CLAIMS

What is claimed is:

1. An immunoconjugate comprising:
a recombinant antibody comprising:
a first heavy chain comprising SEQ ID NO: 9,
a first light chain comprising SEQ ID NO: 10,
a second heavy chain comprising SEQ ID NO: 9, and
a second light chain comprising SEQ ID NO: 10; and
one, two, three or four pairs of adducts;
wherein each adduct of said one, two, three or four pairs of adducts comprises a monomethylauristatin E (MMAE) that is conjugated to said recombinant antibody via a maleimidocaproyl-valine-citrulline-para-amino benzyloxycarbonyl (mc-vc-PAB) linker;
wherein each of said one, two, three, or four pairs of adducts is conjugated to a pair of cysteine residues of said recombinant antibody,
wherein said pairs of cysteine residues are selected from:
C219 of the first heavy chain and C214 of the first light chain;
C219 of the second heavy chain and C214 of the second light chain;
C225 of the first heavy chain and C225 of the second ~~light~~ heavy chain; and
C228 of the first heavy chain and C228 of the second ~~light~~ heavy chain.

2. The immunoconjugate of claim 1 comprising two pairs of said adducts.

3. A pharmaceutical composition comprising the immunoconjugate of claim 1 at a concentration of about 10.0 ± 1.0 mg/mL, about 20 mM histidine buffer at pH 6.0, about 8.0% sucrose, and about 0.01% polysorbate 80.

~~4. A pharmaceutical composition that comprises an immunoconjugate at a concentration of about 10.0 ± 1.0 mg/mL, about 20 mM histidine buffer, about 8.0% sucrose, about 0.01% polysorbate 80; and wherein said immunoconjugate comprises:~~
~~(a) a recombinant antibody that specifically binds CD46 that comprises a heavy chain (HC) variable region that comprises three complementarity determining regions (CDRs): HC CDR1, HC CDR2 and HC CDR3 and a light chain (LC) variable region that comprises three CDRs: LC CDR1, LC CDR2, and LC CDR3, wherein said HC CDR1, HC CDR2, HC CDR3 comprise an amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, and SEQ ID NO: 3, respectively, and said LC CDR1, LC CDR2, and LC CDR3 comprise an amino acid sequence of SEQ ID NO: 4, SEQ ID NO: 5, and SEQ ID NO: 6, respectively; and~~
~~(b) monomethylauristatin E (MMAE) that is conjugated to said recombinant antibody via a maleimidocaproyl-valine-citrulline-para-amino benzyloxycarbonyl (mc-vc-PAB) linker.~~
~~5. A pharmaceutical composition comprising an immunoconjugate, a pharmaceutically acceptable buffer, and a pharmaceutically-acceptable stabilizing agent;~~

wherein said immunoconjugate comprises

(a) a recombinant antibody that specifically binds CD46 that comprises a heavy chain (HC) variable region that comprises three complementarity determining regions (CDRs): HC CDR1, HC CDR2 and HC CDR3 and a light chain (LC) variable region that comprises three CDRs: LC CDR1, LC CDR2, and LC CDR3, wherein said HC CDR1, HC CDR2, HC CDR3 comprise an amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, and SEQ ID NO: 3, respectively, and said LC CDR1, LC CDR2, and LC CDR3 comprise an amino acid sequence of SEQ ID NO: 4, SEQ ID NO: 5, and SEQ ID NO: 6, respectively;

(b) an effector agent that is conjugated to said recombinant antibody.

6. The pharmaceutical composition of claim 5, wherein said pharmaceutical composition has a pH from about 5.0 to about 7.0.

7. The pharmaceutical composition of any one of claims 5-6, wherein the buffer comprises citrate, phosphate, acetate, tromethamine, histidine, succinate, malate, or α-ketoglutaric acid.

8. The pharmaceutical composition of any one of claims 5-7, wherein the buffer comprises from about 10 mM to about 30 mM histidine and the pH is from about 5 to about 7.

9. The pharmaceutical composition of claim 7, wherein the buffer comprises about 20 mM histidine and the pH is about 6.0.

10. The pharmaceutical composition of any one of claims 5-9, wherein the stabilizing agent prevents denaturation of said recombinant antibody, prevents aggregation of said immunoconjugates, or both.

11. The pharmaceutical composition of any one of claims 5-10, wherein the stabilizing agent comprises a non-ionic surfactant.

12. The pharmaceutical composition of claim 11, wherein the stabilizing agent comprises a polysorbate.

13. The pharmaceutical composition of claim 12, wherein the stabilizing agent is about 0.01% polysorbate-80.

14. The pharmaceutical composition of any one of claims 5-13, further comprising a pharmaceutically acceptable cryoprotectant.

15. The pharmaceutical composition of claim 14, wherein the cryoprotectant comprises a saccharide.

16. The pharmaceutical composition of claim 15, wherein the saccharide comprises about 6% to about 10% sucrose or trehalose.

17. The pharmaceutical composition of claim 16, wherein the cryoprotectant is about 8.0% sucrose.

18. The pharmaceutical composition of any one of claims 5-17, wherein said recombinant antibody is conjugated to an effector agent wherein said effector agent comprises a drug (or a prodrug thereof), a peptide, a protein, a detectable label, a liposome containing a drug (or prodrug thereof), a radionuclide, a viral particle, or a chelate.

19. The pharmaceutical composition of claim 18, wherein said effector agent comprises a drug.

20. The pharmaceutical composition of claim 19, wherein said drug is an anti-cancer drug.

21. The pharmaceutical composition of claim 19 or claim 20, wherein said drug is a chemotherapeutic agent.

22. The pharmaceutical composition of claim 19, claim 20, or claim 21, wherein said drug is a microtubule inhibitor, a DNA-damaging agent, or a polymerase inhibitor.

23. The pharmaceutical composition of claim 22, wherein said drug is a microtubule inhibitor.

24. The pharmaceutical composition of claim 23, wherein said microtubule inhibitor is an auristatin (or a derivative thereof), dolastatin 10 (or a derivative thereof), or maytansine (or a derivative thereof).

25. The pharmaceutical composition of claim 22 or claim 23, wherein said microtubule inhibitor is monomethylauristatin F (MMAF), auristatin E (AE), monomethylauristatin E (MMAE), valine-citrulline MMAE (vcMMAE), or valine-citrulline MMAF (vcMMAF).

26. The pharmaceutical composition of claim 25, wherein said microtubule inhibitor is monomethylauristatin E (MMAE).

27. The pharmaceutical composition of any one of claims 5 - 26, wherein a ratio of said effector agent to said recombinant antibody in said population of immunoconjugates is from about 3 to about 5.

28. The pharmaceutical composition of claim 27, wherein the ratio of said effector agent to said recombinant antibody in said population of immunoconjugates is about 4.

29. The pharmaceutical composition of any one of claims 5 - 28, wherein said effector agent is conjugated to said recombinant antibody via a linker.

30. The pharmaceutical composition of claim 29, wherein said linker is a peptide linker, a small molecule linker, or a linker that comprises a peptide and a small molecule.

31. The pharmaceutical composition of claim 29 or claim 30, wherein said linker comprises maleimidocaproyl-valine-citrulline-para-amino benzyloxycarbonyl (mc-vc-PAB).

32. A method of treating a cancer comprising a cell expressing CD46 in a human subject in need thereof, said method comprising administering to said subject an immunoconjugate comprising:

a recombinant antibody comprising:

a first heavy chain comprising SEQ ID NO: 9,

a first light chain comprising SEQ ID NO: 10,

a second heavy chain comprising SEQ ID NO: 9, and

a second light chain comprising SEQ ID NO: 10; and

one, two, three or four pairs of adducts;

wherein each adduct of said one, two, three or four pairs of adducts comprises a monomethylauristatin E (MMAE) that is conjugated to said recombinant antibody via a maleimidocaproyl-valine-citrulline-para-amino benzyloxycarbonyl (mc-vc-PAB) linker;

wherein each of said one, two, three, or four pairs of adducts is conjugated to a pair of cysteine residues of said recombinant antibody,

wherein said pairs of cysteine residues are selected from:

C219 of the first heavy chain and C214 of the first light chain;

C219 of the second heavy chain and C214 of the second light chain;

C225 of the first heavy chain and C225 of the second light chain; and

C228 of the first heavy chain and C228 of the second light chain.

33. The method of claim 32, wherein said cancer is relapsed or refractory multiple myeloma (RRMM).

34. The method of claim 32, wherein said cancer is metastatic castration resistant prostate cancer (mCRPC).

35. The method of any one of claims 32 - 34, wherein said immunoconjugate comprises two pairs of said adducts.

36. The method of any one of claims 32 - 35, further comprising detecting said CD46 in said cell.

37. The method of claim 36, wherein said detecting comprises immunofluorescence microscopy or immunohistochemistry.

38. The method of claim 36, wherein said detecting comprises flow cytometry.

39. The method of claim 36, wherein said detecting comprises detecting an amplification of chromosome location 1q21.

40. The method of any one of claims 32 - 39, wherein said immunoconjugate is administered to said human subject via intravenous infusion.

41. The method of any one of claims 32 - 40, wherein said immunoconjugate is administered to said human subject every 7 days, every 14 days, every 18 days, every 21 days, or every 30 days.

42. The method of claim 41, wherein said immunoconjugate is administered to said human subject every 21 days over at least three cycles.

43. The method of any one of claims 32 - 42, wherein said immunoconjugate is administered at a dose from about 1.2 to about 3.0 mg/kg.

44. The method of claim 43, wherein said recombinant antibody is administered at a dose of about 1.8, about 2.4, about 2.7, or about 3.0 mg/kg.

45. The method of any one of claims 43 - 44, wherein the weight, in kg, of said human subject is an actual body weight.

46. The method of any one of claims 43 - 44, wherein the weight, in kg, of said human subject is an adjusted body weight.

47. The method of any one of claims 43 - 44, wherein the weight, in kg, of said human subject is:

an actual body weight of said human subject if the actual body weight of said human subject is less than an adjusted body weight of said subject;

an adjusted body weight of said human subject if

the actual body weight of said human subject is greater than or equal to an adjusted body weight of said subject, and

the adjusted body weight of said human subject is less than 100 kg; or

100 kg if the adjusted body weight of said human subject is greater than or equal to 100 kg

48. A method of treating metastatic castration resistant prostate cancer in a human subject in need thereof, said method comprising administering to said subject an immunoconjugate comprising,

(i) a recombinant antibody that specifically binds CD46 that comprises heavy chain (HC) variable region that comprises three complementarity determining regions (CDRs): HC CDR1, HC CDR2 and HC CDR3 and the light chain comprises a light chain (LC) variable region comprising three CDRs: LC CDR1, LC CDR2, and LC CDR3, wherein

said HC CDR1, HC CDR2, HC CDR3 comprise an amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, and SEQ ID NO: 3, respectively, and LC CDR1, LC CDR2, and LC CDR3 comprise an amino acid sequence of SEQ ID NO: 4, SEQ ID NO: 5, and SEQ ID NO: 6, respectively; conjugated to

(ii) monomethylauristatin E (MMAE) via a linker, wherein said linker comprises maleimidocaproyl-valine-citrulline-para-amino benzyloxycarbonyl (mc-vc-PAB),

wherein said immunoconjugate is administered at a dose of from about 1.2 to about 3.0 mg/kg.

49. A method of treating relaxed or refractory multiple myeloma in a human subject in need thereof, said method comprising administering to said subject an immunoconjugate comprising,

(i) a recombinant antibody that specifically binds CD46 that comprises heavy chain (HC) variable region that comprises three complementarity determining regions (CDRs): HC CDR1, HC CDR2 and HC CDR3 and the light chain comprises a light chain (LC) variable region comprising three CDRs: LC CDR1, LC CDR2, and LC CDR3, wherein said HC CDR1, HC CDR2, HC CDR3 comprise an amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, and SEQ ID NO: 3, respectively, and LC CDR1, LC CDR2, and LC CDR3 comprise an amino acid sequence of SEQ ID NO: 4, SEQ ID NO: 5, and SEQ ID NO: 6, respectively; conjugated to

(ii) monomethylauristatin E (MMAE) via a linker, wherein said linker comprises maleimidocaproyl-valine-citrulline-para-amino benzyloxycarbonyl (mc-vc-PAB),

wherein said immunoconjugate is administered at a dose of from about 1.8 to about 3.0 mg/kg.

50. The method of any one of claims 48-49, wherein the weight, in kg, of said human subject is an actual body weight.

51. The method of any one of claims 48-49, wherein a calculated weight, in kg, of said human subject is an adjusted body weight.

52. The method of any one of claims 48-49, wherein a calculated weight, in kg, of said human subject is:

an actual body weight of said human subject if the actual body weight of said human subject is less than an adjusted body weight of said subject;

an adjusted body weight of said human subject if

the actual body weight of said human subject is greater than or equal to an adjusted body weight of said subject, and

the adjusted body weight of said human subject is less than 100 kg; or

100 kg if the adjusted body weight of said human subject is greater than or equal to 100 kg.

53. The method of any one of claims 48 - 52, further comprising detecting said CD46 in said cell.

54. The method of claim 53, wherein said detecting comprises immunofluorescence microscopy or immunohistochemistry.

55. The method of claim 53, wherein said detecting comprises flow cytometry.

56. The method of claim 53, wherein said detecting comprises detecting an amplification of chromosome location 1q21.

57. The method of any one of claims 48 - 56, wherein said immunoconjugate is administered to said human subject via intravenous infusion.

58. The method of any one of claims 48 - 57, wherein said immunoconjugate is administered to said human subject every 7 days, every 14 days, every 18 days, every 21 days, or every 30 days.

59. The method of claim 58, wherein said immunoconjugate is administered to said human subject every 21 days over at least three cycles.

60. A method of treating cancer in a human subject in need thereof, said method comprising administering to said human subject an immunoconjugate that comprises:

(a) a recombinant antibody that specifically binds CD46 that comprises a heavy chain (HC) variable region that comprises three complementarity determining regions (CDRs): HC CDR1, HC CDR2 and HC CDR3 and a light chain (LC) variable region that comprises three CDRs: LC CDR1, LC CDR2, and LC CDR3, wherein said HC CDR1, HC CDR2, HC CDR3 comprise an amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, and SEQ ID NO: 3, respectively, and said LC CDR1, LC CDR2, and LC CDR3 comprise an amino acid sequence of SEQ ID NO: 4, SEQ ID NO: 5, and SEQ ID NO: 6, respectively;

(b) an effector agent that is conjugated to said recombinant antibody; and

wherein said immunoconjugate is administered at a dose from about 1.0 to about 5.0 mg/kg.

61. The method of claim 60, wherein said cancer is prostate cancer.

62. The method of claim 61, wherein said prostate cancer is metastatic castration resistant prostate cancer.

63. The method of claim 60, wherein said cancer is multiple myeloma.

64. The method of claim 63, wherein said multiple myeloma is relapsed or refractory multiple myeloma

65. The method of any one of claims 60 - 64, further comprising detecting CD46 expression in a cell of said cancer.

66. The method of claim 65, wherein said detecting comprises immunofluorescence microscopy or immunohistochemistry.

67. The method of claim 65, wherein said detecting comprises flow cytometry.

68. The method of claim 65, wherein said detecting comprises detecting an amplification of chromosome location 1q21.

69. The method of any one of claims 60 - 68, wherein said cancer has higher CD46 expression than a non-cancerous tissue of the same tissue type from the subject or from a healthy individual.

70. The method of any one of claims 60 - 68, wherein said cancer comprises a copy number increase of chromosome band 1q21.

71. The method of any one of claims 60 - 70, wherein said immunoconjugate is administered at a dose from about 1.0 to about 4.5 mg/kg, about 1.0 to about 4.0 mg/kg, about 1.0 to about 3.5 mg/kg, about 1.0 to about 3.0 mg/kg, about 1.0 to about 2.7 mg/kg, about 1.0 to about 2.5 mg/kg, about 1.0 to about 2.4 mg/kg, about 1.5 to about 4.5 mg/kg, about 1.5 to about 4.0 mg/kg, about 1.5 to about 3.5 mg/kg, about 1.5 to about 3.0 mg/kg, about 1.5 to about 2.7 mg/kg, about 1.5 to about 2.5 mg/kg, about 1.5 to about 2.4 mg/kg, about 1.5 to about 2.0 mg/kg, about 1.8 to about 4.5 mg/kg, about 1.8 to about 4.0 mg/kg, about 1.8 to about 3.5 mg/kg, about 1.8 to about 3.0 mg/kg, about 1.8 to about 2.7 mg/kg, about 1.8 to about 2.5 mg/kg, about 1.8 to about 2.4 mg/kg, or about 1.8 to about 2.0 mg/kg.

72. The method of claim 71, wherein said immunoconjugate is administered at a dose of from about 1.2 to about 3.0 mg/kg.

73. The method of any one of claims 60 - 70, wherein said immunoconjugate is administered at a dose of about 1.0, about 1.1, about 1.2, about 1.3, about 1.4, about 1.5, about 1.6, about 1.7, about 1.8, about 1.9, about 2.0, about 2.1, about 2.2, about 2.3, about 2.4, about 2.5, about 2.6, about 2.7, about 2.8, about 2.9, about 3.0, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, or about 4.0 mg/kg.

74. The method of claim 73, wherein said immunoconjugate is administered at a dose of about 1.8, about 2.4, about 2.7, or about 3.0 mg/kg.

75. The method of claim 74, wherein said immunoconjugate is administered at a dose of about 1.8 mg/kg.

76. The method of claim 74, wherein said immunoconjugate is administered at a dose of about 2.4 mg/kg.

77. The method of claim 74, wherein said immunoconjugate is administered at a dose of about 2.7 mg/kg.

78. The method of claim 74, wherein said immunoconjugate is administered at a dose of about 3.0 mg/kg.

79. The method of any one of claims 71 - 78, wherein the weight, in kg, of said human subject is an actual body weight.

80. The method of any one of claims 71 - 78, wherein the weight, in kg, of said human subject is an adjusted body weight.

81. The method of any one of claims 71 - 78, wherein the weight, in kg, of said human subject is:

an actual body weight of said human subject if the actual body weight of said human subject is less than an adjusted body weight of said subject;

an adjusted body weight of said human subject if

the actual body weight of said human subject is greater than or equal to an adjusted body weight of said subject, and

the adjusted body weight of said human subject is less than 100 kg; or

100 kg if the adjusted body weight of said human subject is greater than or equal to 100 kg

82. The method of any one of claims 60 - 81, wherein said recombinant antibody is administered to said human subject via intravenous infusion.

83. The method of any one of claims 60 - 82, wherein said recombinant antibody is administered to said human subject every 7 days, every 14 days, every 18 days, every 21 days, or every 30 days.

84. The method of claim 83, wherein said recombinant antibody is administered to said human subject every 21 days over at least three cycles.

85. The method of any one of claims 60 - 84, wherein said effector agent comprises a drug (or a prodrug thereof), a peptide, a protein, a detectable label, a liposome containing a drug (or prodrug thereof), a radionuclide, a viral particle, or a chelate.

86. The method of claim 85, wherein said effector agent comprises a drug.

87. The method of claim 86, wherein said drug is an anti-cancer drug.

88. The method of claim 86 or claim 87, wherein said drug is a chemotherapeutic agent.

~~89. The method of claim 86, claim 87, or claim 88, wherein said drug is a microtubule inhibitor, a DNA-damaging agent, or a polymerase inhibitor.~~

~~90. The method of claim 89, wherein said drug is a microtubule inhibitor.~~

~~91. The method of claim 90, wherein said microtubule inhibitor is an auristatin (or a derivative thereof), dolastatin-10 (or a derivative thereof), or maytansine (or a derivative thereof).~~

~~92. The method of claim 90 or 91, wherein said microtubule inhibitor is monomethylauristatin F (MMAF), auristatin E (AE), monomethylauristatin E (MMAE), valine-citrulline MMAE (vcMMAE), or valine-citrulline MMAF (vcMMAF).~~

~~93. The method of claim 92, wherein said microtubule inhibitor is monomethylauristatin E (MMAE).~~

~~94. The method of any one of claims 60 - 93, wherein a ratio of said effector agent to said recombinant antibody is from about 3 to about 5.~~

~~95. The method of claim 94, wherein the ratio of said effector agent to said recombinant antibody is about 4.~~

~~96. The method of any one of claims 60 - 95, wherein said effector agent is conjugated to said recombinant antibody via a linker.~~

~~97. The method of claim 96, wherein said linker is a peptide linker, a small molecule linker, or a linker that comprises a peptide and a small molecule.~~

~~98. The method of claim 97, wherein said linker comprises maleimidocaproyl-valine-citrulline-para-amino benzyloxycarbonyl (mc-vc-PAB).~~

~~99. The method of any one of claims 60 - 98, wherein said immunoconjugate binds CD46 expressed on the surface of a cell and is internalized into said cell.~~

~~100. The method of claim 99, wherein said immunoconjugate is internalized into said cell via macropinocytosis.~~

~~4~~101. Use of an~~An~~ immunoconjugate or pharmaceutical composition of any one of claims 1 to 3~~comprising:~~

~~a recombinant antibody comprising:~~

~~a first heavy chain comprising SEQ ID NO: 9,~~

~~a first light chain comprising SEQ ID NO: 10,~~

~~a second heavy chain comprising SEQ ID NO: 9, and~~

~~a second light chain comprising SEQ ID NO: 10; and~~

~~one, two, three or four pairs of adducts;~~

~~wherein each adduct of said one, two, three or four pairs of adducts comprises a monomethylauristatin E (MMAE) that is conjugated to said recombinant antibody via a maleimidocaproyl-valine-citrulline-para-amino benzyloxycarbonyl (mc-vc-PAB) linker;~~

~~wherein each of said one, two, three, or four pairs of adducts is conjugated to a pair of cysteine residues of said recombinant antibody,~~

~~wherein said pairs of cysteine residues are selected from:~~

~~C219 of the first heavy chain and C214 of the first light chain,~~

~~C219 of the second heavy chain and C214 of the second light chain,~~

~~C225 of the first heavy chain and C225 of the second light chain, and~~

~~C228 of the first heavy chain and C228 of the second light chain;~~

in the manufacture of a medicament for the treatment of a cancer in a human subject comprising a cell expressing CD46.

5102. The ~~immunoconjugate~~use of claim 4101, wherein said cancer is relapsed or refractory multiple myeloma (RRMM).

6103. The ~~immunoconjugate~~use of claim 4101, wherein said cancer is metastatic castration resistant prostate cancer (mCRPC).

~~104. The immunoconjugate of any one of claim 101 - 103, wherein said immunoconjugate comprises two pairs of said adducts.~~

7105. The ~~immunoconjugate~~use of any one of claim 4101 - 6104, wherein said cell comprises CD46 as determined by immunofluorescence microscopy or immunohistochemistry~~.~~ or

~~106. The immunoconjugate of any one of claim 101 - 104, wherein said cell comprises CD46 as determined~~ by flow cytometry.

8107. The ~~immunoconjugate~~use of any one of claim 4101 - 6104, wherein said cell comprises an amplification of chromosome location 1q21.

9108. The ~~immunoconjugate~~use of any one of claim 4101 - 8107, wherein said immunoconjugate is formulated for intravenous infusion.

10109. The ~~immunoconjugate~~use of any one of claim 4101 - 9108, wherein said immunoconjugate is to be administered to said human subject every 7 days, every 14 days, every 18 days, every 21 days, every 28 days, or every month, most preferably~~.~~

~~110. The immunoconjugate of claim 109, wherein said immunoconjugate is administered to said human subject~~ every 21 days.

11111. The ~~immunoconjugate~~use of any one of claims 4101 - 10110, wherein said immunoconjugate is to be administered at a dose from about 1.2 to about 3.0 mg/kg, which is optionally~~.~~

~~112. The immunoconjugate of claim 111, wherein said recombinant antibody is administered at a dose of~~ about 1.8, about 2.4, about 2.7, or about 3.0 mg/kg.

12113. The ~~immunoconjugate~~use of ~~any one of~~ claim~~s~~ 11111 - 112, wherein the weight, in kg, of said human subject is an actual body weight.

13114. The ~~immunoconjugate~~use of ~~any one of~~ claim~~s~~ 11111 - 112, wherein the weight, in kg, of said human subject is an adjusted body weight.

14115. The ~~immunoconjugate~~use of ~~any one of~~ claim~~s~~ 11111 - 112, wherein the weight, in kg, of said human subject is:

an actual body weight of said human subject if the actual body weight of said human subject is less than an adjusted body weight of said subject;

an adjusted body weight of said human subject if

the actual body weight of said human subject is greater than or equal to an adjusted body weight of said subject, and

the adjusted body weight of said human subject is less than 100 kg; or

100 kg if the adjusted body weight of said human subject is greater than or equal to 100 kg.

~~116. An immunoconjugate for the treatment of metastatic castration resistant prostate cancer in a human subject in need thereof comprising,~~

~~(i) a recombinant antibody that specifically binds CD46 that comprises heavy chain (HC) variable region that comprises three complementarity determining regions (CDRs): HC CDR1, HC CDR2 and HC CDR3 and the light chain comprises a light chain (LC) variable region comprising three CDRs: LC CDR1, LC CDR2, and LC CDR3, wherein said HC CDR1, HC CDR2, HC CDR3 comprise an amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, and SEQ ID NO: 3, respectively, and LC CDR1, LC CDR2, and LC CDR3 comprise an amino acid sequence of SEQ ID NO: 4, SEQ ID NO: 5, and SEQ ID NO: 6, respectively; conjugated to~~

~~(ii) monomethylauristatin E (MMAE) via a linker, wherein said linker comprises maleimidocaproyl-valine-citrulline-para-amino benzyloxycarbonyl (mc-vc-PAB), wherein said immunoconjugate is administered at a dose of from about 1.2 to about 3.0 mg/kg.~~

~~117. An immunoconjugate for the treatment of refractory multiple myeloma in a human subject in need thereof comprising,~~

~~(i) a recombinant antibody that specifically binds CD46 that comprises heavy chain (HC) variable region that comprises three complementarity determining regions (CDRs): HC CDR1, HC CDR2 and HC CDR3 and the light chain comprises a light chain (LC) variable region comprising three CDRs: LC CDR1, LC CDR2, and LC CDR3, wherein said HC CDR1, HC CDR2, HC CDR3 comprise an amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, and SEQ ID NO: 3, respectively, and LC CDR1, LC CDR2, and LC CDR3 comprise an amino acid sequence of SEQ ID NO: 4, SEQ ID NO: 5, and SEQ ID NO: 6, respectively; conjugated to~~

~~(ii) monomethylauristatin E (MMAE) via a linker, wherein said linker comprises maleimidocaproyl-valine-citrulline-para-amino benzyloxycarbonyl (mc-vc-PAB), wherein said immunoconjugate is administered at a dose of from about 1.8 to about 3.0 mg/kg.~~

~~118. The immunoconjugate of any one of claims 116 - 117, wherein the weight, in kg, of said human subject is an actual body weight.~~

~~119. The immunoconjugate of any one of claims 116 - 117, wherein a calculated weight, in kg, of said human subject is an adjusted body weight.~~

~~120. The immunoconjugate of any one of claims 116 - 117, wherein a calculated weight, in kg, of said human subject is:~~

~~an actual body weight of said human subject if the actual body weight of said human subject is less than an adjusted body weight of said subject;~~

~~an adjusted body weight of said human subject if~~

~~the actual body weight of said human subject is greater than or equal to an adjusted body weight of said subject, and~~

~~the adjusted body weight of said human subject is less than 100 kg; or~~

~~100 kg if the adjusted body weight of said human subject is greater than or equal to 100 kg.~~

~~121. The immunoconjugate of any one of claim 116 - 120, wherein said cell comprises CD46 as determined by immunofluorescence microscopy or immunohistochemistry.~~

122. The immunoconjugate of any one of claim 116 - 120, wherein said cell comprises CD46 as determined by flow cytometry.

123. The immunoconjugate of any one of claim 116 - 120, wherein said cell comprises an amplification of chromosome location 1q21.

124. The immunoconjugate of any one of claim 116 - 123, wherein said immunoconjugate is formulated for intravenous infusion.

125. The immunoconjugate of any one of claims 116 - 124, wherein said immunoconjugate is administered to said human subject every 7 days, every 14 days, every 18 days, every 21 days, every 28 days, or every month.

126. The immunoconjugate of claim 125, wherein said immunoconjugate is administered to said human subject every 21 days over at least three cycles.

127. An immunoconjugate for treating cancer in a human subject in need thereof comprising:

(a) a recombinant antibody that specifically binds CD46 that comprises a heavy chain (HC) variable region that comprises three complementarity determining regions (CDRs): HC CDR1, HC CDR2 and HC CDR3 and a light chain (LC) variable region that comprises three CDRs: LC CDR1, LC CDR2, and LC CDR3, wherein said HC CDR1, HC CDR2, HC CDR3 comprise an amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, and SEQ ID NO: 3, respectively, and said LC CDR1, LC CDR2, and LC CDR3 comprise an amino acid sequence of SEQ ID NO: 4, SEQ ID NO: 5, and SEQ ID NO: 6, respectively;

(b) an effector agent that is conjugated to said recombinant antibody; and

wherein said immunoconjugate is administered at a dose from about 1.0 to about 5.0 mg/kg.

128. The immunoconjugate of claim 127, wherein said cancer is prostate cancer.

129. The immunoconjugate of claim 128, wherein said prostate cancer is metastatic castration resistant prostate cancer.

130. The immunoconjugate of claim 127, wherein said cancer is multiple myeloma.

131. The immunoconjugate of claim 130, wherein said multiple myeloma is relapsed or refractory multiple myeloma.

132. The immunoconjugate of any one of claims 127 - 131, wherein said cancer comprises a cell that expresses CD46 as determined by immunofluorescence microscopy or immunohistochemistry.

133. The immunoconjugate of any one of claims 127 - 131, wherein said cancer comprises a cell that expresses CD46 as determined by flow cytometry.

134. The immunoconjugate of any one of claims 127 - 131, wherein said cancer comprises an amplification of chromosome location 1q21.

135. The immunoconjugate of any one of claims 127 - 131, wherein said cancer has higher CD46 expression than a non-cancerous tissue of the same tissue type from the subject or from a healthy individual.

136. The immunoconjugate of any one of claims 127 - 135, wherein said immunoconjugate is administered at a dose from 1.0 to 4.5 mg/kg, 1.0 to 4.0 mg/kg, 1.0 to 3.5 mg/kg, 1.0 to 3.0 mg/kg, 1.0 to 2.7 mg/kg, 1.0 to 2.5 mg/kg, 1.0 to 2.4 mg/kg, 1.5 to 4.5 mg/kg, 1.5 to 4.0 mg/kg, 1.5 to 3.5 mg/kg, 1.5 to 3.0 mg/kg, 1.5 to 2.7 mg/kg, 1.5 to 2.5 mg/kg, 1.5 to 2.4 mg/kg, 1.5 to 2.0 mg/kg, 1.8 to 4.5 mg/kg, 1.8 to 4.0 mg/kg, 1.8 to 3.5 mg/kg, 1.8 to 3.0 mg/kg, 1.8 to 2.7 mg/kg, 1.8 to 2.5 mg/kg, 1.8 to 2.4 mg/kg, or 1.8 to 2.0 mg/kg.

~~137. The immunoconjugate of claim 136, wherein said immunoconjugate is administered at a dose of from about 1.2 to about 3.0 mg/kg.~~

~~138. The immunoconjugate of any one of claims 127 - 137, wherein said immunoconjugate is administered at a dose of 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, or 4.0 mg/kg.~~

~~139. The immunoconjugate of claim 138, wherein said immunoconjugate is administered at a dose of 1.8, 2.4, 2.7, or 3.0 mg/kg.~~

~~140. The immunoconjugate of claim 139, wherein said immunoconjugate is administered at a dose of about 1.8 mg/kg.~~

~~141. The immunoconjugate of claim 139, wherein said immunoconjugate is administered at a dose of about 2.4 mg/kg.~~

~~142. The immunoconjugate of claim 139, wherein said immunoconjugate is administered at a dose of about 2.7 mg/kg.~~

~~143. The immunoconjugate of claim 139, wherein said immunoconjugate is administered at a dose of about 3.0 mg/kg.~~

~~144. The immunoconjugate of any one of claims 136 - 143, wherein the weight, in kg, of said human subject is an actual body weight.~~

~~145. The immunoconjugate of any one of claims 136 - 143, wherein the weight, in kg, of said human subject is an adjusted body weight.~~

~~146. The immunoconjugate of any one of claims 136 - 143, wherein the weight, in kg, of said human subject is:~~

~~an actual body weight of said human subject if the actual body weight of said human subject is less than an adjusted body weight of said subject;~~

~~an adjusted body weight of said human subject if~~

~~the actual body weight of said human subject is greater than or equal to an adjusted body weight of said subject, and~~

~~the adjusted body weight of said human subject is less than 100 kg; or~~

~~100 kg if the adjusted body weight of said human subject is greater than or equal to 100 kg~~

~~147. The immunoconjugate of any one of claims 136 - 146, wherein said recombinant antibody is formulated for intravenous infusion.~~

~~148. The immunoconjugate of any one of claims 136 - 147, wherein said recombinant antibody is administered to said human subject every 7 days, every 14 days, every 18 days, every 21 days, or every 30 days.~~

~~149. The immunoconjugate of claim 148, wherein said recombinant antibody is administered to said human subject every 21 days.~~

~~150. The immunoconjugate of any one of claims 136 - 149, wherein said effector agent comprises a drug (or a prodrug thereof), a peptide, a protein, a detectable label, a liposome containing a drug (or prodrug thereof), a radionuclide, a viral particle, or a chelate.~~

~~151. The immunoconjugate of claim 150, wherein said effector agent comprises a drug.~~

~~152. The immunoconjugate of claim 151, wherein said drug is an anti-cancer drug.~~

~~153. The immunoconjugate of claim 150 or claim 151, wherein said drug is a chemotherapeutic agent.~~

~~154. The immunoconjugate of claim 150, claim 151, or claim 152, wherein said drug is a microtubule inhibitor, a DNA-damaging agent, or a polymerase inhibitor.~~

~~155. The immunoconjugate of claim 150, wherein said drug is a microtubule inhibitor.~~
~~156. The immunoconjugate of claim 155, wherein said microtubule inhibitor is an auristatin (or a derivative thereof), dolastatin-10 (or a derivative thereof), or maytansine (or a derivative thereof).~~
~~157. The immunoconjugate of claim 155 or 156, wherein said microtubule inhibitor is monomethylauristatin F (MMAF), auristatin E (AE), monomethylauristatin E (MMAE), valine-citrulline MMAE (vcMMAE), or valine-citrulline MMAF (vcMMAF).~~
~~158. The immunoconjugate of claim 157, wherein said microtubule inhibitor is monomethylauristatin E (MMAE).~~
~~159. The immunoconjugate of any one of claims 127- 158, wherein a ratio of said effector agent to said recombinant antibody is from about 3 to about 5.~~
~~160. The immunoconjugate of claim 159, wherein the ratio of said effector agent to said recombinant antibody is about 4.~~
~~161. The immunoconjugate of any one of claims 127- 160, wherein said effector agent is conjugated to said recombinant antibody via a linker.~~
~~162. The immunoconjugate of claim 161, wherein said linker is a peptide linker, a small molecule linker, or a linker that comprises a peptide and a small molecule.~~
~~163. The immunoconjugate of claim 162, wherein said linker comprises maleimidocaproyl-valine-citrulline-para-amino benzyloxycarbonyl (mc-vc-PAB).~~
~~164. The immunoconjugate of any one of claims 127- 163, wherein said immunoconjugate binds CD46 expressed on the surface of a cell and is internalized into said cell.~~
~~165. The immunoconjugate of claim 164, wherein said immunoconjugate is internalized into said cell via macropinocytosis.~~

15~~166~~. Use of ~~A~~a pharmaceutical formulation in the manufacture of a medicament for the treatment of metastatic castration resistant prostate cancer in a human subject in need thereof, wherein the pharmaceutical formulation comprises~~ing~~ an immunoconjugate at a concentration of about 10.0 ± 1.0 mg/mL, wherein the immunoconjugate comprises:

a recombinant antibody comprising:

a first heavy chain comprising SEQ ID NO: 9,
a first light chain comprising SEQ ID NO: 10,
a second heavy chain comprising SEQ ID NO: 9, and
a second light chain comprising SEQ ID NO: 10; and

one, two, three or four pairs of adducts;

wherein each adduct of said one, two, three or four pairs of adducts comprises a monomethylauristatin E (MMAE) that is conjugated to said recombinant antibody via a maleimidocaproyl-valine-citrulline-para-amino benzyloxycarbonyl (mc-vc-PAB) linker;

wherein each of said one, two, three, or four pairs of adducts is conjugated to a pair of cysteine residues of said recombinant antibody,

wherein said pairs of cysteine residues are selected from:

C219 of the first heavy chain and C214 of the first light chain;
C219 of the second heavy chain and C214 of the second light chain;
C225 of the first heavy chain and C225 of the second ~~light~~ heavy chain; and
C228 of the first heavy chain and C228 of the second ~~light~~ heavy chain.

about 20 mM histidine buffer at pH 6.0,

about 8.0% sucrose, and

about 0.01% polysorbate 80.

~~167. A pharmaceutical formulation for the treatment of refractory multiple myeloma in a human subject in need thereof comprising an immunoconjugate a concentration of about 10.0 ± 1.0 mg/mL, wherein the immunoconjugate comprises:~~

~~a recombinant antibody comprising:~~

~~a first heavy chain comprising SEQ ID NO: 9,~~

~~a first light chain comprising SEQ ID NO: 10,~~

~~a second heavy chain comprising SEQ ID NO: 9, and~~

~~a second light chain comprising SEQ ID NO: 10; and~~

~~one, two, three or four pairs of adducts;~~

~~wherein each adduct of said one, two, three or four pairs of adducts comprises a monomethylauristatin E (MMAE) that is conjugated to said recombinant antibody via a maleimidocaproyl-valine-citrulline-para-amino benzyloxycarbonyl (mc-vc-PAB) linker;~~

~~wherein each of said one, two, three, or four pairs of adducts is conjugated to a pair of cysteine residues of said recombinant antibody,~~

~~wherein said pairs of cysteine residues are selected from:~~

~~C219 of the first heavy chain and C214 of the first light chain;~~

~~C219 of the second heavy chain and C214 of the second light chain;~~

~~C225 of the first heavy chain and C225 of the second light chain; and~~

~~C228 of the first heavy chain and C228 of the second light chain,~~

~~about 20 mM histidine buffer at pH 6.0,~~

~~about 8.0% sucrose, and~~

~~about 0.01% polysorbate 80.~~

16. The immunoconjugate or pharmaceutical composition of any one of claims 1 to 3 or the pharmaceutical formulation of claim 15 for use in therapy.