or A-R, or an enantiomer or a mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof. In another embodiment, pharmaceutical compositions and dosage forms further comprise one or more excipients.

[00173] In one embodiment, provided herein are pharmaceutical compositions and dosage forms, which comprise (i) Compound A, A-S, or A-R, or an enantiomer or a mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, and (ii) a bispecific antibody provided herein. In another embodiment, pharmaceutical compositions and dosage forms further comprise one or more excipients.

[00174] In certain embodiments, pharmaceutical compositions and dosage forms provided herein also comprise one or more additional active agents in amounts effective for achieving a modulation of disease or disease symptoms, including those described herein. Examples of optional additional active agents are disclosed herein (see, e.g., definitions section).

[00175] In certain embodiments, the pharmaceutical compositions provided herein may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir, preferably by oral administration or administration by injection. Oral delivery formats include, but are not limited to, tablets, capsules, caplets, solutions, suspensions, and syrups, and may also comprise a plurality of granules, beads, powders or pellets that may or may not be encapsulated. In one embodiment, the pharmaceutical compositions may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the

formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compound or its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques. In some embodiments, the pharmaceutical compositions provided herein that comprise the bispecific antibody are administered parentally, and in some embodiments, subcutaneously.

[00176] In certain embodiments, dosage forms provided herein for Compound A, A-S, or A-R, or an enantiomer or a mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof, are suitable for oral, mucosal (e.g., nasal, sublingual, vaginal, buccal, or rectal), parenteral (e.g., subcutaneous, intravenous, bolus injection, intramuscular, or intraarterial), topical (e.g., eye drops or other ophthalmic preparations), transdermal, or transcutaneous administration to a patient. Examples of dosage forms include, but are not limited to: tablets; caplets; capsules, such as soft elastic gelatin capsules; cachets; troches; lozenges; dispersions; suppositories; powders; aerosols (e.g., nasal sprays or inhalers); gels; liquid dosage forms suitable for oral or mucosal administration to a patient, including suspensions (e.g., aqueous or non-aqueous liquid suspensions, oil-in-water emulsions, or a water-in-oil liquid emulsions), solutions, and elixirs; liquid dosage forms suitable for parenteral administration to a patient; eye drops or other ophthalmic preparations suitable for topical administration; and sterile solids (e.g., crystalline or amorphous solids) that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a patient.

[00177] In certain embodiments, dosage forms provided herein for the bispecific antibody, are suitable for oral, mucosal (e.g., nasal, sublingual, vaginal, buccal, or rectal), parenteral (e.g., subcutaneous, intravenous, bolus injection, intramuscular, or intraarterial), topical (e.g., eye drops or other ophthalmic preparations), transdermal, or transcutaneous administration to a patient. Examples of dosage forms include, but are not limited to: tablets; caplets; capsules, such as soft elastic gelatin capsules; cachets; troches; lozenges; dispersions; suppositories; powders; aerosols (e.g., nasal sprays or inhalers); gels; liquid dosage forms suitable for oral or mucosal administration to a patient, including suspensions (e.g., aqueous or non-aqueous liquid suspensions, oil-in-water emulsions, or a water-in-oil liquid emulsions), solutions, and elixirs; liquid dosage forms suitable for parenteral administration to a patient. In some embodiments, the dosage form for the bispecific antibody is for parental administration, and in some embodiments, subcutaneous administration. In one embodiment, the bispecific

antibody is formulated as described in the package insert for ELREXFIO™ (a bispecific BCMA-directed CD3 T-cell engager sold under the trademark of ELREXFIO).

[00178] Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form provided herein depends on a variety of factors, including, but not limited to, the route of administration. For example, oral dosage forms such as tablets may contain excipients not suited for use in parenteral dosage forms. The suitability of a particular excipient may also depend on the specific active ingredients in the dosage form. For example, the decomposition of some active ingredients may be accelerated by some excipients such as lactose, or when exposed to water. Active ingredients that comprise primary or secondary amines are particularly susceptible to such accelerated decomposition. Consequently, encompassed herein are pharmaceutical compositions and dosage forms that contain little, if any, lactose. As used herein, the term "lactose-free" means that the amount of lactose present, if any, is insufficient to substantially increase the degradation rate of an active ingredient.

[00179] Lactose-free compositions provided herein can comprise excipients that are listed, for example, in the U.S. Pharmacopeia (USP) 25-NF20 (2002). In certain embodiments, lactose-free compositions comprise active ingredients, a binder/filler, and a lubricant in pharmaceutically compatible and pharmaceutically acceptable amounts. In certain embodiments, lactose-free dosage forms comprise active ingredients, microcrystalline cellulose, pre-gelatinized starch, and magnesium stearate.

[00180] Further encompassed herein are anhydrous pharmaceutical compositions and dosage forms comprising active ingredients, since water can facilitate the degradation of some compounds. For example, the addition of water (e.g., 5%) is widely accepted in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. See, e.g., Jens T. Carstensen, Drug Stability: Principles & Practice, 2d. Ed., Marcel Dekker, NY, NY, 1995, pp. 379-80. In effect, water and heat accelerate the decomposition of some compounds. Thus, the effect of water on a formulation can be of great significance since moisture and/or humidity are commonly encountered during manufacture, handling, packaging, storage, shipment, and use of formulations.

[00181] Anhydrous pharmaceutical compositions and dosage forms provided herein can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms that comprise lactose and at least one active ingredient that comprises a primary or secondary amine are preferably

anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected.

[00182] An anhydrous pharmaceutical composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, in certain embodiments, provided herein are anhydrous compositions packaged using materials to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (*e.g.*, vials), blister packs, and strip packs.

[00183] Encompassed herein are pharmaceutical compositions and dosage forms that comprise one or more compounds that reduce the rate by which an active ingredient will decompose. Such compounds, which are referred to herein as "stabilizers," include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers.

Oral dosage forms

[00184] In certain embodiments, pharmaceutical compositions provided herein that are suitable for oral administration are formulated as discrete dosage forms, examples of which include, but are not limited to, tablets (e.g., chewable tablets), caplets, capsules, and liquids (e.g., flavored syrups). Such dosage forms contain predetermined amounts of active ingredients and may be prepared by some known methods of pharmacy. See generally, Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing, Easton PA (1990).

[00185] In certain embodiments, the oral dosage forms provided herein are prepared by combining the active ingredients in an intimate admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form of preparation desired for administration. For example, excipients suitable for use in oral liquid or aerosol dosage forms include, but are not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents. Examples of excipients suitable for use in solid oral dosage forms (e.g., powders, tablets, capsules, and caplets) include, but are not limited to, starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents.

[00186] Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid excipients are employed. If desired, tablets can be coated by standard aqueous or nonaqueous techniques. Such dosage forms may be prepared by some known methods of pharmacy. In certain embodiments, pharmaceutical compositions and dosage forms are prepared by uniformly and intimately

admixing the active ingredients with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary.

[00187] In certain embodiments, a tablet is prepared by compression or molding. In certain embodiments, compressed tablets are be prepared by compressing in a suitable machine the active ingredients in a free-flowing form, *e.g.*, powder or granules, optionally mixed with an excipient. In certain embodiments, molded tablets are made by molding in a suitable machine a mixture of a powdered compound moistened with an inert liquid diluent.

[00188] Examples of excipients that can be used in oral dosage forms provided herein include, but are not limited to, binders, fillers, disintegrants, and lubricants. Binders suitable for use in pharmaceutical compositions and dosage forms provided herein include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (e.g., ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, (e.g., Nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof.

[00189] Suitable forms of microcrystalline cellulose include, but are not limited to, AVICEL-PH-101, AVICEL-PH-103 AVICEL RC-581, AVICEL-PH-105 (FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, PA), and mixtures thereof. An specific binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose (e.g., AVICEL RC-581). Suitable anhydrous or low moisture excipients or additives include AVICEL-PH-103™ and Starch 1500 LM.

[00190] Examples of fillers suitable for use in the pharmaceutical compositions and dosage forms provided herein include, but are not limited to, talc, calcium carbonate (e.g., granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. In certain embodiments, the binder or filler in pharmaceutical compositions provided herein is present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form.

[00191] Disintegrants are used in the compositions provided herein to provide tablets the ability to disintegrate when exposed to an aqueous environment. Tablets that contain too much disintegrant may disintegrate in storage, while those that contain too little may not disintegrate at a desired rate or under the desired conditions. Thus, a sufficient amount of disintegrant that is neither too much nor too little to detrimentally alter the release of the active ingredients should be used to form solid oral dosage forms provided herein. The

amount of disintegrant used varies based upon the type of formulation. In certain embodiments, the pharmaceutical compositions provided herein comprise from about 0.5 to about 15 weight percent or from about 1 to about 5 weight percent of disintegrant.

[00192] Disintegrants that are suitable for use in pharmaceutical compositions and dosage forms provided herein include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums, and mixtures thereof.

[00193] Lubricants that are suitable for use in pharmaceutical compositions and dosage forms provided herein include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (*e.g.*, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, and mixtures thereof. Additional lubricants include, but are not limited to, a syloid silica gel (AEROSIL200, W.R. Grace Co., Baltimore, MD), a coagulated aerosol of synthetic silica (Degussa Co. of Plano, TX), CAB-O-SIL (a pyrogenic silicon dioxide, Cabot Co. of Boston, MA), and mixtures thereof. In certain embodiments, if used at all, lubricants are used in an amount of less than about 1 weight percent of the pharmaceutical compositions or dosage forms into which they are incorporated.

[00194] In certain embodiments, provided herein is a solid oral dosage form, comprising Compound A, A-S, or A-R, or an enantiomer or a mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof; and one or more excipients selected from anhydrous lactose, microcrystalline cellulose, polyvinylpyrrolidone, stearic acid, colloidal anhydrous silica, and gelatin.

[00195] In certain embodiments, provided herein is a solid oral dosage form, comprising Compound A, A-S, or A-R, or an enantiomer or a mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof; and anhydrous lactose, microcrystalline cellulose, polyvinylpyrrolidone, stearic acid, colloidal anhydrous silica, and gelatin.

[00196] In certain embodiments, provided herein is a solid oral dosage form, comprising a hydrochloride salt of Compound A, A-S, or A-R, or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically solvate, hydrate, co-crystal, clathrate, or polymorph thereof; and one or more excipients selected from anhydrous lactose,

microcrystalline cellulose, polyvinylpyrrolidone, stearic acid, colloidal anhydrous silica, and gelatin.

[00197] In certain embodiments, provided herein is a solid oral dosage form, comprising a hydrochloride salt of Compound A, A-S, or A-R, or an enantiomer or a mixture of enantiomers thereof, or a pharmaceutically solvate, hydrate, co-crystal, clathrate, or polymorph thereof; and anhydrous lactose, microcrystalline cellulose, polyvinylpyrrolidone, stearic acid, colloidal anhydrous silica, and gelatin.

Delayed release dosage forms

[00198] In certain embodiments, the active ingredients provided herein are administered by controlled release means or by delivery devices. Examples include, but are not limited to, those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719, 5,674,533, 5,059,595, 5,591,767, 5,120,548, 5,073,543, 5,639,476, 5,354,556, and 5,733,566, each of which is incorporated herein by reference in its entirety. In certain embodiments, such dosage forms are be used to provide slow or controlled-release of one or more active ingredients using, for example, hydroxypropyl methyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Encompassed herein are single unit dosage forms suitable for oral administration, including, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled-release.

[00199] All controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled counterparts. Ideally, the use of an optimally designed controlled-release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. Advantages of controlled-release formulations include extended activity of the drug, reduced dosage frequency, and increased patient compliance. In addition, controlled-release formulations can be used to affect the time of onset of action or other characteristics, such as blood levels of the drug, and can thus affect the occurrence of side (*e.g.*, adverse) effects.

[00200] Most controlled-release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic effect, and gradually and continually release of other amounts of drug to maintain this level of therapeutic or prophylactic effect over an extended period of time. In order to maintain this constant level

of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled-release of an active ingredient can be stimulated by various conditions including, but not limited to, pH, temperature, enzymes, water, or other physiological conditions or compounds.

Parenteral dosage forms

[00201] Parenteral dosage forms can be administered to patients by various routes including, but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and intraarterial. Because their administration typically bypasses patients' natural defenses against contaminants, parenteral dosage forms are preferably sterile or capable of being sterilized prior to administration to a patient. Examples of parenteral dosage forms include, but are not limited to, solutions ready for injection, dry products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection, suspensions ready for injection, and emulsions. In certain embodiments, the bispecific antibody is in 40 mg/mL solution for administration to patients by subcutaneous injection.

[00202] Some suitable vehicles that can be used to provide parenteral dosage forms provided herein include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate. Compounds that increase the solubility of one or more of the active ingredients disclosed herein can also be incorporated into the parenteral dosage forms provided herein.

Kits

[00203] In certain embodiments, active ingredients provided herein are not administered to a patient at the same time or by the same route of administration. Therefore, encompassed herein are kits which, when used by the medical practitioner, can simplify the administration of appropriate amounts of active ingredients to a patient. In certain embodiments, a kit provided herein comprises a dosage form of a Compound A, A-S, or A-R, or an enantiomer or a mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof. In certain embodiments, the kits provided herein further comprise the bispecific antibody provided herein. In certain

embodiments, a kit provided herein comprises a dosage form of a bispecific antibody provided herein. In certain embodiments, the kits provided herein further comprises Compound A, A-S, or A-R, or an enantiomer or a mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof. In certain embodiments, the kit provided herein further comprises a device that is used to administer the active ingredients. Examples of such devices include, but are not limited to, syringes, drip bags, patches, and inhalers.

[00204] In certain embodiments, the kit provided herein further comprises cells or blood for transplantation as well as pharmaceutically acceptable vehicles that can be used to administer one or more active ingredients. For example, if an active ingredient is provided in a solid form that must be reconstituted for parenteral administration, the kit can comprise a sealed container of a suitable vehicle in which the active ingredient can be dissolved to form a particulate-free sterile solution that is suitable for parenteral administration. Examples of pharmaceutically acceptable vehicles include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

EXAMPLES

[00205] Certain embodiments of the invention are illustrated by the following non-limiting examples.

Example 1: A Phase 1b, Open-Label Study Of Elranatamab In Combination With Iberdomide In Participants With Relapsed Refractory Multiple Myeloma

A. Study Rationale

[00206] The Example is to evaluate the safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of elranatamab (a BCMA × CD3 bispecific antibody) in combination with iberdomide (a cereblon E3 ligase modulator) in participants with relapsed/refractory multiple myeloma (RRMM). This study is composed of a dose escalation approach (PART 1) to identify recommended Phase 2 doses (RP2Ds) or to select recommended doses for expansion (RDE) that is further evaluated in a randomized dose optimization approach (PART 2).

B. Objectives, Endpoints and Estimands

[00207] **PART 1: Dose Escalation**

Objectives	Endpoints	Estimands
Primary		
To assess safety and tolerability of elranatamab in combination with iberdomide in participants with relapsed/refractory multiple myeloma (RRMM) in order to select recommended Phase 2 dose (RP2D) for the combination (dose optimization PART 2)	Dose-limiting-toxicities (DLTs) during the DLT observation period (defined as Cycle 1).	The primary estimand is DLT rate estimate based on data from DLT-evaluable participants during the DLT observation period.
Secondary		
To evaluate the overall safety profile of elranatamab in combination with iberdomide	Adverse events (AEs) as characterized by type, frequency, severity as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0, timing, seriousness, and relationship to elranatamab in combination with iberdomide. The severity of cytokine release syndrome (CRS) and immune effector cell associated neurotoxicity syndrome (ICANS) is assessed according to American Society for Transplantation and Cellular Therapy (ASTCT) criteria (Lee DW, et al. Biol Blood Marrow Transplant. 2019;25(4):625-38). Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v5.0), and timing.	NA
To evaluate anti-myeloma activity of elranatamab in combination with iberdomide	Objective response rate (ORR) and complete response rate (CRR), per International Myeloma Working Group (IMWG) response criteria as determined by investigator; Time to event endpoints: time to response (TTR), duration of response (DOR), duration of complete response, (DOCR,), progression-free survival (PFS) per IMWG response criteria as determined by investigator, and overall survival (OS); Minimal residual disease (MRD) (assessed by central lab) negativity rate per IMWG sequencing criteria.	NA
To evaluate the PK of elranatamab given alone and in combination with iberdomide	Pre- and postdose concentrations of elranatamab; Trough concentrations of iberdomide at selected cycles.	NA

Objectives	Endpoints	Estimands
To evaluate the PK of iberdomide when administered with elranatamab		
To evaluate immunogenicity of elranatamab in combination with iberdomide	Incidence and titers of antidrug antibodies (ADA) and neutralizing antibodies (NAb) against elranatamab	NA

[00208] **Part 2: Randomized Dose Optimization**

Objectives	Endpoints	Estimands
Primary		
To evaluate the overall safety profile of elranatamab in combination with iberdomide.	AEs as characterized by type, frequency, severity as graded by NCI CTCAE v5.0, timing, seriousness, and relationship to elranatamab in combination with iberdomide. The severity of CRS and ICANS is assessed according to ASTCT criteria (Lee DW, et al. Biol Blood Marrow Transplant. 2019; 25(4): 625-38). Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v5.0), and timing,	The primary estimand is AE rate estimated based on data from the safety analysis set (SAS) during the on-treatment period.
Secondary		
To evaluate anti-myeloma activity of elranatamab in combination with iberdomide	ORR and CRR, per IMWG response criteria as determined by investigator; Time to event endpoints: TTR, DOR, DOCR, PFS per IMWG response criteria as determined by investigator, and OS; MRD (assessed by central laboratory) negativity rate per IMWG sequencing criteria.	NA
To evaluate the PK of elranatamab given alone and in combination with iberdomide; To evaluate the PK of iberdomide when administered with elranatamab	Pre- and postdose concentrations of elranatamab; Trough concentrations of iberdomide at selected cycles.	NA
To evaluate immunogenicity of elranatamab in combination with iberdomide	Incidence and titers of antidrug antibody (ADA) and neutralizing antibodies (NAb) against elranatamab	NA

C. Overall Design

[00209] This study is a Phase 1b, open-label, prospective, multi-center study to evaluate the safety, efficacy, PK, and PD of elranatamab in combination with iberdomide in participants with RRMM. Two clinical trial designs (C1 and C2) are described below.

C1. Overall Design 1

[00210] As illustrated in FIG. 2, the study is composed of 2 parts:

Dose escalation (PART 1) evaluates the tolerability and safety of elranatamab in combination with iberdomide to select recommended dose(s) (combination RP2Ds) for further evaluation in Part 2.

Randomized Dose Optimization (PART 2) further evaluates the safety and preliminary efficacy of elranatamab in combination with iberdomide at RP2Ds.

C1-1. Dose Escalation Design

[00211] Dose escalation design under C1 is illustrated in FIG. 2. For the dose escalation, Dose Level 1 (DL 1) is evaluated followed by Dose Level 2 (DL 2) if DL 1 is deemed tolerable. Dose Level 3 (DL 3) is evaluated after DL 2 is determined tolerable. Two combination dose levels of elranatamab and iberdomide are selected as RP2D(s) for further evaluation as Dose Level A (DL A) and Dose Level B (DL B) in Part 2.

[00212] Approximately 6 to 9 DLT-evaluable participants are treated at each dose level of the combination therapy. At least 6 DLT-evaluable participants are treated at each of the 2 selected combination dose levels that are further evaluated in Part 2. The actual number of participants to be enrolled depends on the number of dose levels evaluated and the number of participants treated at each dose level. It is estimated that approximately up to 27 DLT-evaluable participants are enrolled and treated in Part 1 dose escalation.

[00213] A staggered enrollment strategy is applied for dose escalation: when a dose level opens for enrollment, the first binding participant is dosed and observed for 24 hours after C1D1 (initiation of the elranatamab plus iberdomide combination). If no safety concerns arise during the 24-hour period from C1D1, subsequent participants are enrolled into the same dose level and combination.

[00214] The target DLT rate is $\leq$25% and the dose escalation decisions are guided by a Bayesian Optimal Interval Design (BOIN) approach (Liu S, Yuan Y. Bayesian optimal interval designs for phase I clinical trials. Journal of the Royal Statistical Society: Series C: Applied Statistics. 2015:507-23; Yuan L, Gu ZY, Gao CJ. P53-mediated Regulatory Mechanism of Ran Transcription in Multiple Myeloma Cells. Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2016;24(3):760-4.). The isotonic estimate of the toxicity rate from BOIN

approach guides the determination of the RP2D(s) of elranatamab plus iberdomide. However, other available evidence such as safety data beyond the DLT window, clinical activity, PK, and PD data is also evaluated in the decision to escalate. Dose escalation decisions and RP2D(s) selections are determined with agreement between the investigators and the sponsor at the dose level review meeting (DLRM).

C1-2. Study Arms and Duration:

Treatment Period

[00215] Participants receive elranatamab in combination with iberdomide in 28-day cycles (plus initial 14-day priming dose cycle for elranatamab) as detailed below:

- Cycle 0 Day 1 : Elranatamab subcutaneously (SC) 12 mg
- Cycle 0 Day 4 : Elranatamab SC 32 mg
- Cycle 0 Day 8 : Elranatamab SC 76 mg
- Cycle 1 to Cycle 6 : Elranatamab SC 76 mg weekly (QW) plus iberdomide by mouth (PO) at the specified dose (1.0 mg or 1.3 mg or 1.6 mg daily [QD]) depending on the cohort assigned from Day 1 to 21 of each 28-day cycle.
- Cycle 7 to Cycle 12 : Elranatamab SC 76 mg every 2 weeks (Q2W) (if a participant has received treatment for at least 6 months (6 cycles) and disease response shows at least a partial response (PR) or better with responses persisting for at least 2 months) plus iberdomide by mouth (PO) at the specified dose (1.0 mg or 1.3 mg or 1.6 mg daily [QD]) depending on the cohort assigned from Day 1 to 21 of each 28-day cycle.
- Starting Cycle 13 : Elranatamab subcutaneously (SC) 76 mg every 4 weeks (Q4W) (if disease response shows at least a partial response (PR) or better with responses persisting for at least 2 months) plus iberdomide PO at the specified dose (1.0 mg or 1.3 mg or 1.6 mg QD) depending on the cohort assigned from Day 1 to 21 of each 28-day cycle.
- All participants receive study interventions until disease progression, unacceptable toxicity, withdrawal of consent, or study termination. The total study duration for each participant is at least 2 years because all participants are followed for a minimum of 2 years.

C1-3. Randomized Dose Optimization Design

[00216] Dose optimization design under C1 is illustrated in FIG. 2. Dose optimization phase begins once the combination RP2D(s) are identified in the dose escalation part (PART 1). Approximately up to 60 participants are randomized to DL A and DL B at a 1:1 ratio stratified on the number of prior lines of therapy (1 vs >1).

C1-4. Dose Modification:

[00217] Dose modification can be conducted due to toxicity and efficacy.

Table 4: Dose modifications for iberdomide-related toxicity under C1

Dose Level	Oral Iberdomide Dose (Days 1 to 21 of 28-day cycle)		
Starting Dose	**1.6 mg**	**1.3 mg**	**1 mg**
Dose Level -1	1.3 mg	1 mg	0.75 mg
Dose Level -2	1 mg	0.75 mg	0.60 mg
Dose Level -3	0.75 mg	0.60 mg	-

C2. Overall Design 2

[00218] As illustrated in FIG. 4, the design is also composed of 2 parts:

Dose escalation (PART 1) evaluates the tolerability and safety of elranatamab in combination with iberdomide to select recommended doses (combination RDEs) for further evaluation in Part 2.

Randomized Dose Optimization (PART 2) further evaluates the safety and preliminary efficacy of elranatamab in combination with iberdomide at RDEs.

C2-1. Dose Escalation Design

[00219] Dose escalation design under C2 is illustrated in FIG. 4. For the dose escalation, Dose Level 1 (DL 1) will be evaluated followed by Dose Level 2 (DL 2) if DL 1 is deemed tolerable. If DL 1 (elranatamab weekly [QW]) is not tolerable, Dose Level -1 (DL -1; elranatamab every 2 weeks [Q2W]) will be evaluated, followed by DL 2 should DL -1 be deemed tolerable. If DL -1 is not tolerable, Dose Level -2 (DL -2) will be evaluated. Two dose levels of the elranatamab and iberdomide combination will be selected as recommended doses for expansion (RDE) for further evaluation as Dose Level A (DL A) and Dose Level B (DL B) in Part 2 (Dose Optimization, FIG. 4).

[00220] Approximately 6 to 9 DLT-evaluable participants are treated at each dose level of the combination therapy. At least 6 DLT-evaluable participants are treated at each of the 2 selected combination dose levels that are further evaluated in Part 2. The actual number of participants to be enrolled depends on the number of dose levels evaluated and the number of participants treated at each dose level. It is estimated that approximately up to 27 DLT-evaluable participants are enrolled and treated in Part 1 dose escalation.

[00221] A staggered enrollment strategy is applied for dose escalation at DL1 and DL2: when a dose level opens for enrollment, the first binding participant is dosed and observed for 24

hours after C1D1 (initiation of the elranatamab plus iberdomide combination). If no safety concerns arise during the 24-hour period from C1D1, subsequent participants are enrolled into the same dose level and combination. A staggered enrollment strategy may be used for DL -1 and DL -2 (lower elranatamab and/or lower iberdomide doses), depending on the observed safety at DL 1 and DL 2.

[00222] The target DLT rate is ≤25% and the dose escalation decisions are guided by a Bayesian Optimal Interval Design (BOIN) approach. The isotonic estimate of the toxicity rate from BOIN approach guides the determination of the RDEs of elranatamab plus iberdomide. However, other available evidence such as safety data beyond the DLT window, clinical activity, PK, and PD data is also evaluated in the decision to escalate. Dose escalation decisions and RDEs selections are determined with agreement between the investigators and the sponsor at the dose level review meeting (DLRM).

C2-2. Study Arms and Duration

[00223] **Treatment Period:** Participants will receive elranatamab in combination with iberdomide in 28-day cycles (plus initial 14-day priming dose cycle for elranatamab).

[00224] Part 1 dose levels are detailed below:

Priming (14 days, all dose levels):

- Cycle 0 Day 1: Elranatamab subcutaneously (SC) 12 mg
- Cycle 0 Day 4: Elranatamab SC 32 mg
- Cycle 0 Day 8: Elranatamab SC 76 mg

Dose Level 1 (28-day cycles, DL1):

- Cycle 1 to Cycle 3: Elranatamab SC 76 mg weekly (QW) plus iberdomide by mouth (PO) 1 mg daily [QD] D1-21 of each 28-day cycle.
- Cycle 4 to Cycle 6: Elranatamab SC 76 mg Q2W plus iberdomide PO at 1 mg QD D1-21 of each 28-day cycle.
- Starting Cycle 7: Elranatamab SC 76 mg every 4 weeks (Q4W) plus iberdomide PO 1 mg QD D1-21 of each 28-day cycle.

Dose Level 2 (28-day cycles, DL2):

- Cycle 1 to Cycle 3: Elranatamab SC 76 mg Q2W plus iberdomide PO 1.3 mg QD D1-21 of each 28-day cycle.
- Starting Cycle 4: Elranatamab SC 76 mg Q4W plus iberdomide PO 1.3 mg QD D1-21 of each 28-day cycle.

Dose Level -1 (28-day cycles, DL -1):

- Cycle 1 to Cycle 3: Elranatamab SC 76 mg Q2W plus iberdomide PO 1 mg QD D1-21 of each 28-day cycle.
- Starting Cycle 4: Elranatamab SC 76 mg Q4W plus iberdomide PO 1 mg QD D1-21 of each 28-day cycle.

Dose Level -2 (28-day cycles, DL -2):

- Cycle 1 to Cycle 3: Elranatamab SC 76 mg Q2W plus iberdomide PO 0.75 mg QD D1-21 of each 28-day cycle.
- Starting Cycle 4: Elranatamab SC 76 mg Q4W plus iberdomide PO 0.75 mg QD D1-21 of each 28-day cycle.

[00225] Participants may receive one or more of Priming, Dose Level 1, Dose Level 2, Dose Level -1, or Dose Level -2, or any combination of cycles thereof, based on disease progression, toxicity, and other factors. Exemplary dosing schedules are illustrated in FIGs. 5 and 6.

C2-2. Randomized Dose Optimization

[00226] Dose optimization design under C2 is illustrated in FIG. 4. Dose optimization phase begins once the combination RDEs are identified in the dose escalation part (part 1). Approximately up to 60 participants are randomized to DL A and DL B at a 1:1 ratio stratified on the number of prior lines of therapy (1 vs >1).

C2-4. Dose Modification:

[00227] Dose modification can be conducted due to toxicity and efficacy.

Table 5: Dose reductions for iberdomide-related toxicity under C2

Dose Level	Oral Iberdomide Dose (Days 1 to 21 of 28-day cycle)		
Starting Dose	0.75 mg	1 mg	1.3 mg
Dose Reduction -1	0.60 mg	0.75 mg	1 mg
Dose Reduction -2	-	0.60 mg	0.75 mg
Dose Reduction -3	-	-	0.60 mg

D. Number of Participants

It is estimated that approximately up to 27 DLT-evaluable participants are enrolled and treated in PART 1 and approximately up to 60 participants are randomized in PART 2.

E. Study Population

Key Inclusion Criteria

[00228] Participants must meet the following key inclusion criteria to be eligible for

enrollment into the study:

- Participant age ≥18 years at the time of informed consent. A female participant is eligible to participate if she is not pregnant or breastfeeding; the manufacturer's pregnancy prevention program for iberdomide must be followed.
- Prior diagnosis of MM as defined according to IMWG criteria as defined by at least 1 of the following:
    - Serum M-protein ≥0.5 g/dL by serum protein electrophoresis (SPEP)
    - Urinary M-protein excretion ≥200 mg/24 hours by urine protein electrophoresis (UPEP)
    - Serum immunoglobulin free light chain (FLC) ≥10 mg/dL (≥100 mg/L) and abnormal serum immunoglobulin kappa to lambda free light ratio (<0.26 or >1.65).
- **PART 1**: Participants who have received at least 2 and not more than 4 prior lines of therapy for MM including at least 1 IMiD (lenalidomide or pomalidomide) and at least 1 proteasome inhibitor (PI).
    - All participants in PART 1 must have received prior treatment with at least 2 consecutive cycles of a lenalidomide or pomalidomide-containing regimen and at least 2 consecutive cycles of a PI or a PI-containing regimen.
- **PART 2**: Participants who have received at least 1 but not more than 3 prior lines of therapy for MM including at least 1 IMiD (lenalidomide or pomalidomide) and at least 1 PI.
    - All participants in PART 2 must have received prior treatment with at least 2 consecutive cycles of a lenalidomide or pomalidomide-containing regimen and at least 2 consecutive cycles of a PI or a PI-containing regimen.
- Relapsed or Refractory to the last anti-MM regimen according to IMWG criteria. Primary refractory MM (defined as participants who have never achieved at least a MR with any treatment during the disease course) are not eligible.
- Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1.
- Adequate hepatic, renal and bone marrow function.

Exclusion Criteria

[00229] Participants with any of the following characteristics/conditions are excluded:

- Plasma cell leukemia, Smoldering MM, Waldenström's macroglobulinemia, amyloidosis, polyneuropathy, organomegaly, endocrinopathy, myeloma protein and skin changes (POEMS Syndrome), Known central nervous system (CNS) involvement or clinical signs of myelomatous meningeal involvement, active Graft Versus Host Disease (GVHD),

history of stem cell transplant within 12 weeks prior to enrollment.

- Impaired cardiovascular function or clinically significant cardiovascular diseases within 6 months prior to enrollment.
- Ongoing Grade ≥2 peripheral sensory or motor neuropathy, history of Guillain-Barre Syndrome GBS) or GBS variants, or history of any Grade ≥3 peripheral motor polyneuropathy.
- Participants with active hepatitis B virus (HBV), hepatitis C virus (HCV), severe acute respiratory syndrome coronavirus 2 (COVID-19/SARS-CoV-2), HIV, or any active, uncontrolled bacterial, fungal, or viral infection. Active infections must be resolved at least 21 days prior to enrollment. Treatment with systemic anti-infective agents must have completed at least 28 days prior to enrollment. Prophylactic use of systemic anti-infective agents is permitted.
- Any other active malignancy within 3 years prior to enrollment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ or Stage 0/1 malignancy with minimal risk of recurrence per investigator.
- Gastrointestinal disease that may significantly alter the absorption of iberdomide.
- Previous treatment with a B-cell maturation antigen (BCMA)-directed or cluster of differentiation 3 (CD3) redirecting therapy.
- Previous treatment with iberdomide (CC-220) or Mezigdomide.
- Strong inhibitor or inducer of CYP3A4/5 including grapefruit, St John's Wort or related products within 2 weeks prior to dosing and during the course of study.
- Participant unable or unwilling to undergo study required thromboembolism prophylaxis.

F. Statistical Methods:

[00230] Part 1 Primary Estimand: DLT rate estimated based on data from DLT-evaluable participants during the DLT observation period.

[00231] Part 2 Primary Estimand: AE rate estimated based on data from SAS during the on-treatment period.

[00232] There is no secondary estimand for this study.

[00233] Interim safety assessments are performed on this study. Separate assessments are performed for Part 1 dose escalation and each dose level in Part 2.

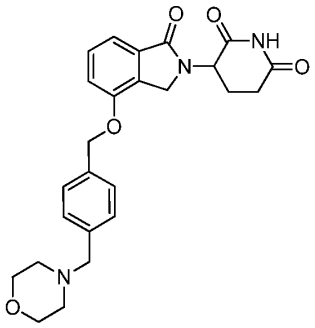
[00234] The examples set forth above are provided to give those of ordinary skill in the art with a complete disclosure and description of how to make and use the claimed

embodiments, and are not intended to limit the scope of what is disclosed herein. Modifications that are obvious to persons of skill in the art are intended to be within the scope of the following claims. All publications, patents, and patent applications cited in this specification are incorporated herein by reference as if each such publication, patent or patent application were specifically and individually indicated to be incorporated herein by reference.

WHAT IS CLAIMED IS:

1. A method of treating or managing multiple myeloma, comprising administering to a patient having multiple myeloma:

(a) a therapeutically effective amount of a compound, wherein the compound is Compound A



Compound A

or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof; in combination with

(b) a therapeutically effective amount of a bispecific antibody comprising a first binding part binding to B cell maturation antigen (BCMA) and a second binding part binding to cluster of differentiation 3 (CD3),

wherein the first binding part binding to BCMA comprises (i) a VH region comprising a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 9, 14, 16, and 17; a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 10, 15, 18, and 23; and a VH CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 11, and 19; and (ii) a VL region comprising a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 12, and 20; a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 7, 13, and 21; and a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8 and 22; and

wherein the second binding part binding to CD3 comprises (i) a VH region comprising a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 26, 32, 37, 39, and 40; a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 27, 33, 38, 41, and 46; and a VH CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 28, 34, and 42; and (ii) a VL region comprising a VL CDR1 having an amino acid sequence selected from the group

consisting of SEQ ID NOs: 29, 35, and 43; a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 30, 36, and 44; and a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 31 and 45.

2. The method of claim 1, wherein the first binding part binding to BCMA comprises:
(a) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:3, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:4, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:5; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:6, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:7, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:8;
(b) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:9, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:10, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:11; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:12, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:13, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:8;
(c) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:14, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:15, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:11; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:12, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:13, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:8;
(d) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:16, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:10, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:11; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:12, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:13, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:8;
(e) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:17, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:18, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:19; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:20, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:21, and a VL CDR3 comprising the amino acid

sequence of SEQ ID NO:22; or

(f) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:16, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:23, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:11; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:12, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:13, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:8.

3. The method of claim 1 or 2, wherein the second binding part binding to CD3 comprises:

(a) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:26, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:27, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:28; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:29, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:30, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:31;

(b) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:32, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:33, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:34; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:35, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:36, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:31;

(c) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:37, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:38, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:34; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:35, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:36, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:31;

(d) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:39, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:33, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:34; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:35, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:36, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:31;

(e) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:40, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:41, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:42; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:43, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:44, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:45; or

(f) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:39, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:46, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:34; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:35, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:36, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:31.

4. The method of any one of claims 1 to 3, wherein

(a) the first binding part binding to BCMA comprises a VH region comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:1 and a VL region comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:2, and

(b) the second binding part binding to CD3 comprises a VH region comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:24 and a VL region comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:25.

5. The method of any one of claims 1 to 4, wherein

(a) the first binding part binding to BCMA comprises a heavy chain and a light chain; and

(b) the second binding part binding to CD3 comprises a heavy chain and a light chain.

6. The method of claim 5, wherein

(a) the heavy chain of the first binding part binding to BCMA comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:47 and the light chain of the first binding part binding to BCMA comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:48, and

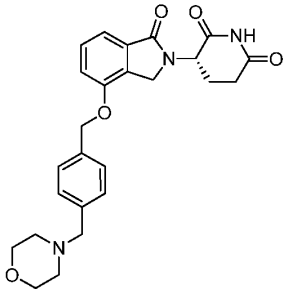
(b) the heavy chain of the second binding part binding to CD3 comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:49 and the light

chain of the second binding part binding to CD3 comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:50.

7. The method of claim 5 or 6, wherein
(a) the heavy chain of the first binding part binding to BCMA comprises the amino acid sequence of SEQ ID NO:47 and the light chain of the first binding part binding to BCMA comprises the amino acid sequence of SEQ ID NO:48, and
(b) the heavy chain of the second binding part binding to CD3 comprises the amino acid sequence of SEQ ID NO:49 and the light chain of the second binding part binding to CD3 comprises the amino acid sequence of SEQ ID NO:50.

8. The method of any one of claims 1 to 7, wherein the bispecific antibody is an IgG2 kappa antibody.

9. The method of any one of claims 1 to 8, wherein the compound is Compound A-S



Compound A-S

or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof.

10. The method of claim 9, wherein the compound is hydrochloride salt of Compound A-S.

11. The method of any one of claims 1 to 10, wherein the multiple myeloma is relapsed, refractory or resistant.

12. The method of claim 11, wherein the multiple myeloma is relapsed or refractory.

13. The method of claim 12, wherein the multiple myeloma is relapsed or refractory to at

least two prior therapies, wherein the prior therapies are selected from lenalidomide, pomalidomide, and a proteasome inhibitor.

14. The method of any one of claims 1 to 10, wherein the multiple myeloma is newly diagnosed multiple myeloma.

15. The method of any one of claims 1 to 14, wherein the compound is administered orally.

16. The method of any one of claims 1 to 15, wherein the compound is administered in an amount of about 0.6 mg, 0.7 mg, 0.75 mg, 0.8 mg, 0.9 mg, 1.0 mg, 1.1 mg, 1.2 mg, 1.3 mg, 1.4 mg, 1.5 mg, or 1.6 mg per day.

17. The method of any one of claims 1 to 16, wherein the compound is administered once daily for 21 days followed by 7 days of rest.

18. The method of any one of claims 1 to 17, wherein the bispecific antibody is administered subcutaneously.

19. The method of any one of claims 1 to 18, wherein the bispecific antibody is administered in an amount of about 12 mg, about 32 mg, or about 76 mg.

20. The method of any one of claims 1 to 19, wherein the bispecific antibody is administered once a week, once every two weeks, or once every four weeks.

21. The method of any one of claims 1 to 20, wherein the bispecific antibody is administered on days 1, 4, and 8 in a 14-day priming dose cycle prior to administration of the compound, and then administered once a week, once every two weeks, or once every four weeks in a 28-day cycle while the compound is administered once a day on days 1 to 21 in the 28-day cycle.

22. The method of claim 21, wherein the bispecific antibody is administered on day 1 in an amount of 12 mg, on day 4 in an amount of 32 mg, and on day 8 in an amount of 76 mg in the 14-day priming dose cycle prior to administration of the compound.

23. The method of claim 21 or 22, wherein, following the priming dose cycle, the bispecific antibody is administered in an amount of 76 mg once a week, once every two

weeks, or once every four weeks in a 28-day cycle while the compound is administered in an amount of 1.0 mg, 1.3 mg or 1.6 mg once a day on days 1 to 21 in the 28-day cycle.

24. The method of claim 21 or 22, wherein, following the priming dose cycle, the bispecific antibody is administered in an amount of 76 mg once a week, once every two weeks, or once every four weeks in a 28-day cycle while the compound is administered in an amount of 0.75 mg once a day on days 1 to 21 in the 28-day cycle.

25. The method of any one of claims 21 to 24, wherein
(a) following the priming dose cycle and subsequent six 28-day cycles, the bispecific antibody is administered in an amount of 76 mg once every two weeks if the patient has received treatment for at least 6 months and a disease response shows at least a partial response or better with responses persisting for at least 2 months; and/or
(b) following the priming dose cycle and subsequent twelve 28-day cycles, the bispecific antibody is administered in an amount of 76 mg once every four weeks if a disease response shows at least a partial response or better with responses persisting for at least 2 months.

26. The method of any one of claims 21 to 23, wherein
(a) following the priming dose cycle and subsequent three 28-day cycles, the bispecific antibody is administered in an amount of 76 mg once every two weeks; and/or
(b) following the priming dose cycle and subsequent six 28-day cycles, the bispecific antibody is administered in an amount of 76 mg once every four weeks.

27. The method of claim 26, wherein the compound is administered in an amount of 1.0 mg once a day on days 1 to 21 of each 28-day cycle.

28. The method of any one of claims 21 to 24, wherein
(a) following the priming dose cycle and subsequent seven or more 28-day cycles, the bispecific antibody is administered in an amount of 76 mg once every two weeks for three 28-day cycles; and/or
(b) following the priming dose cycle and subsequent ten or more 28-day cycles, the bispecific antibody is administered in an amount of 76 mg once every four weeks.

29. The method of any one of claims 21 to 24, wherein
(a) following the priming dose cycle, the bispecific antibody is administered in an amount of

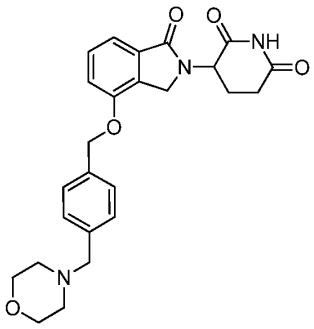
76 mg once every two weeks; and/or

(b) following the priming dose cycle and subsequent three 28-day cycles, the bispecific antibody is administered in an amount of 76 mg once every four weeks.

30. The method of claim 28 or 29, wherein the compound is administered in an amount of 0.75 mg, 1.0 mg, or 1.3 mg once a day on days 1 to 21 of each 28-day cycle.

31. A compound for use in a method of treating multiple myeloma, wherein the method comprises administering to a patient having multiple myeloma:

(a) a therapeutically effective amount of the compound, wherein the compound is Compound A



Compound A

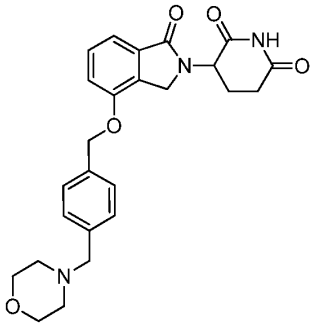
or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof; in combination with

(b) a therapeutically effective amount of a bispecific antibody comprising a first binding part binding to B cell maturation antigen (BCMA) and a second binding part binding to cluster of differentiation 3 (CD3),

wherein the first binding part binding to BCMA comprises (i) a VH region comprising a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 9, 14, 16, and 17; a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 10, 15, 18, and 23; and a VH CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 11, and 19; and (ii) a VL region comprising a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 12, and 20; a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 7, 13, and 21; and a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8 and 22; and

wherein the second binding part binding to CD3 comprises (i) a VH region comprising a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 26, 32, 37, 39, and 40; a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 27, 33, 38, 41, and 46; and a VH CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 28, 34, and 42; and (ii) a VL region comprising a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 29, 35, and 43; a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 30, 36, and 44; and a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 31 and 45.

32. A bispecific antibody for use in a method of treating multiple myeloma, wherein the method comprises administering to a patient having multiple myeloma:
(a) a therapeutically effective amount of the bispecific antibody, where the bispecific antibody comprises a first binding part binding to B cell maturation antigen (BCMA) and a second binding part binding to cluster of differentiation 3 (CD3), wherein the first binding part binding to BCMA comprises (i) a VH region comprising a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 9, 14, 16, and 17; a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 10, 15, 18, and 23; and a VH CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 11, and 19; and (ii) a VL region comprising a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 12, and 20; a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 7, 13, and 21; and a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8 and 22; and wherein the second binding part binding to CD3 comprises (i) a VH region comprising a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 26, 32, 37, 39, and 40; a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 27, 33, 38, 41, and 46; and a VH CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 28, 34, and 42; and (ii) a VL region comprising a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 29, 35, and 43; a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 30, 36, and 44; and a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 31 and 45; in combination with
(b) a therapeutically effective amount of a compound, wherein the compound is Compound A

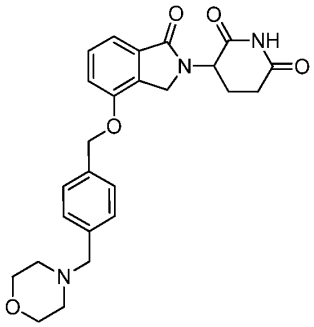


Compound A

or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof.

33. A compound and a bispecific antibody for use in a method of treating multiple myeloma, wherein the method comprises administering to a patient having multiple myeloma:

(a) a therapeutically effective amount of the compound, wherein the compound is Compound A



Compound A

or an enantiomer or mixture of enantiomers, a tautomer, an isotopolog, a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof; in combination with

(b) a therapeutically effective amount of the bispecific antibody comprising a first binding part binding to B cell maturation antigen (BCMA) and a second binding part binding to cluster of differentiation 3 (CD3),

wherein the first binding part binding to BCMA comprises (i) a VH region comprising a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 3,

9, 14, 16, and 17; a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 10, 15, 18, and 23; and a VH CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 11, and 19; and (ii) a VL region comprising a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 12, and 20; a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 7, 13, and 21; and a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8 and 22; and wherein the second binding part binding to CD3 comprises (i) a VH region comprising a VH CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 26, 32, 37, 39, and 40; a VH CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 27, 33, 38, 41, and 46; and a VH CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 28, 34, and 42; and (ii) a VL region comprising a VL CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 29, 35, and 43; a VL CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 30, 36, and 44; and a VL CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 31 and 45.

34. The compound for use of claim 31, the bispecific antibody for use of claim 32, or the compound and the bispecific antibody for use of claim 33, wherein the first binding part binding to BCMA comprises:

(a) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:3, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:4, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:5; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:6, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:7, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:8;

(b) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:9, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:10, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:11; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:12, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:13, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:8;

(c) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:14, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:15, a VH CDR3

comprising the amino acid sequence of SEQ ID NO:11; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:12, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:13, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:8;

(d) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:16, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:10, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:11; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:12, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:13, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:8;

(e) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:17, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:18, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:19; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:20, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:21, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:22; or

(f) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:16, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:23, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:11; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:12, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:13, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:8.

35. The compound for use of claim 31 or 34, the bispecific antibody for use of claim 32 or 34, or the compound and the bispecific antibody for use of claim 33 or 34, wherein the second binding part binding to CD3 comprises:

(a) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:26, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:27, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:28; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:29, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:30, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:31;

(b) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:32, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:33, a VH CDR3

comprising the amino acid sequence of SEQ ID NO:34; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:35, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:36, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:31;

(c) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:37, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:38, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:34; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:35, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:36, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:31;

(d) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:39, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:33, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:34; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:35, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:36, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:31;

(e) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:40, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:41, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:42; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:43, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:44, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:45; or

(f) a VH region comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:39, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:46, a VH CDR3 comprising the amino acid sequence of SEQ ID NO:34; and a VL region comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:35, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:36, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:31.

36. The compound for use of any one of claims 31 and 34 to 35, the bispecific antibody for use of any one of claims 32 and 34 to 35, or the compound and the bispecific antibody for use of any one of claims 33 to 35, wherein

(a) the first binding part binding to BCMA comprises a VH region comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:1 and a VL region

comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:2, and
(b) the second binding part binding to CD3 comprises a VH region comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:24 and a VL region comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:25.

37. The compound for use of any one of claims 31 and 34 to 36, the bispecific antibody for use of any one of claims 32 and 34 to 36, or the compound and the bispecific antibody for use of any one of claims 33 to 36, wherein
(a) the first binding part binding to BCMA comprises a heavy chain and a light chain; and
(b) the second binding part binding to CD3 comprises a heavy chain and a light chain.

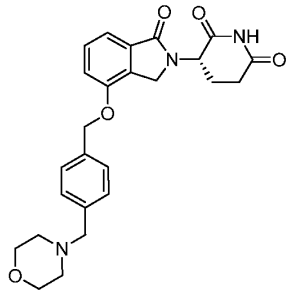
38. The compound for use, the bispecific antibody for use, or the compound and the bispecific antibody for use of claim 37, wherein
(a) the heavy chain of the first binding part binding to BCMA comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:47 and the light chain of the first binding part binding to BCMA comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:48, and
(b) the heavy chain of the second binding part binding to CD3 comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:49 and the light chain of the second binding part binding to CD3 comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:50.

39. The compound for use, the bispecific antibody for use, or the compound and the bispecific antibody for use of claim 37 or 38, wherein
(a) the heavy chain of the first binding part binding to BCMA comprises the amino acid sequence of SEQ ID NO:47 and the light chain of the first binding part binding to BCMA comprises the amino acid sequence of SEQ ID NO:48, and
(b) the heavy chain of the second binding part binding to CD3 comprises the amino acid sequence of SEQ ID NO:49 and the light chain of the second binding part binding to CD3 comprises the amino acid sequence of SEQ ID NO:50.

40. The compound for use of any one of claims 31 and 34 to 39, the bispecific antibody

for use of any one of claims 32 and 34 to 39, or the compound and the bispecific antibody for use of any one of claims 33 to 39, wherein the bispecific antibody is an IgG2 kappa antibody.

41. The compound for use of any one of claims 31 and 34 to 40, the bispecific antibody for use of any one of claims 32 and 34 to 40, or the compound and the bispecific antibody for use of any one of claims 33 to 40, wherein the compound is Compound A-S



Compound A-S

or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, clathrate, or polymorph thereof.

42. The compound for use, the bispecific antibody for use, or the compound and the bispecific antibody for use of claim 41, wherein the compound is hydrochloride salt of Compound A-S.

43. The compound for use of any one of claims 31 and 34 to 42, the bispecific antibody for use of any one of claims 32 and 34 to 42, or the compound and the bispecific antibody for use of any one of claims 33 to 42, wherein the multiple myeloma is relapsed, refractory or resistant.

44. The compound for use, the bispecific antibody for use, or the compound and the bispecific antibody for use of claim 43, wherein the multiple myeloma is relapsed or refractory.

45. The compound for use, the bispecific antibody for use, or the compound and the bispecific antibody for use of claim 44, wherein the multiple myeloma is relapsed or refractory to at least two prior therapies, wherein the prior therapies are selected from lenalidomide, pomalidomide, and a proteasome inhibitor.

46. The compound for use of any one of claims 31 and 34 to 42, the bispecific antibody for use of any one of claims 32 and 34 to 42, or the compound and the bispecific antibody for use of any one of claims 33 to 42, wherein the multiple myeloma is newly diagnosed multiple myeloma.

47. The compound for use of any one of claims 31 and 34 to 46, the bispecific antibody for use of any one of claims 32 and 34 to 46, or the compound and the bispecific antibody for use of any one of claims 33 to 46, wherein the compound is administered orally.

48. The compound for use of any one of claims 31 and 34 to 47, the bispecific antibody for use of any one of claims 32 and 34 to 47, or the compound and the bispecific antibody for use of any one of claims 33 to 47, wherein the compound is administered in an amount of about 0.6 mg, 0.7 mg, 0.75 mg, 0.8 mg, 0.9 mg, 1.0 mg, 1.1 mg, 1.2 mg, 1.3 mg, 1.4 mg, 1.5 mg, or 1.6 mg per day.

49. The compound for use of any one of claims 31 and 34 to 48, the bispecific antibody for use of any one of claims 32 and 34 to 48, or the compound and the bispecific antibody for use of any one of claims 33 to 48, wherein the compound is administered once daily for 21 days followed by 7 days of rest.

50. The compound for use of any one of claims 31 and 34 to 49, the bispecific antibody for use of any one of claims 32 and 34 to 49, or the compound and the bispecific antibody for use of any one of claims 33 to 49, wherein the bispecific antibody is administered subcutaneously.

51. The compound for use of any one of claims 31 and 34 to 50, the bispecific antibody for use of any one of claims 32 and 34 to 50, or the compound and the bispecific antibody for use of any one of claims 33 to 50, wherein the bispecific antibody is administered in an amount of about 12 mg, about 32 mg, or about 76 mg.

52. The compound for use of any one of claims 31 and 34 to 51, the bispecific antibody for use of any one of claims 32 and 34 to 51, or the compound and the bispecific antibody for use of any one of claims 33 to 51, wherein the bispecific antibody is administered once a week, once every two weeks, or once every four weeks.

53. The compound for use of any one of claims 31 and 34 to 52, the bispecific antibody

for use of any one of claims 32 and 34 to 52, or the compound and the bispecific antibody for use of any one of claims 33 to 52, wherein the bispecific antibody is administered on days 1, 4, and 8 in a 14-day priming dose cycle prior to administration of the compound, and then administered once a week, once every two weeks, or once every four weeks in a 28-day cycle while the compound is administered once a day on days 1 to 21 in the 28-day cycle.

54. The compound for use, the bispecific antibody for use, or the compound and the bispecific antibody for use of claim 53, wherein the bispecific antibody is administered on day 1 in an amount of 12 mg, on day 4 in an amount of 32 mg, and on day 8 in an amount of 76 mg in the 14-day priming dose cycle prior to administration of the compound.

55. The compound for use, the bispecific antibody for use, or the compound and the bispecific antibody for use of claim 53 or 54, wherein, following the priming dose cycle, the bispecific antibody is administered in an amount of 76 mg once a week, once every two weeks, or once every four weeks in a 28-day cycle while the compound is administered in an amount of 1.0 mg, 1.3 mg or 1.6 mg once a day on days 1 to 21 in the 28-day cycle.

56. The compound for use, the bispecific antibody for use, or the compound and the bispecific antibody for use of claim 53 or 54, wherein, following the priming dose cycle, the bispecific antibody is administered in an amount of 76 mg once a week, once every two weeks, or once every four weeks in a 28-day cycle while the compound is administered in an amount of 0.75 mg once a day on days 1 to 21 in the 28-day cycle.

57. The compound for use, the bispecific antibody for use, or the compound and the bispecific antibody for use of any one of claims 53 to 56, wherein
(a) following the priming dose cycle and subsequent six 28-day cycles, the bispecific antibody is administered in an amount of 76 mg once every two weeks if the patient has received treatment for at least 6 months and a disease response shows at least a partial response or better with responses persisting for at least 2 months; and/or
(b) following the priming dose cycle and subsequent twelve 28-day cycles, the bispecific antibody is administered in an amount of 76 mg once every four weeks if a disease response shows at least a partial response or better with responses persisting for at least 2 months.

58. The compound for use, the bispecific antibody for use, or the compound and the bispecific antibody for use of any one of claims 53 to 55, wherein

(a) following the priming dose cycle and subsequent three 28-day cycles, the bispecific antibody is administered in an amount of 76 mg once every two weeks; and/or
(b) following the priming dose cycle and subsequent six 28-day cycles, the bispecific antibody is administered in an amount of 76 mg once every four weeks.

59. The compound for use, the bispecific antibody for use, or the compound and the bispecific antibody for use of claim 58, wherein the compound is administered in an amount of 1.0 mg once a day on days 1 to 21 of each 28-day cycle.

60. The compound for use, the bispecific antibody for use, or the compound and the bispecific antibody for use of any one of claims 53 to 56, wherein
(a) following the priming dose cycle and subsequent seven or more 28-day cycles, the bispecific antibody is administered in an amount of 76 mg once every two weeks for three 28-day cycles; and/or
(b) following the priming dose cycle and subsequent ten or more 28-day cycles, the bispecific antibody is administered in an amount of 76 mg once every four weeks.

61. The compound for use, the bispecific antibody for use, or the compound and the bispecific antibody for use of any one of claims 53 to 56, wherein
(a) following the priming dose cycle, the bispecific antibody is administered in an amount of 76 mg once every two weeks; and/or
(b) following the priming dose cycle and subsequent three 28-day cycles, the bispecific antibody is administered in an amount of 76 mg once every four weeks.

62. The compound for use, the bispecific antibody for use, or the compound and the bispecific antibody for use of claim 60 or 61, wherein the compound is administered in an amount of 0.75 mg, 1.0 mg, or 1.3 mg once a day on days 1 to 21 of each 28-day cycle.