

What is claimed is:

1. Use of a bispecific antibody in the manufacture of a medicament for~~A method of~~ treating a BCMA+ cancer in a subject in need thereof, ~~wherein comprising administering to the~~ subject a bispecific antibody comprises comprising a first antigen-binding domain that specifically binds a human B-cell maturation antigen (BCMA) on a target tumor cell, and a second antigen-binding domain that specifically binds human CD3, wherein the ~~medicament-bispecific antibody~~ is for administration administered to the subject at a dose of at least 1 mg of the bispecific antibody weekly, and wherein:-

~~2. — The method of claim 1, wherein the BCMA+ cancer is multiple myeloma.~~

~~3. — The method of claim 1 or 2, wherein~~ the first antigen-binding domain comprises:

(a) three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 66; and

(b) three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO:82, and

the second antigen-binding domain comprises:

(a) three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 90 or SEQ ID NO: 98; and

(b) three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO:82..

24. The use~~method~~ of claim 13, wherein the BCMA+ cancer is multiple myeloma.

3. The use of claim 1 or 2, wherein the first antigen-binding domain comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO:68, a HCDR2 comprising the amino acid sequence of SEQ ID NO:70, and a HCDR3 comprising the amino acid sequence of SEQ ID NO:72.

4.5. The usemethod of claim ~~3 or 4~~, wherein the first antigen-binding domain comprises a LCDR1 comprising the amino acid sequence of SEQ ID NO:84, a LCDR2 comprising the amino acid sequence of SEQ ID NO:86, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:88.

56. The usemethod of any one of claims 1-4~~claim 3~~, wherein the first antigen-binding domain comprises a HCVR comprising the amino acid sequence of SEQ ID NO: 66, and a LCVR comprising the amino acid sequence of SEQ ID NO: 82.

67. The usemethod of any one of claims 1-56, ~~wherein the second antigen-binding domain comprises:~~

~~(a) — three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 90 or SEQ ID NO: 98; and~~

~~(b) — three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO:82.~~

~~8. — The method of claim 7,~~ wherein the second antigen-binding domain comprises:

(a) a HCDR1 comprising the amino acid sequence of SEQ ID NO: 92 or SEQ ID NO: 100;

(b) a HCDR2 comprising the amino acid sequence of SEQ ID NO: 94 or SEQ ID NO: 102; and

(c) a HCDR3 comprising the amino acid sequence of SEQ ID NO: 96 or SEQ ID NO: 104.

79. The usemethod of claim 67 or 8, wherein the second antigen-binding domain comprises a LCDR1 comprising the amino acid sequence of SEQ ID NO:84, a LCDR2 comprising the amino acid sequence of SEQ ID NO:86, and a LCDR3 comprising the amino acid sequence of SEQ ID NO:88.

~~810.~~ The usemethod of claim 97, wherein the second antigen-binding domain comprises:

(a) HCDR1, HCDR2, HCDR3 domains, respectively, comprising the amino acid sequences of SEQ ID NOs: 92, 94, 96; and LCDR1, LCDR2, LCDR3 domains, respectively, comprising the amino acid sequences of SEQ ID NOs: 84, 86, 88; or

(b) HCDR1, HCDR2, HCDR3 domains, respectively, comprising the amino acid sequences of SEQ ID NOs: 100, 102, 104; and LCDR1, LCDR2, LCDR3 domains, respectively, comprising the amino acid sequences of SEQ ID NOs: 84, 86, 88.

911. The usemethod of claim 810, wherein the second antigen-binding domain comprises:

(a) a HCVR comprising the amino acid sequence of SEQ ID NO: 90, and a LCVR comprising the amino acid sequence of SEQ ID NO: 82; or

(b) a HCVR comprising the amino acid sequence of SEQ ID NO: 98, and a LCVR comprising the amino acid sequence of SEQ ID NO: 82.

1012. The usemethod of claim 1 or 2, wherein the bispecific antibody comprises:

(a) a first antigen-binding domain that comprises HCDR1, HCDR2, HCDR3 domains, respectively, comprising the amino acid sequences of SEQ ID NOs: 68, 70, 72, and LCDR1, LCDR2, LCDR3 domains, respectively, comprising the amino acid sequences of SEQ ID NOs: 84, 86, 88; and

(b) a second antigen binding domain that comprises HCDR1, HCDR2, HCDR3 domains, respectively, comprising the amino acid sequences of SEQ ID NOs: 92, 94, 96, and LCDR1, LCDR2, LCDR3 domains, respectively, comprising the amino acid sequences of SEQ ID NOs: 84, 86, 88.

1113. The usemethod of claim 1 or 2, wherein the bispecific antibody comprises:

(a) a first antigen-binding domain that comprises HCDR1, HCDR2, HCDR3 domains, respectively, comprising the amino acid sequences of SEQ ID NOs: 68, 70, 72, and LCDR1, LCDR2, LCDR3 domains, respectively, comprising the amino acid sequences of SEQ ID NOs: 84, 86, 88; and

(b) a second antigen binding domain that comprises HCDR1, HCDR2, HCDR3 domains, respectively, comprising the amino acid sequences of SEQ ID NOs: 100, 102, 104, and LCDR1, LCDR2, LCDR3 domains, respectively, comprising the amino acid sequences of SEQ ID NOs: 84, 86, 88.

1214. The usemethod of claim 1 or 2, wherein

(a) the bispecific antibody comprises:

(a) a first antigen binding domain that comprises a HCVR comprising the amino acid sequence of SEQ ID NO: 66, and a LCVR comprising the amino acid sequence of SEQ ID NO: 82; and

~~(b)~~ — a second antigen binding domain that comprises a HCVR comprising the amino acid sequence of SEQ ID NO: 90, and a LCVR comprising the amino acid sequence of SEQ ID NO: 82, or

~~(b)~~ —

~~15.~~ — The ~~method of claim 13, wherein the bispecific~~ antibody comprises:

~~(a)~~ — a first antigen binding domain that comprises a HCVR comprising the amino acid sequence of SEQ ID NO: 66, and a LCVR comprising the amino acid sequence of SEQ ID NO: 82; and

~~(b)~~ — a second antigen binding domain that comprises a HCVR comprising the amino acid sequence of SEQ ID NO: 98, and a LCVR comprising the amino acid sequence of SEQ ID NO: 82.

~~1316.~~ The ~~use~~method of claim ~~1 or 2, wherein the antibody comprises:~~

~~(a)~~ — a first antigen-binding domain comprising the CDRs of a HCVR comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 50, 66, 122, and 124, and the CDRs of a LCVR comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 10, 26, 42, 58, 74, 82, 123, and 125; and

~~(b)~~ — a second antigen-binding domain that specifically binds human CD3.

~~17.~~ — The method of claim 16, wherein the first antigen-binding domain comprises the CDRs from a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 122/123, 124/125, 2/82, 18/82, 34/82, 50/82, 66/82, 122/82, and 124/82.

~~18.~~ — The method of claim 17, wherein the first antigen-binding domain comprises HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 domains, respectively, selected from the group consisting of SEQ ID NOs: ~~4-6-8-12-14-16, 20-22-24-28-30-32, 36-38-40-44-46-48, 52-54-56-60-62-64, 68-70-72-76-78-80, 4-6-8-84-86-88, 20-22-24-84-86-88, 36-38-40-84-86-88, 52-54-56-84-86-88, and 68-70-72-84-86-88.~~

~~19.~~ — The method of claim 18, wherein the first antigen-binding domain comprises the a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 122/123, 124/125, 2/82, 18/82, 34/82, 50/82, 66/82, 122/82, and 124/82.

~~20.~~ — The method of any one of claims 16-19, wherein the second antigen-binding domain comprises the CDRs of a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 90/82 and 98/82.

~~21.~~ — The method of any one of claims 1-20, wherein the bispecific antibody comprises a human IgG heavy chain constant region.

~~22. The method of claim 21, wherein the bispecific antibody comprises a first heavy chain comprising a constant region comprising the amino acid sequence of SEQ ID NO: 130.~~

~~23. The method of claim 21 or 22, wherein the bispecific antibody comprises a second heavy chain comprising a constant region comprising the amino acid sequence of SEQ ID NO: 131.~~

~~24. The method of any one of claims 1-23, wherein the bispecific antibody comprises a first heavy chain comprising the amino acid sequence of SEQ ID NO: 126, a second heavy chain comprising the amino acid sequence of SEQ ID NO: 127 or SEQ ID NO: 128, and a common light chain comprising the amino acid sequence of SEQ ID NO: 129.~~

~~1425. Use The method of a bispecific antibody in the manufacture claim 21, wherein the human IgG heavy chain constant region is isotype IgG1 of a medicament for~~

~~26. The method of claim 21, wherein the human IgG heavy chain constant region is isotype IgG4.~~

~~27. The method of claim 25 or 26, wherein the bispecific antibody comprises a chimeric hinge that reduces Fcγ receptor binding relative to a wild-type hinge of the same isotype.~~

~~28. A method of treating multiple myeloma in a subject in need thereof, wherein the method comprising administering to the subject a bispecific antibody comprising a first heavy chain and common light chain pair comprising a first antigen-binding domain that specifically binds a human B-cell maturation antigen (BCMA), and a second heavy chain and common light chain pair comprising a second antigen-binding domain that specifically binds human CD3, wherein the first antigen-binding domain comprises three heavy chain complementarity determining regions (CDRs) and three light chain CDRs comprising the amino acid sequences of SEQ ID NOs: 68, 70, 72, 84, 86, and 88, respectively, the second antigen-binding domain comprises three heavy chain CDRs and three light chain CDRs comprising the amino acid sequences of SEQ ID NOs: 92, 94, 96, 84, 86, and 88, respectively and wherein the medicament bispecific antibody is for administration administered to the subject at a dose of at least 1 mg of the bispecific antibody weekly.~~

~~1529. The use method of claim 1428, wherein the first heavy chain comprises a first heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 66, the second heavy chain comprises a second heavy chain variable region comprising the amino acid~~

sequence of SEQ ID NO: 90, and the common light chain comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 82.

1630. The use method of claim 1529, wherein the first heavy chain comprises the amino acid sequence of SEQ ID NO: 126, the second heavy chain comprises the amino acid sequence of SEQ ID NO: 127, and the common light chain comprises the amino acid sequence of SEQ ID NO: 129.

1731. Use of a bispecific antibody in the manufacture of a medicament for A method ~~of~~ treating multiple myeloma in a subject in need thereof, ~~wherein the method comprising administering to the subject a~~ bispecific antibody ~~comprises comprising~~ a first heavy chain and common light chain pair comprising a first antigen-binding domain that specifically binds a human B-cell maturation antigen (BCMA), and a second heavy chain and common light chain pair comprising a second antigen-binding domain that specifically binds human CD3, wherein the first antigen-binding domain comprises three heavy chain complementarity determining regions (CDRs) and three light chain CDRs comprising the amino acid sequences of SEQ ID NOs: 68, 70, 72, 84, 86, and 88, respectively, the second antigen-binding domain comprises three heavy chain CDRs and three light chain CDRs comprising the amino acid sequences of SEQ ID NOs: 100, 102, 104, 84, 86, and 88, respectively and wherein the ~~medicament bispecific antibody~~ is for administration administered to the subject at a dose of at least 1 mg of the bispecific antibody weekly.

1832. The use method of claim 1728, wherein the first heavy chain comprises a first heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 66, the second heavy chain comprises a second heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 98, and the common light chain comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 82.

1933. The use method of claim 1829, wherein the first heavy chain comprises the amino acid sequence of SEQ ID NO: 126, the second heavy chain comprises the amino acid sequence of SEQ ID NO: 128, and the common light chain comprises the amino acid sequence of SEQ ID NO: 129.

2034. The use method of any one of claims 1-1933, ~~wherein the further comprising administering a second therapeutic agent or therapeutic regimen.~~

~~35. The method of claim 34, wherein the second therapeutic agent or therapeutic regimen comprises a chemotherapeutic drug, DNA alkylators, immunomodulators, proteasome inhibitors, histone deacetylase inhibitors, radiotherapy, a stem cell transplant, a different bispecific antibody that interacts with a different tumor cell surface antigen and a T cell or immune cell antigen, an antibody drug conjugate, a bispecific antibody conjugated to an anti-tumor agent, a PD-1, PD-L1, or CTLA-4 checkpoint inhibitor, or combinations thereof.~~

~~36. The method of any one of claims 1-35, wherein the bispecific antibody is administered in a dosing regimen comprising a split initial dose.~~

~~37. The method of any one of claims 1-36, wherein the dose of the bispecific antibody is administered to the subject at a dose of from 3 mg to 900 mg weekly.~~

~~38. The method of any one of claims 1-37, wherein the BCMA+ cancer is multiple myeloma, and the subject has been previously treated with an anti-CD38 antibody therapy.~~

~~39. The method of claim 38, wherein the anti-CD38 antibody is daratumumab or isatuximab.~~

~~40. The method of any one of claims 1-37, wherein the BCMA+ cancer is multiple myeloma, and the subject has been previously treated with a proteasome inhibitor or an immunomodulatory drug.~~

~~2141. The usemethod of claim 40, wherein the proteasome inhibitor is bortezomib, carfilzomib or ixazomib.~~

~~42. The method of claim 40, wherein the immunomodulatory drug is lenalidomide or pomalidomide.~~

~~43. The method of any one of claims 2-201-42, wherein the subject has been diagnosed with a multiple myeloma immune subtype selected from immunoglobulin G, immunoglobulin A, lambda light chain, or kappa light chain, or the subject has an extramedullary plasmacytoma.~~

~~2244. The usemethod of any one of claims 2-201-42, wherein the multiple myeloma subject has an extramedullary plasmacytoma.~~

~~45. The method of any one of claims 1-44, wherein the BCMA+ cancer is relapsed or refractory multiple myeloma.~~

~~4623. The usemethod of any one of claims 1-2245, wherein the subject is at least triple-refractory to prior therapies.~~

~~4724. The usemethod of claim 2346, wherein the subject is quad-refractory or penta-refractory to prior therapies.~~

~~4825. A dosing regimen~~ Use of a bispecific antibody in the manufacture of a medicament for use in a dosing regimen~~method~~ for treating multiple myeloma in a subject in need thereof, wherein the dosing regimen comprises administration of a bispecific antibody to the subject at an initial dose during week one of the dosing regimen, at a secondary dose during week two of the dosing regimen, and at a tertiary dose during week three of the dosing regimen, wherein the tertiary dose is equal to or greater than the secondary dose, and the secondary dose is greater than the initial dose,

wherein the bispecific antibody comprises:

(a) a first heavy chain and common light chain pair comprising a first antigen-binding domain that specifically binds a human B-cell maturation antigen (BCMA), and a second heavy chain and common light chain pair comprising a second antigen-binding domain that specifically binds human CD3, wherein the first antigen-binding domain comprises three heavy chain complementarity determining regions (CDRs) and three light chain CDRs comprising the amino acid sequences of SEQ ID NOs: 68, 70, 72, 84, 86, and 88, respectively, the second antigen-binding domain comprises three heavy chain CDRs and three light chain CDRs comprising the amino acid sequences of SEQ ID NOs: 92, 94, 96, 84, 86, and 88, respectively, or

(b) a first heavy chain and common light chain pair comprising a first antigen-binding domain that specifically binds a human B-cell maturation antigen (BCMA), and a second heavy chain and common light chain pair comprising a second antigen-binding domain that specifically binds human CD3, wherein the first antigen-binding domain comprises three heavy chain complementarity determining regions (CDRs) and three light chain CDRs comprising the amino acid sequences of SEQ ID NOs: 68, 70, 72, 84, 86, and 88, respectively, the second antigen-binding domain comprises three heavy chain CDRs and three light chain CDRs comprising the amino acid sequences of SEQ ID NOs: 100, 102, 104, 84, 86, and 88, respectively.

~~49. The dosing regimen of claim 48, wherein the bispecific antibody comprises a first heavy chain and common light chain pair comprising a first antigen-binding domain that specifically~~

~~binds a human B-cell maturation antigen (BCMA), and a second heavy chain and common light chain pair comprising a second antigen-binding domain that specifically binds human CD3, wherein the first antigen-binding domain comprises three heavy chain complementarity determining regions (CDRs) and three light chain CDRs comprising the amino acid sequences of SEQ ID NOs: 68, 70, 72, 84, 86, and 88, respectively, the second antigen-binding domain comprises three heavy chain CDRs and three light chain CDRs comprising the amino acid sequences of SEQ ID NOs: 92, 94, 96, 84, 86, and 88, respectively.~~

~~50. — The dosing regimen of claim 48, wherein the bispecific antibody comprises a first heavy chain and common light chain pair comprising a first antigen-binding domain that specifically binds a human B-cell maturation antigen (BCMA), and a second heavy chain and common light chain pair comprising a second antigen-binding domain that specifically binds human CD3, wherein the first antigen-binding domain comprises three heavy chain complementarity determining regions (CDRs) and three light chain CDRs comprising the amino acid sequences of SEQ ID NOs: 68, 70, 72, 84, 86, and 88, respectively, the second antigen-binding domain comprises three heavy chain CDRs and three light chain CDRs comprising the amino acid sequences of SEQ ID NOs: 100, 102, 104, 84, 86, and 88, respectively.~~

~~51. — The dosing regimen of claim 49, wherein the first heavy chain comprises a first heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 66, the second heavy chain comprises a second heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 90, and the common light chain comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 82.~~

~~52. — The dosing regimen of claim 51, wherein the first heavy chain comprises the amino acid sequence of SEQ ID NO: 126, the second heavy chain comprises the amino acid sequence of SEQ ID NO: 127, and the common light chain comprises the amino acid sequence of SEQ ID NO: 129.~~

~~53. — The dosing regimen of claim 50, wherein the first heavy chain comprises a first heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 66, the second heavy chain comprises a second heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 98, and the common light chain comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 82.~~

~~54. — The dosing regimen of claim 53, wherein the first heavy chain comprises the amino acid sequence of SEQ ID NO: 126, the second heavy chain comprises the amino acid~~

sequence of SEQ ID NO: 128, and the common light chain comprises the amino acid sequence of SEQ ID NO: 129.

55. — The dosing regimen of any one of claims 48-54, wherein the initial dose is from 1 to 5 mg.

56. — The dosing regimen of any one of claims 48-55, wherein the secondary dose is from 3 mg to 400 mg.

57. — The dosing regimen of any one of claims 48-56, wherein the tertiary dose is from 3 mg to 800 mg.

58. — The dosing regimen of any one of claims 48-57, wherein the initial dose is 5 mg.

59. — The dosing regimen of any one of claims 48-58, wherein the secondary dose is 25 mg.

60. — The dosing regimen of any one of claims 48-59, wherein the tertiary dose is from 50 mg to 800 mg.

61. — The dosing regimen of any one of claims 48-60, comprising administration of the tertiary dose weekly for at least 12 weeks during a weekly dosing period of the dosing regimen.

62. — The dosing regimen of claim 61, further comprising administration of the tertiary dose once every two weeks during a biweekly dosing period of the dosing regimen that follows the weekly dosing period of the dosing regimen.

63. — The dosing regimen of any one of claims 48-62, wherein the subject has been previously treated with an anti-CD38 antibody therapy, a proteasome inhibitor, or an immunomodulatory drug.

64. — The dosing regimen of claim 63, wherein the anti-CD38 antibody is daratumumab or isatuximab.

65. — The dosing regimen of claim 63, wherein the proteasome inhibitor is bortezomib, carfilzomib or ixazomib.

66. — The dosing regimen of claim 63, wherein the immunomodulatory drug is lenalidomide or pomalidomide.

~~67. — The dosing regimen of any one of claims 48-62, wherein the multiple myeloma is relapsed or refractory multiple myeloma.~~

~~68. — The dosing regimen of any one of claims 48-67, wherein the subject is at least triple-refractory to prior therapies.~~

~~69. — The dosing regimen of claim 68, wherein the subject is quad-refractory or penta-refractory to prior therapies.~~